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Clinical Risk Factors for Fracture in Diabetes: A Matched Cohort Analysis

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Abstract

The objective was to determine which individuals with diabetes are at increased risk for fracture. It is unknown whether traditional clinical risk factors (CRFs) can be used in this population to identify individuals at higher risk of fracture. Using the Manitoba Bone Density Program database, we identified 3054 diabetic women and 9151 matched nondiabetic controls. The independent association of specific CRFs with incident osteoporotic fracture risk was assessed separately in those with diabetes and in controls, with subsequent examination of the interaction between diagnosed diabetes and each CRF. Prior major fractures were more prevalent in the diabetic group compared with the nondiabetic group (16.2% vs 14.3%, $p < 0.001$). During mean 4 yr of observation, 259 (8.5%) of diabetic women and 559 (6.5%) of nondiabetic women experienced an incident major osteoporotic fracture (unadjusted hazard ratio [HR] for diabetes 1.49 [95% confidence interval (CI): 1.28–1.72], $p < 0.001$; adjusted HR 1.14 [95% CI: 1.10–1.18], $p < 0.001$). There were no significant differences between the 2 groups in the HRs for incident fracture associated with any of the CRFs studied (all p-for-interaction >0.1). Diabetes is a risk factor for major fracture. The ability of traditional CRFs to predict osteoporotic fractures is not influenced by the diagnosis of diabetes.

Keywords

Clinical risk factor; diabetes; fracture; osteoporosis

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Introduction

Multiple studies have found that men and women with diabetes (type 1 or type 2) are at increased fracture risk at the hip, spine, and other skeletal sites (1–5). Although hyperglycemia has been shown to have a negative impact on skeletal health (6), it does not fully explain the increased fracture risk (1) and various other diabetes-specific mechanisms have been implicated (7,8). Bone mineral density (BMD) measurement, a tool used to diagnose osteoporosis and make decisions around initiating protective therapies, has not been found to be a reliable predictor of fractures in diabetic patients (4). Although individuals with type 1 diabetes have decreased BMD in many studies, this decrease is not proportional to the increased fracture risk observed (1). Individuals with type 2 diabetes have been found to have normal or increased BMD, but have paradoxically elevated fracture risk (1,9).

Both osteoporosis and diabetes are global diseases of epidemic proportions. Over 25% of Canadian women and 5% of Canadian men older than 50 yr have osteoporosis (10). In Canada, 9 million people are affected by diabetes or prediabetes (11). Globally, it is estimated that 285 million people are affected by diabetes (11). With rapidly rising obesity rates worldwide, this number is expected to increase dramatically (12). As the rate of diabetes rises, so will the numbers of fractures occurring in these individuals. It is therefore of critical importance that clinicians be able to identify diabetic patients who are at increased risk of fracture so that protective strategies can be implemented. Traditional osteoporosis risk factors include female sex, age, lower body mass index (BMI), prior fragility fracture, parental hip fracture, rheumatoid arthritis, corticosteroid use, smoking, alcohol use, and secondary causes of osteoporosis (13). To our knowledge, only 1 prospective cohort study involving 1964 individuals with type 2 diabetes has investigated the contribution of osteoporosis risk factors (5). In this study, Melton et al found age, female gender, prior osteoporotic fracture, use of corticosteroids, and secondary osteoporosis to be associated with increased fracture risk. The findings from this report are limited by the small sample size and lack of control group.

We performed a study looking at traditional clinical risk factors (CRFs) for osteoporotic fractures in a large cohort of diabetic women and a matched group of nondiabetic women from the Manitoba Bone Density Program database. Our objective was to determine whether the diagnosis of diabetes interacts with the classic CRFs to alter their predictive association with major osteoporotic fracture risk.

Research Design and Methods

Data Sources

A population-based matched case-control cohort study was carried out using the Population Health Information System (POPULIS) data repository at the Manitoba Center for Health Policy (MCHP). The data repository contains information regarding patient’s demographics; date/type of service received; inpatient, outpatient, and office-based procedures performed; up to 16 International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) codes; and prescription medications dispensed to outpatients since April 1, 1995. The

POPULIS databases have been found to be both accurate and valid (14). The Manitoba Bone Density Program database is linked to the MHCP data repository through an anonymized personal health identification number. The construction and validation of the Manitoba Bone Density Program database has been described previously (15). Briefly, the database contains all BMD measurements for individuals tested in the province of Manitoba since January 1, 1990. In Manitoba's publicly funded health care system, BMD testing is covered in women older than 65 yr of age and younger women who have: experienced a fragility fracture; used systemic corticosteroids for more than 3 mo/yr; have X-ray evidence of osteopenia; or other CRFs that put them at increased risk of osteoporosis and fracture. This study was approved by the Research Ethics Board for the University of Manitoba and the Health Information Privacy Committee (HIPC) of Manitoba Health.

Population

We identified women in the Manitoba Bone Density Program database up to March 31, 2007, who were older than 50 yr at the time of BMD measurement, had a recorded weight and height, and had a BMD measurement for the femoral neck (FN). For those who had multiple dual-energy X-ray absorptiometry (DXA) assessments, we used their first BMD measurement for analysis. Women with diabetes diagnosed prior to BMD testing were identified by a previously validated definition: 2 separate physician claims for diabetes within 2 yr or a single hospitalization with a diagnosis of diabetes (ICD-9-CM code 250.0–250.9) (16). Administrative data cannot reliably determine whether diabetes is type 1 or type 2, although the vast majority would be type 2 among older women. Each diabetic case was then matched to 3 control patients who did not have diabetes. Cases and controls had BMD testing performed at the same facility within 1 yr of each other and were the same age (±2.5 yr).

BMD Measurements and CRFs

DXA measurements were performed at the lumbar spine and hip, using either a pencil-beam instrument if the measurement was performed before 2000 (Lunar DPX; GE Lunar, Madison, WI) or a fan-beam instrument (Lunar Prodigy; GE Lunar, Madison, WI) if the measurement was performed after 2000. There were no clinically significant differences between the analyses using the different instruments (T-score differences <0.2). FN T-scores and Z-scores were calculated based on reference data for white females from the NHANES III survey (17).

Risk factors that we investigated included age at time of BMD measurement; BMI; previous osteoporotic fracture; diagnosis with chronic obstructive pulmonary disease (COPD) as a proxy for smoking history, substance and alcohol abuse diagnosis, rheumatoid arthritis, hyperthyroidism, and dementia; recent systemic corticosteroid use (≥90 d at a mean of ≥7.5 mg/d dispensed in the year prior to BMD testing); and the use (2 or more pharmacy dispensations) of hormone therapy (HT) and non-HT osteoporosis medications (bisphosphonate, raloxifene, calcitonin, parathyroid hormone analog) during the year prior to the BMD test.

Outcomes

Incident osteoporotic fractures up to March 31, 2007 that occurred after BMD testing were identified from the following ICD-9-CM codes: ICD-9-CM 820-821 with site-specific fracture fixation code (hip); ICD-9-CM 813 with site-specific fracture fixation or casting code (forearm); ICD-9-CM 805 (clinical spine); and ICD-9-CM 812 (proximal humerus). Case definitions required the presence of 2 or more relevant ICD-9-CM codes. Fractures that were associated with trauma codes were excluded from the analysis. Major fractures that occurred prior to BMD testing were also recorded (maximum look back to April 1, 1987). To minimize the potential for counting health care interactions related to the same injury, fracture codes for the same site that occurred within 180 d were ignored.

Statistical Analysis

Descriptive cohort characteristics were calculated as mean ± standard deviation or frequency (percent). Differences in means between the groups for each variable were evaluated using parametric unpaired *t*-tests for continuous variables and chi-square tests for categorical variables. A Cox proportional hazards regression model was used to estimate the hazard ratio (HR) of incident osteoporotic fracture in women with diabetes and women without diabetes. Interaction terms were introduced into the regression model to evaluate the interaction between diabetes and each of the CRFs. Statistical analyses were performed using Statistica version 8.0 (StatSoft, Tulsa, OK) and SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL). The criterion for statistical significance was set at a p value of 0.05.

Results

Of 12,205 women included in the cohort, 3054 were women with diabetes and 9151 were matched controls. Mean age was 68 (±9) yr in the diabetic group and 68 (±9) yr in the nondiabetic group (Table 1). Statistically significant differences were identified between the groups in BMI, COPD diagnoses, corticosteroid use, HT use, BMD, and prior major fractures. Individuals with diabetes had higher FN BMD with 13.1% having a T-score ≤−2.5 compared with 15.8% in the nondiabetic group ($p < 0.001$). Despite this difference in BMD, prior major fractures (hip, clinical vertebral, proximal humerus, and wrist) were more prevalent in the diabetic group compared with the nondiabetic group (16.2% vs 14.3%, $p < 0.001$).

During mean 4.8 yr of observation, 259 (8.5%) of diabetic women and 559 (6.5%) of nondiabetic women experienced an incident major osteoporotic fracture. The fracture rate was significantly greater among diabetic women (unadjusted HR 1.49 [95% confidence interval (CI): 1.28–1.72], $p < 0.001$; covariate-adjusted HR 1.14 [95% CI: 1.10–1.18], $p < 0.001$). HRs for risk factors stratified by diabetes diagnosis are shown in Table 2. Prior fracture, age, and BMD were found to increase the risk of fracture in both groups ($p < 0.001$). A higher BMI was found to decrease fracture risk in individuals with diabetes (HR 0.80, $p = 0.003$) but not in those without diabetes (HR 0.93, $p = 0.276$). Diagnosed substance abuse, dementia, and corticosteroid use increased fracture risk in women without diabetes (HR 1.99, $p = 0.008$; HR 1.89, $p = 0.007$; HR 1.66, $p = 0.014$, respectively) but were not statistically significant risk factors in women with diabetes; 95% CIs for the HRs overlapped

in the diabetic and nondiabetic groups in all the CRFs examined. Diabetes was not found to significantly interact with any of the CRFs studied (all *p*-for-interaction >0.1).

Discussion

In this large cohort of women, we found an increased risk of fracture associated with the diagnosis of diabetes. The predictive ability of traditional CRFs for fracture, including previous osteoporotic fracture, age, FN BMD, BMI, smoking, substance abuse diagnosis, rheumatoid arthritis, hyperthyroidism, dementia, and corticosteroid use, was not influenced by the diagnosis of diabetes. Our study supports the notion that these traditional CRFs can be used in diabetic patients to predict fracture risk.

The pathophysiology of bone fragility in individuals with diabetes differs from postmenopausal osteoporosis, as it is influenced by advanced glycation end products, insulin, and differences in bone geometry and cortical density (7). Therefore, we cannot assume that the same risk factors influence fracture risk in a similar way in these 2 different populations. The traditional CRFs that were examined in our study have been shown to be independent risk factors for fractures in the general population. Traditional CRFs including age, BMI, prior fracture, secondary osteoporosis, and corticosteroid use were all previously found to be associated with greater fracture risk in individuals with diabetes living in Rochester, Minnesota (5). Our study expands on this, examining additional CRFs such as diagnosed COPD, substance abuse, rheumatoid arthritis, hyperthyroidism, and dementia. We were also able to evaluate a larger number of diabetic women (n = 3054) with a matched control group, whereas the Melton et al.'s study looked at a smaller group (n = 1964) and did not compare with a control group. Prior to our study, it was not clear if traditional CRFs maintain the same predictive ability in diabetic populations. Our study suggests that diabetes status does not modulate the ability of traditional risk factors to predict fractures.

Other studies looking at risk factors for fracture in diabetic populations have not focused on traditional CRFs but have mostly looked at factors specific to diabetes. These studies aim to differentiate why fracture risk is higher in individuals with diabetes, but the predictive utility of traditional risk factors has been overlooked. Increased visceral fat and elevated BMI, which are commonly seen in type 2 diabetes, have been found in some studies to have a protective effect increasing BMD and decreasing the risk of fracture (18,19). Our results support a protective effect of BMI with respect to fracture incidence. The increased skeletal loading associated with increased weight and a net positive effect of adipokines, which have been found to actively affect the skeleton, are thought to mediate this protection (8). Micro and macrovascular complications of diabetes, including retinopathy, neuropathy, peripheral vascular disease, stroke, and myocardial infarction, have been found to be associated with increased fracture rates in diabetic patients (20,21). These findings coincide with other studies that have found the duration of diabetes is predictive of fracture risk (2,9). Patients with long-standing diabetes are more likely to suffer from diabetes-related complications and are likely to be older and have more comorbidities. Diabetic patients who fall are also at increased risk of fracture, and therefore it is possible that the associations between diabetic complications (neuropathy, stroke, etc.) and fracture are mediated by an increased fall risk secondary to these complications (20). Results for insulin use as a risk factor for fracture

have been mixed. Insulin use has been associated with increased fracture risk in some studies (21). It may be that insulin is a marker of more severe, long-standing disease in type 2 diabetes and is also associated with increased incidence of hypoglycemia and hence increased falls. However, other studies have found insulin use to be associated with a decreased fracture risk (3), perhaps relating to the fact that insulin has an important anabolic effect on bone. Likewise, insulin therapy has been found to be associated with enhanced bone formation (22,23). In keeping with this, the hyperinsulinemia associated with early type 2 diabetes may be protective against fracture (19). Other diabetic medications have also been found to impact bone health. Both sulfonylureas and metformin have been associated with a deceased fracture risk (3), whereas rosiglitazone was found to be associated with a 2-fold increase in fracture risk in the ADOPT study (24). Hyperglycemia and subsequent advanced glycation end products have also been implicated in multiple studies with increased fracture risk (7,21).

We found higher rates of prior major osteoporotic fracture and higher incident fracture rates in women diagnosed with diabetes compared with those without diabetes in our study. These findings are in keeping with other reports in the literature (1–5).

Our study looked at a large cohort of diabetic women and we were able to directly compare these women with a matched control group. The study does however have several limitations. The databases used did not distinguish diabetic patients as being type 1 or type 2. This is important as different mechanisms of bone fragility have been proposed in these 2 different groups of patients. However, given the mean age and BMI of our diabetic group and the frequency of type 2 (compared with type 1) diabetes in the adult population, we expect that the vast majority of our subjects had type 2 diabetes. Fracture risk in type 2 diabetes may be influenced by diabetes-specific medications (e.g., insulin or thioglitazones) but this information was not available to us (3,24). Other risk factors for fracture, including neuropathy, falls, calcium intake, and vitamin D levels, cannot be reliably ascertained in our data sources. Our study used administrative data and therefore we cannot be certain of the accuracy of the diagnosis of diabetes or fracture. Also, we only studied women and therefore our results cannot be extrapolated to men. Lastly, we found several significant differences in baseline characteristics between the diabetic and nondiabetic groups; therefore, we cannot be sure that these differences were not responsible for the differences in fracture risk, which we recorded.

In conclusion, our study supports the use of traditional CRFs in diabetic patients to identify those who are at increased fracture risk. Although the cause of increased bone fragility in diabetes is still not definitively known, the increased fracture risk has been replicated in multiple studies and therefore deserves attention. Patients diagnosed with diabetes usually have frequent interactions with the health care system during scheduled follow-up appointments and regular screening; therefore, this is an ideal group to target with fracture prevention strategies. If we can identify which individuals with diabetes are at highest fracture risk, then future research can specifically evaluate the effectiveness of antiosteoporosis therapies in this population.

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Table 1

Descriptive Characteristics

Characteristic	Diabetic women (N = 3054); Number (%)[a]	Nondiabetic women (N = 9151); Number (%)	*p* Value
Demographics			
Age (yr); mean (SD)	68.0 (9.3)	67.9 (9.2)	0.773
BMI (kg/m^2); mean (SD)	29.9 (6.3)	26.6 (5.0)	<0.001
Medical conditions			
COPD	323 (10.6)	750 (8.2)	<0.001
Substance abuse diagnosis	64 (2.1)	181 (2.0)	0.688
Rheumatoid arthritis	113 (3.7)	316 (3.5)	0.521
Hyperthyroidism	74 (2.4)	206 (2.3)	0.583
Dementia	65 (2.1)	185 (2.0)	0.718
Medications			
Recent systemic corticosteroid use[b]	188 (6.2)	331 (3.6)	<0.001
Recent HT	368 (12.1)	1546 (16.9)	<0.001
Recent non-HT osteoporosis medication	256 (8.4)	862 (9.4)	0.085
BMD; mean (SD)			
FN T-score	−1.33 (1.05)	−1.57 (0.95)	<0.001
FN Z-score	0.36 (1.11)	0.09 (0.98)	<0.001
FN T-score ≤−2.5; n (%)	395 (13.1)	1441 (15.8)	<0.001
Prior major fracture[c]	496 (16.2)	1310 (14.3)	<0.001

Abbr: BMI, body mass index; COPD, chronic obstructive pulmonary disease; HT, hormone therapy; BMD, bone mineral density; SD, standard deviation; FN, femoral neck.

[a] Unless otherwise stated.

[b] >7.5 mg/d for more than 3 mo.

[c] Includes fractures of the hip, vertebra, proximal humerus, and wrist.

Table 2

Risk of Incident Fracture Given Different Clinical Risk Factors in Diabetic Women and Nondiabetic Women

	Women with diabetes			Women without diabetes		
Risk factor	**HR**	**95% CI**	***p* Value**	**HR**	**95% CI**	***p* Value**
Prior osteoporotic fracture	1.69	1.23–2.31	0.001	1.79	1.44–2.24	<0.001
Age increase per 10 yr	1.24	1.05–1.47	0.011	1.42	1.26–1.61	<0.001
BMI increase per SD	0.80	0.69–0.93	0.003	0.93	0.82–1.06	0.276
FN BMD decrease per SD	1.52	1.40–1.81	<0.001	1.71	1.61–1.96	<0.001
COPD	1.29	0.86–1.93	0.222	0.99	0.72–1.36	0.953
Substance use	1.18	0.46–3.00	0.728	1.99	1.20–3.32	0.008
Rheumatoid arthritis	1.49	0.78–2.85	0.225	1.16	0.75–1.80	0.510
Hyperthyroidism	0.95	0.39–2.31	0.911	0.67	0.33–1.35	0.261
Dementia	1.59	0.72–3.49	0.251	1.89	1.19–3.01	0.007
Systemic corticosteroid use	1.00	0.56–1.80	0.990	1.66	1.11–2.48	0.014
Osteoporosis medication use	0.74	0.50–1.09	0.125	1.02	0.82–1.28	0.852

Abbr: HR, hazard ratio; CI, confidence interval; BMI, body mass index; SD, standard deviation; FN, femoral neck; BMD, bone mineral density; COPD, chronic obstructive pulmonary disease.