Longer Duration of Diabetes Strongly Impacts Fracture Risk Assessment: The Manitoba BMD Cohort

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Context: Type 2 diabetes is associated with a higher risk for major osteoporotic fracture (MOF) and hip fracture than predicted by the World Health Organization fracture risk assessment (FRAX) tool.

Objective: The objective of the study was to examine the impact of diabetes duration on fracture risk.

Methods: Using a clinical dual-energy x-ray absorptiometry registry linked with the Manitoba administrative databases, we identified all women age 40 years or older with 10 or more years of prior health care coverage undergoing hip dual-energy x-ray absorptiometry measurements (1996–2013). Incident MOF and incident hip fractures were each studied over 7 years. Cox proportional hazards models were adjusted for FRAX (FRAX adjusted) and then FRAX plus comorbidity, falls, osteoporosis therapy, or insulin (fully adjusted). FRAX calibration was assessed comparing observed vs predicted probabilities.

Results: There were 49 098 women without and 8840 women with diabetes (31.4% >10 y duration; 20.1% 5–10 y; 23.7% <5 y; 24.8% new onset). In FRAX-adjusted analyses, only duration longer than 10 years was associated with a higher risk for MOF (hazard ratio [HR] 1.47, 95% confidence interval [CI] 1.30–1.66), and this was similar in the fully adjusted models (HR 1.34, 95% CI 1.17–1.54). In contrast, a higher risk for hip fracture was seen for all durations in a dose-dependent fashion (eg, FRAX adjusted HR 2.10, 95% CI 1.71–2.59 for duration >10 y vs HR 1.32, 95% CI 1.03–1.69 for new onset). FRAX significantly underestimated the MOF risk (calibration ratio 1.24, 95% CI 1.08–1.39) and hip fracture risk (1.93, 95% CI 1.50–2.35) in those with a diabetes duration longer than 10 years.

Conclusion: Diabetes is a FRAX-independent risk factor for MOF only in women with a long duration of diabetes, but diabetes increases hip fracture risk, regardless of duration. Those with diabetes longer than 10 years are at particularly high risk of fracture, and this elevated risk is currently underestimated by FRAX. (*J Clin Endocrinol Metab* 101: 4489–4496, 2016)

Osteoporosis and type 2 diabetes are both common chronic diseases that are increasing in prevalence and share some risk factors such as older age, current smoking, and exposure to glucocorticoids. Furthermore, each condition alone increases the risk of fracture, with type 2 diabetes a bone mineral density (BMD)-indepen-

Abbreviations: ADG, aggregated diagnosis group; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; DXA, dual-energy x-ray absorptiometry; FRAX, fracture risk assessment; HR, hazard ratio; ICD-9-CM, *International Classification of Diseases*, ninth revision, Clinical Modification; MOF, major osteoporotic fractures; RR, risk ratio.

dent and fracture risk assessment (FRAX) tool -independent risk factor for major osteoporotic fractures (MOF) and hip fractures (1–3). The reasons that type 2 diabetes increases the risk of fracture are complex and multifactorial and include skeletal (eg, compromised bone strength or bone quality, suppressed bone turnover, increased cortical porosity) and nonskeletal factors (eg, increased risk of injurious falls related to hypoglycemia, obesity, decreased visual acuity, and impaired mobility and balance) (1, 2). All of the putative mechanisms for the associations between type 2 diabetes and fracture require time to accrue, and a better understanding of the time course between a diagnosis of diabetes and the risk of fracture is of clinical value in stratifying the risk of fracture for a given patient with type 2 diabetes.

Prior studies of different designs among different populations and from different time periods have consistently demonstrated that type 2 diabetes increases the risk of MOF by about 20%–30% and the risk of hip fracture by 70%–80% (4). There has been, however, much less consistency when trying to examine the duration of type 2 diabetes as a risk factor for osteoporotic fractures, with studies demonstrating no association with duration (5, 6), increased risk only with long duration of diabetes (7–10), increased risk with even a short duration of diabetes (11, 12), and even a reduction in the risk of fracture with new-onset diabetes (13). Larger studies with longer follow-up and more consistent definitions of diabetes and osteoporosis risk are needed to bring clarity to this topic.

Therefore, we undertook the present analysis in a large population-based sample of women with and without type 2 diabetes undergoing dual-energy x-ray absorptiometry (DXA) for clinical indications. We hypothesized that the duration of diabetes might be more important than its mere presence or absence and that a longer duration of diabetes would be positively associated with an increased risk of incident fracture in a dose-dependent fashion. Furthermore, given that FRAX (with or without BMD) already tends to underestimate the risk of fracture in patients with type 2 diabetes (2, 3), we hypothesized that any potential miscalibration would result in clinically important underestimation of fracture risk, particularly in those with the longest duration of diabetes.

Materials and Methods

Subjects and setting

Using a registry containing all clinical DXA results for Manitoba, Canada, we identified all women aged 40 years and older with at least 10 years of health care coverage before undergoing their first (baseline) DXA in the years 1996–2013. In the Province of Manitoba, Canada, health services are provided to nearly all residents through a single public health care system (14, 15). DXA testing has been managed as an integrated program since 1997, and this program maintains a database of all DXA results that can be linked with other population-based databases through an anonymous personal identifier (16). The DXA database has completeness and accuracy in excess of 99% and has been described in detail (16–18). This study was approved by the University of Manitoba Health Research Ethics Board and data access granted by the Manitoba Health Information Privacy Committee.

Diabetes diagnosis and duration of disease

Women were first categorized according to the presence or absence of diabetes using a validated algorithm for identifying individuals with diabetes in population-based health services data (15). Using data sources since 1987, diabetes was ascertained from the presence of at least two physician billing claims for diabetes within 2 years (coded using *International Classification of Diseases*, ninth revision, Clinical Modification [ICD-9-CM]) or at least one hospitalization with a diabetes diagnosis (coded using the ICD-9-CM prior to 2004 and *International Classification of Diseases*, 10th revision, Canada thereafter) (15). Then we defined our independent variable of interest, namely the duration of diabetes, based on the earliest applicable diagnosis code for diabetes. We classified the duration of diabetes as new onset (ie, not present at the time of baseline DXA test but diagnosed within the subsequent 5 y) vs short duration (less than 5 y prior to DXA) vs intermediate duration (5–10 y prior to DXA) vs long duration (10 y or more prior to DXA). Because of the relatively long asymptomatic period associated with type 2 diabetes, changes in definitions and screening, and the observation that at least one-third of prevalent diabetes is undiagnosed, we included new-onset diabetes as a separate category rather than altogether exclude them or include them in the no-diabetes category. Given the age of the cohort, subjects in this analysis were presumed to have type 2 diabetes. As a sensitivity analysis, we reran our analyses after excluding those with a long duration of diabetes treated with only insulin because this subgroup was most likely to have type 1 diabetes.

Incident fractures

The main study outcome was incident fracture that occurred after the baseline DXA test through the observation period ending March 31, 2013. Fractures were ascertained through a combination of hospital discharge abstracts and physician billing claims because this method allows complete capture of any fractures that require treatment irrespective of hospital admission (3, 13, 16–18). Longitudinal health service records were assessed for the presence of hip, clinical vertebral, forearm, and humerus fracture codes (collectively designated as MOF) that were not also associated with the presence of trauma codes (3, 13, 16–18). Hip fractures and forearm fractures were required to have a site-specific fracture reduction, fixation, or casting code to enhance specificity for an acute fracture event. To minimize potential misclassification of prior incident fractures, we required that there be no hospitalization or physician visit(s) with the same fracture type in the 6 months preceding an incident fracture diagnosis.

DXA measurements

Proximal femur DXA scans were performed and analyzed by technicians according to the manufacturer's guidelines using

pencil beam (Lunar DPX; GE Lunar) if the measurement was taken before the year 2000 or fan beam (Lunar Prodigy; GE Lunar) if the measurement was taken after the year 2000. These densitometers have been cross-calibrated and demonstrated no clinically important differences across scanners (eg, within 0.1 SD at the femoral neck) and have shown stable long-term performance (eg, coefficient of variation <0.5%) and good in vivo precision (eg, coefficient of variation of 1.1% for the total hip) (16–18). Femoral neck T-scores (number of SDs above or below young adult mean BMD) were calculated based on reference data for US white females from the National Health and Nutrition Examination Survey III survey (19).

Potential confounders and other measurements

Ten-year probability of MOF risk and hip fracture risk was calculated using the World Health Organization FRAX tool, Canadian version (FRAX Desktop Multi-Patient Entry, version 3.7). The Canadian FRAX tool was calibrated using nationwide hip fracture data, and its predictions agreed closely with observed fracture risk (17). Weight and height were obtained by self-report at the time of the DXA examination before the year 2000; thereafter height was assessed with a wall-mounted stadiometer and weight was assessed without shoes using a standard floor scale. Body mass index (BMI [in kilograms per square meter]) was calculated as weight (in kilograms) divided by height (in meters) squared. Prior fracture, other FRAX input variables, and falls requiring hospitalization were assessed using hospital discharge abstracts and physician billing claims as previously described (3, 13, 16–18). We defined prior fragility fracture as any nontraumatic MOF that occurred before the baseline DXA test using records back to 1987 and used both hospital discharge abstracts and physician billing claims to capture any fracture that required treatment whether or not the patient was hospitalized. Prolonged oral corticosteroid use (>90 d dispensed in the 1 y prior to DXA), as well as any use of prescription osteoporosis therapy (ie, bisphosphonates, calcitonin, systemic estrogen products, raloxifene, teriparatide) or any oral antidiabetic agents or insulin in the 1 year prior to baseline DXA test, was obtained from the provincial pharmacy system. Lastly, to define burden of comorbidity in the 1 year prior to their baseline DXA test for each subject, we used the Johns Hopkins Adjusted Clinical Group (ACG) Case-Mix System (version 9) (20, 21). Aggregated diagnosis groups (ADGs) represent 32 comorbidity clusters of every ICD-9-CM diagnostic codes (20, 21). The number of ADGs was categorized as less than three (reference group) vs three to five vs six or more (22).

Statistical analysis

Sociodemographic and clinical characteristics of subjects with and without type 2 diabetes at the time of the baseline DXA test were described using means and SDs for continuous variables and frequencies and percentages for categorical variables; between-group comparisons were conducted using appropriate statistical tests (eg, χ^2 tests of independence for categorical variables). Cumulative incidence of fractures, MOF, and hip fracture, stratified by the presence and duration of diabetes, were plotted. Then multivariable Cox proportional hazards regression models were used to test the independent association between a diagnosis of type 2 diabetes and incident fractures. After this, we examined the independent association between the duration of diabetes (no diabetes [reference] vs new onset diabetes

vs <5 y duration vs 5–10 y duration vs >10 y duration) and incident fracture. The model was first adjusted for FRAX scores computed with femoral neck BMD (log transformed due to a skewed distribution), hereafter referred to as FRAX adjusted. Then another model was fit to the data that adjusted for FRAX scores in addition to burden of comorbidity, hospitalized falls, prescription osteoporosis treatment, and insulin therapy, hereafter referred to as fully adjusted. The proportional hazards assumption was confirmed for each model by testing scaled Schoenfeld residuals vs time, and no violations were detected.

Lastly, we examined the calibration of FRAX computed with femoral neck BMD according to different durations of diabetes. The magnitude of potential miscalibration of FRAX was evaluated by calculating ratios for the observed 10-year incident fracture probability to the expected 10-year fracture probability predicted by FRAX across each strata of diabetes duration. These ratios explicitly considered the effect of competing mortality, which is a component of the FRAX methodology (23). A priori, we considered observed fracture rates within 10% of FRAX predicted rates (ie, an observed to expected calibration ratio anywhere between 0.90 and 1.10) to represent good calibration (18). All statistical analyses were performed with Statistica (version 10.0; StatSoft Inc).

Results

The final study cohort included 8840 women with type 2 diabetes and 49 098 women without diabetes. Women with diabetes were significantly older and heavier with a greater burden of comorbidity and more prior falls than women without diabetes (Table 1). Women with diabetes were also significantly more likely to have had a prior fracture, and had higher predicted risk of MOF and hip fractures, than women without diabetes (Table 1). Over more than 420 000 person-years of follow-up (mean 7 y per subject), women with diabetes were significantly more likely to suffer an incident MOF than women without diabetes (814 [9.2% or 14.3 per 1000 person-years] vs 4211 [8.6% or 11.5 per 1000 person-years]; FRAX-adjusted hazard ratio [HR] 1.19, 95% [CI] 1.10–1.28, $P <$ .001; fully adjusted HR 1.11, 95% CI 1.03–1.21, $P =$ .007) and significantly more likely to suffer a hip fracture than women without diabetes (279 [3.2% or 4.9 per 1000 person-years] vs 1109 [2.3% or 3.0 per 1000 person-years]; FRAX adjusted HR 1.66, 95% CI 1.45–1.89, $P <$ .001; fully adjusted HR 1.56, 95% CI 1.36–1.79, $P <$ .001). Unlike these osteoporotic fractures, incident ankle fractures were not associated with the presence of diabetes ($P =$ .2; Table 1).

Duration of diabetes and incident fractures

Most diagnoses of diabetes preceded DXA testing (n = 2776 [31.4%] >10 y duration; n = 1776 [20.1%] 5–10 y; n = 2098 [23.7%] <5 y duration) with a minority of diabetes being diagnosed after DXA testing (n = 2190

Table 1.   Characteristics and Outcomes Stratified According to the Presence or Absence of Diabetes

	Diabetes (n = 8840), %	No Diabetes (n = 49 098), %	P Value for Difference
Characteristics			
Age, y	67.1 ± 10.4	63.8 ± 11.1	<.0001
BMI, kg/m²	30.3 ± 6.4	26.5 ± 5.1	<.0001
Height, cm	159.2 ± 6.5	160.5 ± 6.6	<.0001
Weight, kg	76.9 ± 17.2	68.3 ± 13.9	<.0001
Prior fracture	1462 (16.5)	7045 (14.3)	<.0001
Insulin use	832 (9.4)	0 (0)	<.0001
Osteoporosis treatment	1103 (12.5)	8054 (16.4)	<.0001
Fracture probability (FRAX MOF with BMD)	12.7 ± 8.7	11.3 ± 8.6	<.0001
Fracture probability (FRAX hip with BMD)	2.8 ± 4.6	2.6 ± 4.5	<.0001
Femoral neck T-score	−1.3 ± 1.1	−1.4 ± 1	<.0001
Femoral neck Z-score	0.3 ± 1	0,0 ± 0.9	<.0001
Femoral neck osteoporosis (T-score ≤−2.5)	974 (11)	6136 (12.5)	<.0001
Hospitalization for a fall in the last 3 y	428 (4.8)	1610 (3.3)	<.0001
ADG score	5.6 ± 2.8	4.6 ± 2.6	<.0001
Observation time, y	6.5 ± 3.9	7.5 ± 4.2	<.0001
Outcomes			
Incident hip fractures	279 (3.2)	1109 (2.3)	<.0001
Incident vertebral fractures	200 (2.3)	945 (1.9)	.04
Incident humerus fractures	201 (2.3)	844 (1.7)	<.0001
Incident forearm fractures	248 (2.8)	1793 (3.7)	<.0001
Incident MOF fractures	814 (9.2)	4211 (8.6)	.05
Incident ankle fractures	153 (1.7)	751 (1.5)	.20
Deaths	1666 (18.8)	5454 (11.1)	<.0001

[24.8%] new onset). If we considered any subject who ever used insulin but never used an oral antidiabetes agent to represent type 1 diabetes, only 207 of 8840 (2.3%) women with diabetes in our population met this definition, supporting our assumption that our cohort contained predominantly type 2 diabetes.

Table 2 provides selected baseline characteristics according to the duration of diabetes. Compared with those without diabetes, there was a statistically significant (P for linear trend <.001) gradient in age, BMI, prior fractures, and FRAX scores (but not femoral neck bone density) according to the duration of diabetes (Table 2). A similar linear gradient in observed rates of incident fracture was seen according to the duration of diabetes for both MOF and hip fracture, with a greatest risk of both types of frac-

tures observed in those with more than 10 years of diabetes duration (Table 3).

Multivariable analyses of diabetes duration

With respect to MOF, in FRAX-adjusted analyses, only diabetes present for a duration longer than 10 years was independently associated with incident fracture, and this association remained statistically significant in the fully adjusted model (adjusted HR 1.34, 95% CI 1.17–1.54, P < .001; Table 4). Treatment with insulin was not associated with MOF (P = .5), and excluding the 207 women with possible type 1 diabetes did not affect either the magnitude or statistical significance of these findings (data not shown).

With respect to hip fracture, however, any duration of diabetes was independently associated with an increased

Table 2.   Selected Baseline Characteristics Stratified According to the Presence and Duration of Diabetes

	No Diabetes (n = 49 098)	New-Onset Diabetes (n = 2190)	Duration, <5 y (n = 2098)	Duration, 5–10 y (n = 1776)	Duration, >10 y (n = 2776)
Characteristics, mean (±SD)					
Age, y	63.8 ± 11.1	65.6 ± 10.7	66.5 ± 10.3	67.9 ± 9.9	68.4 ± 10.4
Body mass index, kg/m²	26.5 ± 5.1	30.4 ± 6.2	30.5 ± 6.4	30.4 ± 6.4	30.0 ± 6.4
Prior fracture, %	14.3 ± 0.3	14.5 ± 0.4	16.0 ± 0.4	15.9 ± 0.4	19.0 ± 0.4
Fracture probability (FRAX MOF with BMD)	10.9 ± 8.0	11.1 ± 8.0	11.2 ± 7.8	11.7 ± 8.2	12.3 ± 7.9
Fracture probability (FRAX hip with BMD)	2.6 ± 4.5	2.6 ± 4.6	2.6 ± 4.4	2.9 ± 5.2	3.1 ± 4.5
Femoral neck T-score	−1.4 ± 1.0	−1.2 ± 1.0	−1.2 ± 1.1	−1.2 ± 1.0	−1.4 ± 1.1
Femoral neck Z-score	0.0 ± 0.9	0.3 ± 0.9	0.3 ± 1.0	0.4 ± 1.0	0.2 ± 1.0

Table 3. Rates per 1000 Person-Years (95% Confidence Intervals) of Major Osteoporotic Fracture, Hip Fracture, and Death According to the Presence and Duration of Diabetes

	n	Major Osteoporotic Fractures	Hip Fractures	Deaths
No diabetes	49 098	11.4 (10.5–12.4)	3.0 (2.5–3.5)	14.8 (13.8–15.9)
Diabetes	8840	14.3 (11.8–16.7)	4.9 (3.4–6.3)	29.2 (25.7–32.7)
Diabetes duration				
New onset	2190	11.9 (7.4–16.4)	3.9 (1.3–6.5)	22.4 (16.2–28.6)
<5 y	2098	13.3 (8.4–18.2)	4.5 (1.7–7.4)	27.5 (20.5–34.5)
5–10 y	1776	13.9 (8.5–19.4)	4.8 (1.6–8)	29.3 (21.4–37.1)
>10 y	2776	18.0 (13.1–23.0)	6.4 (3.5–9.4)	38.3 (31.2–45.5)

risk of incident fracture (Table 4). A dose-response gradient was present with diabetes duration longer than 10 years associated with the greatest risk of hip fracture in both the FRAX-adjusted models (adjusted HR 2.10, 95% CI 1.71–2.59, $P < .001$) and fully adjusted models (adjusted HR 1.94, 95% CI 1.54–2.44, $P < .001$; see Table 4). Treatment with insulin was not associated with hip fracture ($P = .7$) and excluding 207 women with presumptive type 1 diabetes did not materially affect either the magnitude or statistical significance of these findings (data not shown).

FRAX calibration and diabetes duration

FRAX was well calibrated for MOF prediction in women without diabetes (ie, desirable range for the calibration ratio 0.90–1.10). With respect to MOF in women with diabetes, FRAX was well calibrated in fully adjusted models except when diabetes duration was longer than 10 years (Figure 1). In those with a long duration of diabetes, the observed to expected calibration ratio was 1.24 (95% CI 1.08–1.39), representing a statistically significant and clinically important underestimation of MOF risk (Table 5).

FRAX calibration for hip fracture prediction was again within the desirable range in women without diabetes. FRAX was not well calibrated in women with diabetes of any duration (Figure 1). Irrespective of statistical significance, the observed to expected calibration ratios ex-

ceeded in magnitude the 1.10 threshold across all durations of diabetes and statistically significantly exceeded 1.90 in those with the longest duration of diabetes (1.93, 95% CI 1.50–2.35; see Table 5). This represents a clinically important and substantial underestimation of the hip fracture risk in those with diabetes, particularly in those with the longest durations of diabetes.

Discussion

In a large cohort of more than 50 000 women undergoing DXA testing for clinical indications, we confirmed that type 2 diabetes is a FRAX-independent risk factor for MOF and hip fractures and demonstrated that the duration of diabetes is important in terms of understanding and quantifying this increased risk. Indeed, at least 10 years of a diagnosis with diabetes needed to be present before women were at a significantly increased risk of MOF, whereas the risk of hip fracture was increased even before the diagnosis of diabetes. That said, the risk of hip fracture increased with duration of diabetes, such that women with 10 years or more of diabetes had almost a doubling in their hip fracture risk when compared with women without diabetes, even after adjusting for FRAX with BMD, comorbidity, falls, osteoporosis treatment, and insulin therapy. Whereas FRAX is known to underestimate the risk of

Table 4. FRAX-Adjusted and Fully Adjusted[a] Associations With Incident Fractures According to the Duration of Diabetes[b]

		Major Osteoporotic Fractures		Hip Fractures	
	n	FRAX-Adjusted HR (95% CI)	Fully Adjusted HR (95% CI)	FRAX-Adjusted HR (95% CI)	Fully Adjusted HR (95% CI)
No diabetes	49 098	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
New onset	2190	1.02 (0.89–1.17)	0.99 (0.86–1.14)	**1.32 (1.03–1.69)**	**1.30 (1.01–1.65)**
<5 y	2098	1.13 (0.98–1.32)	1.07 (0.92–1.25)	**1.59 (1.23–2.06)**	**1.54 (1.19–1.99)**
5–10 y	1776	1.16 (0.99–1.37)	1.10 (0.93–1.29)	**1.61 (1.21–2.13)**	**1.55 (1.17–2.06)**
>10 y	2776	**1.47 (1.30–1.66)**	**1.34 (1.17–1.54)**	**2.10 (1.71–2.59)**	**1.94 (1.54–2.44)**

[a] Fully adjusted models included FRAX scores (computed with BMD), burden of comorbidity, falls, prescription osteoporosis treatments, and insulin therapy.

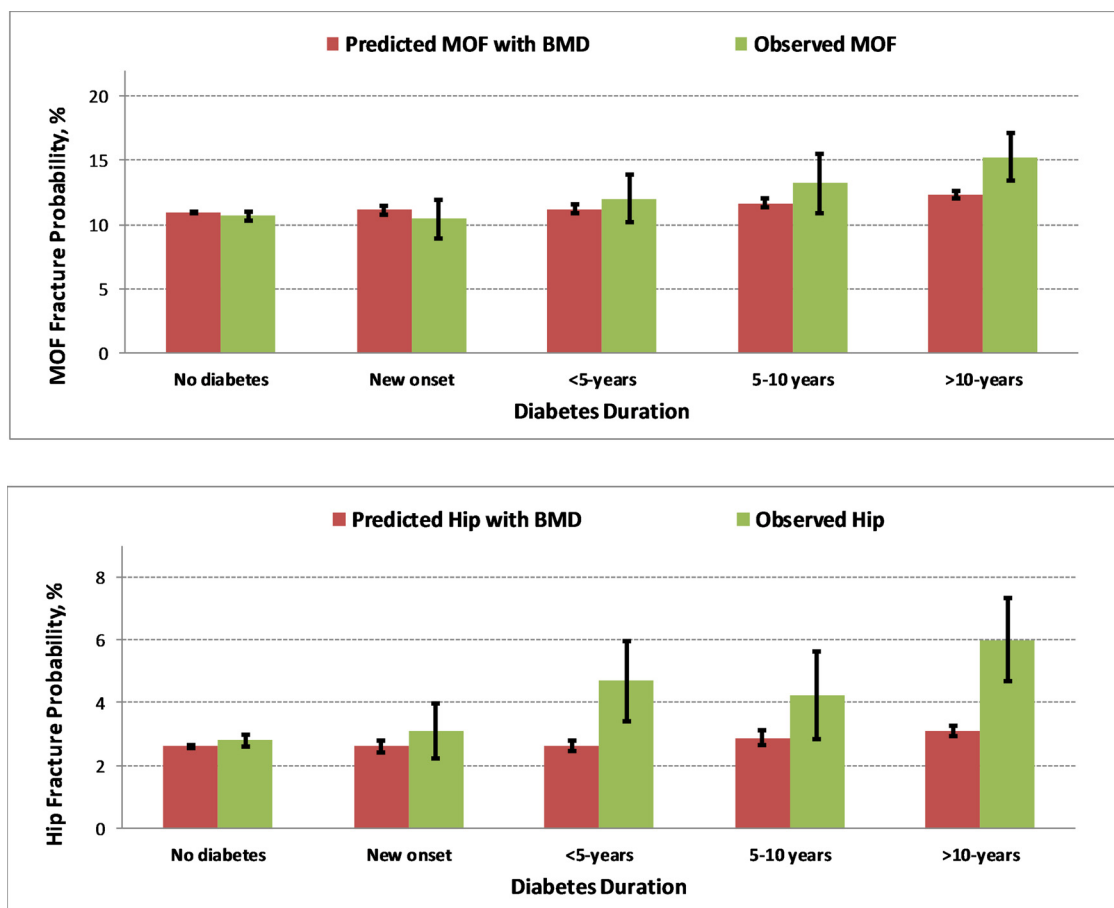[b] Statistically significant ($P < .05$) HRs in bold.

Figure 1. FRAX calibration plots: observed vs predicted 10-year probabilities and their associated observed to predicted ratios for major osteoporotic fractures and hip fractures. A priori, we considered observed to predicted ratios between 0.9 and 1.10 to represent good calibration and values outside these bounds to represent clinically important miscalibration. *, Values of $P < .05$ represents a statistically significant miscalibration.

fractures in women with type 2 diabetes (2, 3), we demonstrated that it is most severely miscalibrated for both MOF and hip fractures in those with 10 years or longer of duration of diabetes.

The findings from the prior literature are inconsistent and difficult to synthesize, likely because different studies have included very different sample sizes, examined different geographic populations over different eras, been restricted to certain fracture types, or ascertained diabetes diagnoses and

durations using variable methods (5–13). Strotmeyer et al (Health, Aging, Body Composition Study [5]) and Ahmed et al (Tromso Study [6]) reported no association between any type of fracture and duration of diabetes. Schwartz et al (Study of Osteoporotic Fractures [7]) reported all fracture types increased with long (>14 y) duration of diabetes compared with shorter durations of diabetes, although this reached statistical significance only for hip fracture (risk ratio [RR] 2.40 [95% CI 1.55–3.71] compared with no diabetes

Table 5. Effect of Diabetes Duration on FRAX Calibration According to Observed Versus Predicted 10-Year Fracture Probability Ratio[a]

		Major Osteoporotic Fractures		Hip Fractures	
	n	**Observed vs Predicted Ratio**	**95% Confidence Intervals**	**Observed vs Predicted Ratio**	**95% Confidence Intervals**
Diabetes					
No Diabetes	49 098	0.98	0.95–1.01	**1.08**	**1.01–1.15**
New onset	2190	0.94	0.80–1.07	1.18	0.85–1.51
<5 y	2098	1.07	0.90–1.24	**1.79**	**1.30–2.27**
5–10 y	1776	1.13	0.94–1.33	1.46	0.98–1.95
>10 y	2776	**1.24**	**1.08–1.39**	1.93	**1.50–2.35**

[a] Statistically significant ($P < .05$) ratios in bold.

and RR 1.46 [95% CI 0.98–2.17] compared with short duration of diabetes). This association with a longer duration has been confirmed by Forsen et al (Nord-Trondelag Health Study [8]), Ivers et al (Blue Mountains Eye Study [9]), and Melton et al (Rochester Minnesota cohort [10]), who observed significantly an increased risk of fracture only after 5 years, 10 years, and 10 years of duration of diabetes, respectively. Janghorbani et al (Nurses' Health Study [11]) reported an increased risk of hip fracture with any diabetes duration, although the risk was greatest with a long (>11 y) duration of disease, findings nearly identical with that of Nicodemus and Folsom (Iowa Women's Health Study [12]).

Finally, in a population-based case-control study drawn from the same province as the current study, Leslie et al (13) showed that a longer (>5 y) duration of diabetes was associated with an increased risk of MOF (RR 1.15, 95% CI 0.86–0.95) and hip fractures (RR 1.40, 95% CI 1.28–1.53). These investigators also found a biphasic association with diabetes wherein subjects with new-onset diabetes during follow-up had a 9% reduced risk of MOF and a 17% reduced risk of hip fracture (13). This latter finding has not been replicated by others and is not consistent with our current work or the findings of Nicodemus and Folsom (12) in which new-onset diabetes was very similar in fracture risk to established diabetes of less than 5 years' duration. This protective benefit of a new diagnosis of diabetes is also difficult to interpret, given that type 2 diabetes often has a 5- to 10-year asymptomatic latency period and that at the time of diagnosis most patients already have some diabetes-related complications or comorbidities (24).

Although the literature is not straightforward to interpret, we believe that the totality of evidence indicates that type 2 diabetes increases the risk of MOF and hip fractures and that the longer the duration of disease, the greater the risk of fracture, particularly a decade after the diagnosis. What does this imply for fracture risk assessment? For type 1 diabetes, the current consensus is to consider it a secondary osteoporosis FRAX input and assumes that some (although not all) of the increased risk relates to reduced BMD in this population (2, 25). For type 2 diabetes, FRAX computed with BMD is miscalibrated and underestimates the risk, especially for hip fracture and especially for those with a long duration of disease. Although more work needs to be done and our findings need to be replicated, type 2 diabetes of 10 years' duration should be considered a red flag for greater attention to osteoporosis, perhaps thought of as a previous fracture equivalent at the bedside (24) in the way that a long duration of diabetes is sometimes considered a coronary heart disease equivalent when undertaking cardiac risk stratification (26).

This study has several strengths, including its large and population-based sample size, its long look-back and follow-up periods, its capture of both BMI and BMD, and its use of previously validated methods to capture both exposure (diabetes) and outcome (fractures). Nevertheless, it also has several important limitations. First, we cannot distinguish type 1 from type 2 diabetes, and this may be an important pathophysiological distinction. Given the age of cohort entry (40 y) and the look-back period (10 y), only a very small proportion (maximum 2.3%) of those with diabetes in our study potentially had type 1 diabetes. Furthermore, sensitivity analyses in which we excluded all 207 subjects who ever used insulin and never used oral antidiabetes agents did not materially affect any of our findings, confirming that this was a study dominated by those with type 2 diabetes as was intended.

Second, diagnoses of diabetes were based on administrative data, and we did not have measurements of fasting glucose or glycated hemoglobin, and thus, we could not examine the role of impaired fasting glucose or prediabetes on the one hand nor guarantee that our control group did not have undiagnosed diabetes on the other hand. Third, we did not have any measures of glycemic control or, related to this, measures of bone strength or quality as influenced by glycemic control. Fourth, we had no detailed information on smoking; physical activity; falls not requiring hospitalization or mediators of falling such as hypoglycemia; or measures of diabetic complications such as neuropathy, myopathy, retinopathy, or nephropathy; or chronic kidney disease. Fifth, we did not examine time-updated covariates such as changes in BMI, BMD, or FRAX clinical risk factors or the addition of new medications during follow-up but rather examined only covariates at the time of the baseline DXA test. Sixth, our fracture data were based on claims data and procedure codes, and although validated and specific (27, 28), we did not have information with respect to asymptomatic or nonclinical vertebral fractures. Lastly, our findings may lack generalizability because the population was drawn from one province in Canada and the subjects were predominantly white, and we examined only women.

In conclusion, confirming a diagnosis of type 2 diabetes significantly increases the risk of hip fracture, and once a woman has had type 2 diabetes for a decade (all else being equal), she has more than a 30% increased risk of MOF and more than a 90% increased risk of hip fracture when compared with a woman without diabetes. These substantially elevated risks as they relate to duration of disease have not been captured using conventional fracture risk assessment tools such as FRAX.

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