Increased rate of spinal trabecular bone loss in patients with inflammatory bowel disease

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SUMMARY   The rate of spinal trabecular bone loss during one year was measured in 54 patients with inflammatory bowel disease. The mean change in spinal bone mineral content was $-5 \cdot 1$ mg/ml K_2HPO_4, representing 3% of the initial bone mineral content. The rate of bone loss showed a significant negative correlation with body mass index ($r = -0 \cdot 276$, $p < 0 \cdot 05$) but no other significant correlations were found with other clinical or biochemical indices, including the total amount of prednisolone taken during the course of the study. Eleven patients had bone loss greater than 15 mg/ml/year; these included four non-steroid treated patients, two of whom had disease confined to the large bowel. The results indicate rapid rates of bone loss in some patients with inflammatory bowel disease over the course of one year. Although steroid therapy and malnutrition are likely to be contributory factors in some patients, other, as yet unidentified, risk factors also operate. The rapid bone loss observed in some patients emphasises the need for effective prophylactic regimes.

Osteoporosis has been reported in association with intestinal disease[1-4] and we have recently shown an increased prevalence of spinal osteoporosis in a large unselected group of patients with inflammatory bowel disease, using quantitative computed tomography.[5] In some patients, particularly young women with amenorrhoea and high dose steroid therapy, severe clinical manifestations of osteoporosis were seen with bone pain, spinal deformity and height loss resulting from vertebral crush fractures.

The development of quantitative computed tomography[6] for the assessment of bone mineral content has enabled, for the first time, measurements at these clinically relevant sites of sufficient precision for rates of bone loss to be calculated; however, to date no longitudinal measurements of spinal bone density have been reported in intestinal disease. We have done repeat measurements of spinal trabecular bone mineral content in 54 patients with inflammatory bowel disease after a period of one year, in order to assess the rate of bone loss in such patients and to identify further the risk factors involved in the

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development of osteoporosis associated with intestinal disease.

Methods

PATIENTS
Seventy five consecutive patients, 46 women, with inflammatory bowel disease who were attending a gastroenterology clinic had initial measurements of spinal trabecular bone mineral content. Fifty four (72%) of these aged 22–78 years (mean 47), 33 women, attended after a period of 10–18 months (mean 13·8) for repeat measurement. Of these 54 patients, 27 had small intestinal disease (Crohn's disease 26, carcinoid one) and 21 had large intestinal disease (19 ulcerative colitis, two Crohn's colitis). Six patients had Crohn's disease affecting both small and large bowel. Of the 34 patients with Crohn's disease, all but three had undergone at least one small intestinal resection. The total lifetime dose of prednisolone at the start of the study ranged between 0 and 81 g (median 3·5 g). During the year between the initial study and the repeat measurement, 29 of the 54 patients received prednisolone, the total dose during this period ranging from 0·32–7·3 g (median

2·75 g). Four patients were taking 1 α-hydroxyvitamin D_3, three were taking calcium and vitamin D tablets BPC, one was taking calcium supplements, and two were taking hormone replacement therapy. The body mass index was calculated as weight/(height)^2.

BIOCHEMISTRY

Non-fasting serum calcium, phosphate, alkaline phosphatase, and albumin were measured by standard Technicon Autoanalyser methods.

MEASUREMENT OF BONE MINERAL CONTENT

Mineral concentrations in the anterior part of the first, second, and third lumbar vertebral bodies were measured with a Philips 350 x-ray computed tomography (CT) scanner, using a modification of the method of Cann and Genant.[7] 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 mean CT number within the vertebral body of L_1, L_2, and L_3 was compared with those of the salt solutions. In this way, mineral concentrations were calculated in terms of the equivalent concentration of K_2HPO_4 solution, a salt which has similar radiographic attenuation properties to 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. The
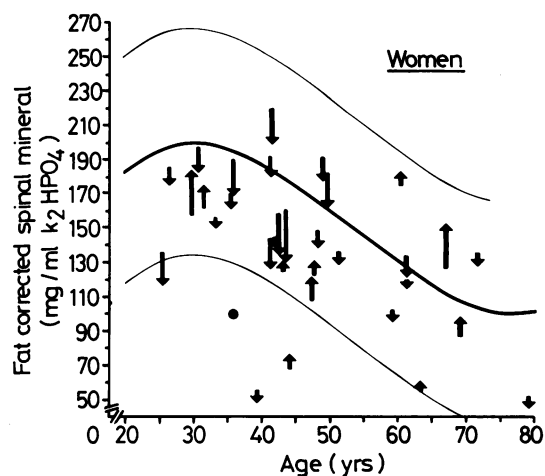

Fig. 1 *Rates of spinal trabecular bone loss in female patients with inflammatory bowel disease. Results are expressed in terms of the equivalent concentration of K_2HPO_4. The arrows indicate the magnitude and direction of change. The normal values, taken from the data of Cann and Genant[7] are shown as the mean value (heavy line) ±2SD (light lines).*
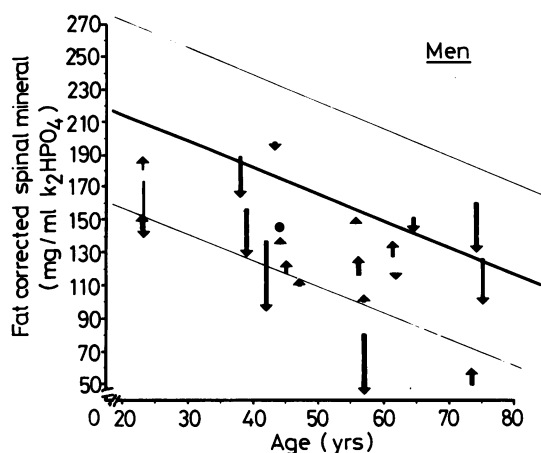

Fig. 2 *Rates of spinal trabecular bone loss in male patients with inflammatory bowel disease. Results are expressed in terms of the equivalent concentration of K_2HPO_4. The arrows indicate the magnitude and direction of change. The normal values taken from the data of Cann and Genant[7] are shown as the mean value (heavy line) ±2SD (light lines).*

non-mineral or soft tissue component consists of red marrow, yellow marrow, and the collagen matrix, the partial attenuation coefficients of each of these tissues being found from published values of density and percentage by weight of constituent elements, together with interpolated values of atomic cross sections.[8] Normal values were obtained from the data of Cann and Genant,[7] to which the same correction procedure had been applied. The short term *in vivo* reproducibility of the measurement in our hands, assessed by repeat measurements in six subjects over a period of six hours or less, is 2·3%. The long term *in vitro* precision, studied by carrying out repeat measurements on a phantom after a period of 12–18 months (total 14 measurements) was 1·2%. The combined precision was calculated as $\sqrt{(2·3^2+(1·2)^2}$ =2·6%, corresponding to 3·1 mg/ml K_2HPO_4.[9]

STATISTICAL ANALYSIS

For normally distributed data, correlations were examined by linear regression analysis. Where data were non-normally distributed, a Mann-Whitney rank correlation was used. The significance of correlation coefficients was established using a two-tailed *t* test.

Results

The change in spinal bone mineral content, corrected in each patient to give the rate of bone loss or gain per annum, is shown for women in Figure 1 and for men in Figure 2. Twenty nine patients (54%) showed a

decrease, 16 (30%) showed an increase, and 9 (16%) did not change. The change in spinal bone mineral content, expressed in absolute terms, ranged from +10·8 mg/ml K_2HPO_4 to −37·0 mg/ml (mean −5·1). Expressed as a percentage of the initial bone mineral content, the change ranged from +27·0% to −47·0% (mean −3). No significant correlation was found between the rate of bone loss and serum calcium, phosphate, albumin, alkaline phosphatase, body weight, body height, duration of disease or total dose of prednisolone during the time over which the study was carried out. There was a significant negative correlation, however, between the body mass index and rate of bone loss (r= −0·276, p<0·05).

As the combined precision of the method of measurement was 2·6% or 3·1 mg/ml K_2HPO_4, differences greater than 9·3 mg/ml K_2HPO_4 should be reliably detectable in an individual; to allow for some margin of additional error we chose a point of 15 mg/ml above which changes could definitely be regarded as significant. Eleven patients, seven men, aged 23–74 years (median 42) showed a decrease in bone mineral content >15 mg/ml K_2HPO_4/year. The decrease ranged from 17–37 mg/ml (mean 25), representing a decrease of 7·7–46.3% (mean 18) of the initial bone mineral content. Of these 11 patients, four had ulcerative colitis, six Crohn's disease and one carcinoid. Further details of these patients are shown in the Table. The total dose of prednisolone during the course of the study ranged from 0–7·9 g (median 2·95); seven of the 11 patients (64%) had received prednisolone during the study. Of the four patients with rapid bone loss who had not received steroids, two had small bowel disease with resections and two had ulcerative colitis. All the four women in this group were premenopausal and menstruating regularly. Of the two patients receiving hormone

replacement therapy, one showed an increase of 5 mg/ml K_2HPO_4/yr and the other a decrease of 8 mg/ml K_2HPO_4/yr.

Two patients, both women, aged 30 and 67 years, showed an increase in bone mineral content >15 mg/ml K_2HPO_4 (30 and 20 mg/ml respectively) representing percentage increases of 19 and 15·9% of the initial bone mineral content. Neither of these patients was receiving oestrogen therapy and both had been treated with prednisolone during the course of the study (total dose 1·7 and 0·4 g respectively).

Discussion

Our results show rapid rates of bone loss over the course of one year in some patients with inflammatory bowel disease. As would be expected in this group of patients, in whom the mean age was 47 years, the mean change in spinal bone mineral content was negative (−5·1 mg/ml K_2HPO_4/yr or 3% of the original bone mineral content). Eleven patients (20%) showed a decrease of 15 mg/ml or more whilst two female patients showed increases of >15 mg/ml. The cut off point of 15 mg/ml K_2HPO_4 was chosen as one above which changes could definitely be regarded as significant, bearing in mind the combined precision of the method and allowing some margin for additional errors. Although it may be important to identify these patients for clinical reasons, they should not be regarded as a separate group and it would be statistically invalid to compare them with the remaining patients. In one of the patients with an increase >15 mg/ml who was aged 30 years, this may have represented a normal increment in bone mineral content during the attainment of peak bone mass but in the other, who was aged 67 years, the increase is more difficult to explain and was

Table   *Clinical details of patients with a decrease in bone mineral content >15 mg/ml/year*

Patient no	Sex	Age (yrs)	Disease	SB disease	LB disease	SB resection	Serum albumin (g/l)	Body weight (kg)	Total dose prednisolone* (g)	Absolute decrease BMC (mg/ml/yr)	% Decrease BMC %/yr
1	M	59	CD	+	−	×2	37	43·5	3·7	37	46·3
2	F	42	CD	+	−	×1	40	52·8	2·4	21	13·2
3	M	23	CD	−	+	0	51	91·8	7·9	31	17·8
4	M	39	UC	−	+	0	43	82·8	3·2	26	16·7
5	F	42	CD	+	−	×1	35	47·2	7·6	24	14·9
6	M	38	UC	−	+	0	36	53·4	6·2	22	11·6
7	M	41	CD	+	−	×2	41	56·6	8·0	37	27·0
8	F	42	CD	+	−	×2	41	55·2	0·00	17	7·7
9	F	49	UC	−	+	0	50	58·3	0·00	17	9·3
10	M	74	UC	−	+	0	41	78·2	0·00	22	17·5
11	M	73	Carcinoid	+	−	×3	35	59·8	0·00	25	15·5

SB=small bowel; LB=large bowel; *=represents total dose of prednisolone given over the course of the study.

not associated with any marked change in her clinical condition.

The rate of bone loss from the spine in normal subjects varies with age and sex, bone loss being most rapid in women during and immediately after the menopause. The approximate expected rate of bone loss in normal subjects can be inferred from the slopes shown in Figures 1 and 2, although these are derived from cross sectional data; both the data from Cann and Genant[10] and others from another cross sectional study[11] indicate a curvilinear decrease of 2·4% in spinal bone mineral content in women whilst in men, there is a linear decrease of 1·2.[12] The age of onset of bone loss is disputed, but may be as early as 30–35 years in women.[13] Rather lower rates of bone loss were reported in normal women by Riggs *et al* in a longitudinal study;[13] using dual photon absorptiometry to measure bone mineral content in the spine, these workers found a mean annual rate of bone loss of 1·2% and were unable to show any difference in the rate of bone loss between pre and postmenopausal women. In contrast, Genant *et al*[14] reported a rate of bone loss of 6%/year in a longitudinal study of women who had undergone oophorectomy; these differences may be because of the different techniques used to measure bone mineral content, as quantitative computed tomography measures trabecular bone only, whereas dual photon absorptiometry includes cortical bone and any extraskeletal calcification in the field of measurement. Alternatively, the rate of bone loss after oophorectomy may be faster than after a natural menopause. It is also important to remember that bone loss may be phasic[15] and thus results from longitudinal studies carried out over relatively short periods of time may be misleading. This reservation also applies to the present study and further studies are in progress to see if the rapid rates of bone loss observed in some patients are maintained.

The pathogenesis of osteoporosis associated with inflammatory bowel is incompletely understood, but corticosteroid therapy is likely to contribute in some patients. The deleterious effects of steroids on trabecular bone mass are well documented[16 17] and in our previous study of patients with inflammatory bowel disease those patients with osteoporosis had received a significantly higher lifetime dose of prednisolone than those with a normal bone mineral content.[5] In the present study, we were unable to show any significant correlation between the rate of bone loss and prednisolone therapy during the course of the study, and 36% of patients with the most rapid bone loss had not received steroids over the preceding year whilst other patients who were receiving high doses of steroids did not show such rapid bone loss. These findings indicate that whilst steroid therapy

may play a role in the pathogenesis of osteoporosis associated with inflammatory bowel disease, other factors are also important and can operate in the absence of steroid therapy; conversely, even relatively high doses of steroids are not inevitably accompanied by rapid bone loss.

Another factor which may contribute to osteoporosis in some women with inflammatory bowel disease is oestrogen deficiency and amenorrhoea appears to be a major risk factor in young women.[5] All four women in the group with the most rapid bone loss were premenopausal and menstruating regularly and none had menopausal symptoms. In view of their age, however, some degree of oestrogen deficiency cannot be excluded and, if present, may have contributed to bone loss.[18]

The relationship between the body mass index and rate of bone loss observed in this study suggests that the nutritional status and hence disease activity may be important determinants of bone loss in patients with inflammatory bowel disease. Disease activity could affect bone mass in several ways – for example, by increasing the likelihood of steroid therapy or by increasing calcium malabsorption in patients with active small bowel disease as a result of vitamin D deficiency,[19 20] rapid transit time, mucosal inflammation or intraluminal binding of calcium salts to fatty acids.[21] In addition, the nutritional status may directly affect bone mass, particularly if protein-calorie malnutrition is present.[22]

The increased prevalence of osteoporosis in association with inflammatory bowel disease and the presence of severe clinical effects of bone loss in some relatively young patients emphasise the importance of identifying those most at risk and establishing effective prophylaxis, particularly in view of the good prognosis of Crohn's disease in most patients.[23] The pathogenesis of increased bone loss in these patients is likely to be multifactorial and whilst steroid therapy, oestrogen deficiency and malnutrition are all probable contributory factors, further studies are required to define risk factors more clearly. Until effective forms of prophylaxis have been established it seems advisable to advocate hormone replacement therapy for female patients with secondary amenorrhoea and for those entering the menopause; implant or percutaneous preparations may be preferable to oral forms because of variable intestinal absorption in some patients. In addition, steroid therapy should be constantly reviewed and kept to a minimum and a daily calcium intake of at least 1·5 g should be recommended.

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