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ORIGINAL CONTRIBUTIONS

Fracture Risk in Patients with Celiac Disease, Crohn's Disease, and Ulcerative Colitis: A Nationwide Follow-up Study of 16,416 Patients in Denmark

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The authors studied fracture risk among 16,416 Danish patients with bowel disease. All patients diagnosed with celiac disease (n = 1,021), Crohn's disease (n = 7,072), or ulcerative colitis (n = 8,323) in Denmark between January 1, 1983, and December 31, 1996, were included. Each patient was compared with three age- and gender-matched controls randomly drawn from the background population. No increase in fracture risk could be demonstrated for celiac disease before or after diagnosis. In patients with Crohn's disease, overall fracture risk was increased both before diagnosis (incidence rate ratio = 1.15, 95% confidence interval (CI): 1.00, 1.32) and after diagnosis (incidence rate ratio = 1.19, 95% CI: 1.06, 1.33). Bowel surgery was associated with a decreased risk of sustaining a fracture before diagnosis (odds ratio = 0.70, 95% CI: 0.54, 0.90) and after diagnosis (hazard ratio = 0.81, 95% CI: 0.67, 0.99). Overall fracture risk was not increased in patients with ulcerative colitis, except for a small increase around the time of diagnosis. Increasing age and having a fracture before diagnosis increased the risk of sustaining a new fracture after diagnosis. Crohn's disease was associated with a minor increase in overall fracture risk in contrast to ulcerative colitis and celiac disease. The severity of the inflammatory process and the amount of corticosteroids given may explain the difference in fracture risk. *Am J Epidemiol* 2002;156:1–10.

celiac disease; colitis, ulcerative; Crohn disease; fractures; inflammatory bowel diseases

Abbreviations: CI, confidence interval; ICD, *International Classification of Diseases*; IRR, incidence rate ratio.

Intestinal disease may affect the skeleton through several mechanisms (1). Malabsorption leads to deficiencies in calcium and vitamin D (2, 3). The increased production of cytokines in inflammatory bowel disease induces bone loss (1). Treatment with corticosteroids contributes to bone loss in both Crohn's disease and ulcerative colitis (4–7). These processes decrease bone mineral density (4, 8–10) and increase fracture risk (11).

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Crohn's disease

Crohn's disease is a regional inflammation in the jejunum and ileum, but it may also affect the colon, mouth, esophagus, and stomach (12). The disease occurs at all ages, with peak incidence appearing between the ages of 15 and 35 years (12). More women than men are affected (13).

In Crohn's disease, malabsorption and increased cytokine production due to inflammation are present. The disease often requires surgery and treatment with systemic corticosteroids and cytostatic agents.

Previous studies have demonstrated decreased bone mineral density in Crohn's disease (9, 14–18). One study (11) demonstrated an increased risk of fracture after diagnosis (incidence rate ratio (IRR) = 1.7, 95 percent confidence interval (CI): 1.2, 2.3). Fracture risk was linked to use of corticosteroids, while bowel surgery was associated with a decreased risk of fractures among users of corticosteroids (11).

Ulcerative colitis

Ulcerative colitis occurs in all age groups. Incidence peaks between the ages of 15 and 35 years, and there are no major gender differences (12).

Ulcerative colitis affects only the colon and is not accompanied by malabsorption (12); thus, it affects bone density less than does Crohn's disease (1, 17). Use of corticosteroids in these patients can often be limited to treatment with topical preparations (12).

Previous studies have demonstrated a marginal decrease in bone mineral density among persons with ulcerative colitis compared with normal controls. The decrease is smaller than in Crohn's disease (9, 14–18). A previous study (11) failed to demonstrate an increase in fracture risk (IRR = 1.1, 95 percent CI: 0.8, 1.6).

Celiac disease (nontropical sprue)

Celiac disease affects the small intestine through intolerance to gluten (19). The disease may be seen in children as well as in adults, with more women than men being affected.

Celiac disease is often accompanied by severe malabsorption but no systemic inflammation (19), and the patients do not require corticosteroids. Previous studies have demonstrated decreased bone mineral density (20–26). One study reported an increased risk of peripheral fractures (odds ratio = 3.5, 95 percent CI: 1.8, 7.2) and a trend toward more spinal fractures (odds ratio = 2.8, 95 percent CI: 0.7, 11.5) (27). Most fractures were observed before the diagnosis was made or in patients who were not compliant with their gluten-free diet (27). After the introduction of a gluten-free diet, bone mineral density may increase to normal values (23).

The present study

The aim of the present study was to assess fracture risk among persons with Crohn's disease, ulcerative colitis, and celiac disease before and after diagnosis. This allowed for evaluation of a possible time lag before diagnosis and the effect of treatment on fracture risk after diagnosis. Furthermore, it was possible to obtain information on risk factors for such fractures because of the differences in pathophysiology and treatment between the three disorders.

MATERIALS AND METHODS

Study population

All patients diagnosed with new cases of celiac disease (*International Classification of Diseases*, Eighth Revision (ICD-8), code 269.00 (n = 822) and *International Classification of Diseases*, Tenth Revision (ICD-10), code K90.0 (n = 199)), Crohn's disease (ICD-8 codes 563.00 (n = 1,136), 563.01 (n = 3,903), 563.02 (n = 30), 563.08 (n = 121), and 563.09 (n = 405) and ICD-10 codes K50.0 (n = 438), K50.1 (n = 259), K50.8 (n = 123), and K50.9 (n = 657)), or ulcerative colitis (ICD-8 code 563.19 (n = 6,068) and ICD-10 codes K51.0 (n = 466), K51.1 (n = 28), K51.2 (n = 408), K51.3 (n = 59), K51.8 (n = 47), and K51.9 (n = 1,247)) in Denmark between January 1, 1983, and December 31, 1996, were included. Fracture occurrence was assessed for the period 1980–1996. The number of person-years of follow-up between 1980 and 1996 was 14,449 for the 1,021 patients with celiac disease, 114,992 for the 7,072 patients with Crohn's disease, and 135,161 for the 8,323 patients with ulcerative colitis.

Patients were identified through the National Patient Discharge Register, a computer-based register of all admissions to and discharges from Danish hospitals that includes both ICD-8 and ICD-10 diagnoses and surgical procedures (28). The register covered only inpatient admissions until 1994 and has covered both inpatient and outpatient admissions since 1995. The register was founded in 1977 and is linked with other Danish registers through the nationwide Civil Registration Number. This Civil Registration Number is a unique identifying code given to each citizen in Denmark.

Almost all patients with inflammatory bowel disease or celiac disease are hospitalized early in the course of the disease to undergo diagnostic tests and are subsequently transferred to an outpatient clinic for follow-up. Thus, hospital-based discharge diagnosis dates are a valid marker for the time of diagnosis of these conditions.

A more liberal definition of Crohn's disease was used than in other studies (these studies used the codes 563.01, K50.0, and K50.1 or equivalents (13)). This was done because many patients later progressed from an initial diagnosis of an illness such as terminal ileitis to the more narrow definition of Crohn's disease (35 percent of the 2,472 patients with diagnosis codes other than 563.01, K50.0, and K50.1 later progressed to Crohn's disease). Limiting the analysis to the more narrow definition of Crohn's disease did not change the results.

Comorbidity among the patients and controls was examined by assessing hospital admissions for some conditions that may affect the risk of fractures. These conditions included diseases of calcium metabolism (hyper- and

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hypoparathyroidism, hyper- and hypothyroidism) and those that entail a risk of falls (epilepsy).

Patients who were not residing in Denmark were excluded. For each patient, the first date on which the diagnosis of an intestinal disorder was made was recorded. The observation period was subsequently divided into the periods before and after this date. This division permitted analysis of limited time periods before and after diagnosis (e.g., the period 1–5 years after diagnosis) through calculation of the number of person-years in a given time interval and the number of fractures sustained within that interval.

From the coding of surgical procedures, an assessment was made of whether the patient had undergone surgery of the jejunum, ileum, colon, or rectum. Both laparoscopic procedures and procedures involving open abdominal surgery were included. The procedures included bowel resection, formation of stomas, resection of fistulas, etc.

Controls

Each patient was compared with three age-, gender-, and status-matched controls. The controls were age-matched to the case by birth year. The status match regarded death or emigration. If the case subject had died or emigrated, a control subject who had died or emigrated on the same date or later was chosen. The Danish Ministry of the Interior performed this matching using standard procedures involving the Civil Registration Number, as previously described (29). Each control's assigned "date of diagnosis" was the date on which the corresponding case had had his or her intestinal disease diagnosed. The follow-up period for controls was divided into the periods before and after this dummy "date of diagnosis" (29).

Table 1 gives numbers of control subjects, and table 2 gives person-years of follow-up. In a few cases it was not possible to find control subjects because they had died or emigrated.

Outcome variable

For both cases and controls, any fracture diagnosis (ICD-8 and ICD-10 codes) registered between January 1, 1980, and December 31, 1996, was retrieved from the National Patient Discharge Register (28). The diagnoses included fractures of the skull and face (codes 800.00–803.99, S02.0–S02.9, and S07.0–S07.9), spine, rib, and pelvis (codes 805.00–808.09, S12.0–S12.9, S22.0–S22.9, and S23.0–S23.9), clavicle, scapula, and humerus (codes 810.99–812.99 and S42.0–S42.9), forearm (codes 813.00–813.99 and S52.0–S52.9), hand and finger (codes 814.00–816.09 and S62.0–S62.9), hip and femur (codes 820.00–821.99 and S72.0–S72.9), lower leg (codes 823.00–824.09 and S82.0–S82.9), and foot and toe (codes 825.00–826.09 and S92.0–S92.9); other fractures (codes 822.00, 818.99, and 827.99); and osteoporosis (codes 723.09 and M80.0–M81.9).

The follow-up period began at birth or on January 1, 1980, whichever came last, and ended on the date of death or on December 31, 1996. The number of person-years before diagnosis was calculated as (date of diagnosis – January 1, 1980)/365.25, and the number of person-years after diagnosis was calculated as (December 31, 1996 – date of diagnosis)/365.25. Data for outpatient contacts were available from 1995 and 1996; however, results were not changed when this period was analyzed in comparison with the period in which only inpatient records were available.

Validity

The validity of diagnoses in the present study was evaluated in random samples of patients using clinical, radiologic, pathoanatomic, and paraclinical findings (12). Validity ranged from 64 percent for ulcerative colitis ($n = 22$) to 78 percent for celiac disease ($n = 9$) and 95 percent for Crohn's disease ($n = 19$). The main reason for deviations in the diagnosis of ulcerative colitis was the fact that, in many of these cases, the diagnosis should have been Crohn's disease. If the criterion of validity was expanded to include any inflammatory bowel disease, validity was 73 percent among persons classified as having ulcerative colitis. In our study, the validity of fracture reports was 97 percent in a random sample of diagnoses ($n = 35$) compared with patient files.

The National Patient Discharge Register has nationwide coverage and almost 100 percent capture of records (28, 30, 31).

Statistics

Mean values and standard deviations were used as descriptive statistics. Numbers were compared by Mann-Whitney U test or χ^2 test for contingency tables, where appropriate. Incidence rates were calculated as the number of subjects with at least one fracture divided by the observation time. Incidence rates were compared by IRRs, and statistical significance was tested by Mantel-Haenszel-type χ^2 statistics. Relative risks were compared using Poisson regression analysis. Cox regression and conditional logistic regression were applied to analyze risk factors for fracture among the patients. All calculations were performed using SPSS for Windows, version 6.1.3 (SPSS, Inc., Chicago, Illinois).

RESULTS

Table 1 shows the baseline characteristics of the patients. In general, there were more females than males. Patients with celiac disease were younger at diagnosis (31 years) than patients with Crohn's disease (38 years) or ulcerative colitis (43 years). Ages at diagnosis were similar for men and women among persons with Crohn's disease and ulcerative colitis, while men with celiac disease were younger at diagnosis than women. Fewer patients with celiac disease had had a fracture before diagnosis (2 percent) than patients with Crohn's disease or ulcerative colitis (4 percent).

The presence of comorbidity as defined in Materials and Methods was approximately equal in patients and controls: for Crohn's disease, 1.7 percent in patients and 1.5 percent in controls; for ulcerative colitis, 2.0 percent in patients and 1.9 percent in controls; and for celiac disease, 2.8 percent in

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TABLE 1. Baseline characteristics of patients with Crohn's disease, ulcerative colitis, or celiac disease diagnosed between January 1, 1983, and December 31, 1996, Denmark

Disease and variable	Females		Males		Total		*p* value
	No. or mean	%	No. or mean	%	No. or mean	%	
Crohn's disease							
No. of subjects	4,109	58	2,963	42	7,072		
Age (years) at diagnosis	38.8 (19.9)*		37.6 (19.0)		38.3 (19.5)		0.14†
Person-years before diagnosis	9.8 (4.1)		9.8 (4.0)		9.8 (4.0)		0.96†
Person-years after diagnosis	6.5 (4.1)		6.4 (4.1)		6.5 (4.1)		0.36†
No. of patients with at least one fracture before diagnosis	153	4	134	4	287	4	0.09‡
Age (years) at first fracture after diagnosis	57.7 (22.0)		41.0 (19.8)		50.7 (22.7)		<0.01†
No. with bowel surgery before diagnosis	259	6	183	6	442	6	0.83‡
No. with bowel surgery after diagnosis	1,621	39	1,087	37	2,708	38	0.02‡
Ulcerative colitis							
No. of subjects	4,309	52	4,014	48	8,323		
Age (years) at diagnosis	43.2 (20.2)		43.7 (19.4)		43.5 (19.8)		0.09†
Person-years before diagnosis	10.4 (4.2)		10.4 (4.1)		10.4 (4.2)		0.93†
Person-years after diagnosis	5.9 (4.2)		5.8 (4.1)		5.9 (4.1)		0.16†
No. of patients with at least one fracture before diagnosis	190	4	174	4	364	4	0.87‡
Age (years) at first fracture after diagnosis	61.3 (20.6)		51.5 (21.4)		57.0 (21.5)		<0.01†
No. with bowel surgery before diagnosis	134	3	108	3	242	3	0.26‡
No. with bowel surgery after diagnosis	792	18	786	20	1,578	19	0.16‡
Celiac disease							
No. of subjects	588	58	433	42	1,021		
Age (years) at diagnosis	34.7 (23.9)		27.2 (25.1)		31.5 (24.7)		<0.01†
Person-years before diagnosis	8.0 (4.7)		7.1 (4.8)		7.6 (4.8)		<0.01†
Person-years after diagnosis	6.7 (4.1)		6.4 (4.2)		6.5 (4.2)		0.22†
No. of patients with at least one fracture before diagnosis	14	2	10	2	24	2	0.94‡
Age (years) at first fracture after diagnosis	48.6 (26.4)		31.1 (26.5)		40.2 (27.7)		0.01†

* Numbers in parentheses, standard deviation.
† Mann-Whitney *U* test.
‡ χ^2 test for contingency tables.

patients and 2.6 percent in controls (in all cases, $p > 0.05$ for patients vs. controls). Comorbidity did not influence fracture risk.

Table 2 shows fracture risks before and after diagnosis. There were only small and borderline-significant changes in relative fracture risk in the period before diagnosis as compared with the period after diagnosis. The overall risk of fracture was slightly increased among patients with Crohn's disease both before and after diagnosis. More femur and skull fractures were observed before diagnosis, while more fractures of the spine, hands, and feet were seen after diagnosis (table 2). The risk of hip fractures decreased among patients with Crohn's disease after diagnosis, while the risk of hand fractures increased (table 2). Patients with ulcerative colitis had no increase in overall fracture risk, except for an increase in fractures of the spine before diagnosis (table 2) and small increases in the first year before diagnosis and the first 5 years after diagnosis. The IRRs were not significantly different in patients with Crohn's disease and patients with ulcerative colitis (two-sided $p = 0.21$ by Poisson regression).

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TABLE 2. Incidence rate ratios for fracture before and after diagnosis among patients with Crohn's disease, ulcerative colitis, or celiac disease diagnosed between January 1, 1983, and December 31, 1996, Denmark

Disease and fracture site	Period before diagnosis				Period after diagnosis				*p* value*
	No. of patients†	No. of controls	IRR‡	95% CI‡	No. of patients†	No. of controls	IRR	95% CI	
Crohn's disease	(69,314 P-Y‡)	(207,668 P-Y)			(45,678 P-Y)	(146,402 P-Y)			
All fractures	287	748	1.15	1.00, 1.32	418	1,126	1.19	1.06, 1.33	0.71
Skull and jaws	18	27	2.00	1.11, 3.58	15	38	1.27	0.70, 2.30	0.28
Spine, rib, and pelvis	19	44	1.29	0.76, 2.21	35	60	1.87	1.24, 2.82	0.28
Upper arm	36	90	1.20	0.81, 1.76	44	127	1.11	0.79, 1.56	0.77
Forearm	44	137	0.96	0.69, 1.35	66	203	1.04	0.79, 1.38	0.72
Colles' fracture	26	84	0.93	0.60, 1.44	50	154	1.04	0.76, 1.43	0.69
Hand and finger	13	59	0.66	0.36, 1.20	76	182	1.34	1.03, 1.75	0.03
Hip and femur	78	153	1.53	1.17, 2.00	100	292	1.10	0.87, 1.38	0.07
Femoral neck	56	106	1.58	1.15, 2.18	80	253	1.01	0.79, 1.30	0.03
Lower leg	85	238	1.07	0.84, 1.37	73	216	1.08	0.83, 1.41	0.96
Foot	14	43	0.98	0.53, 1.78	46	102	1.45	1.02, 2.04	0.26
Osteoporosis	10	21	1.43	0.67, 3.02	36	46	2.51	1.65, 3.82	0.20
Ulcerative colitis	(86,399 P-Y)	(258,908 P-Y)			(48,762 P-Y)	(158,013 P-Y)			
All fractures	364	982	1.11	0.98, 1.25	448	1,346	1.08	0.97, 1.20	0.74
Skull and jaws	27	55	1.47	0.93, 2.33	12	37	1.05	0.55, 2.02	0.41
Spine, rib, and pelvis	30	45	2.00	1.27, 3.14	26	81	1.04	0.67, 1.62	0.04
Upper arm	44	112	1.18	0.83, 1.67	52	167	1.01	0.74, 1.38	0.51
Forearm	66	177	1.12	0.84, 1.48	79	246	1.04	0.81, 1.34	0.70
Colles' fracture	36	115	0.94	0.65, 1.36	59	187	1.02	0.76, 1.37	0.73
Hand and finger	27	77	1.05	0.68, 1.63	77	190	1.31	1.01, 1.71	0.40
Hip and femur	74	234	0.95	0.73, 1.23	127	382	1.08	0.88, 1.32	0.44
Femoral neck	57	172	0.99	0.74, 1.34	114	334	1.11	0.89, 1.37	0.54
Lower leg	107	302	1.06	0.85, 1.32	82	255	1.04	0.81, 1.34	0.91
Foot	21	55	1.14	0.69, 1.89	35	120	0.95	0.65, 1.38	0.57
Osteoporosis	15	37	1.21	0.67, 2.21	30	60	1.62	1.05, 2.50	0.44
Celiac disease	(7,774 P-Y)	(23,316 P-Y)			(6,675 P-Y)	(21,468 P-Y)			
All fractures	24	103	0.70	0.45, 1.09	65	223	0.94	0.71, 1.24	0.27
Skull and jaws	0	5	0		1	5	0.64	0.08, 5.41	
Spine, rib, and pelvis	5	7	2.14	0.70, 6.57	5	15	1.07	0.39, 2.95	0.37
Upper arm	2	10	0.60	0.13, 2.69	9	29	1.00	0.47, 2.11	0.55
Forearm	7	17	1.23	0.51, 2.97	19	70	0.87	0.53, 1.45	0.51
Colles' fracture	4	6	2.00	0.58, 6.91	14	45	1.00	0.55, 1.82	0.32
Hand and finger	2	4	1.50	0.28, 8.09	11	34	1.04	0.53, 2.05	0.69
Hip and femur	7	29	0.72	0.32, 1.65	13	48	0.87	0.47, 1.61	0.72
Femoral neck	5	21	0.71	0.27, 1.89	13	36	1.16	0.62, 2.19	0.41
Lower leg	4	32	0.37	0.14, 1.02	9	27	1.07	0.50, 2.28	0.10
Foot	0	2	0		5	15	1.07	0.39, 2.95	
Osteoporosis	1	1	3.00	0.21, 41.91	4	10	1.29	0.40, 4.09	0.57

* Poisson test; if $p < 0.01$, then the IRR changed significantly from the period before diagnosis to the period after diagnosis.
† No. of patients with at least one incident fracture.
‡ IRR, incidence rate ratio; CI, confidence interval; P-Y, person-years of follow-up.

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TABLE 3. Risk factors for fracture before and after diagnosis among patients with Crohn's disease, ulcerative colitis, or celiac disease diagnosed between January 1, 1983, and December 31, 1996, Denmark

Disease and parameter	Risk estimate	95% CI*
Period before diagnosis†		
Crohn's disease		
Age (years)	1.02	1.02, 1.03
Gender (male/female)	1.26	0.99, 1.60
Bowel surgery (yes/no)	0.70	0.54, 0.90
Ulcerative colitis		
Age (years)	1.02	1.01, 1.02
Gender (male/female)	0.98	0.80, 1.22
Bowel surgery (yes/no)	0.66	0.49, 0.90
Celiac disease		
Age (years)	1.03	1.01, 1.05
Gender (male/female)	1.16	0.51, 2.66
Period after diagnosis‡		
Crohn's disease		
Age (years)	1.03	1.02, 1.03
Fracture before diagnosis (yes/no)	3.37	2.42, 4.70
Gender (male/female)	1.02	0.84, 1.24
Bowel surgery (yes/no)	0.81	0.67, 0.99
Ulcerative colitis		
Age (years)	1.03	1.03, 1.04
Fracture before diagnosis (yes/no)	2.89	2.08, 4.00
Gender (male/female)	0.87	0.72, 1.05
Bowel surgery (yes/no)	0.98	0.78, 1.22
Celiac disease		
Age (years)	1.02	1.01, 1.03
Fracture before diagnosis (yes/no)	2.04	0.49, 8.40
Gender (male/female)	1.52	0.92, 2.50

* CI, confidence interval.
† Odds ratio from logistic regression analysis.
‡ Hazard ratio from Cox regression analysis.

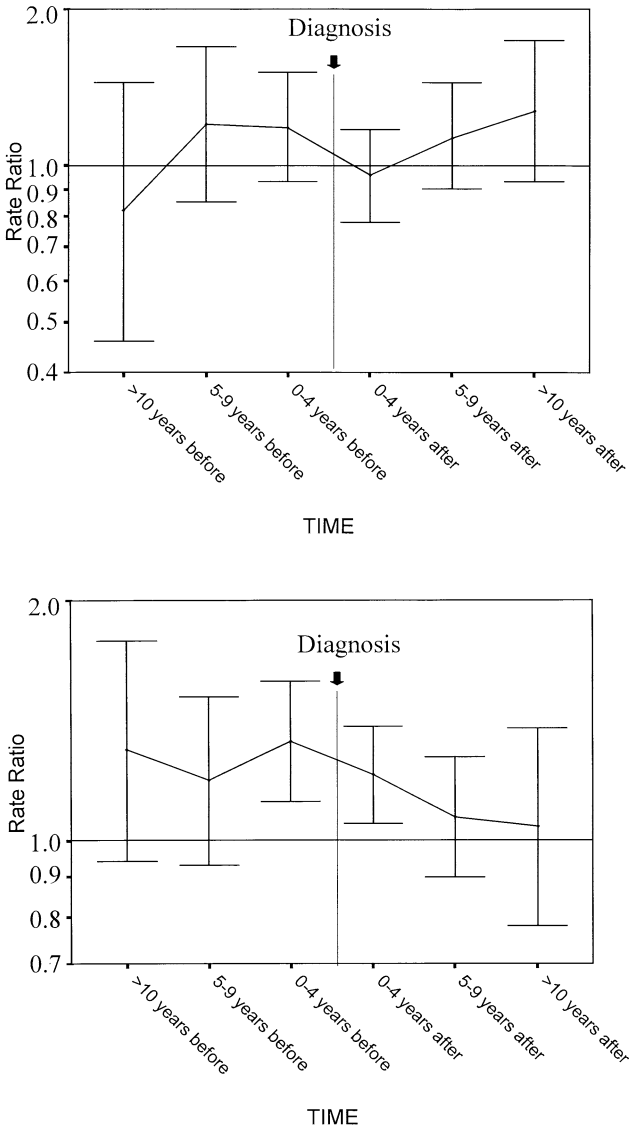

FIGURE 1. Risks of fracture during various time periods before and after diagnosis, according to bowel surgery, among patients with Crohn's disease diagnosed between January 1, 1983, and December 31, 1996, Denmark. Rate ratios are presented on a log scale; the T-shaped bars show 95 percent confidence intervals. Top, Crohn's disease with surgery; bottom, Crohn's disease without surgery.

Sustaining a fracture before diagnosis was associated with an increased risk of sustaining a new fracture after diagnosis (table 3).

Bowel surgery was associated with a borderline-significant reduction in fracture risk after diagnosis in patients with Crohn's disease (figure 1) but not in patients with ulcerative colitis (figure 2). Before diagnosis, patients with Crohn's disease and patients with ulcerative colitis who later underwent bowel surgery had lower fracture risks than those who did not undergo surgery (table 3).

Patients with celiac disease had no increase in fracture risk before or after diagnosis (table 2 and figure 3). Age was the only significant risk factor (table 3).

The incidence rate of celiac disease was stable during the observation period at 1.39 (standard deviation 0.29) new cases per 100,000 inhabitants per year.

DISCUSSION

In this study of fracture risk among persons with bowel disease, only a limited increase in overall fracture risk could be demonstrated in a subset of patients, despite the presence of several predisposing factors for fracture.

Fracture risk

The finding of an increase in fracture risk after diagnosis among patients with Crohn's disease but not patients with

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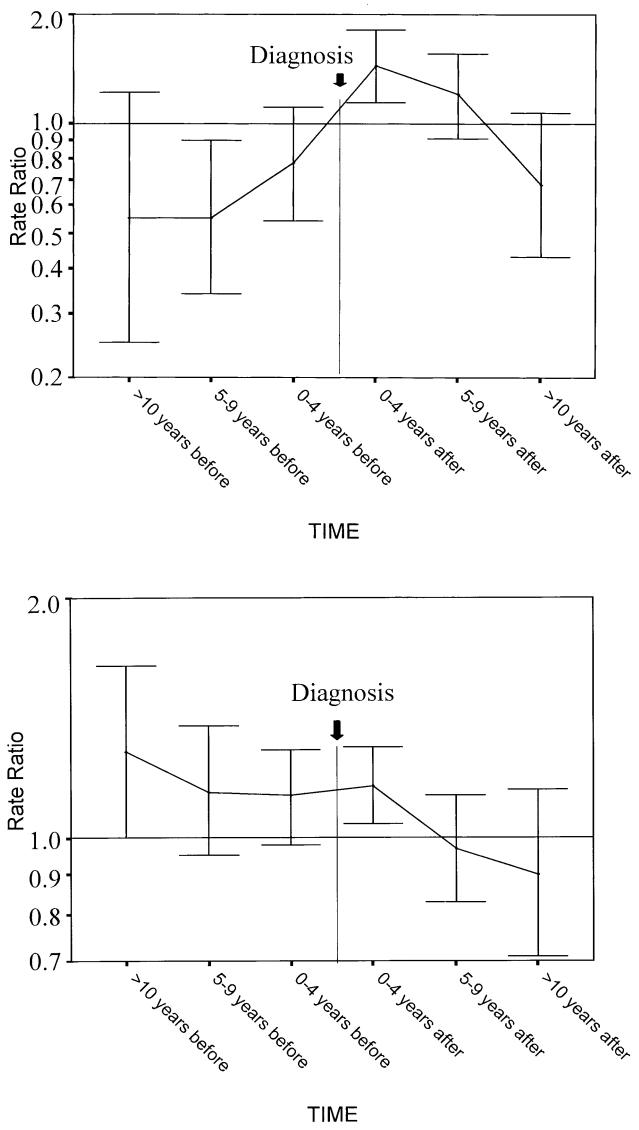

FIGURE 2. Risks of fracture during various time periods before and after diagnosis, according to bowel surgery, among patients with ulcerative colitis diagnosed between January 1, 1983, and December 31, 1996, Denmark. Rate ratios are presented on a log scale; the T-shaped bars show 95 percent confidence intervals. Top, ulcerative colitis with surgery; bottom, ulcerative colitis without surgery.

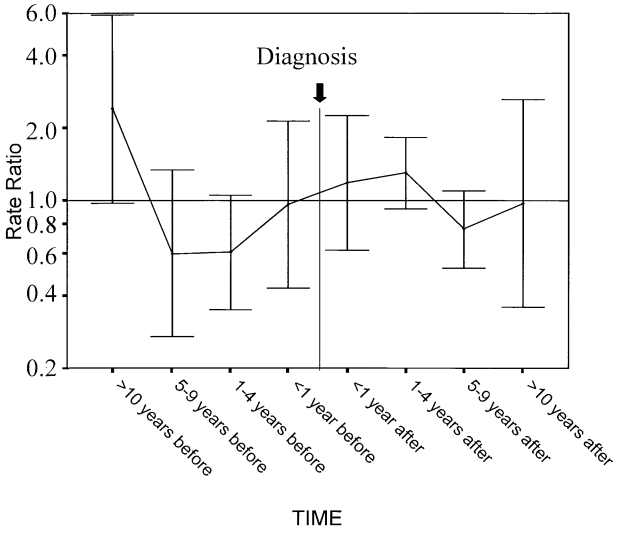

FIGURE 3. Risks of fracture before and after diagnosis among patients with celiac disease diagnosed between January 1, 1983, and December 31, 1996, Denmark. Rate ratios are presented on a log scale; the T-shaped bars show 95 percent confidence intervals.

ulcerative colitis matches that of a previous report (11). The increase in fracture risk after diagnosis among persons with Crohn's disease was smaller in our study (IRR = 1.19, 95 percent CI: 1.06, 1.33) than in the previous study (IRR = 1.7, 95 percent CI: 1.2, 2.3) (11). This could be related to differences in study design. The present study was population-based and might have included patients with milder disease than the previous study, which was based on questionnaires issued to members of a patient association (11). The observation that only 38 percent of the patients with Crohn's disease in the present study had bowel surgery after diagnosis, versus 60 percent in the previous study (11), supports the possibility that patients in the present study had less severe disease. Patients may also be more willing to answer a questionnaire on fractures if they have experienced a fracture.

The increased risk of fracture before diagnosis in persons with Crohn's disease and persons with ulcerative colitis could indicate that the disease may have been present for some time before the diagnosis was established. A delay in seeking medical attention by the patient or a delay in making or registering a definite diagnosis by the doctor (e.g., if the patient had undergone outpatient treatment before being admitted to a hospital) may also explain this.

The presence of a bone deficit before disease diagnosis is supported by the findings of Ghosh et al. (14), who reported decreased bone mineral density at diagnosis among patients with Crohn's disease but not among patients with ulcerative colitis. In the study by Ghosh et al. (14), the mean estimated duration of disease at diagnosis was 18.6 weeks for Crohn's disease and 12.3 weeks for ulcerative colitis.

The differences in fracture risk between different types of bowel disease may point to an effect of the inflammatory process and corticosteroid treatment. These factors are more prevalent in Crohn's disease than in celiac disease and ulcerative colitis. This potential inflammation effect may explain the reduction in fracture risk following bowel surgery among patients with Crohn's disease (11). After surgery, the need for corticosteroids is reduced and the inflammatory tissue has been removed (1).

Previous studies of bone mineral density in persons with intestinal disorders have disclosed a limited deficit among Crohn's disease patients of approximately 0.44 z score in the

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lumbar spine and 0.34 z score in the femoral neck (z score is bone mineral density normalized to the mean value of an age- and gender-matched normal control group). The corresponding figures for patients with ulcerative colitis were 0.31 and 0.19 (9, 14–18). Using the estimates presented by Marshall et al. (26), these figures should be associated with increases in overall fracture risk in Crohn's disease (odds ratio = 1.1–1.2) and ulcerative colitis (odds ratio = 1.1). These numbers are close to the observed excess fracture risks in table 2 and figures 1 and 2, indicating that the present fracture estimates are closer to those of the general population than the estimates in the previous study (11).

For celiac disease, previous studies have revealed a mean decrease in lumbar spine z score of 1.03 in newly diagnosed patients versus 0.69 in treated patients (20–24, 27). These decreases should be accompanied by a relative risk of 1.5 before diagnosis and 1.3 after diagnosis (26). In the femoral neck, the corresponding figures were decreases of 0.91 at diagnosis and 0.41 after treatment, yielding an expected relative risk of 1.5 at diagnosis and 1.2 after treatment. The present study had a power of 94 percent for demonstrating an IRR of 1.5 in persons with celiac disease, and thus it should have had adequate power for demonstrating an increase of 1.2–1.5. However, the validity of a diagnosis of celiac disease was low (78 percent) in this study; in addition, this information was not available in the design phase of the study and was not included in the power calculations. The misclassification may have affected the results. Since a substantial proportion of the patients diagnosed with celiac disease or inflammatory bowel disease did not have bowel disease, the IRR estimates in this study were probably underestimates. Furthermore, the observed IRR of 0.94 (95 percent CI: 0.71, 1.24; table 2) after diagnosis and treatment is in accordance with bone mineral density measurements in studies reporting normal bone mineral density after appropriate treatment (20, 23).

The higher fracture risk before diagnosis in patients with Crohn's disease or ulcerative colitis versus patients with celiac disease was due to differences in age.

Although surgically treated patients with Crohn's disease had a lower fracture risk after diagnosis than controls, this trend was also present before diagnosis. The reduced fracture risk before diagnosis could indicate selection bias: It may be that only patients fit for bowel surgery were offered this treatment. In patients with ulcerative colitis, there was an increase in fracture risk after diagnosis among persons who received bowel surgery (figure 2), which indicates that only patients with more severe cases of ulcerative colitis—for example, those exposed to the greatest inflammatory activity and the highest dosages of corticosteroids—were selected for bowel surgery.

Study strengths and limitations

Besides the size of the study, the advantages of the present study were that it was population-based and that data were gathered without the necessity of collecting information from each individual patient. These circumstances may have reduced selection and information bias. Because probably all incident cases diagnosed during the study period were included, as well as the cases of persons who had died or emigrated, significant selection bias seems unlikely. Information bias related to imprecision in the diagnosis of bowel disease was mainly present in cases of ulcerative colitis. The relative fracture risk for this disease may have been overestimated because of the presence of patients with Crohn's disease. Information bias related to fracture diagnosis seems to have been limited, owing to the high accuracy of diagnoses.

The study by Vasquez et al. (27) used patients from a malabsorption clinic and may have included patients with more severe degrees of celiac disease. Thus, the present study may provide more reliable estimates of fracture risk.

The observed incidence rate of celiac disease in our study was close to the very low incidence rates previously reported for the Danish population (32). The observed number of patients with ulcerative colitis was also close to that previously reported for the Danish population, while the number of patients with Crohn's disease was higher (13). This was due to our use of a less restrictive definition of Crohn's disease (13). This wider definition did not change the fracture estimate for Crohn's disease but captured the patients early in the diagnostic process.

Our population-based controls were not specifically selected to be healthy, and thus they included subjects with diseases such as epilepsy, which may increase fracture risk. This reduced bias induced by selecting controls without competing diseases. The mere fact that some of the controls had a disease may have led to more fractures than would appear in healthier controls, but the excess fracture risk was limited.

Patients in this study were selected from an inpatient hospital register; this may have resulted in selection of more severe cases, causing an overestimate of the association between bowel disease and fracture risk. However, two factors mitigate against this: 1) the number if patients was close to that expected from other studies of celiac disease and ulcerative colitis (i.e., it did not seem that any major patient groups were left out) and 2) the risk estimates for Crohn's disease and celiac disease were lower than those seen in previous studies (11, 27).

The main disadvantage of the study was the absence of information on disease activity, use of medications, biochemical variables (including calcitropic hormones and bone markers), bone mineral density, and confounding factors such as smoking. We also lacked information on vitamin D deficiency, which may lead to muscle weakness (11) or other debility, resulting in more falls and fractures. Also absent were data on body mass index, immobilization, menopausal status, postmenopausal hormone therapy, alcohol abuse, and use of such medications as nonsteroidal antiinflammatory drugs, psychotropic drugs, and bisphosphonates, which may also influence fracture outcome. In addition, the available information on comorbidity in this study did not include all types of diseases.

Because the hospital discharge register was not complete for fractures treated on an outpatient basis, such as forearm fractures, the possibility of bias from more patients' than controls' being hospitalized with fractures cannot be elimi-

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nated. However, since no significant excess of forearm fractures was present, any bias arising from this source would seem to have been limited. All patients with femur fractures are hospitalized, which eliminates bias for this type of fracture.

A Berkson bias may be responsible for the peak in fracture risk around the time of diagnosis among patients with Crohn's disease and ulcerative colitis. A general health screening and a search for causes of secondary osteoporosis may reveal a previously unknown intestinal disease following a diagnosis of low-energy fractures. Conversely, detection of intestinal disease may lead to increased awareness of osteoporosis, with subsequent detection of reduced bone mineral density and asymptomatic spinal fractures. However, a peak in fracture risk at diagnosis was not seen among patients with celiac disease. Since the peak phenomenon was not universally present, a significant Berkson bias seems less likely. Furthermore, the decrease in the relative risk of spinal fractures after diagnosis in persons with ulcerative colitis also mitigates against a Berkson bias. Theoretically, patients should be more likely than controls to undergo radiography of the spine (or chest) and to have spinal fractures detected after diagnosis because of a higher frequency of hospital contact, but this was not the case.

In conclusion, in this study of 16,416 Danish patients with bowel disease, Crohn's disease was accompanied by a small increase in fracture risk before and after diagnosis, while ulcerative colitis was not. No increase in fracture risk could be detected on a population level in patients with celiac disease. Age and having a previous fracture were risk factors for sustaining a new fracture.

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