Crohn Disease and Fracture Risk Assessment With FRAX

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Background: Studies are inconsistent whether people with Crohn disease (CD) have an increased fracture risk.

Methods: Forty-nine CD and 49 controls participated. All 98 completed a health questionnaire. A score with the fracture assessment tool FRAX > 15% was considered risk factor for fracture.

Results: Mean FRAX score for 49 CD was 10.1 ± 10.3% and for 49 controls 5.0 ± 3.9% ($P = 0.002$). The variables correlated with fracture were being female ($P = 0.04$) and having a fractured mother ($P = 0.002$).

Conclusion: The CD group had significantly higher FRAX scores and more fractures, but the proportion of CD subjects with a fracture was not significantly higher than that of controls.

Key Words: bone fracture, colitis, inflammatory bowel disease, osteoporosis

INTRODUCTION

Crohn disease (CD) is a chronic granulomatous inflammation, which may affect one or more parts of the gastrointestinal tract. It is most common in the distal ileum, and less common in the rectum and mouth.[1] The disease affects a patient's daily life due to its unpredictable course with exacerbations and remissions, physical symptoms such as bloody diarrhea, abdominal pain, and fatigue, the risk of malignancy, and side effects of medication. One side effect is an increased risk of reduced bone mineral density (BMD).[2–4] Decreased BMD is associated with a low body mass index (BMI) and glucocorticoid use, with exercise as a potential countermeasure.[3] Studies differ on whether CD subjects have an increased fracture rate compared with healthy controls. Previously, a significantly increased fracture rate and a deterioration of the connectivity of the trabeculae of the mandibular alveolar bone have been demonstrated in a sample of CD subjects compared with a matched control group.[5] No significant correlation was found between fracture and the connectivity of the trabeculae, probably because of the relatively young ages in the material and the small sample size.[5]

The fracture assessment tool FRAX has been developed to evaluate the 10-year probability of hip and other major fractures (clinical spine, forearm, and shoulder fractures).[6] The FRAX algorithm integrates the risks associated with clinical risk factors (age, sex, weight, height, prior fracture, parental fracture (heredity), smoking, use of oral glucocorticoids, rheumatoid arthritis, secondary osteoporosis, and alcohol intake, and may also include BMD at the femoral neck). The weights of the components used in the algorithm are those from large population-based cohorts from Europe, North America, Asia, and Australia. The performance of the clinical factors has been validated in independent, population-based cohorts with over a million person-years of observation. The FRAX algorithms are based on cohorts of people over 40 and have been poorly validated in populations with inflammatory bowel disease (IBD), which frequently affects young people. Also, the use of BMD measurement with dual X-ray absorptiometry (DXA) to predict fracture risk is mainly derived from work in postmenopausal osteoporosis, and reference material for CD subjects is still lacking.

The present case–control study aimed to test the use of FRAX without BMD for fracture risk assessment in relatively young persons and to evaluate possible differences in FRAX scores between CD subjects and sex and age-matched controls.

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METHODS

Population

Sixty-three individuals with an established CD diagnosis treated at the Clinic of Medicine, NÄL, Trollhättan, Sweden consented to participate in the study.[5] Exclusion criteria were edentulousness, radiotherapy for cancer, and age over 60. Nine CD subjects could not be reached for an appointment, and 5 missed their scheduled appointments. One subject was 60 years old at inclusion but 61 when examined. Forty-nine CD subjects (33 women and 16 men) consented to participate, allowed extraction of information from their medical files, and completed medical questionnaires. A dental hygienist examined oral status, and dental radiographs were taken.

An age- and sex-matched control group of 49 subjects was selected from a public dental clinic in the same geographical area. They had participated in other research projects[7,8] regarding the association between BMD and mandibular alveolar bone structure. The initial inclusion criteria were at least one mandibular premolar present and no current periodontal disease. None were excluded due to systemic diseases (Table 1).

Both CD and control subjects completed a questionnaire regarding medication, lifestyle factors, smoking, height, weight, calcium intake, medical history, fractures, and whether their mother had sustained a fracture (Table 1). The CD subjects answered supplementary questionnaires regarding nutrition, specific medication, CD history, and heredity. Only factors from the questionnaires were considered in the analyses.

FRAX

The FRAX risk factors are age, sex, weight, length, prior fracture, parental fracture, smoking, use of oral glucocorticoids, rheumatoid arthritis, secondary osteoporosis, alcohol intake 3 or more units/day, and BMD.[9] For the calculation of FRAX, a "yes" or "no" response is called for. If the field is left blank, then a "no" response is assumed.[9] In 11 CD subjects and all control subjects, BMD measurements were available, but not used in our FRAX calculations because the aim was to test fracture risk assessment without the use of BMD. Three small modifications to the FRAX calculation were applied: (1) for parental fractures we used the mother with a history of a major fracture instead of a hip fracture (none had a hip fracture); (2) alcohol intake was not included in our questionnaire; (3) the minimum value for age in the FRAX tool is 40, but 14 subjects were younger than 40. This means that the calculated risks are slightly elevated for young people (equally for the CD group and controls), whereas missing answers (alcohol use) may have led to a slightly underestimated 10-year probability of fracture.

The FRAX tool for Sweden was used for calculating the 10-year probability of "major fractures".[9] We only calculated the probability for major fractures because no CD and no controls had suffered a hip fracture. Major fragility fractures are low-impact fractures such as those of the wrist, arm, spine, and hip, not jaws, fingers, or toes. Jaw fractures are nearly always high-impact fractures, due to accidents, violence, etc. Fragility hip fractures occur mostly late in life. In this study, the continuous variable FRAX was transformed into a categorical dichotomous variable using the cut-off value >15% for risk according to the recommendation from the Swedish National Board of Health and Welfare.[10] The recommendation is that a FRAX score (without DXA) higher than 15% should be used as a threshold for medical examination and referral to BMD with DXA, and a FRAX determined risk of >30% for prescribing medication with antiresorptive drugs.[10]

TABLE 1. FRAX Variables

	CD Group (n = 49)	Controls (n = 49)	*P*
Female (male)	33 (16)	33 (16)	
Age (y)	48.7 ± 9.9 (23–61)	49.0 ± 9.9 (22–62)	0.98
Weight (kg)	76.9 ± 13.1 (42–115)	70.2 ± 9.8 (54–94)	0.005
Height (cm)	170.4 ± 8.9 (151–190)	171.0 ± 7.1 (148–187)	0.69
BMI	26.5 ± 3.6 (17–38)	23.9 ± 2.4 (19–29)	0.001
Prior fracture	18%	8%	0.14
Heredity of fracture	23%	2%	0.002
Smoking	33%	18%	0.10
Glucocorticoids	28%	8%	0.012
Rheumatoid arthritis	0	0	
Secondary osteoporosis[a]	49	0	
FRAX	10.1 ± 10.3 (1.8–55)	5.0 ± 3.9 (1.2–18)	0.002

[a]Diabetes, osteogenesis, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 y), chronic malnutrition/CD, and chronic liver disease.

Statistical Methods

Power calculation had shown that 45 subjects were needed in each group, and therefore, all 49 CD subjects and 49 age- and sex-matched controls were included. Student *t* test (independent 2-sample test) was used for significance testing of continuous data, and the Mann–Whitney *U* test or Kruskal–Wallis nonparametric tests were used for significance testing of ordinal data. Bivariate and multiple regression analyses with fracture as the dependent variable were used to evaluate the associations between fracture and separate FRAX components. A *P* value below 0.05 was considered statistically significant. Epi Info version 3.5 was used for significance and regression analyses (Centers for Disease Control and Prevention, Atlanta, GA).

Ethical Considerations

The study was approved by the Ethics Committee of the University of Gothenburg (DNr 693–08; date: January 13, 2010), and participants had granted their informed consent. The investigation was observational, not experimental.

RESULTS

CD Subjects

Mean disease duration was 18.0 ± 11.4 years (range 1–40 years), and the diagnosis age was ≤16 years for 6 CD patients, 17–40 years for 28, and >40 years for 15. Twenty-four subjects (9 men and 15 women) had undergone intestinal surgery. One CD subject had been operated on 25 times, 3 patients 3 times, 9 patients twice, and 11 patients once. In these 24 subjects, a mean of 60.0 + 63.5 cm (range 2–300 cm) of the small intestine was removed.

Twenty-three percent had a mother, who had sustained a fragility fracture. Furthermore, 1 CD subject had cancer, 4 had anemia, 7 were allergic, 2 had Bechterew disease, 1 had asthma, 1 had goiter, and 1 had heart disease. FRAX does not take these conditions into account. One subject was diagnosed with osteoporosis, but the CD had already led to a "yes" for secondary osteoporosis.

Controls

Two percent had a mother, who had sustained a fragility fracture. Two controls had cancer, 1 had asthma, 2 had Bechterew disease, 4 had hysterectomies, 1 had ovariectomy, 1 had heart disease, 4 had goiters, 4 had hypertensions, and 1 had allergy.

Fracture and Smoking

Twenty-eight previous fractures were reported, including both osteoporotic and non-osteoporotic fractures (Table 2). Nineteen fractures were found in CD subjects and 9 fractures in controls ($P < 0.05$). One CD subject had sustained "several fractures," but she did not indicate how many; we supposed 3. Two controls had 2 fractures and 1 control 4 fractures. When finger and toe fractures, and fractures in childhood were excluded, the number of individuals who had suffered major fractures in adulthood was 13 (9 CD subjects and 4 controls). Mean age for subjects with major fractures in adulthood was 51.9 ± 10.0 (range 36–61). In all the following analyses, individuals who sustained fractures on more than one occasion were included only with the first fracture, and individuals with fracture in childhood (<20) were registered as not fractured.

TABLE 2. Number of Sustained Fractures in Each Reported and Not-Reported Site in Adulthood and Childhood (<20 Years), Followed by Number of Adult Individuals With Major Fractures[a]

	Fracture Number		
Fracture site	CD Adult	CD Child	Control
Arm	2		2
Wrist	1		4
Leg	4	1	3
Not-reported site	4	2	
Finger	2		
Toe	1	1	
Collar bone		1	
Total number of fractures[b]	14	5	9
Adults with major fracture[a]	9		4
Adults without major fracture	40		45

[a]Major fractures mean hip, arm, wrist, spine, leg, etc. (finger and toe fractures excluded).
[b]Nine CD subjects had sustained a total of 19 fractures (14 + 5); 4 controls had a total of nine fractures. One CD subject had 3 fractures, 2 controls had 2 fractures, and 1 control 4 fractures.

More women (n = 12 of 66 women, 18%) than men (n = 1 of 32 men, 3%, $P = 0.04$) had sustained fracture. More CD subjects (n = 9, 18%) but not significantly more, had sustained a fracture than the subjects in the control group (n = 4, 8%, $P = 0.14$).

Sixteen subjects were smokers in the CD group (33%) and 9 in the control group (18%, $P = 0.11$). In the CD group, 25% of the smokers (n = 4) and 15% of the nonsmokers had sustained a fracture (n = 5, $P = 0.41$); the smokers had significantly lower BMIs (25.0) than the nonsmokers (27.2, $P = 0.045$). In the control group, 22% of the smokers (n = 2) and 5% of the nonsmokers (n = 2, $P = 0.09$) had sustained a fracture.

In the total group (n = 98), 2 variables were correlated with fracture; female sex ($r = 0.20$, $P = 0.04$) and having a mother who had sustained a fracture ($r = 0.32$; $P = 0.002$), whereas having CD ($r = 0.14$; $P = 0.14$), and smoking ($r = 0.14$; $P = 0.15$) were not significant.

When analyzing the CD group separately, fracture was no longer significantly correlated with having a mother who had

sustained a fracture ($P = 0.09$). Furthermore, fracture was not correlated with smoking ($P = 0.41$), the amount of intestinal resection ($P = 0.29$), the number of disease location ($P = 0.18$), or disease duration ($P = 0.31$).

In the control group, fracture was significantly correlated with having a mother having sustained a fracture ($r = 0.48$, $P < 0.001$) and with height ($r = 0.30$, $P < 0.04$).

FRAX

The mean FRAX value for the total group (n = 98) was 7.6% ± 8.16% (range 1.2%–55%). The mean FRAX value for 49 CD subjects was 10.1% ± 10.3% (range 1.8%–55%) and for 49 controls 5.0% ± 3.9% (range 1.2%–18%, $P = 0.002$). The FRAX components are presented in Table 1. The FRAX-score variation is illustrated in Figure 1. Data for the 4 CD subjects with the highest FRAX scores are presented in Table 3.

In the total group with FRAX < 15% (n = 85), 5 individuals (5.9%) had sustained a fracture (one of them was 36 years old with a FRAX score of 3.6). In the group with FRAX > 15% (n = 13), 8 individuals (61.5%) had sustained fracture ($P < 0.001$).

When the CD group was analyzed separately, 39 subjects had a FRAX score < 15% and 4 of these sustained a fracture (10.3%), whereas in the group with FRAX scores > 15%, consisting of 10 subjects, 5 sustained a fracture (50%, $P < 0.001$). In a multiple regression analysis, 31% of the variance in CD FRAX score was explained by the amount of intestinal resection ($P = 0.001$), sex ($P = 0.01$), and a family history of CD ($P = 0.02$).

In the control group, 46 individuals had a FRAX score < 15% and 1 individual had sustained a fracture (2.2%). Three subjects had FRAX scores > 15%, and all 3 had sustained a fracture (100%, $P < 0.001$).

DISCUSSION

A FRAX value > 15% was an adequate indicator of fracture risk in both the CD and the control group, and in the total group. The CD subjects had significantly higher FRAX scores compared to sex- and age-matched controls. Particular traits in the CD group were the high fracture rate, high BMI, and the many smokers. In the total group of 98 subjects, 14 individuals were under 40, meaning a slightly elevated FRAX score was calculated, but applied equally to the CD and control group.

Twenty-three percent of the CD subjects had a mother, who had sustained a fragility fracture compared with 2% in the control group. Less calcium intake in the CD group, as found previously,[5] may increase fracture risk, which is in line with other studies.[11] In the present sample, the variance in CD FRAX score (the 10-y fracture risk) was correlated with the amount of intestinal resection, whereas sustained fracture was not significantly correlated with the amount of intestinal resection or with disease duration. The latter is in line with findings from another study, where no association between BMD and disease duration was found.[11]

Traditionally, CD is thought to be associated with undernutrition and wasting due to malabsorption, inadequate dietary intake, and the effect of inflammation. However, this trend is changing, and the incidence of obesity is rising in CD subjects as well. It is hypothesized that increased incidences in common obesity and CD could be pathogenically linked because obesity predisposes a low-grade inflammation such as that occurring in CD.[12] An explanation may be that adipocytes release a variety of proinflammatory cytokines and peptides.[12] Also, the frequent use of oral glucocorticoids may partly explain the high BMI in the CD group.

Thirty-three percent of the CD subjects in our study were smokers compared with 18% in the control group. In

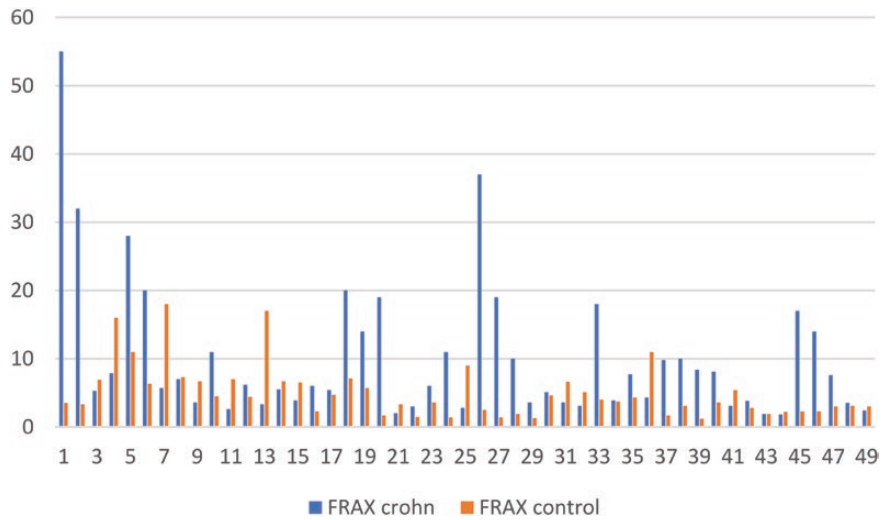

FIGURE 1. Variations in FRAX values of CD subjects and their age- and sex-matched controls.

TABLE 3. Four CD Subjects With High FRAX Score

ID	1	2	5	26
FRAX	55	32	28	37
Sex	Female	Female	Female	Female
Age	61	58	59	51
Years with diagnosis	16	32	32	39
CD locations	5	5	2	4
Number operations	3	0	0	25
Resection cm	92	0	0	300
Cortisone	Yes	No	Yes	Yes
Immunosuppression	Yes	Yes	Yes	No
CD heredity	No	No	No	Yes
Fracture	Yes	Yes	No	Yes
Maternal fracture	Yes	Yes	Yes	Yes
Smoking	No	No	Yes	Yes

an investigation of a cohort of 160 CD subjects, 91% were smokers at the time of diagnosis and 74% at study enrollment.[13] It seems that smoking increases the risk of developing CD, and it is associated with more frequent intestinal penetrating complications.[14] The course of CD disease varies considerably among patients and the progression in the individual patient is unpredictable, but clinical severity and intestinal lesions usually progress. However, individuals with 4 healthy factors (lifelong nonsmoker, BMI lower than 30, 3.5 h of weekly physical activity, prudent diet with a high intake of fruits, vegetables, whole-grain bread, and low meat consumption) have a lower risk of developing a chronic disease.[15]

In a systematic review article from 2017 regarding FRAX and the prediction of fracture risk in patients with IBD, 4 full-text references were found for adult patients, 1 regarding ulcerative colitis, and 3 CD.[16] In their subjects with CD, the mean risk of major osteoporotic fractures calculated with FRAX was 6.65%,[16] which was between the mean value for the control group (5.0%) and the mean value for the CD group (10.1%) in our study.

There is a consensus that subjects with IBD have reduced bone mass, but a controversy over an increased risk of fracture. In one study, patients with IBD had an increased risk of vertebral and hip fracture, which was greater in CD subjects compared with those with ulcerative colitis.[17] In the present study, the CD group had significantly higher FRAX scores and significantly more fractures, but the proportion of CD subjects with fractures was not significantly higher than that of controls.

We used the dichotomous variable FRAX > 15% as a risk indicator because it is recommended by the Swedish National Board of Health and Welfare,[10] and tested in a longitudinal study of women.[18] An extensive study of 647 patients with IBD and 38,165 controls over the age of 50 used FRAX as a continuous variable,[19] and it was found that IBD was not associated with a significantly increased risk for major osteoporotic fracture, but may be associated with an increased risk for hip fracture. Results were similar when CD subjects and subjects with ulcerative colitis were tested separately.[19] The researchers concluded that although subjects with IBD may be at an increased fracture risk, the increased risk may be due to factors (low BMI and glucocorticoid use) other than their diagnosis.[19] In another investigation, the conclusion was that a FRAX score alone can predict fracture risk and thereby reduce the need for DXA scans and unnecessary anti-osteoporosis treatment in patients with IBD.[20]

It seems that FRAX predictions ameliorate substantially with increasing age. In a younger group, 50–66 years of age, those with both FRAX > 15% and mandibular sparse trabeculation, had 6 times the risk of future fracture, whereas in the older group, 62–78 years of age, they had a 23 times greater risk compared with those without these risk factors.[18] It was concluded that a FRAX score > 15%, without BMD measurements, was an effective fracture predictor, and mandibular sparse trabeculation had a substantial additive effect.[18] The participants in the present investigation were younger, 22–62 years, and sparse trabeculation did not add to the prediction. This may change, if the group of CD subjects is followed up after, for instance, 10 years, or a larger, older group is examined.

The main limitation of the present investigation is the relatively low number of CD subjects and fractures, but the power calculation seems to be correct because a significant difference in FRAX scores was found between CD and matched control group. FRAX as a tool for fracture risk prediction has some limitations because it does not include risk of falling, number of prior fractures, and doses of glucocorticoid treatment, alcohol, and smoking. In our study, alcohol consumption and bone mineral density were not included in the FRAX calculation. Another small deviation from the standard in the FRAX calculation of fracture risk was that we used any maternal fracture instead of maternal hip fracture. Nevertheless, the results were in line with what could be expected from other studies, and the method was sensitive enough to capture some of the risk differences as measured in this case–control study.

CONCLUSION

The CD group had a significantly higher FRAX score and significantly more fractures, but the proportion of CD subjects with a fracture was not significantly higher than that of controls. FRAX score > 15%, without BMD measurements, was a useful fracture predictor also in this relatively young sample.

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