Disorders of mineral and bone metabolism in patients with Crohn's disease

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ABSTRACT: Crohn's disease is known to produce malabsorption of calcium and vitamin D which affect the skeleton. A variety of techniques were used to assess the prevalence of mineral and bone abnormalities in 53 consecutive patients with Crohn's disease. Twenty healthy controls were compared with 28 men and 25 women with Crohn's disease. In males, the mean corrected serum calcium concentration was elevated, the mean winter plasma 25-hydroxyvitamin D was low, as was the bone volume on biopsy and the fractional absorption of ^{47}Ca. In females, the corrected serum calcium was also higher than in controls, as was the serum alkaline phosphatase activity. The female patients had significant decreases in both summer and winter plasma vitamin D levels, metacarpal cortical thickness and fractional absorption of ^{47}Ca. The disturbances in bone and mineral metabolism were generally mild and were not associated with use of glucocorticosteroids but were more severe in patients with a history of bowel resection. Thus, patients with Crohn's disease are at risk of developing metabolic bone disease and consideration should be given for an assessment of the skeleton in patients with Crohn's disease, especially in women and in patients with previous ileal resection. A battery of tests may be needed to exclude the diagnosis of metabolic bone disease but a 25-hydroxyvitamin D assay and hand x-rays using industrial grade film are recommended as a valuable preliminary assessment. **Can J Gastroenterol 1987;1(1):11-17**

Key Words: *Crohn's disease, Inflammatory bowel disease, Metabolic bone disease, Osteoporosis*

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This work was supported in part by grants from the MSI Foundation of Alberta and Special Services Research Fund of the University of Alberta Hospital

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Received for publication June 4, 1987. Accepted July 31, 1987

CROHN'S DISEASE HAS BEEN ASSOCIated with malabsorption of a variety of nutrients (1-4) and with growth failure (5-9). Vitamin D absorption and serum vitamin D levels have been reported to be abnormal in patients with inflammatory bowel disease (10), although not all studies have shown this (10-17). Skeletal abnormalities have been described in patients with Crohn's disease (6-9, 14, 18) and diminished 25-hydroxyvitamin D absorption has been reported in patients who underwent small bowel resection for treatment of Crohn's disease (19). Most studies have tended to use one technique to assess the skeletal and metabolic abnormalities. The present authors used a variety of techniques to evaluate the mineral and bone status of an unselected group of Crohn's patients.

MATERIALS AND METHODS

Patient population: A total of 53 consecutive patients with an established diagnosis of Crohn's disease was studied (Table 1). The diagnosis was established by the usual criteria including typical clinical presentation, radiological findings,

TABLE 1
Patient population characteristics

Sex (n)	Age (years)	Disease (years)	Resections (number of patients)	Prednisone (number of patients)	Dose of prednisone (mg/day)	Duration of dose (years)
Male (28)	32.0±14.8	5.4±5.2	17	18	17.9±11.3	1.7±2.6
Female (25)	32.7±11.1	6.4±6.7	8	13	14.8±4.6	1.4±1.2

Values are mean±SD

rectal biopsy or pathology, or the findings at surgery. Twenty-eight men (mean ±SD age 32±14.8 years) and 25 women (32.7±11.1 years) were compared with 20 healthy controls.

Blood samples: Blood was obtained by venipuncture in the morning while the patients were fasting. Serum calcium, phosphorus, albumin, alkaline phosphatase and creatinine were measured by Technicon autoanalyzer. Serum magnesium was determined by means of a Perkin-Elmer Model 303 atomic absorption spectrophotometer. Serum calcium was normalized to an albumin of 4.0 g/dL (20) to take account of the variability of serum proteins in patients with Crohn's disease and to allow a comparison to be made with normal controls.

25-hydroxyvitamin D: Plasma 25-hydroxyvitamin D (25[OH]D) was assayed by a modification of the method of Haddad and Chyu (21). The vitamin D standard was 25-hydroxycholecalciferol hydrate (Upjohn, Don Mills, Ontario). The ^{3}H-25(OH)D_3 (SA 94 Ci/mmol, 235 mCi/mg) was obtained from Amersham (Oakville, Ontario). The vitamin D binding protein was derived from a kidney cytosol preparation extracted from weanling Sprague-Dawley rats. The interassay coefficient of variation was 10.6% for a plasma 25(OH)D level of 24 ng/mL. The intra-assay variation was 5.4%. Samples collected from November to April were analyzed separately from the summer samples collected from May to October to identify seasonal variations that might occur in the northern latitude in which this study was conducted.

Urine samples: Twenty-four hour urine collections were timed with the blood samples and calcium, phosphorus and creatinine levels were determined by standard laboratory methods. Calcium excretion was recorded as mg calcium/mg creatinine. Phosphorus excretion was converted to maximum tubular reabsorption of phosphorus per unit of glomerular filtration (Tm/GFR) (22).

Bone assessment: The bone density and thickness were assessed, when possible, by three different techniques. Cortical bone thickness was measured in both second metacarpal bones visualized on industrial grade radiographs of the hands (23-26). The percentage cortical area ratio was calculated according to the method of Garn (23) and the published normal population was used as the control groups with whom the Crohn's patients were compared (24, 25). The metacarpal bones, as well as the other phalanges, were assessed as described by Meema et al (25). Cortical bone mineral content was measured by ^{125}I photon absorptiometry at the distal one-third site in the nondominant radius (27). The bone histology was evaluated directly using undecalcified biopsy samples obtained from the posterior iliac spine by means of a Vilaghy-Zellerman needle (28). Samples without fracture artefact were quantified for percentage bone volume and percentage osteoid by point counting 16 fields using a 25 point integrating eyepiece grid (29,30). Bone resorption was graded as described by Huffer et al (31) with grade 2 or higher being considered as increased resorption. Sections were stained using both von Kossa and toluidine blue stain (32).

Calcium absorption: In 14 of these

TABLE 2
Laboratory data on males with Crohn's disease

		Blood					Urine	
Number	Age (years)	Ca (mg%)	Alb (mg%)	AP (iu/mL)	Vit D (ng/mL)	Ca Abs (%)	Ca/Cr (mg/mg)	GFR (Tm/100 mL)
1	34	8.7	3.0	77	—	33	0.213	2.52
2	24	9.6	3.8	82	23.5	—	0.283	3.18
3	21	9.5	4.6	106	—	—	0.012	3.82
4	38	9.1	3.2	95	16.3	—	0.076	3.26
5	31	7.9	2.9	67	—	—	0.077	2.85
6	21	9.4	3.6	47	22.1	—	0.128	4.05
7	37	7.8	2.5	82	23.1	—	0.013	2.46
8	39	10.9	2.9	408	20.7	—	0.273	2.65
9	68	8.3	3.0	109	—	—	0.225	4.22
10	38	7.5	2.6	51	5.1	—	0.167	2.46
11	38	9.0	3.4	78	ND	—	0.068	3.03
12	17	10.1	4.0	66	27.4	—	0.153	3.78
13	26	9.5	4.0	80	16.9	—	0.178	3.62
14	62	8.7	3.7	54	—	—	0.091	1.54
15	51	9.1	3.1	137	5.8	—	0.134	4.72
16	60	8.9	3.9	74	—	—	—	—
17	31	9.0	3.4	78	57.5	—	0.094	1.70
18	20	9.0	3.4	78	28.7	—	0.130	3.70
19	17	8.4	3.3	75	29.9	39	0.087	4.08
20	20	9.5	3.5	102	11.0	—	0.320	4.17
21	30	9.0	2.5	76	6.0	13.6	1.13	3.49
22	44	9.0	3.8	193	—	31.0	0.011	3.27
23	14	10.0	4.3	288	ND	—	—	—
24	21	9.9	4.7	77	26.3	—	0.223	2.04
25	31	8.8	4.2	65	60.6	—	0.36	3.11
26	14	11.6	3.7	207	—	—	0.089	2.99
27	36	9.4	3.9	66	41.0	37.6	0.045	3.67
28	12	8.6	3.5	82	17.9	17.4	0.307	2.69
Mean ± SD (n=9)				97.8±72.7*				
Control males								
Mean ± SD (n=9)				60.6±13.8				

* *Four patients with immature bones excluded. Ca Calcium; Alb Albumin; AP Alkaline phosphatase; Abs Absorption; Cr Creatinine; Tm Maximum tubular reabsorption; GFR Glomerular filtration rate; ND Not detected*

patients, fractional calcium absorption from the gut was measured using a radioisotope method similar to that described by Chanard et al (33). The protocol was as follows: on day 1 of the test the subject received 1.0 $\mu Ci^{47}Ca^{2+}$ as calcium chloride intravenously after an 8 h fast. Four hours later, while still fasting, the radioactivity in the contralateral forearm was measured using a low background, two crystal gamma ray spectrometer. On day 3 of the study, following another 8 h fast, residual activity in the forearm was measured immediately before the subject received an oral dose of 4 $\mu Ci^{47}Ca^{2+}$ together with 180 mg elemental calcium (as 10% gluconate). Four hours following this oral dose, while still fasting, the forearm radioactivity was again measured. Fractional calcium absorption was calculated as follows:

$$\% \text{ Fractional absorption} = \frac{\text{Fractional oral uptake} \times 100\%}{\text{Fractional intravenous uptake}}$$

TABLE 4
Plasma 25-hydroxyvitamin D and percentage fractional calcium absorption

	Sex		Crohn's (n)	Controls (n)
Calcium absorption (%) (mean ± SD)	Male and female		22.6 ± 10.8 (14)*	39.5 ± 19.5 (23)
Plasma 25(OH)D (ng/mL) (mean ± SD)	Male	Winter	11.1 ± 8.3 (7)*	22.33 ± 8.2 (19)
		Summer	28.6 ± 15.9 (13)	27.1 ± 8.4 (8)
	Female‡	Winter	13.3 ± 6.1 (12)†	25.5 ± 9.9 (18)
		Summer	14.1 ± 11.6 (7)*	25.7 ± 8.5 (19)

** P<0.01 compared with controls; † P<0.001 compared with controls; ‡ Three subjects on supplements not included*

The gamma ray spectrometer system, specially constructed for these measurements, was carefully calibrated and arm positioning devices were used to assure consistent repeat measurements of forearm radioactivity. The radiation background of the gamma ray spectrometer system was low and stable and was screened against radioactivity from parts of the subject's body other than the measured forearm. For normal subjects, the error in the measurement (including counting and repositioning errors) was less than ± 1% (coefficient of variation); for subjects with fractional absorptions less than 25% the corresponding error was less than ± 2%. For very low absorption (less than 10%) the error increased to about ± 10%.

Data analysis: The results were analyzed by the Student's *t* test for statistical significance, using two tailed probability tables.

TABLE 3
Laboratory data on females with Crohn's disease

		Blood					Urine	
Number	Age (years)	Ca (mg%)	Alb (mg%)	AP (iu/mL)	Vit D (ng/mL)	Ca Abs (%)	Ca/Cr (mg/mg)	GFR (Tm/100 mL)
29	40	9.2	3.7	111	8.1	—	0.122	3.45
30	34	8.6	2.5	62	—	—	—	—
31	40	9.9	4.2	84	ND	—	0.22	2.45
32	20	8.7	3.4	187	10.9	—	0.148	2.83
33	46	9.0	4.4	74	25.3	—	0.281	2.83
34	46	8.4	3.0	75	8.0	—	0.112	3.70
35	28	9.6	4.3	83	53.8	26.1	0.116	2.82
36	40	9.0	3.1	103	18.0	—	0.274	3.29
37	27	9.8	4.3	63	11.1	—	0.280	3.23
38	18	8.5	3.0	116	—	—	0.404	3.16
39	20	8.8	2.8	78	—	—	0.150	—
40	21	9.2	3.3	157	15.3	12.9	0.225	3.40
41	27	9.6	3.7	122	16.9	—	0.251	4.84
42	40	8.9	4.4	74	10.3	—	0.100	2.92
43	29	9.0	3.9	123	5.8	—	0.216	3.08
44	25	8.6	3.0	45	13.4	—	0.323	3.08
45	28	9.1	3.7	47	8.9	22.4	0.063	3.88
46	23	8.9	3.4	60	7.7	8.4	0.400	1.69
47	21	7.9	3.3	76	7.0	5.9	0.377	3.99
48	24	8.6	3.6	160	20.2	—	0.040	—
49	25	8.4	3.3	151	10.9	20.6	0.110	5.18
50	56	9.3	4.8	52	39.5	33.2	0.730	2.67
51	49	9.4	4.8	110	15.3	—	0.370	3.29
52	49	8.8	3.3	265	47.5	15.3	0.062	4.56
53	42	9.1	3.8	85	13.5	—	0.019	1.78
Mean ± SD (n=32)*		9.1 ± 14.8	3.5 ± 0.87‡	107.1 ± 0.6§	22.5 ± 78.9	16.0	0.175 ± 0.215	3.23 ± 0.82
Controls								
Mean ± SD (n=20)		9.3 ± 0.3	4.3 ± 0.2		46.9 ± 10.9	n=(11)	0.145 ± 0.074	3.05 ± 0.63

** Means for both sexes except AP; † Two patients with frank hypercalcemia excluded; ‡ P<0.001 compared with controls; § P<0.02 compared with controls. Abbreviations, see Table 2*

RESULTS

No significant difference was found in the urinary and serum biochemistry between the Crohn's patients and a group of 20 healthy normal individuals consisting of medical personnel and healthy spouses of diabetics attending the outpatient diabetic centre. Two Crohn's patients had serum calcium levels much higher than the normal range, one of whom was later proven to have a parathyroid adenoma. Even when excluding these individuals to avoid biasing the results, the mean calcium level (when normalized to an albumin of 4.0 g/dL), was significantly ($P<0.01$) higher for all Crohn's patients at 9.4 ± 0.5 mg/100 mL than the mean of 8.9 ± 0.3 mg/100 mL in the control group; nevertheless, both mean values were within the accepted normal range. However, the uncorrected mean calcium level was higher in the controls at 9.3 ± 0.3 mg/100 mL than in the Crohn's patients at 9.1 ± 0.9 mg/100 mL ($P<0.005$). This reflects a higher mean albumin level in the controls as compared to 3.5 ± 0.6 g/dL in the Crohn's patients ($P<0.001$) (Tables 2 and 3).

Alkaline phosphatase was higher in all patients with Crohn's disease, but only in females was this difference significant

TABLE 5
Bone analysis in males with Crohn's disease

Number	Bone (%)	Osteoid (%)	Bone mineral content	Percentage cortical area ratio
1	24.5	0.3	0.80	78.9
2	25.8	0.3	0.76	81.8
3	19.8	6.4	0.64	66.5
4	20.3	0.9	0.57	73.7
5	–	–	–	88.7
6	26.2	0.7	0.90	68.5
7	20.7	0.3	0.70	72.2
8	16.3	7.3	0.77	72.1
9	–	–	–	79.0
10	27.3	1.1	1.01	80.5
11	22.2	5.8	–	69.2
12	14.6	1.7	–	76.6
13	–	–	0.73	88.0
14	–	–	0.64	72.6
15	21.7	1.1	0.61	78.5
16	–	–	0.78	81.5
17	–	–	0.62	73.4
18	–	–	0.69	74.0
19*	11.0	1.7	0.49	55.9
20	16.5	1.0	0.81	94.4
21	–	–	0.99	79.2
22	–	–	–	63.4
23	27.5	4.3	0.50	59.0
24	20.7	4.5	–	75.4
25	–	–	–	85.0
26*	–	–	–	55.2
27	–	–	–	83.6
28*	11.7	0.5	–	68.9
Mean±SD(n)	21.3±3.96(13)†	2.4±2.6(13)	0.75±0.13(16)	77.4±7.42(24)‡§
Controls				
Mean±SD(n)	25.8±4.2(13)†	2.3±1.5(13)	0.77±0.05(32)**	86.3±6.7(465)**

* *Excluded as bone age not adult;* † *P<0.01 compared with controls;* ‡ *P<0.001 compared with controls;* § *P<0.05 compared with females with Crohn's;* ** *P<0.01 compared with female controls*

(P<0.02). The alkaline phosphatase isoenzymes and the serum 5′ nucleotidase activity measured were not routinely identified.

Seasonal variations in plasma 25(OH) D were not found in controls. Males and females with Crohn's had significantly decreased 25(OH)D levels (Table 4) during the winter months. Females' values were also low during the summer months (P<0.01). There was no correlation between 25(OH)D levels and the percentage osteoid volume on bone biopsy, although a number of the patients with low 25(OH)D levels could not be biopsied.

Of those patients biopsied, four of 13 adult males (31%) and one of six (17%) females had osteoid volumes greater than 4% of the total bone volume. This is suggestive of early osteomalacia, although measurement of appositional rate would be necessary to firmly substantiate a diagnosis. Regrettably, biopsies from two additional males and seven female patients could only be evaluated qualitatively (because of processing artefact), but none showed a qualitative increase in osteoid width. Biopsies from the males also showed a significant decrease (P<0.01) in bone volumes compared to controls (Table 5). In patients where adequate bone volume quantification was

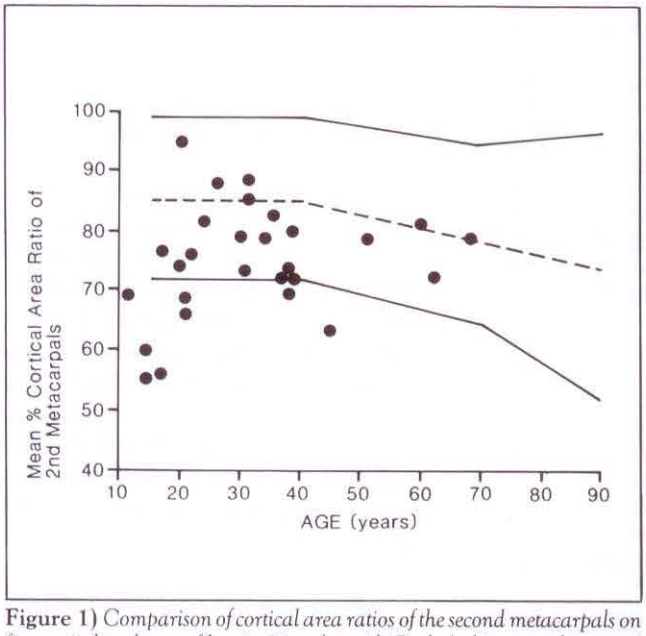

Figure 1) *Comparison of cortical area ratios of the second metacarpals on fine grain hand x-ray films in 24 males with Crohn's disease with normal males (- - - Mean; —— ± 2 SDs of a normal population)*

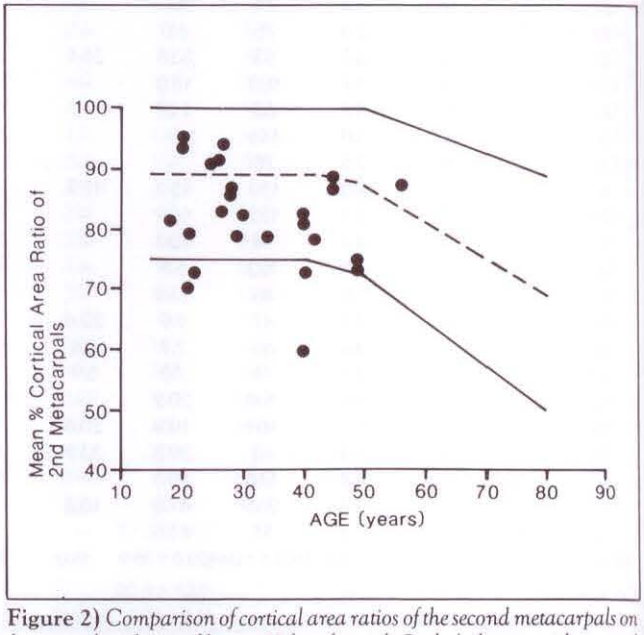

Figure 2) *Comparison of cortical area ratios of the second metacarpals on fine grain hand x-ray films in 25 females with Crohn's disease with normal females (- - - Mean; —— ± 2 SDs of a normal population)*

possible, three of 13 males and two of seven females had bone volumes at or less than 2 SDs below the mean of the control subjects. In addition, two of the three males with immature bone ages who were biopsied also had bone volumes much below that reported in the literature (34).

The data obtained from the hand x-rays showed that males and females with Crohn's disease had thin cortical bone (Tables 5 and 6) when compared to controls ($P<0.01$). Females had a higher percentage cortical area ratio than males ($P<0.05$), but this difference was also seen in the controls and may reflect the smaller metacarpal radius in females relative to the cortical thickness. There was no correlation between the percentage cortical area ratio on hand x-rays and bone biopsy findings, possibly because cortical bone was assessed in the hand x-rays and trabecular bone was examined in the biopsy. The cortical mineral content, as measured by photon absorptiometry, showed the same trends as the bone biopsy data and the percentage cortical area ratio but was not significantly different from controls. In general, the males with Crohn's showed a greater decrease in their bone density, bone biopsy data and percentage cortical area ratio, than the controls, whereas the females appeared less affected in these parameters. In males with mature bone age, the percentage cortical area ratio was at or below 2 SDs in seven of 24 patients (Figure 1), but it was reduced in four of 25 females (Figure 2).

The percentage fractional absorption of ^{47}Ca was significantly lower ($P<0.01$) in the Crohn's patients than in controls (Table 4). The calcium absorption in those individuals who had not taken any vitamin D supplement was positively correlated with the plasma 25(OH)D level (Figure 3) but was negatively correlated with the urinary calcium excretion (Figure 4). Low calcium absorption did not correlate with the percentage cortical area ratio.

No difference was found in percentage bone volumes, vitamin D levels, cortical mineral content or percentage cortical area ratio in patients who did or did not use glucocorticosteroids. However, there was a reduced percentage cortical area ratio when patients with bowel resection were compared to those without any resection ($P<0.025$) but those patients with small bowel resections also had a longer history of Crohn's disease ($P<0.002$). A history of bowel resection was not necessarily associated with glucocorticoid administration.

TABLE 6
Bone analysis in females with Crohn's disease

Number	Bone (%)	Osteoid (%)	Bone mineral content	Percentage cortical area ratio
29	11.4	3.0	0.66	60.0
30	20.0	1.0	0.59	78.5
31	–	–	0.64	81.0
32	–	–	0.69	93.5
33	–	–	0.67	87.9
34	–	–	0.61	88.5
35	15.9	1.0	–	86.5
36	–	–	–	82.8
37	26.8	0.2	0.62	86.0
38	–	–	–	81.2
39	–	–	0.65	94.2
40	13.7	0.1	0.60	78.9
41	–	–	0.50	94.0
42	–	–	0.62	73.0
43	–	–	0.42	83.0
44	–	–	0.84	91.2
45	–	–	–	78.8
46	–	–	–	72.9
47	–	–	–	70.4
48	20.9	4.2	–	92.7
49	–	–	–	84.0
50	–	–	–	87.8
51	–	–	–	74.4
52	11.8	0.1	–	72.8
53	–	–	–	78.4
Mean ± SD(n)	17.9 ± 5.4(7)	1.4 ± 1.6(7)	0.62 ± 0.1(13)†	82.1 ± 8.5(25)*†
Controls				
Mean ± SD(n)	18.4 ± 2.7(9)‡	1.0 ± 1.0(9)	0.67 ± 0.06(13)‡	88.4 ± 6.9(25)‡

* $P<0.001$ compared with controls; † $P<0.05$ compared with males with Crohn's; ‡ $P<0.01$ compared with female controls

DISCUSSION

There are a number of risk factors in patients with Crohn's disease which might predispose to the development of metabolic bone disease. Frequently, their dietary history revealed that patients were either intolerant to dietary products or simply did not consume adequate amounts of either calcium or vitamin D (unpublished observations). Those patients who were more severely affected were in hospital more frequently and would tend to have less sunlight exposure and less physical activity, which could explain their low vitamin D levels (35). These dietary and environmental conditions are considered factors in the generation of osteoporosis (35-40).

Many Crohn's patients require glucocorticoid therapy to control their bowel symptoms. Corticosteroids have been shown to decrease intestinal calcium absorption, to stimulate parathyroid hormone secretion and to promote urinary calcium loss. It is, therefore, likely that glucocorticoids tend to promote a negative calcium balance and so play a role in the appearance of metabolic bone disease (40). However, the present study did not find any obvious associations with glucocorticoid treatment and metabolic bone disease. Bowel resections were associated with low percentage cortical area ratios in both sexes, but not with low bone mineral content or percentage bone volumes. These results confirm that patients with Crohn's disease may have osteoporosis, osteomalacia and a disturbance in vitamin D and calcium metabolism. Low plasma vitamin D levels do not always correspond to histological evidence of osteomalacia (11,41) but of-

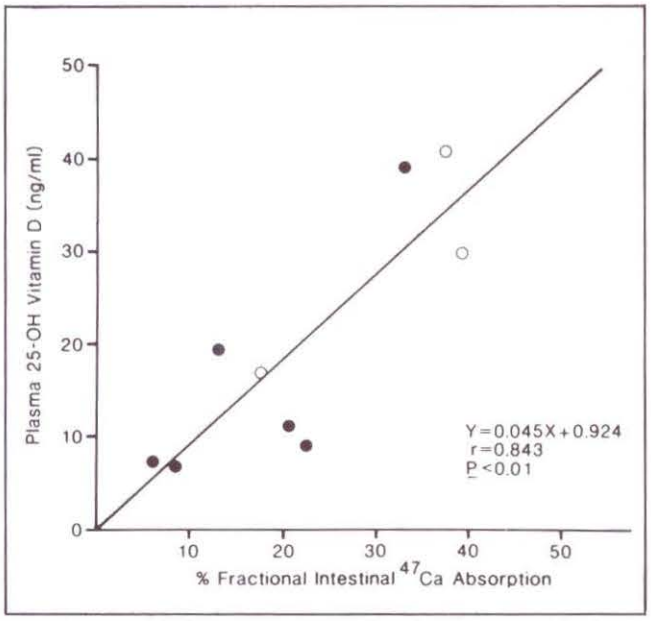

Figure 3) *Correlation between plasma 25-hydroxyvitamin D levels and fractional intestinal absorption of calcium in nine patients with Crohn's who had not been on vitamin D supplementation.* ○*Males;* ● *Females*

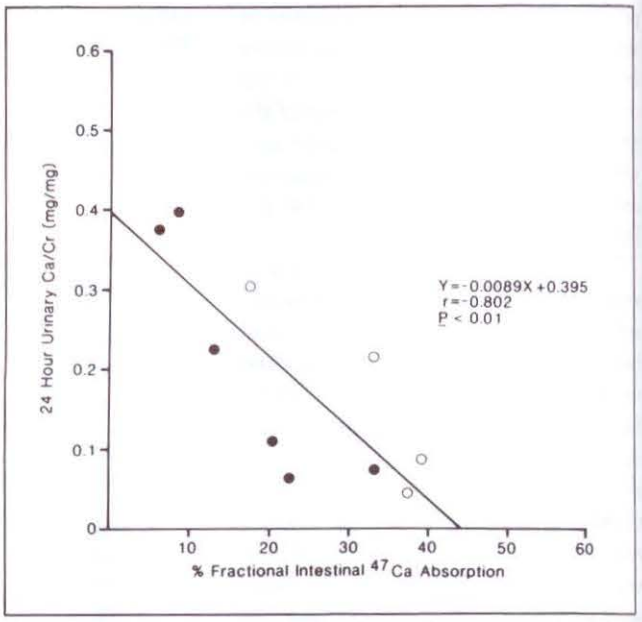

Figure 4) *Correlation between 24-h urinary calcium excretion and fractional intestinal calcium absorption in 10 patients with Crohn's disease.* ○ *Males;* ● *Females*

ten there is such an association (42). Low 25(OH)D levels in Crohn's patients may, in part, explain the low calcium absorption.

There is no good explanation for the observation that urinary calcium was lowest in those with increased intestinal calcium absorption. No correlation was seen between calcium excretion and vitamin D levels in the Crohn's group as a whole, or between serum calcium and calcium excretion. In normal individuals it has been shown that, with intravenous calcium infusions, urinary calcium excretion increases as serum calcium rises, although the relationship is curvilinear in the normal serum calcium range (43). Urinary calcium levels in the present study were standard 24 h collections in the nonfasting state, which may obscure the relationship between blood and urinary calcium. The experimental group also had higher fasting serum calcium levels than normal controls when corrected for differences in serum proteins (20). The patient with a parathyroid adenoma was not recognized initially as his serum calcium was in the normal range in the presence of hypoalbuminemia. Because dietary influences are absent in the fasting state, the serum calcium is likely to be derived from bone resorption, possibly secondary to nocturnal increased parathyroid hormone activity. The evidence for increased bone resorption in the Crohn's patients is tentative, but is suggested by the presence of mild subperiosteal reabsorption seen in 23 of 52 (44%) fine grain film hand x-rays. Of the 31 bone biopsies which could be graded for resorption, 10 (32%) had evidence of increased resorption, grade 2 or greater on biopsy.

Low calcium absorption, decreased serum 25(OH)D levels, increased bone resorption, decreased bone mineralization and bone mineral content were found in the present study in a consecutive series of patients with Crohn's disease. There was no correlation between type or severity of the metabolic problems with site of known bowel involvement, medications or age of the patients. The authors were impressed that no single test allowed exclusion of the presence of metabolic bone disease. Thus, metabolic bone disease must be suspected in patients with Crohn's disease, particularly in those with a previous small bowel resection, and a battery of tests may need to be performed to make or to exclude this diagnosis. For this, the authors recommend a 25(OH)D assay and hand x-rays using industrial grade film. If the alkaline phosphatase is elevated, it should be fractionated, as an elevated 5'nucleotidase is not sufficient to exclude alkaline phosphatase of bone origin.

To date, few patients have been symptomatic from their generally mild bone diseases. It remains to be seen whether these patients will become symptomatic sooner than the general population as age related bone loss proceeds. The actual mechanism(s) responsible for the mineral, hormonal and bone abnormalities, have not been identified, but these are undoubtedly multifactorial.

Driscoll and co-workers (11) reported that, in three of their patients with osteomalacia and low serum 25(OH)D levels, there was histoligical improvement in bone biopsy after therapy with oral vitamin D restored serum 25(OH)D levels to normal. Some of the present patients with documented bone abnormalities were started empirically on oral calcium with vitamin D supplementation, sodium fluoride and estrogens, given according to the individual circumstance (44). To date, an insufficient number of patients have been followed longitudinally to assess any progression of the metabolic abnormalities, but one young woman developed a vertebral crush fracture while on calcium (GramCal one per day) and vitamin D (50,000 units twice weekly).

ACKNOWLEDGEMENTS: We thank Mrs Lori Zuk and her staff of the Clinical Investigation Unit for their help in the investigation of these patients; for technical assistance we thank Dorcas Outhet, Rose Breitkreutz, Linda Gray, Marynell Favero, Christine McMichael and Roderick Haarstad; for the illustrations we thank the photographic department of the University of Alberta Hospital and Colleen Gardner and Susan Evans-Davies for help in the preparation of the manuscript. We are also grateful to Dr J. Babcock of the Upjohn Company for the gift of 25-hydroxy-cholecalciferol hydrate and to Dr R. Sherbaniuk and Dr R. Wensel for referring patients to this study.

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