Care Gap in Patients with Early Inflammatory Arthritis with a High Fracture Risk Identified Using FRAX®

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ABSTRACT. ***Objective.*** To determine the proportion of patients with early inflammatory arthritis in a Canadian cohort who are at high risk for a major osteoporotic fracture using the Fracture Risk Assessment Tool (FRAX®), and to determine if a care gap exists in high-risk patients.

Methods. FRAX was applied to 238 patients enrolled in the Canadian Early Arthritis Cohort (CATCH) study based on norms from the United States and the United Kingdom, without the use of bone mineral density measurements.

Results. FRAX identified 5%–13% of patients at high risk for fracture, using a conservative analysis. Based on US norms, there was a significant correlation between increasing fracture risk groups and oral glucocorticoid use ($p = 0.012$) and baseline erosions ($p = 0.040$). Calcium or vitamin D use did not vary among the different fracture risk groups ($p = NS$), nor did bisphosphonate use ($p = NS$). The Disease Activity Score with 28 joint count in the high-risk group was significantly higher compared to the low-risk group ($p = 0.048$).

Conclusion. Patients at increased risk had higher disease activity, more frequent glucocorticoid use, and more baseline erosions compared to patients at low risk. A care gap exists, in that a very low proportion of patients at high risk are being treated with calcium, vitamin D, and/or bisphosphonates. A higher fracture risk was calculated in our cohort using the US FRAX calculation tool compared to the UK calculation tool. These data highlight the need to identify and modify fracture risk in patients with early inflammatory arthritis. (J Rheumatol First Release August 15 2010; doi:10.3899/jrheum.091368)

Key Indexing Terms:
RHEUMATOID ARTHRITIS OSTEOPOROSIS BONE FRACTURES

Rheumatoid arthritis (RA) is an inflammatory disease shown to be associated with a greater risk of fragility fracture and increased bone loss early in the disease course[1,2,3]. The progression of osteoporosis is more rapid in the early stages of RA and if fracture occurs, can result in a loss of mobility and independence in patients who are already restricted by their condition[4,5]. It was reported recently that up to 30% of patients with early RA had vertebral deformities consistent with fracture, in accord with estimates for patients over 60 years of age with established RA[6]. Osteoporotic fractures are a common cause of morbidity and mortality and an important healthcare cost worldwide[7]. It has been estimated that the health and longterm costs associated with osteoporosis-related fractures were $13.8 billion in the United States in 1994 and $1.3 billion in Canada in 1993[8]. There is a limited use of clinical decision tools for predicting osteoporosis in patients with RA, and thus an effective fracture prediction tool that includes risk factors independent of bone mineral density (BMD) measurements is of clinical importance[9,10].

The World Health Organization Fracture Risk Assessment Tool (FRAX®) has recently been developed to estimate a 10-year absolute risk of sustaining a hip or other major osteoporotic fracture (clinical spine, forearm, hip, or shoulder fracture). The FRAX calculation tool is available on the Internet (http://www.shef.ac.uk/FRAX)[11]. The tool identifies patients as being at low (< 10%), moderate (10%–20%), or high (> 20%) risk of fracture using validated clinical risk factors for fracture with or without the use of a BMD measurement at the femoral neck. The clinical risk

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Supported by Amgen Canada Inc. and Wyeth Pharmaceuticals.

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Accepted for publication June 18, 2010.

factors include age, sex, body mass index (BMI), history of previous fracture, history of parental hip fracture, current smoking, use of oral glucocorticoids, RA, secondary osteoporosis, and excess alcohol intake.

To our knowledge, no other predominantly Caucasian populations of early inflammatory arthritis (EIA) or patients with early RA have been evaluated for fracture risk using this tool. The aim of our study was to determine the proportion of patients with EIA in the Canadian Early Arthritis Cohort (CATCH) study at high risk for a major osteoporotic fracture using FRAX, and to determine if a care gap exists in those high-risk patients.

MATERIALS AND METHODS

Subjects. Data from the 238 patients successively recruited between July 2007 and January 2009, inclusive, were collected from the CATCH study, a multicenter, observational, prospective, "real-world" cohort of patients with EIA. Inclusion criteria were age > 16 years, between 6 weeks and 12 months of persistent synovitis, and ≥ 2 swollen joints or 1 swollen metacarpophalangeal or proximal interphalangeal joint with ≥ 1 of the following: positive rheumatoid factor, positive anti-cyclic citrullinated peptide (anti-CCP), morning stiffness > 45 minutes, response to nonsteroidal antiinflammatory drugs or painful metatarsophalangeal squeeze test. The majority of CATCH patients were recruited from the higher population provinces, mainly Ontario and Quebec.

Patients were evaluated at baseline and every 3 months according to a standard protocol. Treatment, including disease modifying antirheumatic drug (DMARD) therapy, such as methotrexate, sulfasalazine, and hydroxychloroquine, with the option of oral, intramuscular, or intraarticular glucocorticoid bridging was left to the discretion of the treating physician. Prednisone doses ≤ 10 mg daily were usually used. Therapy was adjusted at every visit with the aim of remission, defined as zero swollen joints.

Data collection. FRAX was applied to the baseline characteristics of patients utilizing the 2008 US norms, without BMD, where the appropriate calculation tool accounted for ethnicities with the following distribution: Caucasian (n = 224), Asian (n = 9), Hispanic (n = 3), and Black (n = 2). Patients were also assessed assuming norms from the United Kingdom, without BMD.

A history of previous fracture was collected using spontaneous reports in the CATCH standard questionnaire during baseline and followup visits. A history of hip fracture in a parent was inconsistently reported by patients participating in the study and was assumed to be absent for purposes of calculating fracture risk (n = 238). Values were imputed for patients with unreported weight (n = 2) and height (n = 17), as well as for patients with both weight and height unreported (n = 57), which were needed to apply the tool. Average Canadian male weight 81.9 kg and height 174.8 cm and average Canadian female weight 67.9 kg and height 161.8 cm were substituted[12]. Since FRAX has a limited age range (40–90 years), 39 (16%) patients were under the age of 40 years and thus fracture risk at the age of 40 was calculated for these patients, and no patient was over the age of 90. Only 6 patients were over the age of 80 years.

Statistical analysis. Our fracture groups were based on FRAX US norms. The chi-square test was used to test independence between the fracture risk group and other categorical groups such as for oral glucocorticoid use, baseline erosions of the hands and/or feet, calcium or vitamin D intake, and bisphosphonate use. The Fisher exact chi-square test was used when the expected cell frequency was less than 5. ANOVA was used to determine whether the Disease Activity Score 28-joint count (DAS28) varied among different fracture risk groups. A sensitivity analysis was conducted on subgroups of Population 1 (whole population, n = 238); Population 2 (without imputation of height and weight, n = 162); and Population 3 (without imputation of height and weight and without premenopausal women, n = 104).

RESULTS

Baseline characteristics of the 238 patients are displayed in Table 1. For the FRAX calculation, RA diagnosis at baseline

Table 1. Baseline characteristics of patients with early inflammatory arthritis (n = 238).

Characteristic	
Age, mean ± SD yrs	52 ± 15
Female, n (%)	189 (79)
Weight, kg, mean ± SD*	76.3 ± 17.4
Height, cm, mean ± SD*	165.5 ± 9.4
Body mass index, mean ± SD*	27.5 ± 5.5
Previous fracture, n (%)	25 (11)
Current smoking, n (%)	56 (24)
Glucocorticoid use meeting FRAX criteria, n (%)	58 (24)
Rheumatoid arthritis, n (%)	175 (74)
Secondary osteoporosis, n (%)	48 (20)
Alcohol 3 or more units per day, n (%)	61 (26)
Symptom duration, median months of new-onset persistent synovitis (IQR)	6.1 (4.42, 9.35)
Meet ACR criteria for RA, n (%)	194 (82)
RF-positive**, n (%)	174 (80)
Anti-CCP-positive†, n (%)	104 (66)
Erosive disease (hands and/or feet)††, n (%)	55 (27)
Tender joint count (68), mean ± SD	12.8 ± 9.9
Swollen joint count (66), mean ± SD	8.8 ± 8.1
ESR, mm/h, normal < 20, mean ± SD	26.6 ± 22.2
C-reactive protein, mg/l, normal < 8, mean ± SD	16.7 ± 29.2
DAS28 ESR score, mean ± SD	4.9 ± 1.5
HAQ score, mean ± SD	1.0 ± 0.7

IQR: interquartile range; ACR: American College of Rheumatology; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide; ESR: erythrocyte sedimentation rate; DAS28: Disease Activity Score with 28-joint count; HAQ: Health Assessment Questionnaire. * Values imputed Canadian averages. ** N = 218. † N = 157. †† N = 201.

was based on the physician's assessment, where the components for determining if a patient meets American College of Rheumatology criteria for RA may not have been available to physicians at the time of diagnosis. The 10-year risk of a major osteoporotic fracture and characteristics of patients according to FRAX US and UK norms are displayed in Table 2. Oral glucocorticoid use in this study was defined as those patients meeting the FRAX criteria for glucocorticoid use at doses ≥ 7.5 mg for ≥ 3 months and those using oral glucocorticoids at a lower dose and duration than the amount considered to be a risk factor in FRAX. Based on US norms, there was a significant correlation between increasing fracture risk groups and oral glucocorticoid use ($p = 0.012$) as well as baseline erosions of the hands and/or feet ($p = 0.040$). At baseline and subsequent visits, the calcium or vitamin D use did not vary among the different fracture risk groups (p = nonsignificant) and neither did bisphosphonate use (p = nonsignificant). The DAS28 with erythrocyte sedimentation rate (DAS28-ESR) in the high-risk group was significantly higher than the DAS28-ESR in the low-risk group ($p = 0.048$).

Considering the subgroups, there remained a strong association between the increasing fracture risk groups and oral glucocorticoid use, determined by the chi-square test. The p values for the subgroups, Population 2 (without imputation of height and weight) and Population 3 (without imputation of height and weight and without premenopausal women), were $p = 0.013$ and $p = 0.024$, respectively. However, considering the subgroups (Populations 2 and 3), there was no longer a significant association between the increasing fracture risk groups and baseline erosions of the hands and/or feet. Consistent with the observations from the whole population, the calcium or vitamin D use and bisphosphonate use in the subgroups (Populations 2 and 3) did not vary among the different fracture risk groups (p = nonsignificant).

A logistic regression analysis was used to evaluate the correlation between FRAX major osteoporotic fracture risk and oral glucocorticoid use as well as baseline erosions of the hands and/or feet in the whole population and the subgroups (Populations 2 and 3), as shown in Table 3. Based on the whole population, for a patient in the moderate-risk group compared to the low-risk group, the odds of having oral glucocorticoid use were 1.924 times higher. For a patient in the high-risk group compared to the low-risk group, the odds of having oral glucocorticoid use were 2.887 times higher.

In total, 197 (83%) patients were taking methotrexate, where 142 (72%) of them used combination DMARD therapy consisting of methotrexate with sulfasalazine and/or hydroxychloroquine. However, 70 (29%) patients were not prescribed a DMARD in the first 3 months of followup and only one patient started biologic therapy.

Of the 238 patients, 136 (57%) received glucocorticoid treatment; 58 (24%) patients were treated with oral glucocorticoids (prednisone) meeting the FRAX criteria for glucocorticoid use at doses ≥ 7.5 mg for ≥ 3 months, 44 (18%) patients received oral glucocorticoids at a lower dose and duration not meeting FRAX criteria, and 93 (39%) patients required intermittent intramuscular or intraarticular glucocorticoids. We found no correlation between DMARD use and fracture risk.

DISCUSSION

A diagnostic and therapeutic care gap exists in these patients with EIA at high risk for fracture. FRAX identified 5%–13% of patients at high risk for fracture, depending on the country calculation tool applied (US/UK), using a conservative analysis. These patients had higher disease activity and had more frequent oral glucocorticoid use and more baseline erosions compared to patients at low risk for fracture. The care gap was assessed using the 2002 Canadian guidelines for osteoporosis from the Scientific Advisory Council of the Osteoporosis Society of Canada (OSC)[13]. These recommendations suggest that "People receiving ≥ 7.5 mg of prednisone daily for more than 3 months should be assessed for initiation of a bone-sparing therapy" and that "Bisphosphonates are the first-line therapy for the prevention of glucocorticoid-induced osteoporosis." Although 58 (24%) of all patients in our cohort met these criteria, only 18 (8%) of all patients were treated with bisphosphonates. Of the patients at high risk for fracture according to US norms, 15 (48%) were treated with any dose of oral glucocorticoids,

Table 2. Ten-year risk of a major osteoporotic fracture and characteristics of patients according to FRAX US and UK norms (n = 238). Values are number (%).

	Low Risk (< 10%)		Moderate Risk (10–20%)		High Risk (> 20%)	
	USA	UK	USA	UK	USA	UK
N (%)	155 (65)	175 (73)	52 (22)	52 (22)	31 (13)	11 (5)
Oral glucocorticoid use	38 (25)	47 (27)	20 (38)	17 (33)	15 (48)	9 (82)
Received calcium or vitamin D	28 (18)	33 (19)	14 (27)	13 (25)	6 (19)	2 (18)
Received a bisphosphonate	11 (7)	11 (6)	3 (6)	6 (12)	4 (13)	1 (9)
Baseline erosions (hands and/or feet)	31/140 (22)	38/157 (24)	16/42 (38)	15/38 (39)	8/19 (42)	2/6 (33)
Baseline DAS28 score, mean ± SD	4.7 ± 1.5	4.8 ± 1.5	5.1 ± 1.6	4.9 ± 1.5	5.3 ± 1.2	5.6 ± 1.4

DAS28: Disease Activity Score with 28-joint count; ESR: erythrocyte sedimentation rate.

Table 3. Logistic regression analysis between FRAX major osteoporotic fracture risk groups and oral glucocorticoid use and baseline erosions of the hands and/or feet, in the whole population and the subgroups (Population 2 and 3).

Population	Fracture Risk	Oral Glucocorticoid Use		Baseline Erosions	
		OR	p	OR	p
1. Whole population (n = 238)	Moderate vs low	1.924	0.055	2.164	0.041
	High vs low	2.887	0.009	2.557	0.064
2. Population without imputation of height and weight (n = 162)	Moderate vs low	2.520	0.024	2.236	0.066
	High vs low	3.360	0.021	2.330	0.172
3. Population without imputation of height and weight and without premenopausal women (n = 104)	Moderate vs low	2.943	0.026	1.947	0.179
	High vs low	3.727	0.023	1.927	0.320

but only 3 (25%) of these patients received a bisphosphonate. Despite awareness that classic risk factors are associated with high fracture risk, a very low proportion of patients are being treated with bisphosphonates, even though these agents have been shown to reduce vertebral fractures by almost 50% in susceptible populations[14]. The OSC guidelines also noted that "Adequate calcium and vitamin D through diet or supplements are essential for the prevention of osteoporosis and, taken together, are essential adjuncts to preventative therapy." Of the 15 patients at high risk for fracture according to US norms and treated with oral glucocorticoids, only 4 (27%) were receiving supplemental calcium and vitamin D. A possible explanation for the observed care gap may be that rheumatologists are primarily concerned with efforts toward treating the primary disease, which consequently results in less attention being paid to managing comorbidities. Early recognition of osteoporosis risk could allow earlier intervention to prevent fracture. This is an important factor in implementing best practices in patients with EIA.

Various data sets have contributed to country-specific calculation tools for FRAX to account for the observed differences in fracture prevalence among countries. In the US, there are sufficient data to allow determination of fracture probability for the major ethnic categories in the country — Caucasian, Black, Hispanic, and Asian. Worldwide, fracture risk assessments with FRAX calculation tools are currently available for 17 countries[11]. A FRAX model calibrated to the epidemiology from Canada is forthcoming, but not yet available. Controversy remains as to which dataset in FRAX is most appropriate for application to the Canadian population. It is postulated that a patient in Canada could have a similar fracture risk potential to a patient in the US given the historical and sociocultural similarities of the 2 populations; however, it can also be argued that the same argument could also apply to the UK population. Some have argued that the risk in Canadian patients should be calculated using the Swedish FRAX tool based on latitude; however, the majority of our patients were from a more southern latitude. Therefore, we evaluated fracture risk according to both US and UK norms. The higher apparent risk of osteoporosis in the US compared to the UK is reflected in our cohort in the comparison between fracture risks after applying their respective calculation tools. Whether this is a true reflection of differences in risk between the 2 populations or an artefact of the underlying databases cannot be determined from our study. Further, this was a study to examine the proportion of patients who might not be receiving care according to guidelines for the management of fracture risk.

The fracture risk reported in our population is likely underestimated. This is due in part to inconsistent reporting of a history of parental hip fracture. This risk factor was assumed to be negative in all patients, when in reality this may not be the case. This study reflects real-world rheumatology practice, where it is not the usual pattern of practice to take a detailed family fracture history. However, as the importance of a history of osteoporotic fracture in first- or second-degree relatives has been emphasized[13], it is apparent that without knowledge of this common risk factor, this study presents a conservative risk estimate of fracture for this population regardless of the calculation tool applied to this cohort. In addition, in some instances we had to impute Canadian averages of weight and height for patients where these data were unreported in our database. Patients with EIA may not be accurately represented by the average Canadian due to disease. The actual heights of both females and males in CATCH are similar to Canadian averages; however, the weights and thus BMI of both females and males in this cohort were slightly greater than the average Canadian. This observation is in line with a previous study reporting that the mean weight and BMI were higher in RA patients compared to non-RA controls[15]. However, it has been reported that a low BMI and weight loss are associated with increased fracture risk[16]. Lastly, FRAX does not take into account all fractures when calculating the major osteoporotic fracture risk[17]. Other evidence does indicate that the occurrence of any low-trauma fracture in the older adult population is likely to increase the risk of an osteoporotic fracture in first- and second-degree relatives. These issues singly or combined could have the result that the care gap documented in these patients is larger than presented here.

Our study has further limitations. CATCH is a real-world EIA cohort designed to evaluate clinical outcomes and best

practices. CATCH was not designed to validate FRAX. However, due to the ease of use of the FRAX tool, it can be utilized in this cohort to evaluate fracture risk. The estimate of fracture risk in our cohort did not include BMD measurements, as they were not available from all patients (a situation common to routine clinical care). It has been reported that the addition of BMD in the FRAX calculation is highly unlikely to change the fracture risk assessment in an ERA population[18]. Nevertheless, treatment decisions should not be based solely on FRAX assessment. Instead, patients at high risk for fracture according to FRAX may benefit most from BMD testing, and treatment should be based on the diagnosis of osteoporosis, defined as a BMD value less than –2.5 standard deviations. It remains to be determined if decision tools to assist physicians in selecting patients at risk for fracture (and thus candidates for BMD testing) are superior, and the superiority of FRAX in this context needs to be examined further. Additional research validating the use of FRAX in patients with EIA is warranted.

Overall, data from our cohort study provided the opportunity to assess the osteoporosis care gap, and thus highlighted the need to identify and modify fracture risk in patients presenting with EIA. Rheumatologists should be more aware of the prevalence of osteoporosis in their RA and inflammatory arthritis population and ensure that the patients are investigated and managed accordingly.

ACKNOWLEDGMENT

The authors gratefully acknowledge the NEAR Researchers for contributing to patient enrollment in the CATCH study: Diane Mosher, Vandana Ahluwalia, Bill Bensen, Maggie Larché, Michel Zummer, Majed Khraishi, Bindu Nair, Alice Klinkhoff, and Alf Cividino. We thank Lyn Maguire, the National Study Coordinator, and Ludmila Mironyuk, the CATCH Database Manager. We also acknowledge the contributions of CATCH Study Coordinators and research assistants: Lorna Bain, Sofia Barbosa, Cathy Cheng, Karen Doyle, Diane Ferland, Chantal Guillet, Bob Harris, Debbie Kislinsky, Jolaine L'Archevêque, Tiffany Larsen, Lindsay Luc, Cheryl Magnusson, Julie Matthews, Donna McBain, Mary-Grace Milton, Neomie Poirier, Michèle Ouellet, Angelo Papachristos, Irene Smolik, Jayne Strecko, Lilian Urroz, and Karen White.

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