

Comparison of FRAX in postmenopausal Asian women with and without type 2 diabetes mellitus: a retrospective observational study

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Abstract

Objective: To compare the fracture risk in postmenopausal Asian women with or without type 2 diabetes mellitus (T2DM).

Methods: The study cohort comprised data from consecutive postmenopausal women with T2DM that were retrieved from a prospectively maintained institutional database from 2001 to 2009. Postmenopausal women without DM from the Medical Examination Center from 2001 to 2009 formed the control cohort. The primary endpoint was the World Health Organization Fracture Risk Algorithm (FRAX, revised 2013) score. The secondary endpoint was bone mineral density (BMD).

Results: There were 1014 individuals included for the assessment (T2DM, n=500 and non-DM, n=514). Based on the FRAX model, the risk of major osteoporotic fractures and hip fractures over the next 10 years was higher in the T2DM group compared with the non-DM group. Compared with the T2DM group, the non-DM group had a lower BMD. After adjusting for age, gender, history of alcohol consumption, smoking status, body mass index, and low-density lipoprotein, the differences were statistically significant.

Conclusions: Compared with postmenopausal women without DM, postmenopausal women with T2DM had a significantly higher fracture risk calculated using the FRAX model. Early intervention for postmenopausal women with T2DM may be necessary, although T2DM is associated with a high BMD.

Keywords

Diabetes mellitus, fracture risk assessment tool, bone mineral density, postmenopausal, osteoporotic fracture, FRAX, osteoporosis, hip fracture

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Introduction

Type 2 diabetes mellitus (T2DM) tends to be associated with higher bone mineral density (BMD) and, illogically, with an increase in bone fragility.¹⁻³ It is increasingly recognized that postmenopausal women with T2DM have a high fracture risk that is associated with osteoporosis^{1,4} and that previously established methods for predicting fracture events can be very variable in patients with T2DM because a higher BMD is associated with increased fracture events in these patients.⁵ Conceptually, osteoporosis is defined as a systemic skeletal disease that is characterized by bone mass impairment and micro-architectural deterioration

of bone tissue with a consequent decrease in bone strength and susceptibility to fracture.^{1,6,7} With an aging population, the incidence of osteoporotic fractures in postmenopausal women is higher than that in the non-DM population, which is the main cause of long-term severe pain and/or dysfunction and it seriously affects patients' quality of life.⁸ Therefore, preventive identification and prompt intervention for the risk of osteoporotic fracture in these patients are needed.

Although BMD measured by dual-energy X-ray absorptiometry (DXA) is the foremost determinant of bone strength and fracture risk, BMD values in many patients with fragility fractures tend to be in the

osteopenic or even normal range.^{1,9,10} Multiple studies have also shown that BMD in T2DM patients is higher than that in non-DM individuals of the same age and gender, which does not seem to explain the increased risk of fracture.^{1,4,11} BMD can only reflect 70% of the bone strength and it ignores the risk factors for osteoporosis, such as gender, age, previous fracture history, and smoking history, although studies have consistently demonstrated BMD to be associated with fracture risk.^{1,8} Additionally, previous studies have shown that some patients did not meet the diagnostic criteria of osteoporosis but still had osteoporotic fractures.^{12,13} Consequently, some factors other than BMD (age, bone mineralization, bone microdamage, bone turnover, and fracture history) that are captured by the Fracture Risk Algorithm (FRAX) contribute to the overall assessment of fracture risk.^{6,10} However, the FRAX model estimating the 10-year probability of hip and major osteoporotic fracture, which is based on the individual risk factor profile, fails to capture all skeletal determinants of bone strength that tend to be independent of BMD.^{6,11}

A consideration of the manner whereby FRAX-generated probabilities should warrant intervention, both for an intervention threshold and for an assessment threshold, is necessary for the application of the FRAX model in clinical decision making.^{6,13} To overcome specific limitations of FRAX, relatively straightforward arithmetic procedures have been applied to conventional FRAX estimates of fracture probabilities to adjust the probability assessment (e.g. information on trabecular bone score [TBS], hip structural analysis [HSA], concurrent data on lumbar spine BMD, and high moderate and low exposure to glucocorticoids).² Currently, no guidelines for the prediction or assessment of fracture probabilities in postmenopausal women with T2DM have been reported.

In our study, the FRAX model (revised 2013) was applied to compare the risk of fractures between T2DM and non-DM postmenopausal women over the next 10 years to verify the effectiveness of the FRAX model in estimating the 10-year probability of hip and major osteoporotic fractures in postmenopausal women with T2DM. To the best of our knowledge, previous studies do not appear to be available on fracture prediction in postmenopausal women with T2DM using BMD, although preliminary data have demonstrated an incremental improvement in fracture prediction when BMD is used in combination with other risk factors.⁶ Additionally, there is no FRAX model that is currently available in a Chinese clinical setting, mainly because of significant differences in fracture rates that are described among the different studies.^{1,7,11}

Methods

Study population

This study was reviewed and approved by the review board at Pu'ai Hospital, Tongji Medical College, Huazhong University of Science and Technology. Consent to participate was not applicable because this was a retrospective study, and an exemption was obtained from the Investigational Ethical Review Board. All clinical investigations were conducted in accordance with the Declaration of Helsinki. Individual-level data regarding the general condition of postmenopausal women with T2DM from February 1, 2001 to February 28, 2009 were retrieved from a prospectively maintained institutional database with adjudicated fracture outcomes, and these patients formed the study cohort (the T2DM group). The data with adjudicated fracture outcomes regarding postmenopausal women without DM who underwent a physical examination at the Medical

Examination Center, Pu'ai Hospital, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China) from February 1, 2001 to February 28, 2009 formed the control cohort (the non-DM group). Women had a postmenopausal status based on the Straw classification.¹⁴ The main inclusion criteria were as follows: women ≥ 55 years old; women with a clinically confirmed diagnosis of T2DM or women without DM; and women with T2DM who were treated with antihyperglycemic medications (e.g., metformin, glimepiride, pioglitazone, acarbose, and/or insulin). The main exclusion criteria were as follows: premature menopause (< 45 years old); poor medical data with regard to the FRAX risk factors; repeat admissions for the same fracture; a history of tumor; women with pituitary, thyroid, parathyroid, adrenal, or gonadal diseases; serious infections; organ failure; severe circulatory or metabolic diseases; long-term use of calcium, vitamin D, or other drugs that affect bone metabolism or that are associated with increased fracture risk; a history of drug or alcohol abuse; a New York Heart Association classification of 3,¹⁵ or vascular cognitive impairment (VCI), as reported previously.¹⁶ The primary endpoint was FRAX fracture risk. The secondary endpoint was BMD.

Outcomes and assessments

According to the 2012 American Diabetes Association (ADA) definition,¹⁷ the diagnostic criteria for DM and impaired glucose regulation (IGR) include the following: patients with typical hyperglycemia or hyperglycemic crisis, with random blood glucose ≥ 200 mg/dL (11.1 mmol/L); women with fasting blood glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L); oral glucose tolerance test (OGTT) 2-h results of blood glucose ≥ 200 mg/dL (11.1 mmol/L); or hemoglobin A1c (HbA1c) $\geq 6.5\%$. If there

was no definite hyperglycemia, the test was repeated to verify the results. DXA examination was performed using a Discovery type A dual-energy X-ray bone density analyzer (CV $< 1\%$) (Hologic, Bedford, MA, USA). The DXA measurements included the lumbar spine (L1–L4) and bilateral proximal femur (total hip, femoral neck).

Osteoporosis was diagnosed based on the WHO criteria for osteoporosis diagnosis (1994 version), as follows:^{18,19} T value ≤ -2.5 for osteoporosis; $-2.5 < T \text{ value} < 1$ for bone mass reduction; T value ≥ -1 for normal bone mass (of which the Z-value evaluation was applied to postmenopausal women, and the diagnostic standard was the same as the T value). Major osteoporotic fractures were defined as clinical spine, hip, forearm, and humeral fractures.¹¹ Fractures were calculated based on radiograph confirmation. Glucose and lipid metabolism indicators were collected, including FPG, total cholesterol (TC), triacylglycerol (TG), HDL cholesterol (HDL-c), and LDL cholesterol (LDL-c).

The collection of fracture risk factors involved in the FRAX model was based on the previous description.^{9,11} The WHO 10-year absolute risk of hip and osteoporotic fracture (FRAX scores) was calculated based on the Chinese FRAX model⁶ (a computer-based algorithm), which is available online at the Web site <http://www.shef.ac.uk/FRAX>. A uniform survey form was used to inquire about and document the fracture risk factors that are involved in the FRAX model, including age, BMD T score, height, weight, BMI, previous history of brittle fracture, parental history of fracture, oral history of adrenal corticosteroids, current smoking status, drinking more than three alcoholic beverages per day, a history of rheumatoid arthritis, and diseases closely related to osteoporosis (including type 1 DM, adult osteogenesis immaturity, long-term treatment-naive hyperthyroidism, hypogonadism or premature menopause,

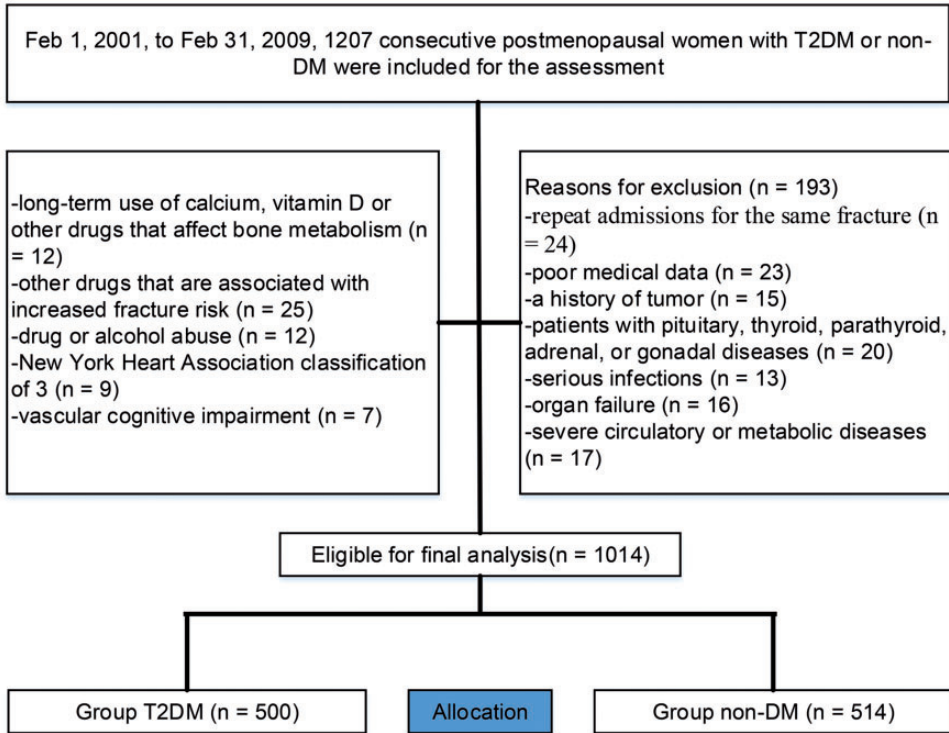


Figure 1. Flow diagram demonstrating the methods for identifying studies to compare the fracture risk in postmenopausal Asian women with type 2 diabetes mellitus (T2DM) or without diabetes mellitus (DM).

chronic malnutrition or malabsorption, and chronic liver disease).¹⁰ A sensitivity analysis was performed to exclude patients, and the results were consistent with previous reports.^{9,20}

Statistical Analysis

Variables were compared using the chi-squared test for categorical variables and the Mann–Whitney U test for continuous variables. In the univariate and multivariate analyses, hazard ratios (HRs) and appropriate 95% confidence intervals (CIs) were calculated using a logistic regression model and a Cox proportional hazard model, respectively. Interactions of the T score with age in patients with T2DM were assessed. All statistical tests were

two-sided, and the significance level was set at 0.05. Ten-year cumulative risks were estimated using the Cox proportional hazards regression model baseline survival function, which was evaluated at 10 years, raised to the power of the relative hazard. Patient-related data extracted from a prospectively maintained database were initially stored in Excel software and subsequently analyzed using SPSS software, v 24.0 (IBM Corp., Armonk, NY, USA).

Results

Comparison of baseline data

Overall, 1207 individuals were enrolled in the study, 193 of whom were considered

Table 1. Demographic and baseline characteristics between groups.

Variable	T2DM (n=500)	Non-DM (n=514)	p-value
Age (years)	68.7±13.5	68.5±12.7	0.214
Menopause age (years)	50.2±2.2	50.6±2.7	0.107
Age structure, n (%) (years)			0.095
55–59	152 (30.4)	143 (27.8)	
60–69	197 (39.4)	189 (36.8)	
70–79	102 (20.4)	117 (22.8)	
80–89	49 (9.8)	65 (12.6)	
Height (cm)	162.1±7.3	162.3±6.8	0.335
Weight (kg)	67.4±9.3	67.6±8.8	0.126
BMI (kg/m ²)	23.5±2.4	23.3±2.8	0.251
FPG (mmol/L)	8.6±2.1	4.5±1.1	0.001*
HbA1c, % (mean, range)	7.7 (6.1–9.4)	4.7 (4.3–5.8)	0.031*
Blood lipid			
TC	4.3±0.7	4.8±1.4	0.013*
TG	1.8±1.3	1.8±0.8	0.274
HDL-c (mmol/L)	1.2±1.1	1.4±0.7	0.038*
LDL-c (mmol/L)	2.7±0.5	2.4±0.4	0.003*
Time from diagnosis of T2DM (months), n (%)			0.054
<6	135 (27.0)	126 (24.5)	
6–12	215 (43.0)	200 (38.9)	
>12	150 (30.0)	188 (36.6)	
Smoking status			0.149
Never a smoker	387 (77.4)	380 (73.9)	
Former smokers	78 (15.6)	82 (16.0)	
Current smokers	35 (7.0)	52 (10.1)	
Alcohol consumption, n (%)			0.994
Never	15 (3.0)	17 (3.3)	
Former	344 (68.8)	351 (68.3)	
Current (3 ≥units/day)	141 (28.2)	146 (28.4)	
Parental fractured hip, n (%)	10 (2.0)	10 (1.9)	0.950

*Statistically significant values.

T2DM, type 2 diabetes mellitus; non-DM, non-diabetes mellitus; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; TC, total cholesterol; TG, Total triglyceride; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol.

to be ineligible based on the exclusion criteria, and 1014 patients (T2DM, n=500, mean age, 68.7 years [standard deviation (SD) 13.5] and non-DM, n=514, 68.5 years [SD 12.7]) were eligible to be included in the study (Figure 1), suggesting that there was no bias in data availability between the groups. At the time of our analyses, patient demographics and other characteristics of the individuals with available data, which were used for validation, are summarized

in Table 1. There were statistically significant differences in FPG, HbA1c, TC, HDL-c, and LDL-c between the groups. Considering that bone metabolism is greatly influenced by age, patients were divided into four groups based on age for comparative analysis. In this study, the non-DM group was collected from a physical examination cohort, and there were no individuals over 90 years old, so this group was

Table 2. The complete distribution of FRAX clinical risk factors.

	T2DM (n=500)				Non-DM (n=514)			
	50–59 (n = 152)	60–69 (n = 197)	70–79 (n = 102)	80–89 (n = 49)	50–59 (n = 143)	60–69 (n = 189)	70–79 (n = 117)	80–89 (n = 65)
BMD (%)	45.0	34.0	25.0	23.0	36.0	44.0	14.0	16.0
BMI (%)	10.0	8.0	13.0	21.0	11.0	2.0	6.0	22.0
Previous fracture (%)	61.0	47.0	51.0	45.0	53.0	33.0	43.0	54.0
Parental hip fracture (%)	18.0	6.0	5.0	14.0	16.0	3.0	3.0	3.0
Corticotherapy (%)	6.4	15.0	16.0	7.0	5.0	7.0	16.0	11.0
RA (%)	0.0	2.0	5.0	0.0	0.0	4.0	4.0	0.0
Alcohol (%)	47.0	36.0	11.0	6.0	35.0	332.0	15.0	2.0
Tobacco(%)	46.0	45.0	21.0	6.0	43.0	41.0	33.0	7.0

T2DM, type 2 diabetes mellitus; non-DM, non-diabetes mellitus; BMD, bone mineral density; BMI, body mass index; RA, rheumatoid arthritis.

combined with patients aged 80 to 89 years for analysis. The complete distribution of FRAX clinical risk factors is showed in Table 2.

Comparison of fracture risk

Among 500 postmenopausal women with T2DM, 65 had a hip fracture and 163 had an osteoporotic fracture during a mean (SD) follow-up of 14.2 (6.8) years. Among 514 postmenopausal women without DM, 31 had a hip fracture, and 72 had an osteoporotic fracture during a mean (SD) follow-up of 14.4 (7.8) years. The risk of hip fractures and major osteoporotic fractures over the next 10 years was assessed based on the FRAX model. The risk of hip fracture was higher in the T2DM group compared with the non-DM group (HR 1.722, 95% CI 1.582–1.903; $P=0.002$) (Figure 2). The risk for major osteoporotic fractures was higher in the T2DM group compared with the non-DM group (HR 1.371, 95% CI 1.120–1.864; $P=0.015$) (Figure 3). In different age groups, patients with T2DM, based on the FRAX model, had a higher risk of hip fractures and major osteoporotic fractures in the next 10 years compared with patients in the non-

DM group. For these types of fractures, the risk of fracture increases with age. Additionally, this trend was significant for the risk of major osteoporotic fractures, especially in the group aged 60 years or older.

Comparison of BMD

The differences in BMD corresponded to an HR of 1.463 (95% CI 1.103–1.917; $P=0.024$) for the femoral neck, 1.572 (95% CI 1.201–2.136; $P=0.033$) for the total hip, and 1.303 (95% CI 1.124–1.567; $P=0.016$) for lumbar vertebrae 1 to 4 (Table 3). BMD in the T2DM group was higher than that in the non-DM group, especially in individuals aged 80 to 89 years. There were significantly more individuals with bone mass reduction in the T2DM group compared with the non-TD group (154 [95% CI, 101.3–182.7] vs. 89 [95% CI, 73.5–122.4]; HR 1.573, 95% CI 1.313–1.839; $P=0.021$). The risk of bone mass reduction in patients with T2DM was further analyzed using the logistic regression model (Table 4), which showed that the risk of bone mass reduction in the T2DM group was similar to that in the non-DM group (OR = 0.748, $P=0.237$). After

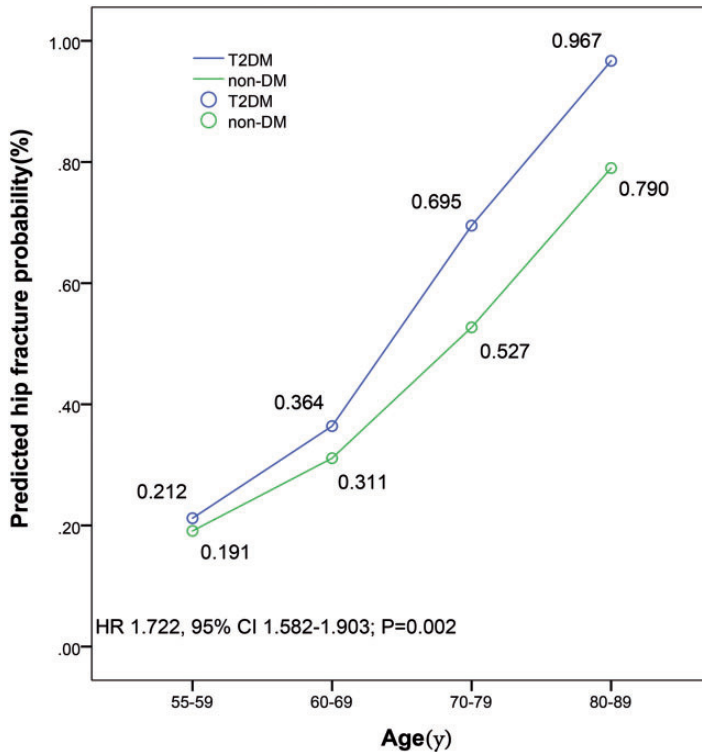


Figure 2. Comparison of the FRAX fracture risk in predicted hip fracture probability between groups. Ten-year probability of a predicted hip fracture in Asian postmenopausal women with type 2 diabetes mellitus (T2DM). The risk of hip fracture is higher in the T2DM group compared with the non-DM group (HR 1.722, 95% CI 1.582–1.903; P=0.002). FRAX, Fracture Risk Assessment Tool; T2DM, type 2 diabetes mellitus; non-DM, non-diabetes mellitus; HR, Hazard ratio; CI, Confidence interval.

adjusting for age, the results were OR = 0.655 and P = 0.004; after further adjustment for alcohol consumption, smoking status, and BMI, the results were OR = 0.811 and P = 0.002. After adjusting for LDL-c, the results were OR = 0.872 and P = 0.003. The differences were statistically significant for each adjustment.

Discussion

Our study demonstrates that compared with postmenopausal women without DM, postmenopausal women with T2DM had significantly higher fracture risk, as calculated using the FRAX model.

The applicability of the FRAX model in the clinical setting tends to be positive, which is consistent with previous studies involving postmenopausal women with T2DM.^{21–24} Although the fracture probability can be underestimated in the FRAX model, particularly for hip fractures because treatment effects were not included in the model, it is commonly accepted as a way of characterizing discriminatory models and as a good predictive tool in postmenopausal women with T2DM. This may be related to the contribution of treatment-induced changes in BMD.^{1,20} Additionally, although it may be influenced by the distribution of risk factors in

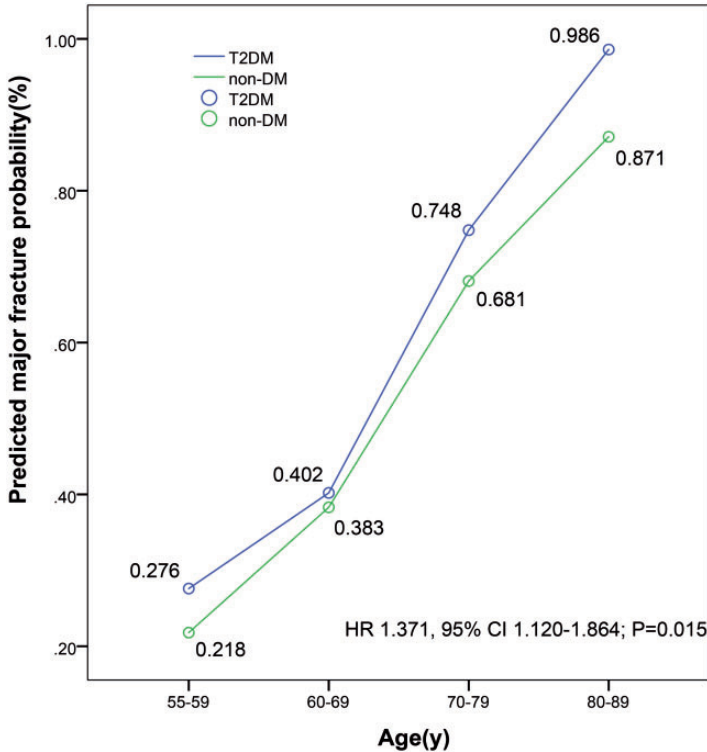


Figure 3. Comparison of the FRAX fracture risk in predicted major fracture probability between groups. Ten-year probability of a predicted major fracture in Asian postmenopausal women with type 2 diabetes mellitus (T2DM). The risk of hip fracture is higher in the T2DM group than in the non-DM group (HR 1.371, 95% CI 1.120–1.864; $P=0.015$). FRAX, Fracture Risk Assessment Tool; T2DM, type 2 diabetes mellitus; non-DM, non-diabetes mellitus; HR, Hazard ratio; CI, Confidence interval.

dissimilar populations, the fracture risk can change frequently based on the timeframe or it can remain consistent across studies.^{9,10} A lack of appreciation of these facts can result in a faulty comparison among predictive tools across study populations.⁶

Our findings are consistent with those of previous studies.^{1,23–25} Whereas previous studies did not focus on the differences in the study population with T2DM, such as estrogen interference, our study provides an independent analysis of a postmenopausal cohort. With the increasing prevalence of T2DM and osteoporosis, the relationship between T2DM and bone metabolism has

increasingly become the focus of research.^{2,4} Metabolic disorders induced by T2DM tend to affect bone metabolism in different ways.^{4,26} However, there is no consensus about the changes in BMD in patients with T2DM.²⁷ An association between BMD and the fracture risk in T2DM failed to be detected.^{1,27} Additionally, the relationship between BMD and fracture risk in T2DM was not completely consistent because of the study design, measurement method, case selection, diabetes complications, and other problems.^{28,29} Currently, several studies have shown that T2DM patients with poor blood glucose control have higher

Table 3. Comparison of BMD between groups.

BMD (g/cm ²)	T2DM (n=500)	non-DM (n=514)	p-value
Femoral neck			
55–59	0.71 ± 0.11	0.70 ± 0.16	0.052
60–69	0.69 ± 0.08	0.64 ± 0.13	0.026*
70–79	0.65 ± 0.08	0.60 ± 0.12	0.033*
80–89	0.61 ± 0.09	0.53 ± 0.14	0.011*
55–89	0.67 ± 0.12	0.62 ± 0.17	0.024*
Total hip			
55–59	0.98 ± 0.15	0.94 ± 0.13	0.023*
60–69	0.95 ± 0.14	0.93 ± 0.11	0.041*
70–79	0.90 ± 0.12	0.86 ± 0.10	0.025*
80–89	0.82 ± 0.13	0.77 ± 0.08	0.014*
55–89	0.92 ± 0.16	0.89 ± 0.14	0.033*
Lumbar 1–4			
55–59	1.03 ± 0.09	1.01 ± 0.12	0.043*
60–69	0.97 ± 0.08	0.92 ± 0.13	0.021*
70–79	0.90 ± 0.11	0.84 ± 0.15	0.013*
80–89	0.82 ± 0.03	0.77 ± 0.05	0.017*
55–89	0.95 ± 0.15	0.90 ± 0.18	0.016*

*Statistically significant values.

T2DM, type 2 diabetes mellitus; non-DM, non-diabetes mellitus; BMD, bone mineral density.

BMD compared with T2DM patients with good blood glucose control.^{28,30–32} Potential explanations for the worse-than-expected BMD performance could be the choice of the study population or that understanding of how estrogen affects BMD should not be ignored. Regardless of the patient's BMI, the power to draw dependable conclusions may be reduced because several studies have shown a positive correlation between BMI and BMD.^{28,31,32} Although the effects of estrogen on BMD are not yet acknowledged,^{33,34} a significant effect of estrogen on BMD was of interest in the early stages of T2DM and it showed little effect thereafter.³⁴ An interaction in the early stages of T2DM appeared to be associated with superior BMD benefit in patients, in whom insulin resistance and hyperinsulinemia may be common.^{29,35} The mechanisms underlying

Table 4. The risk of bone mass reduction for T2DM patients.

Factors	OR (95%CI)	P-value
Crude	0.748 (0.693–1.216)	0.237
Model 1 ^a	0.655 (0.531–0.857)	0.004*
Model 2 ^b	0.811 (0.714–0.922)	0.002*
Model 3 ^c	0.872 (0.785–0.916)	0.003*

*Statistically significant values. T2DM, type 2 diabetes mellitus

^aAdjusted for age

^bFurther adjustment for drinking, smoking status and body mass index (BMI)

^cFurther adjustment for low-density lipoprotein cholesterol (LDL-c).

the relationship between LDL and bone loss have not been fully elucidated.³⁶ The LDL receptor-related protein 5 (LRP5) is considered to be a candidate susceptibility gene for osteoporosis that regulates BMD and/or fracture risk in the general population.^{36,37} LRP5 loss-of-function mutations, which were associated with impaired insulin sensitivity and dysregulated lipid metabolism, have been shown to lead to extreme osteoporosis.³⁶

Frequent debate occurs about the group of postmenopausal women who tend to have an increased risk of fracture, especially hip fracture. BMD was consistently an independent contributor to the assessment of fracture risk.^{1,36,37} Previous studies have shown that although BMD increases in patients with T2DM, the probability of osteoporotic fractures increases.^{1,38} Additionally, osteoporotic fractures tend to occur in some T2DM patients without reaching the diagnostic criteria of osteoporosis, indicating that BMD does not accurately reflect the risk of fractures in these cases.^{4,39} Considering the high disability and mortality rates of osteoporosis, the FRAX model was recommended by the WHO in 2008.¹¹ Currently, no guidelines have been proposed for the prediction or assessment of fracture risk in

postmenopausal women with T2DM,^{6,38} and the application of the FRAX model in the assessment of fracture risk in the cohort has been reported less frequently.¹¹ Schwartz et al.¹ found that in patients with T2DM, both femoral neck T-value and FRAX score are associated with the risk of hip and non-hip fractures, but these patients actually have a higher risk of fracture for the same femoral neck T-value and FRAX score. Although the ability of the FRAX score to predict fracture is undeniable, the FRAX score underestimates the fracture risk in T2DM patients compared with the actual risk of major osteoporotic fractures and hip fractures that are observed.^{1,40} Bridges et al.⁴⁰ reported 770 women with T2DM who had brittle fractures and found that 39.1% (770/1969) of participants were determined to have a low risk of fracture based on the FRAX model (HRs for a one-unit increase in FRAX score, 1.05; 95% CI, 1.03–1.07), suggesting that the FRAX score may underestimate the fracture risk of participants with T2DM. A multicentric cross-sectional study by Carnevale et al.²² showed that DM had a significantly lower FRAX-estimated probability of both major osteoporotic fracture and hip fracture compared with control subjects ($6.35 \pm 5.07\%$ vs. $7.75 \pm 6.93\%$, $p < 0.001$, and $2.17 \pm 3.07\%$ vs. $2.91 \pm 4.56\%$, $p = 0.023$, respectively).

As predicted, according to the FRAX model, the risk of major osteoporotic fractures and hip fractures in the T2DM cohort in the next 10 years was higher compared with the non-DM cohort. Additionally, in previous cohort studies, fracture risk was higher in patients with T2DM compared with non-DM individuals.^{1,7} Although the FRAX model can estimate the risk of major osteoporotic fractures and hip fractures in the next 10 years in patients with T2DM, there is a concern that the model for predicting fracture risk might be performed inadequately in patients with T2DM. This

may be related to some of the risk factors in the FRAX model (e.g., smoking, which is less common in patients with T2DM) and to other common risk factors in the cohort (e.g., falls), which are not included in the FRAX model. It is also suggested that the FRAX model should be further improved to evaluate the risk of major osteoporotic fractures and hip fractures in the next 10 years.

Some limitations should be acknowledged in the present study. First, the retrospective nature of this study has inherent limitations and potential confounding variables (i.e., underlying diseases) that were not addressed. Additionally, because this is a descriptive study with a lack of follow-up data, it is impossible to analyze the time variable and the power tends may be underestimated. Second, generalizability is lacking because our study population included only postmenopausal women. Third, our data were gathered from several institutions, where differences in the number of diagnostic procedures could introduce statistical errors. However, these data were merged based on standardized methods, which, to some extent, provides reliability.

In conclusion, the results reported here provide additional evidence that postmenopausal women with T2DM had a significantly higher fracture risk compared with postmenopausal women without DM, as calculated using the FRAX model, and that application of this model in these patients requires further improvement. Some variables, such as HbA1c, the number of hypoglycemic seizures and diabetes complications, should be considered in future studies.

Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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