Fracture risk is increased in Crohn's disease, but not in ulcerative colitis

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***Aims*—To study fracture rates and risk factors for fractures in patients with Crohn's disease and ulcerative colitis.**
***Methods*—998 self administered questionnaires were issued to members of the Danish Colitis/Crohn Association, and 1000 questionnaires were issued to randomly selected control subjects. 845 patients (84.5%) and 645 controls (65.4%) returned the questionnaire (p<0.01). 817 patients and 635 controls could be analysed.**
***Results*—Analysis was performed on 383 patients with Crohn's disease (median age 39, range 8–82 years; median age at diagnosis 26, range 1–75 years), 434 patients with ulcerative colitis (median age 39, range 11–86 years; median age at diagnosis 29, range 10–78 years), and 635 controls (median age 43, range 19–93 years, p<0.01). The fracture risk was increased in female patients with Crohn's disease (relative risk (RR) = 2.5, 95% confidence interval (CI) 1.7–3.6), but not in male patients with Crohn's disease (RR = 0.6, 95% CI 0.3–1.3) or in patients with ulcerative colitis (RR = 1.1, 95% CI 0.8–1.6). An increased proportion of low energy fractures was observed in patients with Crohn's disease (15.7% versus 1.4 % in controls, 2p<0.01), but not in patients with ulcerative colitis (5.4%, 2p=0.30). The increased fracture frequency in Crohn's disease was present for fractures of the spine, feet, and toes and fractures of the ribs and pelvis. Fracture risk increased with increasing duration of systemic corticosteroid use in Crohn's disease (2p=0.028), but not in ulcerative colitis (2p=0.50).**
***Conclusions*—An increased risk of low energy fractures was observed in female patients with Crohn's disease, but not in male patients with Crohn's disease or in patients with ulcerative colitis.**
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Keywords: fracture; Crohn's disease; ulcerative colitis; inflammatory bowel disease; osteoporosis

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Recent research has shown decreased bone mineral density and thus possibly an increased fracture risk in both adults,[1–4] and children[5] with inflammatory bowel disease (IBD). Furthermore, bone loss rates have been shown to be increased in patients with IBD.[6 7]

This decreased bone mineral density is thought to be the result of vitamin D deficiency,[8 9] malabsorption in general, treatment with glucocorticoids,[3 10–12] hypogonadism,[13] and the inflammatory process itself.[14]

Jahnsen and colleagues[15] have shown normal bone mineral in patients with ulcerative colitis, but decreased bone mineral in patients with Crohn's disease. Silvennoinen and colleagues[12] reported that bone mineral density was correlated to life time intake of corticosteroids, but not to the type of disease or to prior resections of parts of the small bowel.

However, despite the many reports on decreased bone mineral density a search of Medline and Excerpta Medica using any combination of the MESH term fracture versus inflammatory bowel disease, ulcerative colitis, ileitis, Crohn's disease, or enteritis produced only case reports[16–19] and prevalence studies[1 8 20] of fracture occurrence. None of the prevalence studies compared the fracture occurrence with control groups.[1 8 20] It thus remains unclear whether fracture incidence is increased in patients with IBD.

We therefore conducted a study in a large group of patients with IBD to assess the risk of fractures and identify potential risk factors for fractures.

Material and methods

A self administered questionnaire was mailed to 998 patients with IBD, who were members of the Danish Colitis/Crohn Association and to 1000 randomly selected controls, who were drawn from population lists on subjects aged at least 18 years in the region of interest. After six weeks the questionnaire was reissued to non-respondents.

The study was approved by the regional ethics committee (Aarhus County 1998/4294).

The questionnaire was based on a historical follow up design reported previously.[21] The study was designed with a power of 94% to detect a doubling of crude fracture incidence, with 400 patients and 650 controls followed for a median of seven years. In the subgroup of approximately 120 male subjects the power was 84%. Tables 1 and 2 show variables covered by the questionnaire. A family history of fracture was defined as at least one previous fracture reported among either parents or siblings. In case of fractures the participants were asked—in their own words—to describe in detail, which bone(s) had fractured, what had caused each individual fracture (for example, a fall, an automobile accident, etc), whether or not he or she had undergone surgery for each fracture, whether or not he or she had been

Abbreviation used in this paper: IBD, inflammatory bowel disease.

Table 1 Baseline characteristics

Variable	*Crohn's disease (n=383)*	*Ulcerative colitis (n=434)*	*Normal controls (n=635)*	*p Value*
Male	117 (31%)	160 (37%)	324 (51%)	<0.001†
Female	266 (69%)	274 (63%)	311 (50%)	
Age (median, range)	39 (8–82)	39 (11–86)	43 (19–93)	<0.001‡
Smoking				<0.001†
Never smoked	106 (28%)	209 (48%)	252 (40%)	
Current smoker	188 (49%)	72 (17%)	215 (34%)	
Previous smoker	87 (23%)	151 (35%)	167 (26%)	
Use of corticosteroids§	324 (85%)	386 (89%)	34 (5%)	<0.001†
Age at first use of corticosteroids (median, range)	28 (3–76)	30 (10–78)	35 (11–75)	0.028‡
Duration of corticosteroid use				1.00†
<1 year	151 (47%)	179 (47%)	15 (47%)	
⩾1 year	173 (53%)	205 (53%)	17 (53%)	
Ever diagnosed with osteoporosis	14 (4%)	9 (2%)	5 (1%)	0.007†
Family history of osteoporosis¶	22 (6%)	23 (5%)	22 (4%)	0.37†
Family history of fractures¶	166 (38%)	169 (39%)	225 (40%)	0.87†
Use of oral contraceptives*	221 (84%)	220 (80%)	227 (74%)	0.01†
Age at first use of oral contraceptives (median, range)*	18 (12–37)	18 (15–42)	19 (13–40)	0.002‡
Duration of oral contraceptive use*				0.006†
<5 years	71 (32%)	88 (40%)	105 (47%)	
⩾5 years	150 (68%)	132 (60%)	119 (53%)	
Premenopausal* Postmenopausal*	206 (77%) 60 (23%)	214 (78%) 59 (22%)	226 (73%) 84 (27%)	0.25†
Age at menopause in years (median, range)*	47 (34–54)	50 (30–55)	48 (30–58)	0.003‡
Use of HRT after menopause*	37 (63%)	29 (49%)	31 (36%)	0.008†
Age at first HRT use in years (median, range)*	48.5 (37–60)	49 (35–56)	48 (40–60)	0.92†
Duration of HRT use*				0.95†
<5 years	20 (54%)	15 (52%)	15 (50%)	
>5 years	17 (46%)	14 (48%)	15 (50%)	

*Only female respondents.
†χ^2 for contingency tables (p).
‡Kruskal-Wallis test (2p).
§Any type of corticosteroids (oral, enemas, inhaled, topical, etc).
¶A family history means occurrence of any fracture among parents or siblings.
Owing to missing values, sums may not add up.
HRT, hormone replacement therapy.

treated with plaster of Paris for each fracture, and whether each individual fracture had been treated on an inpatient or outpatient basis.

Based on the participants' accounts of the fractures, the energy (force) associated with each fracture was categorised in a blinded design by one of the investigators (PV) into: low energy fracture (a fracture occurring after minor or no trauma); medium energy fracture (a fracture occurring after a fall at the same level, dropping medium weight objects onto/squeezing fingers or toes, etc); and high energy trauma (a fracture occurring after a fall from one level to another, car accidents, etc). The blinded intraobserver kappa value for this classification was 0.87. The location of the fractures was categorised in a blinded design by one of the investigators (PV), based on the descriptions made by the patients into the categories shown in table 3. This classification had an intraobserver kappa of 0.90. The validity of fracture reports has been evaluated in an independent sample. Among these subjects 10 of 163 fractures could not be verified as being fractures (6.1%, 95% confidence interval (CI) 3–11%) on review of files from hospitals,

Table 2 Patients stratified by type of disease

Characteristic	*Crohn's disease (n=383)*	*Ulcerative colitis (n=434)*	*p Value*
Age at diagnosis in years (median, range)	26 (1–75)	29 (10–78)	0.028†
Time since diagnosis in years, (median, range)	8 (0–51)	7 (0–46)	0.31†
Use of corticosteroid enemas	82 (21%)	313 (72%)	<0.001‡
Use of systemic corticosteroids	308 (80%)	311 (72%)	0.004‡
Current use of vitamin D supplements	70 (18%)	36 (8%)	<0.001‡
Current use of calcium supplements	112 (29%)	60 (14%)	<0.001‡
Current use of multivitamin supplements			0.001‡
No	89 (23%)	139 (32%)	
Entire year	203 (53%)	176 (41%)	
Part of the year	90 (24%)	118 (27%)	
Sunbathing	285 (75%)	302 (70%)	0.11‡
Current use of systemic cytostatic agents§	72 (19%)	65 (15%)	0.14‡
Current use of systemic 5-aminosalicylates¶	186 (49%)	267 (61%)	<0.001‡
Current use of B_{12} supplements	42 (11%)	5 (1%)	<0.001‡
Current use of folic acid supplements	13 (3%)	3 (1%)	0.005‡
Current use of iron supplements	20 (5%)	4 (1%)	<0.001‡
Current use of cholestyramine therapy	31 (8%)	0 (0%)	<0.001‡
Undergone bowel surgery	212 (60%)	77 (18%)	<0.001‡
Age at first bowel surgery in years (median, range)	29 (14–75)	32 (10–59)	0.16†
Number of surgical procedures (median, range)	2 (1–20)	2 (1–10)	0.07†
Had a stoma	71 (19%)	65 (15%)	0.19‡

*Only female respondents.
†Mann-Whitney test (2p).
‡χ^2 for contingency tables (p).
§Current systemic therapy with azathioprine or cyclosporin.
¶Current systemic therapy with mesalazine, olsalazine, or sulphasalazine.
Owing to missing values, sums may not add up.
HRT, hormone replacement therapy.

Table 3 Age and sex adjusted relative risk and 95% confidence interval of individual fracture types compared with normal controls, before and after diagnosis

Fracture type	*Crohn's disease*	*Ulcerative colitis*
Before diagnosis		
All fracture types	0.7 (0.6 to 1.0)* [91]	0.9 (0.7 to 1.1) [121]
After diagnosis		
All fracture types	1.7 (1.2 to 2.3)* [51]	1.1 (0.8 to 1.6) [37]
All fracture types (women)	2.5 (1.7 to 3.6)* [46]	1.1 (0.7 to 1.8) [20]
All fracture types (premenopausal women)	2.9 (1.8 to 4.8)* [32]	1.4 (0.7 to 2.5) [15]
All fracture types (postmenopausal women)	1.8 (1.0 to 3.3)† [14]	0.6 (0.3 to 1.6) [5]
All fracture types (men)	0.6 (0.3 to 1.3) [6]	1.4 (0.8 to 2.3) [17]
Skull and jaws	1.1 (0.1 to 15.4) [1]	0.0 [0]
Spine	6.7 (2.1 to 21.7)* [5]	2.4 (0.5 to 11.9) [2]
Forearm	2.0 (0.8 to 5.1) [8]	1.2 (0.1 to 13.8) [5]
Upper arm	1.1 (0.7 to 1.7) [3]	0.3 (0.1 to 1.7) [1]
Hand and fingers	1.4 (0.2 to 9.4) [9]	1.3 (0.1 to 17.2) [9]
Femur	1.5 (0.2 to 11.7) [2]	0.6 (0.1 to 4.9) [1]
Lower leg	1.1 (0.3 to 4.6) [5]	1.5 (0.4 to 5.3) [7]
Feet and toes	3.3 (1.5 to 7.5)* [11]	1.7 (0.5 to 6.5) [6]
Clavicles	0.0 [0]	1.5 (0.1 to 19.6) [3]
Other (ribs and pelvis)	4.9 (1.8 to 13.3)* [7]	2.1 (0.4 to 12.8) [3]

Numbers in square brackets are actual number of fractures.
*p<0.01 compared with normal controls.
†Borderline insignificant (p=0.061).

general practitioners, and *x* ray departments. The fractures that could not be verified were three rib fractures, two toe fractures, and fractures of the knee cap, the orbital margin, the upper arm, a finger, and the coccygeal bone. No fractures were detected among subjects not reporting fractures.

The sex and age distribution among the normal control respondents was close to that of the general population in Denmark as compared with information from the Yearbook from the Danish Bureau of Statistics.[22] The fracture rates in the control group were comparable to those from the Danish population in general when compared with tables from the Danish Board of Health.[23] In general the validity of diagnoses of Crohn's disease or ulcerative colitis is high in Denmark[24]; in the actual sample patients who denoted not having had a final diagnosis of ulcerative colitis or Crohn's disease or those who were not sure of their diagnosis were excluded from the analysis. A separate analysis of those responding in the first and second round of the questionnaires did not change the results concerning age and sex distribution, or fracture rates significantly.

If more than one fracture occurred at the same time the largest bone that fractured was counted as the fractured bone. Analyses were made as comparison of incidence rates in patients versus controls. Incidence rates were calculated for fracture episodes (multiple fractures at the same time counted as one fracture episode) as number of fractures per 10 000 observation years.

Based on a careful evaluation, age adjustment was performed using three strata: less than 15 years, 15–49 years, and 50 years and above. The number of person years was calculated as time until actual age and stratified by time before and after diagnosis. The age at each fracture was calculated in years as integers (for example, 40 years). The fractures were then classified as having occurred before or after diagnosis. A person aged 40.5 years, having been diagnosed at the age of 30.2, and having had one fracture at the age of 10 and another at the age of 35 would contribute as follows: (1) before diagnosis: one fracture and 15 person years to the age strata less than 15 years, zero fractures and 30.2 − 15 = 15.2 person years to the age stratum 15–49 years, and zero fractures and zero person years to the age stratum 50 years and above; (2) after diagnosis: zero fractures and zero person years in the age stratum less than 15 years, one fracture and 40.5 − 30.2 = 10.3 person years to the age stratum 15–49 years, and zero fractures and zero person years to the age stratum 50 years and above. Relative risk estimates obtained by the Mantel-Haenszel method outlined and risk estimates obtained by a Cox regression and a logistic regression did not deviate significantly. The Mantel-Haenszel method was chosen for its ability to handle subjects having experienced more than one fracture episode and its ability to handle a small number of fractures.[25]

Incidence rates were compared by relative risks, and statistical comparisons were made using Mantel-Haenszel type χ^2 statistics. Numbers were compared by χ^2 for contingency tables, Fisher's exact test, or Mann-Whitney statistics when appropriate. Mantel-Haenszel statistics were used to compare fracture occurrence in groups. All comparisons were age and sex adjusted. Multiple comparisons were performed by logistic regression or multiple stepwise regression using SPSS for Windows 6.1.3. In the logistic regression analysis (forward likelihood ratio method) occurrence of fractures or not after the diagnosis was the dependent variable, and age (continuous variable), sex (male/female), family fracture history (yes/no/do not know), systemic corticosteroid use after diagnosis (yes/no), current use of calcium supplements (yes/no), current use of vitamin D supplements (yes/no), ever undergone any type of bowel surgery (yes/no), and current smoking (yes/no) were entered as independent variables.

Results

BASELINE CHARACTERISTICS

In total 845 patients (84.7%) and 654 controls (65.4%) returned the questionnaire (p<0.001). Twenty two patients did not have a definite diagnosis of either ulcerative colitis or Crohn's disease or were unaware of the type of disease they had, and six could not be analysed due to missing data, limiting the total number of patients to 817. A total of 635 controls could be analysed. This reduction did not affect the distribution of characteristics of patients or controls. Table 1 shows baseline characteristics of patients and controls. Table 2 shows the patients stratified by type of disease. The fraction of males was much smaller in patients than in controls. The patients were significantly younger than the controls and had a much higher frequency of any corticosteroid use. Patients with Crohn's disease more frequently reported having been diagnosed with osteoporosis (2p=0.007), while there was no difference between patients with ulcerative colitis and controls (2p=0.21). The female patients more frequently had used oral contraceptives and had used these for a longer period than the controls. The patients also reported hormone replacement therapy after the menopause more often than the controls. Patients with Crohn's

Table 4 Fracture energies before and after diagnosis, stratified by diagnosis

Time	*Diagnosis*	*Low energy*	*Medium + high energy*	*2p**
After diagnosis	Crohn's disease	8 (15.7)	43 (84.3)	0.0001
	Ulcerative colitis	2 (5.4)	35 (94.6)	0.30
	Controls	4 (1.4)	275 (98.6)	
Before diagnosis	Crohn's disease	2 (2.2)	88 (97.8)	0.90
	Ulcerative colitis	0 (0.0)	117 (100.0)	0.49
	Controls	4 (1.4)	275 (98.6)	

Numbers in brackets are percentages.
Low energy fractures are fractures occurring after minimal or no trauma; medium and high energy fractures are all other fractures.
*Fisher's exact test for comparison with control subjects.

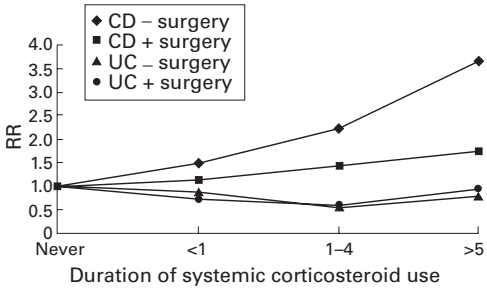

Figure 1 Relative risk (RR) of fractures after diagnosis. CD, Crohn's disease; UC, ulcerative colitis.

disease were younger at diagnosis than patients with ulcerative colitis. In ulcerative colitis there were significantly more ex-smokers than among patients with Crohn's disease. Patients with Crohn's disease were more likely to have had bowel surgery, to have received systemic corticosteroids, and more often used supplements of calcium, vitamin D, vitamin B_{12}, folic acid, multivitamin tablets, or treatment with cholestyramine than patients with ulcerative colitis.

FRACTURE RATES

Table 3 shows an increased fracture rate in female patients with Crohn's disease, but no increase in either male patients with Crohn's disease or patients with ulcerative colitis. The increased risk of fractures in Crohn's disease was limited to the spine, feet, and toes, and to the group of "other fracture sites" (ribs, pelvis). Of the five vertebral fractures occurring after the diagnosis in patients with Crohn's disease, two were diagnosed among 14 patients with known osteoporosis, and three were diagnosed among 369 patients without a diagnosis of osteoporosis. Three vertebral fractures were low energy fractures (spontaneous fractures), one followed a medium impact trauma, and one could not be classified. Among the controls two vertebral fractures were medium energy fractures, and two were high energy fractures. The vertebral fracture rates in the control subjects did not deviate from that of the general Danish population. Before diagnosis the fracture rate was not different from the controls in ulcerative colitis, while it was borderline significantly decreased in Crohn's disease. There was no effect of time since diagnosis on fracture rates in either Crohn's disease or ulcerative colitis (data not shown). In both patients and controls the fracture rate varied in a U shaped manner, fracture rates being higher in subjects less than 15 years and in subjects above 50 years than in subjects between 15 and 49 years.

Table 4 shows that there was an increased proportion of low energy fractures after diagnosis in patients with Crohn's disease, but not in ulcerative colitis. Again, this increase was only present in women with Crohn's disease (seven low energy fractures of 45 fractures in women) and not in men.

RISK FACTORS

Figure 1 shows an increasing relative risk (RR) of fractures in Crohn's disease with increasing duration of use of systemic corticosteroids (2p=0.0062), a trend not present in ulcerative colitis with increasing use of systemic corticosteroids. In Crohn's disease the increase in fracture risk was smaller in those who had ever undergone surgery than in those who had never undergone surgery (2p=0.0209). No such trend was present in ulcerative colitis (multiple linear regression).

Table 5 shows the effect of different risk factors on fracture occurrence. Current, but not previous smoking was associated with an increased fracture risk in ulcerative colitis, but not Crohn's disease. Analysing the risk of fractures after the diagnosis with a logistic regression model among patients with Crohn's disease showed that only a family fracture history (odds ratio (OR) = 3.3, 95% CI 1.5–7.2) was associated with an increased fracture history, while age (2p=0.88), systemic corticosteroid use (2p=0.54), use of calcium supplements (2p=0.52), use of vitamin D supplements (2p=0.13), bowel surgery (2p=0.57), smoking (2p=0.69), and sex (2p=0.09) were not. Among patients with ulcerative colitis the logistic regression confirmed that a family fracture history (OR = 2.5, 95% CI 1.2–5.3) and current smoking (OR = 3.6, 95% CI 1.5–8.9) were associated with fracture risk, while age (2p=0.62), systemic corticosteroid use (2p=0.48), use of calcium supplements (2p=0.11), use of vitamin D supplements

Table 5 Risk factors for fractures stratified by diagnosis

Risk factor	*Crohn's disease*	*Ulcerative colitis*
Family fracture history (yes/no)†	2.4 (1.4 to 4.1)*	1.9 (1.0 to 3.5)
Maternal fracture history (yes/no)	1.4 (0.7 to 2.7)	2.4 (1.2 to 4.7)*
Paternal fracture history (yes/no)	3.6 (1.9 to 6.8)*	1.2 (0.4 to 3.4)
Ever undergone bowel surgery (yes/no)	0.7 (0.4 to 1.3)	0.8 (0.4 to 1.8)
Ever used corticosteroids of any type (yes/no)	1.6 (0.6 to 4.1)	0.8 (0.3 to 2.1)
Ever used corticosteroid enemas only (yes/no)	2.7 (0.6 to 13.1)	0.5 (0.1 to 1.9)
Current use of calcium supplements (yes/no)	1.5 (0.9 to 2.5)	2.4 (1.1 to 5.0)*
Current use of vitamin D supplements (yes/no)	1.9 (1.1 to 3.4)*	1.8 (0.6 to 4.9)
Use of oral contraceptives (only females)	1.3 (0.6 to 2.8)	0.9 (0.3 to 2.4)
Use of HRT after menopause (only females)	0.7 (0.2 to 1.9)	0.7 (0.1 to 3.9)
Current smoking versus never smoking	1.3 (0.6 to 2.8)	3.8 (1.9 to 7.8)*
Previous smoking versus never smoking	1.4 (0.6 to 3.1)	1.2 (0.5 to 2.6)
Current alcohol intake (≥1 drink/week versus <1 drink/week)	0.7 (0.4 to 1.2)	0.6 (0.3 to 1.1)
Current use of systemic cytostatic agents‡ (yes/no)	1.4 (0.7 to 2.6)	1.1 (0.4 to 2.9)
Current use of systemic 5-aminosalicylates§ (yes/no)	1.0 (0.6 to 1.6)	1.2 (0.6 to 2.3)
Current use of B_{12} supplements (yes/no)	0.5 (0.2 to 1.4)	¶
Current use of folic acid supplements (yes/no)	0.7 (0.1 to 4.6)	¶
Current use of iron supplements (yes/no)	0.4 (0.1 to 2.3)	¶
Current use of cholestyramine (yes/no)	1.0 (0.4 to 2.5)	¶

The risks are expressed as relative risk (95% confidence interval) adjusted for age and sex. All significant associations were present both in men and women unless otherwise stated. Insignificant associations were insignificant in both sexes.
*p<0.05.
†Reports of at least one previous fracture among either parents or siblings.
‡Current systemic therapy with azathioprine or cyclosporin versus no such therapy.
§Current systemic therapy with mesalazine, olsalazine, or sulphasalazine versus no such therapy.
¶Too few for analysis.

(2p=0.42), bowel surgery (2p=0.81), and sex (2p=0.10) were not.

Discussion

We have shown an association between Crohn's disease and an increased risk of fractures in women. In particular, low energy fractures of the spine, feet, and toes, and the group of "other sites" (ribs and pelvis) occurred more frequently in Crohn's disease, while no association existed between ulcerative colitis and fracture occurrence. The low energy spine fractures were typical osteoporotic fractures.[26] Jahnsen and colleagues[15] reported no difference in number of fractures among patients with Crohn's disease and patients with ulcerative colitis. Abitbol *et al*,[1] in a series of 84 patients, found six (7%) with vertebral crush fractures, and a retrospective study of 245 patients revealed a total fracture prevalence of 18% and a prevalence of non-accidental fractures of 2.4%.[8] Edwards and Truelove[20] showed a prevalence of 1.4% of osteoporosis in ulcerative colitis based on radiological osteopenia and/or fracture. However, none of these studies[1 8 15 20] compared patients with control groups from the background population. As the vertebral fracture rate in the controls in our study did not deviate from that of the general Danish population,[23] it is unlikely that symptomatic vertebral fractures were missed. However, it should be noted that up to 50% of vertebral fractures at least in elderly subjects may be symptomless.[27]

In our study corticosteroid use per se was not a risk factor for fractures. Although there was an increasing fracture risk with increasing duration of systemic use in Crohn's disease, no such association could be shown in ulcerative colitis. The cause for this difference remains unclear. Several explanations are possible: (1) in Crohn's disease there may be a trend towards continuous steroid treatment, whereas patients with ulcerative colitis tended to be treated with steroids in intermittent periods—a less detrimental treatment form[10]; (2) it may be hypothesised that increasing duration of steroid use was a marker of increasing disease activity, an activity that in Crohn's disease may lead to systemic effects by disturbing the menstrual cycle and thus inducing oestrogen deficiency in women; or (3) it may be hypothesised that the inflammatory process was more pronounced in Crohn's disease, leading to a more profound systemic effect of cytokines and thereby inducing a negative bone mineral balance.[8 14 28] Hyams and colleagues[14] reported that serum from children with Crohn's disease had profound negative effects on bone formation and bone architecture in rat calvariae, an effect not seen with serum from children with ulcerative colitis or from control subjects. Our observations were in accordance with those of Jahnsen *et al*,[15] who found a negative relation between bone mineral density and steroid use in Crohn's disease, but not in ulcerative colitis. Furthermore, Jahnsen *et al* found a relation between cumulative steroid dose and fractures in Crohn's disease, but not in ulcerative colitis. We found that patients with Crohn's disease, who had undergone bowel surgery, were less likely to sustain fractures than those who had not undergone surgery when stratifying for systemic corticosteroid use. As the effects of surgery were not universally demonstrable among the patients with Crohn's disease, it may not be concluded from this study that surgery tends to decrease fracture risk. However, it was an interesting trend, as it may corroborate the hypothesis that the inflammatory process per se—at least in Crohn's disease—was a major determinant of bone loss, because surgery tended to limit the amount of inflammatory tissue. Thus differences between the magnitude or the nature of the systemic inflammatory response in ulcerative colitis and Crohn's disease may perhaps be responsible for the difference in fracture risk between these two types of IBD.

None of the indexes of malabsorption (vitamin B_{12} substitution, folic acid supplements, iron supplements, or cholestyramine treatment; table 5) were associated with an increased fracture risk. Silvennoinen[9] found that in unselected patients with IBD, malabsorption did not seem to play a major role in bone mineral density.

Among the male patients with Crohn's disease there was no trend towards an increase in fracture risk, suggesting a hormonal component in the increased fracture risk among female patients. This suggestion was supported by the finding that the increase in fracture risk was most prominent in premenopausal women, contrary to the findings in the general population where overall fracture risk was higher in postmenopausal women.[29] In the context of sex steroids, surgery may have helped to limit the severity of the disease and thus have helped to correct potential hormonal disturbances in female patients. However, hypogonadism and associated low bone mineral density may also be seen in male patients with Crohn's disease.[13] In our study no specific data on premenopausal amenorrhoea were available. Further studies are needed to assess the relation between disturbances in the menstrual cycle or sex steroids in patients with Crohn's disease and the risk of fractures.

The increased fracture risk seen in users of calcium and vitamin D supplements was more likely to stem from the fact that those with osteoporosis and/or fractures were more likely to receive such therapy than the increased fracture risk being a detrimental effect of the supplements themselves. A small (n=17) randomised controlled study failed to show beneficial effects of calcium (1000 mg/day) and vitamin D (250 IU/day) supplements on changes in bone mineral in patients with inflammatory bowel disease on corticosteroids.[30]

The fact that fracture risk before the diagnosis was borderline significantly lower in subjects with Crohn's disease than in control subjects may be a chance finding. However, it may also be due to a recall bias—the patients recalling fractures which did in fact occur before the diagnosis as having occurred after the diagnosis. Against the latter is the fact that in

ulcerative colitis the fracture reported frequency was the same before and after the diagnosis. Comparison of the fracture reports in the controls with the general Danish population showed no signs of under- or over-reporting.[23] In a questionnaire based study the possibility of false positive reports of fractures must be considered.[31 32] In a separate sample we found a low proportion of false positive fracture reports, mostly for small fractures of fingers and hands. Nevitt and colleagues[31] also found a higher proportion of false positive fracture reports for the fingers and ribs than for other fracture sites, but found that 11% of reported hip fractures could not be verified. However, the study of Nevitt and colleagues[31] was undertaken in a group of women aged 65 years or over. In this age group they[31] reported that fracture reports by relatives were more reliable than those of the study subjects themselves.

The positive association between a family fracture history and fracture occurrence in the study subjects has also been observed in the general population.[33] In accordance with our results, Silvennoinen and colleagues[34] found a higher proportion of smokers among patients with Crohn's disease than among patients with ulcerative colitis. They also found a higher proportion of female patients with osteoporosis—defined as low bone mineral density—among smokers with IBD than among normal controls. In our study no increased fracture risk was present among smokers with Crohn's disease in contrast to patients with ulcerative colitis, a difference that remains unexplained. The fact that so many patients with ulcerative colitis had stopped smoking may also be responsible for the absence of an increased fracture occurrence.

It is concluded that an increased risk of low energy fractures, especially of the spine, feet, and toes, and in the ribs and pelvis was observed among female patients with Crohn's disease. The fracture risk increased with increasing duration of systemic corticosteroid therapy. Among patients with ulcerative colitis the risk of fractures was not increased, and there was no association with systemic corticosteroid use.

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