Osteoporosis in patients with inflammatory bowel disease

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SUMMARY Bone mineral content in spinal trabecular and peripheral cortical bone was measured in 75 unselected patients with small or large intestinal inflammatory bowel disease. Osteoporosis, defined as a bone mineral content >2 SD below the age and sex matched normal mean value was present in 23 patients (30-6%). Three amenorrhoeic females aged 34, 38, and 42 years had severe clinical osteoporosis and a further three patients had one or more vertebral crush fractures. Eighteen of the 23 patients with osteoporosis had small intestinal disease with one or more resections and the mean lifetime steroid dose in those with osteoporosis was significantly higher than in those with normal bone mineral content. Bone mineral content in spinal trabecular bone showed significant negative correlations with lifetime steroid dose and serum alkaline phosphatase and a significant positive correlation with serum albumin. Peripheral cortical bone mineral content was positively correlated with body weight, height and body mass index. We conclude that the prevalence of osteoporosis is increased in patients with inflammatory bowel disease, severe clinical osteoporosis developing in some relatively young patients. The pathogenesis of this bone loss is probably multifactorial; steroid therapy is likely to be an important contributory factor.

Osteoporosis is known to occur in some patients with malabsorption although its prevalence has not been established using accurate diagnostic methods; possible pathogenetic factors include steroid therapy, calcium malabsorption, vitamin D deficiency and, in women, oestrogen deficiency. The accurate and reproducible measurement of bone mineral content at clinically relevant sites such as the vertebrae, femoral neck and radius, where osteoporotic fractures occur, using techniques such as quantitative computerised tomography and dual photon absorptiometry have greatly improved diagnostic sensitivity in osteoporosis, which can be defined as a bone mineral content at the chosen site >2 SD below the mean age and sex matched control value. Using this definition, we have examined the prevalence of spinal trabecular osteoporosis by quantitative computed tomography and of cortical osteoporosis at the radius using single photon absorptiometry in 75 unselected patients with small or large intestinal inflammatory bowel disease.

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Methods

Patients
Between November 1984 and July 1985 all patients with inflammatory bowel disease attending a gastroenterology clinic were asked by one of several doctors to take part in the study. A total of 75 accepted, 29 men, aged 20-81 years (median 41). Forty six had small intestinal disease (Crohn’s disease 45, carcinoid one) and of these, 39 had undergone one or more intestinal resections. Ten of the 46 patients with small bowel disease also had some large bowel involvement. Twenty nine patients had disease confined to the large bowel (idiopathic proctitis or proctocolitis 17, Crohn’s disease six, proctocolitis/Crohn’s undetermined four, collagenous colitis one). Sixteen patients (eight small bowel disease, eight large bowel disease) had never received steroid therapy; in the remaining patients, the total lifetime dose ranged from 560 mg–81 g (median 5.4 g). The duration of disease ranged from 0.2-32 years (median 10 years). Three patients, aged 34, 38, and 42 were amenorrhoeic; in the other women, the menstrual history was normal. Six patients were
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Taking 1α-hydroxyvitamin D₃, 1–3 μg daily, and three others were taking calcium and vitamin D tablets, BPC, one to three daily. Sixteen patients were taking oestrogen preparations, 10 for contraceptive purposes and six for menopausal symptoms.

**Body Mass Index**
The body mass index was calculated as weight/(height)² and expressed in kg/m².

**Dietary Calcium Intake**
Dietary calcium intake was assessed by an experienced dietician using the recall method.

**Biochemistry**
Non-fasting serum calcium, phosphate, total alkaline phosphatase and albumin were measured by standard Technicon Autoanalyser methods. Serum immunoreactive parathyroid hormone (iPTH) was measured by an N-terminal immunoradiometric assay using an antibody raised in sheep to synthetic 1–34 PTH peptide. Serum 25-hydroxyvitamin D (250HD) was measured by radioimmunoassay using antibody code 02282 (kindly supplied by Prof A D Care) after lipid extraction and reverse phase high performance liquid chromatography.

**Measurement of Bone Mineral Content**
Bone mineral content was measured at two sites—the left radius and the lumbar spine. The forearm measurement was done using single photon absorptiometry at a point a third of the distance between the styloid of the radius and the lateral epicondyle of the humerus. The absorption profile thus generated was analysed to yield the bone mineral content (in g/cm) and the bone width for the radius, and the ratio bone mineral content/bone width (in g/cm²). The reproducibility of the method in our hands is 2.5%. Results were compared with the normal values of Ringe, Rehpenning, and Kuhlencordt. Mineral concentrations in the anterior part of the first, second, and third lumbar vertebral bodies were measured with a Philips 350 x-ray CT scanner, using a modification of the method of Cann and Genant. 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 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 K₂HPO₄ solution, a salt which has similar radiograph 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. This 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. The results were then compared with similarly corrected published normal data. The reproducibility of the method in our hands is 2%.

**Statistical Analysis**
For normally distributed data, differences between groups were analysed using Student’s two-tailed unpaired t test and correlations were examined by linear regression analysis. Where data was non-normally distributed, Wilcoxon’s rank-sum-tests and Spearman’s rank correlation were used. Correlation coefficients were adjusted for age effects by calculating the partial correlation coefficient.

**Results**
Twenty three patients (30.7%) had cortical and/or trabecular osteoporosis, as defined by a bone mineral
content >2 SD below the age and sex matched control mean value (Figs 1-4). Altogether 18 patients had cortical osteoporosis (10 men, eight women) and 12 had trabecular osteoporosis (six men, six women). Seven patients (four women, three men) had both cortical and trabecular osteoporosis. Eleven of the 23 osteoporotic patients were men (37.9% of men studied) and 12 women (25.5% of women studied). Five of the patients with spinal trabecular osteoporosis and one patient with cortical osteoporosis had radiological evidence of one or more vertebral crush fractures. Three women, two with combined cortical and trabecular osteoporosis and one with trabecular osteoporosis only, aged 34, 38, and 42 years had severe clinical osteoporosis with multiple vertebral crush fractures, bone pain, kyphosis and loss of height. All three were amenorrhoeic and had received high dose steroid therapy (15, 36, and 37 g total lifetime dose respectively). Clinical details of these and the other three patients with vertebral fracture are shown in Table 1.

Comparison between patients with and without osteoporosis revealed no significant difference in age, duration of disease or serum biochemistry. The mean body weight and body mass index of patients with osteoporosis, however, was significantly less than in those without: in addition, the lifetime steroid dose was significantly higher in the patients with osteoporosis (Table 2). Eighteen of the 23 patients with osteoporosis had small bowel Crohn's disease with one or more resections; one had small bowel disease without resection and four had large bowel disease only. All but three of the patients with osteoporosis had received steroid therapy.

The bone mineral content in the lumbar spine showed a significant positive correlation with bone mineral content in the radius (r=0.370, p<0.005). Spinal bone mineral content also showed significant correlations with serum total alkaline phosphatase (r=-0.236, p<0.05) and serum albumin (r=0.302, p<0.05). There was a negative correlation with total lifetime steroid dose (r=-0.241; p<0.05). There were significant correlations between bone mineral content at the radius and body weight (r=0.412, p<0.001) height (r=0.335, p<0.005) and body mass index (r=0.276, p<0.05). Osteoporosis was present in four of the nine patients receiving vitamin D therapy. Four patients with osteoporosis were taking

Fig. 2 Fat corrected spinal trabecular bone mineral content in the male patients. Results are expressed as in Fig. 1, and the normal data are taken from Cann and Genant. The upper horizontal interrupted line indicates the level above which vertebral fractures are rare and the lower horizontal interrupted line indicates the level below which fractures are common.

Fig. 3 Bone mineral content/bone width ratio at the junction of the proximal two-thirds and distal one-third of the radius in the female patients. The normal data are taken from Ringe et al.
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Table 1  Clinical details of patients with vertebral fracture

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Body mass index (kg/m²)</th>
<th>Disease</th>
<th>Lifetime steroid duration of therapy (yr)</th>
<th>BMC/BW (g/cm²)</th>
<th>QCT (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>M</td>
<td>21.5</td>
<td>Crohn's SB, no resection</td>
<td>65</td>
<td>20</td>
<td>0.51</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>M</td>
<td>18.3</td>
<td>Crohn's SB, 1 resection</td>
<td>49</td>
<td>11</td>
<td>0.67</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>F</td>
<td>17.8</td>
<td>Crohn's SB, 3 resections</td>
<td>36</td>
<td>20</td>
<td>0.34</td>
</tr>
<tr>
<td>4</td>
<td>77</td>
<td>F</td>
<td>18.8</td>
<td>Crohn's SB, 1 resection</td>
<td>15</td>
<td>4</td>
<td>0.32</td>
</tr>
<tr>
<td>5</td>
<td>34</td>
<td>F</td>
<td>15.6</td>
<td>Crohn's SB, 2 resections</td>
<td>15</td>
<td>10</td>
<td>0.68</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>F</td>
<td>20.9</td>
<td>Crohn's SB, 5 resections</td>
<td>37</td>
<td>18</td>
<td>0.47</td>
</tr>
</tbody>
</table>

SB = small bowel; BMC/BW = bone mineral content/bone width ratio in radius; QCT = quantitative computed tomography.

Table 2  Clinical and biochemical parameters in patients with and without osteoporosis

<table>
<thead>
<tr>
<th></th>
<th>With (n =23) osteoporosis</th>
<th>without (n =52) osteoporosis</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>43.4±13.6</td>
<td>45.9±15.9</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>55.6±29.6</td>
<td>65.1±12.2</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>20.6±2.8</td>
<td>25.4±11.2</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Steroids (total lifetime dosage g)</td>
<td>14.6±7.2</td>
<td>2.4*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Duration of disease (yr)</td>
<td>12.0*</td>
<td>9.0*</td>
<td>NS</td>
</tr>
<tr>
<td>Corrected serum calcium mmol/l (Normal 2.6–2.60)</td>
<td>2.28±0.10</td>
<td>2.27±0.09</td>
<td>NS</td>
</tr>
<tr>
<td>Serum phosphate mmol/l (Normal 0.8–1.45)</td>
<td>1.10±0.16</td>
<td>1.12±0.18</td>
<td>NS</td>
</tr>
<tr>
<td>Serum alkaline phosphatase IU/l (Normal 30–115)</td>
<td>113±10*</td>
<td>49*</td>
<td>NS</td>
</tr>
<tr>
<td>Serum albumin g/l (Normal 35–45)</td>
<td>41.4±6.3</td>
<td>43.4±4.5</td>
<td>NS</td>
</tr>
<tr>
<td>Serum PTH ng/ml (Normal &lt;1)</td>
<td>0.4±0.3</td>
<td>0.3±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Serum 25OH D mmol/l (Normal 20–100)</td>
<td>42.3±9.0*</td>
<td>44.3±*</td>
<td>NS</td>
</tr>
<tr>
<td>Dietary calcium intake mmol/day</td>
<td>27±5.1</td>
<td>23±3.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

Results are expressed as mean±SD or median (*).

Discussion

Osteoporosis is a bone disease characterized by decreased bone mass and increased risk of fracture. It is a common condition in postmenopausal women, elderly people, and patients with various medical conditions, including inflammatory bowel disease. Evidence for an increased prevalence of peripheral cortical osteoporosis was also reported in these two studies and more recently Hylander et al1 found decreased bone mineral content in the radius in 11% of 64 patients with small intestinal resection. In the present study, the prevalence of cortical osteoporosis was 24%; possible reasons for the lower prevalence in the former study include the use of calcium supplementation in nearly one-third of patients and less frequent use of steroid therapy.

Although normal data published from other centres were used for comparison with our patients, the methodology for both the quantitative computed tomography and the single photon absorptiometry were very similar to those used by those centres and the small number of controls studied by us have been well within these normal ranges. Geographical differences in bone mineral content might also contribute to differences in normal ranges, particularly in the case of the spinal trabecular measurements which were carried out in California; however, Banks and Stevenson, using a similar method, reported values well within this normal range in 70 British postmenopausal women.16

As would be expected, the majority of patients with osteoporosis had small intestinal disease with one or more resections. The significance of the correlation between spinal bone mineral content and serum alkaline phosphatase is unclear; in the majority of patients with osteoporosis, osteomalacia was excluded by bone biopsy. Bone mineral content at both skeletal sites was significantly correlated with body weight; this may partly reflect the nutritional effects of severe inflammatory bowel disease. The relationship between peripheral cortical bone mineral content and body height as well as weight and body mass index would suggest that small, lean subjects are more prone to osteoporosis, presumably because they have a lower peak bone mass at maturity.

The pathogenesis of osteoporosis associated with intestinal disease has not been adequately studied but steroid therapy, calcium malabsorption, altered sex hormonal status, malnutrition and vitamin D...
deficiency are all possible factors. Steroid induced osteoporosis is well documented and in the present study the patients with osteoporosis had received significantly greater doses of steroids than those with normal bone mineral content. Oestrogen deficiency is known to be a major pathogenetic factor in postmenopausal bone loss and the presence of severe clinical osteoporosis in three young, amenorrhoeic women indicates that it may also play a role in osteoporosis associated with malabsorption. Menstrual abnormalities are common in patients with severe inflammatory bowel disease and the fertility rate is reduced in Crohn's disease, although probably normal in idiopathic proctocolitis. In the present study, a higher percentage of men studied than women had osteoporosis; whether this reflects altered sex hormone status in the men is unclear, but the observation is of interest in the light of a recent report of a high prevalence of oligosperma in patients with Crohn’s disease not receiving salazopyrine.

Calcium deficiency has been shown to cause osteoporosis in animals although its effects in man are more controversial. Calcium malabsorption is common in patients with inflammatory bowel disease and may result from vitamin D deficiency, reduced intestinal absorptive surface area, or binding of calcium salts to fatty acids within the intestinal lumen. Vitamin D deficiency is also well established in patients with small intestinal disease; this may be accompanied by secondary hyperparathyroidism which in turn may lead to osteopenia. In the present study, however, vitamin D status and serum immunoreactive parathyroid hormone levels were normal in most patients and there were no significant differences between the normal and osteoporotic groups.

In view of the relationship between bone mineral content and fracture rate, the increased prevalence of a low bone mineral content in patients with malabsorption indicates an increased risk of osteoporotic fracture; this is supported by the demonstration of vertebral crush fractures in six patients. Because the prognosis of Crohn’s disease is now good in the majority of patients it is clearly important to prevent the development of osteoporosis. Those most at risk appear to be patients with long standing, severe, small intestinal disease, with intestinal resection, high dose steroid therapy and secondary amenorrhoea or premature menopause. Unfortunately it is often impossible to avoid steroid therapy in inflammatory bowel disease but it should be kept to a minimum with frequent revision of the required dose. A daily calcium intake of 1-5 g or more should be recommended although the percentage absorbed may be small in some individuals.

Oestrogen replacement is probably indicated in patients with secondary amenorrhoea or premature menopause but absorption from oral preparations is likely to be variable and implant or transdermal preparations may be preferable. In addition, it is unknown whether oestrogens, or other agents such as anabolic steroids and sodium fluoride can prevent bone loss in the face of continuing steroid therapy. Further studies are required to establish effective prophylaxis and treatment of bone loss associated with inflammatory bowel disease.

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