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 and/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 malabsorption¹⁻⁴ although its prevalence has not been established using accurate diagnostic methods; possible pathogenetic factors include steroid therapy,⁵ calcium malabsorption,⁶ vitamin D deficiency⁷ and, in women, oestrogen deficiency.⁸ 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 tomography⁹ and dual photon absorptiometry¹⁰ 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.¹¹ 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.

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 μ g 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.¹² Serum 25-hydroxyvitamin D (25OHD) was measured by radioimmunoassay¹³ 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 absorptiometry¹⁴ 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, Rehenning, and Kuhlencordt.¹⁵ 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.¹⁶ 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.¹⁷ The results were then compared with similarly corrected published normal data.¹¹ 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

Fig. 1 Fat corrected spinal trabecular bone mineral content in the female patients. Results are expressed in terms of the equivalent concentration of dipotassium hydrogen phosphate. The normal data are taken from Cann and Genant.¹⁶ 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.³¹

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.¹⁶ 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.¹¹

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

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.¹⁵

Fig. 4 Bone mineral content/bone width ratio at the junction of the proximal two-thirds and distal one-third of the radius in the male patients. The normal data are taken from Ringe et al.¹⁵

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

Table 1 Clinical details of patients with vertebral fracture

Patient no	Age (yr)	Sex	Body mass index (kg/m ²)	Disease	Lifetime steroid dose (g)	Duration of disease (yr)	BMC/BW (g/cm ²)	QCT (mg/ml)
1	72	M	21.5	Crohn's SB, no resection	65	20	0.51	60
2	56	M	18.3	Crohn's SB, 1 resection	49	11	0.67	90
3	38	F	17.8	Crohn's SB, 3 resections	36	20	0.34	61
4	77	F	18.8	Crohn's SB, 1 resection	15	4	0.32	60
5	34	F	15.6	Crohn's SB, 2 resections	15	10	0.68	16
6	42	F	20.9	Crohn's SB, 5 resections	37	18	0.47	73

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

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

	With (n=23) osteoporosis	without (n=52) osteoporosis	p value
Age (yr)	43.4±13.6	45.9±15.9	NS
Weight (kg)	55.6±9.6	65.1±12.2	<0.005
Body mass index (kg/m ²)	20.6±2.8	25.4±11.2	<0.005
Steroids (total lifetime dosage g)	14.6*	2.4*	<0.01
Duration of disease (yr)	12.0*	9.0*	NS
Corrected serum calcium mmol/l (Normal 2.26–2.60)	2.28±0.10	2.27±0.09	NS
Serum phosphate mmol/l (Normal 0.8–1.45)	1.10±0.16	1.12±0.18	NS
Serum alkaline phosphatase IU/l (Normal 30–115)	113*	89*	NS
Serum albumin g/l (Normal 35–45)	41.4±6.3	43.4±4.5	NS
Serum iPTH ng/ml (Normal <1)	0.4*	0.3*	NS
Serum 25OHD nmol/l (Normal 20–100)	42.3*	44.3*	NS
Dietary calcium intake mmol/day	27.65±11.75	23.30±9.25	NS

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

oestrogens; the duration of therapy in these four was six months, two, four, and six years.

Discussion

Our results show that the prevalence of both spinal trabecular and peripheral cortical osteoporosis is increased in patients with inflammatory bowel disease and that severe clinical osteoporosis may occur in young amenorrhoeic women. Spinal trabecular bone mineral content has not previously been reported in intestinal disease; however, using the less accurate radiological criteria of skeletal demineralisation, vertebral biconcavity and vertebral crush fractures, an increased prevalence of spinal osteoporosis was reported by Nordin² in patients with steatorrhoea and by Genant *et al*³ in a group of adults and adolescents with inflammatory

bowel disease. Evidence for an increased prevalence of peripheral cortical osteoporosis was also reported in these two studies and more recently Hylander *et al*⁴ 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.¹⁸

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 documented⁵ 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,¹⁹ although probably normal in idiopathic proctocolitis.²⁰ 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 oligospermia in patients with Crohn's disease not receiving salazopyrine.²¹

Calcium deficiency has been shown to cause osteoporosis in animals²² although its effects in man are more controversial. Calcium malabsorption is common in patients with inflammatory bowel disease²³ and may result from vitamin D deficiency, reduced intestinal absorptive surface area, or binding of calcium salts to fatty acids within the intestinal lumen.²⁴ Vitamin D deficiency is also well established in patients with small intestinal disease;²⁵⁻²⁷ this may be accompanied by secondary hyperparathyroidism which in turn may lead to osteopenia.⁷ 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^{28,29} 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 patients³⁰ 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.

References

- 1 Salvesen HA, Boe J. Osteomalacia in sprue. *Acta Med Scand* 1953; **146**: 290-9.
- 2 Nordin BEC. Effects of malabsorption syndrome on calcium metabolism. *Proc R Soc Med* 1961; **54**: 497-500.
- 3 Genant HK, Mall JC, Wagonfeld JB, Horst JV, Lanzl LH. Skeletal demineralisation and growth retardation in inflammatory bowel disease. *Invest Radiol* 1976; **11**: 541-9.
- 4 Hylander E, Ladefoged K, Madsen S. Calcium balance and bone mineral content following small intestinal resection. *Scand J Gastroenterol* 1981; **16**: 167-76.
- 5 Hahn TJ, Boisseau VC, Avioli LV. Effect of chronic corticosteroid administration on diaphyseal and metaphyseal bone mass. *J Clin Endocrinol Metab* 1974; **39**: 274-82.
- 6 Bullamore JR, Gallagher JC, Wilkinson R, Nordin BEC, Marshall DH. Effect of age on calcium absorption. *Lancet* 1970; **2**: 535-7.
- 7 Parfitt AM, Gallagher JC, Heaney RP, Johnston CC, Neer R, Whedon GD. Vitamin D and bone health in the elderly. *Am J Clin Nutr* 1982; **36**: 1014-31.
- 8 Aitken JM, Hart DM, Anderson JB, Lindsay R, Smith DA, Speirs CF. Osteoporosis after oophorectomy for non-malignant disease in pre-menopausal women. *Br Med J* 1973; **iii**: 515-8.
- 9 Genant HK, Cann CE, Ettinger B, Gilbert SG. Quantitative computed tomography of vertebral spongiosa: a sensitive method for detecting early bone loss after oophorectomy. *Ann Intern Med* 1982; **97**: 699-705.
- 10 Krølner B, Pors Nielson S. Measurement of bone mineral content (BMC) of the lumbar spine. 1 Theory and application of a new two-dimensional dual-photon attenuation method. *Scand J Clin Lab Invest* 1980; **40**: 653-63.
- 11 Genant HK, Cann CE, Boyd DP, Kolb FO, Ettinger B, Gordon GS. Quantitative computed tomography for vertebral mineral determination. In: Frame B, Potts JT, eds. *Proceedings of Henry Ford Hospital symposium on clinical disorders of bone and mineral metabolism*. Amsterdam: Excerpta Medica, 1983; 40-7.
- 12 Addison GM, Hales CN, Woodhead JS, O'Riordan JLH. Immunoradiometric assay of parathyroid hormone. *J Endocrinol* 1971; **49**: 521-30.
- 13 Clemens T, Hendry G, Papapoulos S, Fraher L, Care A, O'Riordan JLH. Measurement of 1,25-dihydroxy-

- cholecalciferol in man by radioimmunoassay. *Clin Endocrinol* 1979; **11**: 225–34.
- 14 Cameron JR, Sorenson J. Measurement of bone mineral in vivo: an improved method. *Science* 1963; **142**: 230–2.
- 15 Ringe J-D, Rehpenning W, Kuhlencordt F. Physiologische Änderung des Mineralgehalts von Radius und Ulna in Abhängigkeit von Lebensalter und Geschlecht. *Fortschr Röntgenstr* 1977; **126**: 376–80.
- 16 Cann CE, Genant HK. Precise measurement of vertebral mineral content using computed tomography. *J Comput Ass Tomogr* 1980; **4**: 493–500.
- 17 Crawley EO, Evans WD, Owen GM. A correction procedure for the influence of soft tissue in single energy CT bone mineral measurement. *5th International Workshop on Bone and Soft Tissue Densitometry, Bretton Woods, 1985; USA* (in press).
- 18 Banks LM, Stevenson JC. A modified method of spinal computed tomography for trabecular bone mineral measurements. *J Comput Ass Tomogr* 1986; **10**: 463–7.
- 19 Mayberry JF, Weterman IT. European survey of fertility and pregnancy in women with Crohn's disease. A case control study. *Gut* (in press).
- 20 Willoughby CP, Truelove SC. Ulcerative colitis and pregnancy. *Gut* 1980; **2**: 469–74.
- 21 Farthing MJG, Dawson AM. Impaired semen quality in Crohn's disease – drugs, ill health, or undernutrition? *Scand J Gastroenterol* 1983; **18**: 57–60.
- 22 Nordin BEC. The pathogenesis of osteoporosis. *Lancet* 1961; **1**: 1011–4.
- 23 Hylander E, Ladefoged K, Jarnum S. The importance of the colon in calcium absorption following small intestinal resection. *Scand J Gastroenterol* 1980; **15**: 55–60.
- 24 Southgate DAT, Widdowson EM, Smits BJ, Cooke WT, Walker CHM, Mathers NP. Absorption and excretion of calcium and fat by young infants. *Lancet* 1969; **1**: 487–9.
- 25 Compston J, Creamer B. Plasma levels and intestinal absorption of 25-hydroxyvitamin D in patients with small bowel resection. *Gut* 1977; **18**: 171–5.
- 26 Driscoll R, Meredith S, Wagonfeld J, Rosenberg I. Bone histology and vitamin D status in Crohn's disease (CD): assessment of vitamin D therapy. *Gastroenterology* 1977; **72**: 1051.
- 27 Harries AD, Brown R, Heatley RV, Williams LA, Woodhead JS, Rhodes J. Vitamin D status in Crohn's disease: association with nutrition and disease activity. *Gut* 1985; **26**: 1197–203.
- 28 Jensen GF, Christiansen C, Boesen J, Hegedus V, Transbol I. Relationship between bone mineral content and frequency of postmenopausal fractures. *Acta Med Scand* 1983; **213**: 61–3.
- 29 Genant HK, Cann CE, Faul DD. Quantitative computed tomography for assessing vertebral bone mineral. In: Dequeker J, Johnston CC, eds. *Non-invasive bone measurements: methodological problems*. Oxford, Washington DC: IRL Press, 1982: 215–49.
- 30 Binder V, Hendriksen C, Kreiner S. Prognosis in Crohn's disease – based on results from a regional patient group from the county of Copenhagen. *Gut* 1985; **26**: 158–63.
- 31 Cann CE, Genant HK, Kolb FO, Ettinger B. Quantitative computed tomography for prediction of vertebral fracture risk. *Bone* 1985; **6**: 1–8.