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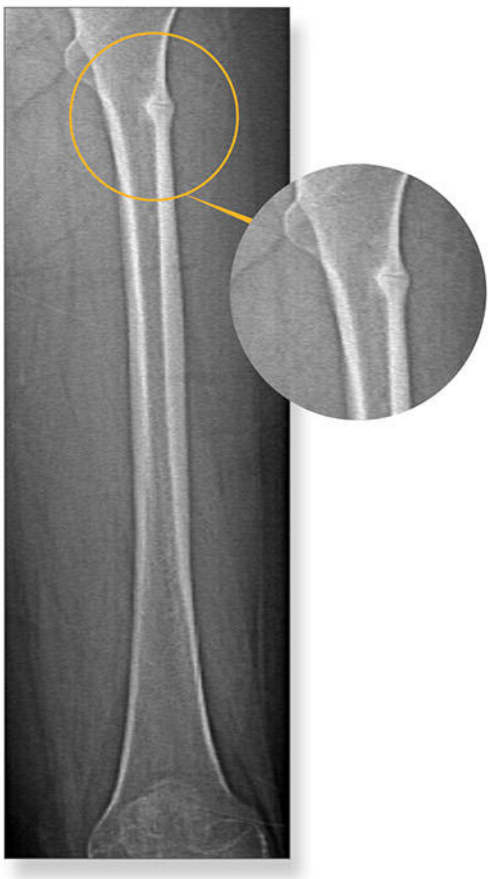

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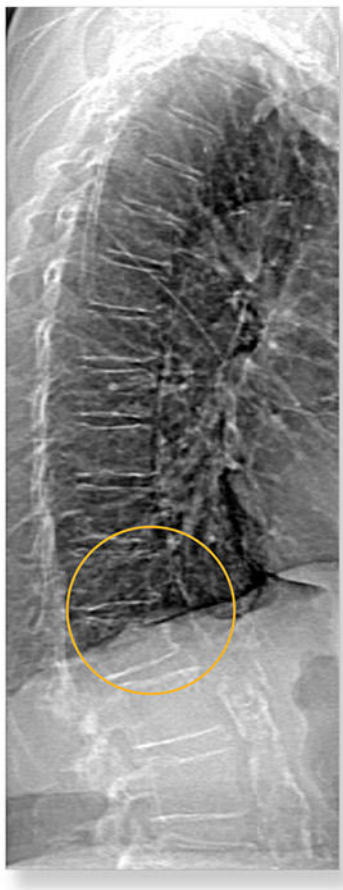

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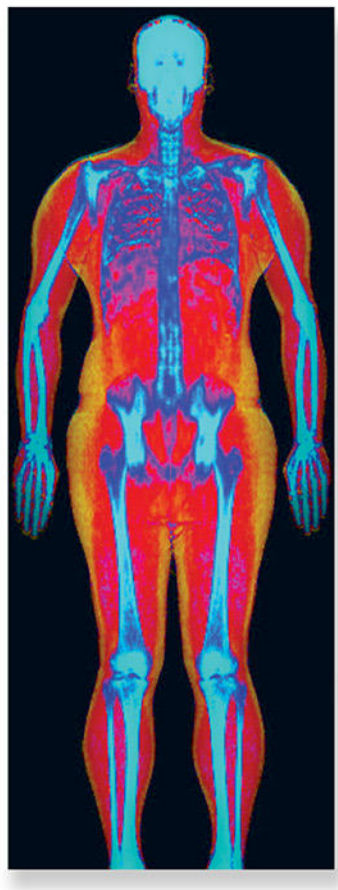

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ORIGINAL ARTICLE

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Comparison of Methods for Improving Fracture Risk Assessment in Diabetes: The Manitoba BMD Registry

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ABSTRACT

Type 2 diabetes is a risk factor for fracture independent of FRAX (fracture risk assessment) probability. We directly compared four proposed methods to improve the performance of FRAX for type 2 diabetes by: (1) including the rheumatoid arthritis (RA) input to FRAX; (2) making a trabecular bone score (TBS) adjustment to FRAX; (3) reducing the femoral neck *T*-score input to FRAX by 0.5 SD; and (4) increasing the age input to FRAX by 10 years. We examined major osteoporotic fractures (MOFs) and hip fractures (HFs) over a mean of 8.3 years observation among 44,543 women and men 40 years of age or older (4136 with diabetes) with baseline lumbar spine and hip DXA from 1999 through 2016. Controlled for unadjusted FRAX probability, diabetes was associated with an increased risk for MOFs and HFs. All four FRAX adjustments attenuated the effect of diabetes, but a residual effect of diabetes was seen on MOF risk after TBS adjustment, and on HF risk after the RA and TBS adjustments. Among those with diabetes, unadjusted FRAX risk underestimated MOF (observed/predicted ratio 1.15; 95% CI, 1.03 to 1.28), but this was no longer significant after applying the diabetes adjustments. HF risk was more severely underestimated (observed/predicted ratio 1.85; 95% CI, 1.51 to 2.20) and was only partially corrected with the diabetes adjustments (still significant for the RA and TBS adjustments). Among those with diabetes, there was moderate reclassification based upon a fixed MOF cut-off of 20% (4.1% to 7.1%) or fixed HF cut-off of 3% (5.7% to 16.5%). Net reclassification improvement increased for MOF with each of the diabetes adjustments (range 3.9% to 5.6% in the diabetes subgroup). In conclusion, each of the proposed methods for addressing limitations in the ability of FRAX to assess fracture risk in individuals with diabetes was found to improve performance, though no single method was optimal in all settings. © 2018 American Society for Bone and Mineral Research.

KEY WORDS: OSTEOPOROSIS; DXA; DIABETES; FRACTURE RISK ASSESSMENT; FRAX; TRABECULAR BONE SCORE

Introduction

The World Health Organization (WHO) defines osteoporosis conceptually as a systemic skeletal disease characterized by low bone mass (decreased quantity) and microarchitectural deterioration of bone tissue (decreased quality) with a consequent increase in bone fragility and susceptibility to fracture.[1] Despite the ability of BMD measurements from DXA to stratify fracture risk, it has low sensitivity.[2] In fact, most fractures occur in individuals who do not have a BMD below the threshold for osteoporosis, implying that factors other than BMD influence bone strength and fracture risk.[3,4] This has stimulated the development of risk algorithms that integrate multiple risk factors for fracture, and new techniques for bone quality assessment. The most widely used tool for fracture risk assessment is FRAX (fracture risk assessment tool), developed by the Collaborating Centre for Metabolic Bone Diseases (Sheffield, UK), which is a computer-based algorithm that computes the 10-year probability of major osteoporotic fracture (MOF; hip, clinical spine, forearm, and humerus fracture) and hip fracture (HF) in the presence of competing mortality.[5] Fracture risk is computed from easily assessed clinical risk factors for fracture and (optionally) femoral neck BMD. FRAX is country-specific and is currently calibrated for over 60 countries.[6]

Notwithstanding the strengths of FRAX, concerns have been raised regarding its performance in those with type 2 diabetes, which is not a direct input variable to FRAX.[7] Despite being associated with higher BMD, type 2 diabetes is a risk factor for

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osteoporotic fracture independent of FRAX probability.[8,9] The underlying mechanisms are unclear, but are clearly multifactorial; they include impaired muscle strength and quality, falls, greater skeletal impact forces related to a fall, and alterations in bone strength.[10,11]

The foregoing has given rise to several proposals on how to improve the performance of FRAX for those with type 2 diabetes, but these have not been directly compared.[12] In the current study, we compare several proposed methods directly, using a large clinical registry that includes all DXA tests for the province of Manitoba, Canada.

Subjects and Methods

Study population

We performed a registry-based cohort study to examine MOF and HF outcomes factors among women and men 40 years of age or older who had undergone baseline DXA of the lumbar spine and hip from 1999 to 2016. In the Canadian province of Manitoba, health services are provided to nearly all residents through a single public health care system.[13] For each health system contact, information is recorded to document the patient's demographics, date and type of service, and diagnostic code(s). Hospital discharge abstracts (diagnoses and procedures) are coded using the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) prior to 2004 and the 10th revision of ICD, Canadian version (ICD-10-CA) thereafter. Physician billing claims are coded using ICD-9-CM for all data years as previously described.[14,15] In previous analyses, we saw no evidence that there was any unexpected change in fracture rates straddling the period of transition from ICD-9-CM to ICD-10-CA for hospitalization data, even in the case of HFs, which are identified solely from hospitalization codes.[16] Medication use is obtained from the provincial pharmacy system.[17] DXA testing through the Manitoba Density Program has been managed as an integrated program since 1997.[18] The Manitoba Density Program maintains a database of all DXA results that can be linked with other population-based databases through an anonymous personal identifier. The associated database exceeds 99% in terms of completeness and accuracy.[19] The study was approved by the Research Ethics Board of the University of Manitoba and the Health Information Privacy Committee of Manitoba Health.

Bone densitometry, trabecular bone score, and fracture probability

All spine and hip DXA scans were performed with a fan-beam DXA configuration (Prodigy or iDXA, GE Healthcare, Madison, WI, USA) and analyzed in accordance with manufacturer recommendations. Femoral neck BMD *T*-scores were calculated using the NHANES III white female reference values.[20] The DXA instruments used were cross-calibrated using anthropomorphic phantoms and no clinically significant differences were identified (*T*-score differences <0.1). Short-term reproducibility (coefficient of variation [CV]) for femoral neck BMD from the multiple technologists was 2.3% (over 400 repeat hip DXA scans performed within 28 days).

Among the clinically applicable techniques developed for bone quality assessment, trabecular bone score (TBS) has been the most extensively studied.[21,22] TBS can help enhance fracture prediction when used in conjunction with FRAX probability estimated with BMD.[23] TBS measurements were performed in the Bone Disease Unit at the University of Lausanne, Switzerland (TBS iNsight Software, Version 2.1, Med-Imaps, Merignac, France), using anonymized spine DXA files to ensure blinding of the Swiss investigators to all clinical parameters and outcomes. We excluded women with BMI outside the range of 15 to 37 kg/m2 as recommended by the TBS manufacturer.[22] No significant calibration differences in mean TBS levels were seen for the DXA scanners used. The lumbar spine TBS CV (from multiple technologists) was 2.1% (92 repeat spine DXA scans performed within 28 days).

Ten-year probability of a major fracture and HF with femoral neck BMD was calculated for each subject using the Canadian FRAX tool (FRAX Desktop Multi-Patient Entry, version 3.8). The Canadian FRAX tool was calibrated using nationwide HF and mortality data.[17] The Manitoba BMD Registry was not used in the creation or calibration of the FRAX tool. Weight and height were measured at the time of DXA, and BMI was calculated as weight (in kg) divided by height (m) squared. Prior fracture and other FRAX input variables were assessed using linkage to the population-based research registry that includes hospital discharge abstracts and physician billing claims as previously described.[24] We defined prior fragility fracture as any non-traumatic MOF that occurred before the baseline DXA test, using records back to 1987. We did not include other fracture sites, but note that MOFs represent the majority of fragility fractures (after excluding head/neck, hand/foot, ankle) and are more strongly associated with recurrent fracture than the remaining sites.[25] Prolonged oral corticosteroid use ($>$90 days dispensed in the 1 year prior to DXA) was obtained from the provincial pharmacy system.[17] Parental HF was by self-report from 2005 onwards, and from linkage to parental hospitalization records in earlier years.[26] Current smoking was by self-report from 2005 onwards and from a proxy variable in earlier years (chronic obstructive lung disease codes). High alcohol use was by self-report from 2012 onwards and from a proxy variable in earlier years (alcohol substance abuse codes). FRAX predictions with the Canadian FRAX tool agree with observed fracture probability in this cohort and in the Canadian population (FRAX with BMD area under the curve for MOF prediction $\sim$0.69 and for HF prediction $>$0.80).[24,27]

Diabetes mellitus case definition and risk adjustments

Diabetes diagnosed prior to the baseline DXA was ascertained from the presence of at least two physician billing claims with a diabetes diagnosis within 2 years or at least one hospitalization with a diabetes diagnosis. These definitions have been well-validated in our population and used as the basis for nationwide diabetes surveillance reporting.[28,29] The duration of diabetes was based upon the time since the earliest qualifying ICD-9-CM or ICD-10-CA diagnosis code, and was included in the analysis plan because a longer duration of diabetes has been shown to increase fracture risk and the extent to which FRAX underestimates this risk.[12,30] More than 90% of the cohort had health coverage exceeding 10 years (mean 32 ± 11 years). Individuals with possible type 1 diabetes (diagnosed before age 50 years, insulin-dependent within 2 years of diagnosis, and no use of oral agents) were excluded. Women without diabetes were retained in the analysis as a referent comparison population.

We compared four options to enhance the performance of FRAX in patients with diabetes. First, we used the rheumatoid arthritis (RA) input to FRAX as a proxy for the effect of diabetes;

this is justified by the similar weights accorded RA and type 2 diabetes in the QFracture algorithm.[31,32] Second, we used the TBS adjustment to the FRAX score; this is justified by the observation in several studies that TBS is lower in those with type 2 diabetes than in the general population. [33–37] Initially, the TBS adjustment was applied to patients with diabetes because the TBS adjustment to FRAX was developed and validated for use in the general population; we secondarily considered its effect for the entire population including those without diabetes.[38,39] Third, we reduced the femoral neck *T*-score input to FRAX by 0.5 SD in patients with diabetes; this follows from the observation that a *T*-score in a woman with diabetes mellitus is associated with HF risk equivalent to a woman without diabetes mellitus with a *T*-score of approximately 0.5 units lower.[8] Finally, we increased the age input to FRAX by 10 years in patients with diabetes; this is comparable to the femoral neck BMD loss of 0.5 SD expected over 10 years.

Assessment of incident fractures

Longitudinal health service records were assessed between April 1, 1987 and March 31, 2016 for the presence of fracture not associated with codes indicative of severe trauma (ie, external injury) using validated definitions.[14] Fragility fracture codes were assessed using hospital discharge abstracts (coded ICD-10-CA) and physician billing claims (coded ICD-9-CM) (Supplementary Table 1). Hip and forearm fractures were required to have a site-specific fracture reduction, fixation, or casting code. To minimize misclassification of prevalent and incident fractures at the same skeletal site, we required that there be no hospitalization or physician visit(s) with the same fracture type in the 6 months preceding an incident fracture. There was no time restriction on prior and incident fractures involving different skeletal sites.

Statistical analyses

Statistical analyses were performed with Statistica (Version 13.0, StatSoft Inc., Tulsa, OK, USA). Descriptive statistics for demographic and baseline characteristics are presented as mean ± SD for continuous variables or number (%) for categorical variables. Cox proportional hazards models were used to study time to first fracture, with diabetes as the covariate of interest, controlled for the effect of FRAX probability before and after application of the proposed diabetes adjustments. We initially considered diabetes as a binary variable (present versus absent [referent]) and then stratified according to duration (<5 years, 5 to 10 years, >10 years versus absent [referent]). Unadjusted and adjusted FRAX scores were log-transformed because of a skewed distribution. Reduction in the model χ^2 statistic for diabetes was used as an ancillary measure of attenuation in the diabetes effect with the adjustment being tested. Risk gradients for the various fracture probability measurements were also estimated and are presented as hazard ratio (HR) per SD decrease with 95% CIs. We also computed calibration ratios (observed versus predicted 10-year fracture probability with 95% CI) overall and for the diabetes subgroup. Observed 10-year fracture probability was derived from the cumulative incidence function for MOF and HF up to 10 years incorporating competing mortality risk.[40,41] Observed fracture probabilities were compared with those predicted from the various fracture probability measurements. An optimal method for capturing and accounting for the fracture risk associated with diabetes would result in a HR for diabetes close to unity (~1.00), a negligible model χ^2 statistic for diabetes (~0), and an observed/predicted calibration ratio close to unity (~1.00).

We also examined reclassification rates and categorical net reclassification improvement (NRI) from using the diabetes adjustments applied to FRAX-based probabilities based upon fixed intervention cut-offs as recommended by the National Osteoporosis Foundation (MOF 20% and HF 3%).[42] NRI was computed separately for individuals with and without incident fractures, and for overall reclassification improvement.[43,44] For individuals who sustain a fracture in follow-up, NRI fracture is the probability of moving to a higher FRAX risk category minus the probability of moving to a lower FRAX risk category. Conversely, for individuals who remain fracture-free in follow-up, NRI nonfracture is the probability of moving into a lower FRAX risk category minus the probability of moving into a higher FRAX risk category. Values of NRI fracture and NRI nonfracture >0 indicate an improvement in risk classification, whereas negative values indicate a worse-risk classification. An asymptotic test of significance for the null hypothesis of NRI = 0 based upon the multinomial distribution was performed.[44]

Results

Baseline characteristics are provided in Table 1. The study cohort consisted of 44,543 individuals, with mean age 63.9 ± 11.0 years. There were 40,059 women and 4484 men. Diagnosed diabetes was present in 4136 (9.3%). Individuals with diabetes tended to be older, male, with greater BMI, greater femoral neck *T*-score, lower lumbar spine TBS, and greater fracture probability even prior to application of the proposed adjustments, which further increased mean fracture probability among those with diabetes (Supplementary Table 2). The prevalence of RA was low and similar among those with diabetes and without diabetes (3.0% versus 2.6%, $P = 0.067$).

During an 8.3-year ± 4.7-year observation, one or more incident MOFs were identified in 3946 (8.9%) of the cohort, including 1162 (2.6%) with an incident HF. The prevalence of diabetes was nonsignificantly greater in those with versus without incident MOF (9.8% versus 9.2%, $P = 0.260$), but was significantly greater for incident HF (12.0% versus 9.2%, $P = 0.001$). Older age, lower BMI, prior fracture, lower femoral neck *T*-score, lower lumbar spine TBS, and higher fracture probability were all significantly associated with incident MOFs or incident HFs.

After controlling for the standard unadjusted FRAX probability, diabetes (all durations combined) was associated with a significantly increased risk for incident MOF (HR 1.32; 95% CI, 1.19 to 1.46) and incident HF (HR 1.76; 95% CI, 1.47 to 2.10). Of the four FRAX adjustments evaluated, all attenuated the effect of diabetes (Table 2). However, there was a significant residual effect of diabetes on MOF risk after TBS adjustment, and on HF risk after the RA and TBS adjustments. Stratification by duration of diabetes, controlled for the standard unadjusted FRAX score, demonstrated a gradient of increasing risk with longer duration, statistically significant for MOF in those with duration exceeding 10 years and significant for all durations of HF. The diabetes adjustments attenuated, but did not eliminate the MOF risk associated with diabetes exceeding 10 years. All methods successfully negated the effect of HF risk on duration of diabetes <10 years, but only partially attenuated this for diabetes duration exceeding 10 years. Figure 1 shows the relative

Table 1. Study Population Baseline Characteristics According to Incident Major Osteoporotic Fracture (MOF) or Incident Hip Fracture (HF)

Variable	Overall $N = 44{,}543$	No MOF $N = 40{,}597$	Incident MOF $N = 3946$	p-value	No HF $N = 43{,}381$	Incident HF $N = 1162$	p-value
Age (years)	63.9 ± 11.0	63.4 ± 10.8	68.6 ± 11.0	<0.001	63.6 ± 10.9	73.3 ± 9.5	<0.001
Sex (men)	4484 (10.1)	4166 (10.3)	318 (8.1)	<0.001	4391 (10.1)	93 (8.0)	0.018
BMI (kg/m^2)	26.4 ± 4.4	26.4 ± 4.4	25.8 ± 4.4	<0.001	26.4 ± 4.4	25.1 ± 4.2	<0.001
Prior fracture	6658 (14.9)	5693 (14.0)	965 (24.5)	<0.001	6359 (14.7)	299 (25.7)	<0.001
Femoral neck T-score	−1.4 ± 1.0	−1.3 ± 1.0	−1.9 ± 0.9	<0.001	−1.3 ± 1	−2.2 ± 0.8	<0.001
FRAX 10-year MOF fracture risk (%)[a]	9.5 ± 6.8	9.2 ± 6.5	13.3 ± 8.4	<0.001	9.4 ± 6.7	16.5 ± 8.7	<0.001
FRAX 10-year HF risk (%)[a]	2.2 ± 3.7	2.0 ± 3.5	4.0 ± 4.8	<0.001	2.1 ± 3.6	5.7 ± 5.2	<0.001
Lumbar spine TBS	1.262 ± 0.123	1.267 ± 0.121	1.211 ± 0.125	<0.001	1.264 ± 0.122	1.188 ± 0.121	<0.001
Diabetes	4136 (9.3)	3750 (9.2)	386 (9.8)	0.260	3997 (9.2)	139 (12.0)	0.001

FRAX = fracture risk assessment tool; TBS = trabecular bone score.
[a]FRAX score computed with femoral neck BMD, but without TBS. Data are mean ± SD or N (%).

importance of diabetes in the model, with the model χ^2 for diabetes reduced by over half in all scenarios.

The calibration analysis given in Table 3 shows excellent agreement between observed and predicted MOF in individuals without diabetes (observed/predicted ratio 1.00; 95% CI, 0.97 to 1.04), but slight underestimation in HF risk (ratio 1.17; 95% CI, 1.08 to 1.25). Among those with diabetes, the standard unadjusted FRAX risk significantly underestimated MOF (ratio 1.15; 95% CI, 1.03 to 1.28), but this was no longer significant after applying the diabetes adjustments. HF risk was even more severely underestimated (observed/predicted ratio 1.85; 95% CI, 1.51 to 2.20) and was partially, but not completely corrected with the diabetes adjustments (still significant for the RA and TBS adjustments).

Reclassification statistics are provided in Table 4. Among the diabetes subgroup, there was a moderate amount of reclassification (predominantly upwards) for MOFs based upon a fixed intervention cut-off of 20% (4.1% to 7.1%) and for HFs based upon a fixed intervention cut-off of 3% (5.7% to 16.5%). The improvement in NRI among fracture cases exceeded the reduction in NRI among fracture noncases, resulting in a significant improvement in overall NRI for MOFs with each of the diabetes adjustments (range 3.9% to 5.6% in the diabetes subgroup). There was a numerical increase in NRI for HFs, but this was not statistically significant (range 1.5% to 4.7% among the diabetes subgroup).

The gradient of risk for MOF and HF prediction was not appreciably different when the diabetes adjustment was only performed in individuals with diabetes (Supplementary Table 3). The TBS adjustment to FRAX (but not the other methods) is also applicable to those without diabetes. When applied to the overall population, the TBS adjustment resulted in a small increase in gradient of risk for both MOFs and HFs (Supplementary Table 3), a larger number with risk reclassification (2.8% overall for MOFs and 4.0% overall for HFs), and a larger improvement in NRI for MOFs (3.1%, $P < 0.001$) and for HFs (2.3%, $P = 0.002$) (Supplementary Table 4).

Supplementary Table 5 gives the calibration analyses according to duration of diabetes. The diabetes adjustments tended to overcorrect MOF risk among those with diabetes duration

Table 2. Effect of Diabetes (Hazard Ratio [HR] With 95% Confidence Interval [CI]) on Incident Major Osteoporotic Fracture (MOF) or Incident Hip Fracture (HF) Controlled for Fracture Probability Using Unadjusted FRAX (Referent) and Four Adjustments Applied to Those With Diabetes

	Diabetes, any duration $N = 4136$	Diabetes <5 years $N = 1323$	Diabetes 5–10 years $N = 922$	Diabetes >10 years $N = 1891$
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
MOF prediction, controlled for:				
FRAX MOF unadjusted (referent)	**1.32 (1.19–1.46)**	1.08 (0.89–1.31)	1.24 (1.00–1.55)	**1.54 (1.34–1.78)**
With RA adjustment	1.02 (0.91–1.13)	0.83 (0.69–1.01)	0.96 (0.77–1.20)	**1.19 (1.03–1.37)**
With TBS adjustment	**1.12 (1.01–1.24)**	0.92 (0.76–1.11)	1.05 (0.84–1.31)	**1.31 (1.13–1.51)**
With T-score lowered 0.5 SD	1.08 (0.98–1.21)	0.89 (0.73–1.08)	1.03 (0.82–1.28)	**1.26 (1.09–1.46)**
With age raised 10 years	1.01 (0.91–1.12)	0.82 (0.68–1.00)	0.95 (0.76–1.18)	**1.19 (1.03–1.37)**
HF prediction, controlled for:				
FRAX HF unadjusted (referent)	**1.76 (1.47–2.10)**	**1.41 (1.01–1.97)**	**1.53 (1.05–2.25)**	**2.12 (1.67–2.68)**
With RA adjustment	**1.30 (1.09–1.55)**	1.04 (0.75–1.45)	1.13 (0.77–1.65)	**1.57 (1.25–1.99)**
With TBS adjustment	**1.48 (1.24–1.77)**	1.19 (0.85–1.65)	1.29 (0.88–1.90)	**1.78 (1.41–2.26)**
With T-score lowered 0.5 SD	1.15 (0.96–1.38)	0.92 (0.66–1.28)	1.01 (0.69–1.47)	**1.40 (1.11–1.77)**
With age raised 10 years	1.12 (0.94–1.34)	0.88 (0.63–1.22)	0.99 (0.67–1.44)	**1.37 (1.08–1.73)**

Boldface indicates p-value <0.05.
FRAX = fracture risk assessment tool; MOF = major osteoporotic fracture; RA = rheumatoid arthritis; TBS = trabecular bone score.

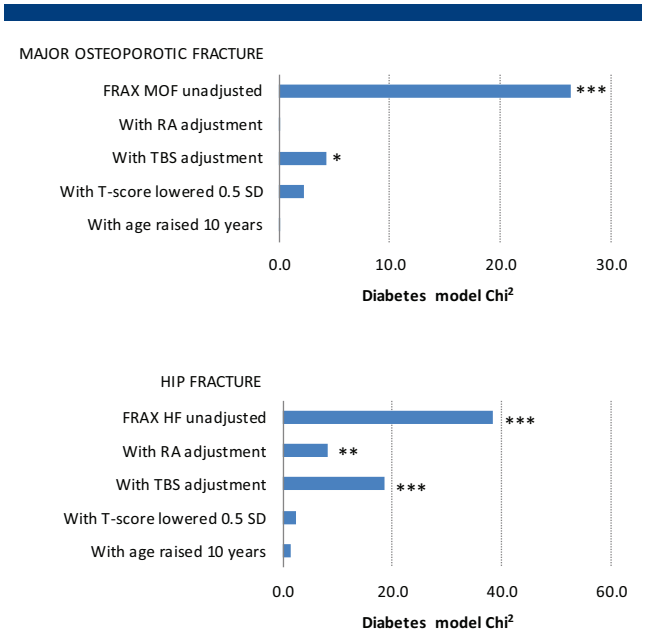

Fig. 1. Diabetes effect (model χ^2) on incident major osteoporotic fracture or incident hip fracture controlled for unadjusted FRAX (fracture risk assessment tool; referent) and after four adjustments applied to those with diabetes. Smaller values are preferred, with zero indicating that the effect of diabetes has been completely captured by the adjustment used. MOF = major osteoporotic fracture; HF = hip fracture; RA = rheumatoid arthritis; TBS = trabecular bone score. $^{*}p$-value < 0.05. $^{**}p$-value < 0.01. $^{***}p$-value < 0.001.

<5 years (nonsignificant for the TBS adjustment). For HFs, all methods showed nonsignificant miscalibration for diabetes duration <10 years, but underestimated risk for those with diabetes duration >10 years (nonsignificant with lowering the femoral neck *T*-score by 0.5).

We performed supplementary analyses to examine for an effect of regular insulin or thiazolidinedione use (medication possession ratio >0.5 in the year prior to BMD testing). After adjusting for the standard unadjusted FRAX score and diabetes (stratified by duration), neither of these had any detectable effect on MOF or HF risk (all *Ps* > 0.4). We also tested for two-way interactions (adjusted for referent FRAX probability) and confirmed that there were no significant differences for diabetes with age, sex, TBS, or BMD (all *Ps* > 0.05).

Discussion

To our knowledge, this is the first study that has directly compared the performance of proposed methods to improve the prediction of fracture risk among individuals with type 2 diabetes when using the FRAX tool. Although individual differences in the performance of these adjustment methods are noted, in general, each approach represented a significant improvement in the performance of FRAX by reducing, or in some cases, eliminating the effect of diabetes on incident MOFs and HFs.

Notably, no single method was optimal for all fracture outcomes and durations of diabetes. Furthermore, only one method (TBS adjustment) can be used in the general population, whereas the others are restricted to use among individuals with diabetes. Therefore, although the TBS adjustment was somewhat less effective in the diabetes subgroup, it had a greater benefit when applied to the overall population that included those without diabetes. Miscalibration (underestimation in risk) has been the primary limitation with using FRAX in those with type 2 diabetes,[8,9] and it follows that this is an important measure to examine in any proposed adjustments. Based upon the calibration ratio (Supplementary Table 5), which considers competing mortality, the TBS adjustment may be preferred for MOFs (nonsignificant miscalibration for all durations of diabetes), whereas lowering the femoral neck *T*-score by 0.5 may be the preferred method for HFs (nonsignificant miscalibration for all durations of diabetes), although the performance of raising age by 10 years was almost equivalent. Using the age adjustment may be less satisfactory in older individuals, however, as the effect of competing mortality may paradoxically reduce fracture probability and could differ between

Table 3. Calibration Ratios for Observed Versus Predicted 10-Year Major Osteoporotic Fracture (MOF) Probability Percent or Hip Fracture (HF) Probability Percent Using Unadjusted FRAX (Referent) and Four Adjustments Applied to Those With Diabetes

	No diabetes $N = 40{,}407$			Diabetes, any duration $N = 4136$		
	Predicted	Observed	Calibration ratio	Predicted	Observed	Calibration ratio
MOF prediction						
FRAX MOF unadjusted	9.5	9.5	1.00 (0.97–1.04)	10.3	11.9	**1.15 (1.03–1.28)**
With RA adjustment				13.1	11.9	0.91 (0.81–1.01)
With TBS adjustment				11.7	11.9	1.02 (0.91–1.12)
With *T*-score lowered 0.5 SD				12.4	11.9	0.96 (0.86–1.06)
With age raised 10 years				12.9	11.9	0.93 (0.83–1.03)
HF prediction						
FRAX HF unadjusted	2.2	2.5	**1.17 (1.08–1.25)**	2.5	4.5	**1.85 (1.51–2.20)**
With RA adjustment				3.4	4.5	**1.35 (1.10–1.60)**
With TBS adjustment				2.8	4.5	**1.63 (1.33–1.93)**
With *T*-score lowered 0.5 SD				3.7	4.5	1.22 (0.99–1.44)
With age raised 10 years				3.7	4.5	1.22 (0.99–1.44)

Boldface indicates *p*-value <0.05. 10-year fracture probability includes competing mortality.
FRAX = fracture risk assessment tool; RA = rheumatoid arthritis; TBS = trabecular bone score.

Table 4. Reclassification and Net Reclassification Improvement (NRI) for Incident Major Osteoporotic Fracture (MOF) or Incident Hip Fracture (HF) Using Four Adjustments Applied to Those With Diabetes (Referent Unadjusted FRAX)

	Reclassified %, total (up, down)	NRI %, fracture cases	NRI %, fracture noncases	NRI %, overall
		MOF 20%		
With RA adjustment	7.1 (7.1, 0.0)	**12.2*****	−**6.5*****	**5.6****
With TBS adjustment	4.1 (3.5, 0.6)	**6.5*****	−**2.5*****	**3.9****
With *T*-score lowered 0.5 SD	6.1 (6.1, 0.0)	**11.1*****	−**5.5*****	**5.6*****
With age raised 10 years	6.7 (6.3, 0.4)	**9.8*****	−**5.4*****	4.4*
		HF 3%		
With RA adjustment	8.4 (8.4, 0.0)	**11.5*****	−**8.3*****	3.2
With TBS adjustment	5.7 (5.2, 0.4)	**7.2****	−**4.7*****	2.5
With *T*-score lowered 0.5 SD	11.5 (11.5, 0.0)	**12.9*****	−**11.4**	1.5
With age raised 10 years	16.5 (16.4, 0.1)	**20.9*****	−**16.2*****	4.7

Analyses limited to the diabetes subgroup. Boldface indicates p-value <0.05.
RA = rheumatoid arthritis; TBS = trabecular bone score.
$^{*}p$-value <0.05. $^{**}p$-value <0.01. $^{***}p$-value <0.001.

populations because FRAX incorporates population-specific mortality data. Lower TBS is associated with increased mortality, and likely explains why the TBS adjustment gave accurate calibration for diabetes (any duration) from 10-year fracture probability that includes competing mortality, whereas there was a significantly increased HR for diabetes from the Cox regression model.[39] Conversely, the RA adjustment was quite effective for both MOFs and HFs at attenuating the effect of diabetes. Additional clinical considerations are the ease with which a method can be applied, availability of the TBS software, and prevalence of RA in the population (because this can only be applied when RA and diabetes do not coexist in the same individual). The data reported here may help to inform future position statements and practice guidelines aimed at enhancing the care of diabetic patients.

Limitations of this analysis are acknowledged. The clinical source of the study cohort is recognized, and referred individuals are likely to be at higher perceived risk of osteoporosis and fracture. This is particularly likely to affect the referral of men for BMD testing. However, because we included all individuals within the geographic region referred for BMD testing, our results are likely to be broadly generalizable to postmenopausal women and older men who are referred for BMD testing. Our study cohort was 98% Caucasian and underpowered to examine the effect of race/ethnicity; other cohorts should be required to address this question. Although we did not have access to x-rays to confirm fractures, particularly vertebral fractures, the definitions for fracture used have been validated and adopted for the national surveillance of osteoporosis and related fractures.[14,15] The definitive differentiation of type 1 and type 2 diabetes within administrative data is not possible, but excluding those with diabetes who were insulin-dependent, diagnosed before age 50 years, and had never used an oral antidiabetes agent would remove almost all individuals with type 1 diabetes. Importantly, none of the methods we tested have been proposed for use in type 1 diabetes, which differs in terms of pathophysiology and fracture risk, particularly for HFs, which is much higher in type 1 diabetes.[45,46]

In conclusion, each of the proposed methods for addressing limitations in the ability of FRAX to assess fracture risk in individuals with type 2 diabetes was found to improve performance. No single method was optimal in all settings, however. Ultimately, incorporating diabetes directly into FRAX would likely be the preferred method, though there are challenges to implementing this approach.[7] Meanwhile, clinical practitioners can choose from among these currently available options to enhance the performance of FRAX.

Disclosures

WDL and HJ declare that they have no conflict of interest. EM has nothing to declare for FRAX and the context of this paper, but has had numerous ad hoc consultancies/speaking honoraria and/or research funding from Amgen, Bayer, General Electric, GSK, Hologic, Lilly, Merck Research Labs, Novartis, Novo Nordisk, Nycomed, Ono, Pfizer, ProStrakan, Roche, Sanofi-Aventis, Servier, Tethys, UBS, and Warner-Chilcott. NH has nothing to declare for FRAX and the context of this paper, but has received consultancy, lecture fees, and honoraria from Alliance for Better Bone Health, AMGEN, MSD, Eli Lilly, Servier, Shire, UCB, Radius, Consilient Healthcare, and Internis Pharma. JAK has received grants from Amgen and Lilly, nonfinancial support from Medimaps, grants from Unigene, nonfinancial support from Asahi, and grants from Radius Health, outside the submitted work. JAK is the architect of FRAX, but has no financial interest. JAK has also received support from the National Institute for Health and Clinical Excellence (NICE), UK; the International Osteoporosis Foundation; INSERM, France; the Ministry of Public Health, China; the Ministry of Health, Australia; the Ministry of Health, Abu Dhabi; National Osteoporosis Guideline Group, UK; and WHO. DH has co-ownership of the TBS patent, stock options or royalties from Med-Imaps, and research grants from Amgen, Radius Pharma, Agnovos, and GE Healthcare.

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