



# Incident Fracture Risk in Type 2 Diabetic Postmenopausal Women in Mainland China: Peking Vertebral Fracture Study

Ruizhi Jiajue<sup>1</sup> · Xuan Qi<sup>1</sup> · Yan Jiang<sup>1</sup> · Qiuping Wang<sup>2</sup> · Wenbo Wang<sup>3</sup> · Yu Pei<sup>4</sup> · Xiran Wang<sup>5</sup> · Wei Huang<sup>6</sup> · Xin Zheng<sup>7</sup> · Zhiwei Ning<sup>8</sup> · Ou Wang<sup>1</sup> · Mei Li<sup>1</sup> · Xiaoping Xing<sup>1</sup> · Wei Yu<sup>9</sup> · Ling Xu<sup>10</sup> · Weibo Xia<sup>1</sup>

Received: 10 May 2019 / Accepted: 10 August 2019 / Published online: 27 August 2019  
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## Abstract

Using data from the Peking Vertebral Fracture Study, we conducted a longitudinal cohort study to investigate the association between type 2 diabetes mellitus (T2DM) and the risk of incident fractures, especially of vertebral fractures (VFs), and we also examined the modifying effect of body mass index (BMI) on this association and the effect of bone mineral density (BMD) *T*-score as a risk factor for incident fractures in T2DM. Chinese postmenopausal women were enrolled ( $n=982$ ), among whom 186 had T2DM. Incident VFs were confirmed by lateral radiographs of the thoracolumbar spine (T4–L5), while incident clinical non-VFs were self-reported. BMDs at the lumbar spine (LS) and femoral neck (FN) were measured by dual-energy X-ray absorptiometry. T2DM and non-DM women were at similar risk for VFs (OR 0.74, 95% CI 0.32–1.74), even adjusting for age, BMI, BMD, and previous fractures. Meanwhile, T2DM women had nearly twice the risk for non-VFs (HR 1.95, 95% CI 1.11–3.35) compared with non-DM women. After stratifying by BMI, the risk of VFs remained similar between diabetics and non-diabetics despite their BMI status ( $p$  for interaction = 0.470), and the risk of non-VFs was positively associated with T2DM only in women with BMI  $\geq 25$  kg/m<sup>2</sup> (HR 3.59, 95% CI 1.68–7.65) ( $p$  for interaction = 0.065). Although LS BMD *T*-score was similarly and negatively associated with incident VFs both in T2DM (OR 0.34, 95% CI 0.12–0.88) and non-DM women (OR 0.60, 95% CI 0.44–0.82) ( $p$  for interaction = 0.430), the FN BMD *T*-score was not found to be significantly associated with either non-VFs or VFs among T2DM women. Comparing T2DM and non-DM women with similar fracture risks, the mean difference in LS *T*-score was  $-0.36$  (95% CI  $-1.77$  to  $1.04$ ) for VF, and difference in FN *T*-score was  $1.61$  (95% CI  $-0.11$  to  $3.34$ ) for non-VF. In conclusion, Chinese postmenopausal women with T2DM had a similar risk of incident VFs, but a significantly higher risk of incident non-VF, compared to women without DM. Higher BMI did not modify the effect of T2DM on risk of VFs, but it increased the association between T2DM and risk of non-VFs. LS BMD *T*-score was similarly and negatively associated with VF risk in T2DM and non-DM women and appear to be useful for clinical evaluation of VF risk.

**Keywords** Type 2 diabetes mellitus · Vertebral fractures · Bone mineral density · Body mass index · Peking vertebral fracture stud

## Introduction

Numerous epidemiological studies have confirmed that type 2 diabetes mellitus (T2DM) is associated with an increased risk of fractures [1–17]. Nevertheless, studies conducted among the Chinese population are rare [6–8]. Chinese people with T2DM have different clinical features from Caucasians, with most having normal weight, a lower prevalence

of abdominal obesity, and lower insulin secretion and sensitivity [18–20]. Therefore, it is possible that the association between T2DM and fractures in the Chinese population is different from that in the Caucasian population. However, the few previous studies performed using Chinese subjects are limited by several factors, including reporting only a single type of fracture [8], cross-sectional study design [6], ignoring important confounders, such as bone mineral density (BMD) and history of previous fractures [7, 8], and self-reporting of fractures unconfirmed by radiographs [7, 8]. In addition, no longitudinal study has been conducted for diabetic subjects in mainland China until now.

✉ Weibo Xia  
xiaweibo8301@163.com

Extended author information available on the last page of the article

There is also less information available on vertebral fractures (VF) in subjects with T2DM. This is most likely due to the difficulty in identifying VFs, most of which are clinically silent [21, 22]. Moreover, studies investigating the risk of incident VFs in individuals with T2DM have reached controversial results, with risk being increased in studies using clinical VFs as the outcome [5, 9, 11], but not different from non-diabetic counterparts in studies based on morphometric VFs [12, 13, 23, 24].

Previous studies have shown that T2DM is usually associated with a 5–10% higher areal BMD than in healthy subjects [6, 25–30]. Thus, it is difficult for clinicians to identify and treat diabetic patients at high risk of fractures as BMD may underestimate fracture risks in these patients. For this reason, other factors are needed to predict fracture risk in patients with T2DM. Suppressed bone turnover is clearly associated with T2DM [6, 25, 31, 32]. However, cross-sectional studies examining the role of bone turnover markers (BTMs) in predicting fracture risk have been conducted with different outcomes [25, 32, 33]. Therefore, a longitudinal study is needed to clarify whether low BTMs contributes to the increased risk of incident fractures in patients with T2DM.

High body mass index (BMI) or obesity was previously considered as a protective factor for fractures, especially for hip fractures [9, 17, 34]. However, higher BMI is normally associated with more severe T2DM, which is speculated to be related to a higher risk of fractures. New emerging cohort studies have shown that the association between T2DM and increased risk of fractures remains unchanged after adjusting for BMI [9, 13, 16, 24], and Holmberg et al. [9] reported that the effect of BMI on diabetes-associated fracture risk differs according to the site.

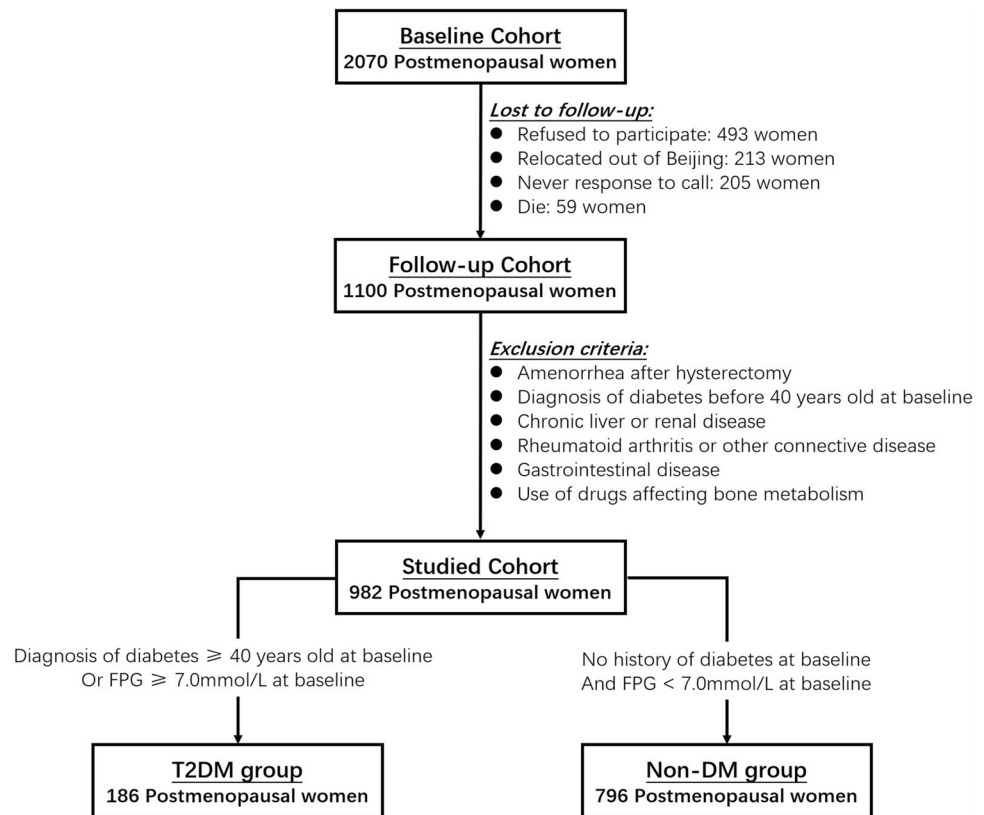
To clarify these issues, we used data from the Peking Vertebral Fracture Study (PK-VF), a large-scale community-based epidemiologic study designed to determine the prevalence and incidence of morphometric vertebral fractures among Chinese postmenopausal women in Beijing, China, from January 2008 through June 2014. We conducted this longitudinal cohort study mainly to examine whether the risk of incident fractures, especially of morphometric VFs, was higher among Chinese postmenopausal women with T2DM than among women without diabetes. We also sought to determine whether BMI has a modifying effect on the association between T2DM and incident fractures. Finally, we investigated whether BMD *T*-score or BTM were significantly associated with incident fractures in T2DM women.

## Subjects and Methods

### Subjects

The PK-VF has already conducted two surveys from January 2008 through January 2009, and from March 2013 through June 2014. The cohort of the first survey (baseline study) was constituted by randomly sampling postmenopausal women from seven districts throughout Beijing, namely Dong Cheng, Chao Yang, Xi Cheng, Hai Dian, Feng Tai, Shi Jing Shan, and Fang Shan. The Coordinating Center was located at the Peking Union Medical College Hospital (PUMCH). The populations of the seven districts in our study ranged from 350,000 to 1,920,000. One or two communities in each district were randomly selected and represented at least 5% of the total population of the district. A community in our study was defined as a group of interacting people characterized by similar culture and lifestyle, living at a specific geographic area, and sharing common spaces. Postmenopausal women were stratified by age and randomly sampled according to the age composition of those communities. Ahead of sampling, written notices explaining the nature of the proposed study were posted on the bulletin board of each community center. Then telephone calls were made to invite the randomly selected participants to join the study. In the end, a total of 2070 postmenopausal women aged 47–108 years without any known metabolic bone diseases were enrolled (Fig. 1). Every participant completed a standardized questionnaire concerning items such as demographic information, years since menopause (YSM), clinical fracture history before the baseline, medical history including diabetes, and usage of different drugs including anti-diabetic medication. Weight and height for each participant were measured by standard methods, and BMI was calculated according to the standard formula:  $BMI = \text{weight}/\text{height}^2$ . Women with  $BMI \geq 24 \text{ kg/m}^2$  were defined as overweight or obese [35]. Measurements of serum bone turnover markers (BTMs) and BMDs, as well as assessment of morphometric VFs were also performed for each participant by certified staff. The full details of the baseline study were previously published [6, 36, 37]. During the second survey (follow-up study), we attempted to call and persuade every woman to participate in a second visit. However, 493 (23.82%) women refused to participate, 418 (20.19%) women had relocated out of Beijing or never responded to a phone call, and another 59 (2.85%) women had died. At last, 1100 (53.14%) postmenopausal women aged 50 to 93 years were successfully recruited in the follow-up study, with a median duration of  $5.2 \pm 1.0$  years in follow-up (Fig. 1). The same aforementioned questionnaire and measurements were performed for each participant again,

**Fig. 1** Flow-chart for the cohort selection and classification. T2DM, type 2 diabetes mellitus; FPG fasting plasma glucose



and incident clinical fractures having occurred during the follow-up period were additionally recorded. In this study, because we mainly aimed to investigate how T2DM affects the risk of incident fractures among women with natural menopause, we excluded women who met one of the following criteria (Fig. 1): 1) menstruation stopped after a hysterectomy; 2) diagnosis of diabetes before 40 years old indicating possible type 1 diabetes; 3) the presence of diseases that likely affect bone metabolism, including chronic liver disease, chronic renal disease, rheumatoid arthritis, or other connective tissue disease and significant gastrointestinal disease; and 4) taking drugs that affect bone metabolism, including corticosteroid, anticonvulsant drugs, bisphosphonates, calcitonin, activated vitamin D, or estrogen and progesterone. Eventually, a total of 982 subjects were included. This study was approved by the Department of Scientific Research, and the ethics committee of PUMCH. All of the subjects agreed to participate in this study and signed informed consent forms.

### Biochemical Measurements

In the baseline study, a fasting blood sample was collected from each woman in the morning (7–9 am). After blood sampling, the serum was separated and cryopreserved at  $-80^{\circ}\text{C}$ . All of the biochemical measurements were

conducted within 3–6 months after sampling. The concentration of fasting plasma glucose (FPG) was assessed by standard methods in the central laboratory of PUMCH. Serum levels of BTMs, including C-terminal telopeptide of type I collagen ( $\beta$ -CTX) and N-aminoterminal prepeptide of type I procollagen (P1NP), were measured by an automated Roche electrochemiluminescence system (E170; Roche Diagnostics, Basel, Switzerland). The measuring ranges of  $\beta$ -CTX and P1NP were 0.01–6 ng/ml and 5–1200 ng/ml, respectively. The intra-assay and inter-assay coefficients of variation were 2.0% and 3.2% for  $\beta$ -CTX, 2.3% and 1.7% for P1NP.

### Ascertainment of Type 2 Diabetes Mellitus

Baseline diabetes status was determined by self-reported diagnosis of diabetes or  $\text{FPG} \geq 7.0$  mmol/L. Self-reported diagnosis of diabetes was confirmed on the basis of an affirmative answer to the questions asked at baseline: “Were you ever diagnosed with diabetes by a doctor when you were not pregnant, and how old were you when you were diagnosed with diabetes? Or did you ever use an anti-diabetic medication such as insulin, metformin, acarbose, sulfonylureas, thiazolidinedione and the like?” In the end, 186 (18.9%) women with probable type 2 diabetes mellitus were included in our longitudinal study, and 161 (16.4%) women

were diagnosed based on self-reporting, while 25 (2.5%) women were diagnosed by high FPG only. Based on the diabetes status, subjects were classified into a T2DM group and non-DM group (Fig. 1 and Table 1). Hemoglobin A1c (HbA1c) was not measured in PK-VF.

### BMD Measurements and Ascertainment of Osteoporosis

In the baseline study, 954 (97.1%) women took BMD measurements at the lumbar spine (LS, including L1 to L4), femoral neck (FN), total hip and greater trochanter, using dual-energy X-ray absorptiometry (DXA) with either Lunar DPX or Norland equipment, from which

*T*-scores were generated. The manufacturer's phantom was calibrated every day before the measurement started. The coefficients of variation were 0.75–1.7% for LS and 0.56–1.0% for FN. Cross-calibration equations between the two kinds of machines are listed below [38].

$$\text{LS BMD (g/cm}^2\text{) Lunar} = 1.012 \times \text{Norland} + 0.0137.$$

$$\text{FN BMD (g/cm}^2\text{) Lunar} = 1.0377 \times \text{Norland} + 0.00026.$$

According to the World Health Organization definition, osteoporosis was defined as *T*-score  $\leq -2.5$ . A woman was defined with osteoporosis if her *T*-score of at least one bone site was not over  $-2.5$ . Accordingly, a woman with FN *T*-score  $\leq -2.5$  or LS *T*-score  $\leq -2.5$  was defined with FN osteoporosis or LS osteoporosis, respectively.

**Table 1** Baseline characteristics and incident fractures according to diabetic status

Characteristics	Overall	Range	Non-DM group	T2DM group	<i>p</i> <sup>a</sup>
Number (%)	982	–	796 (81.1%)	186 (18.9%)	–
Age (years), median (IQR)	62.0 (15.0)	48.0–87.0	61.0 (15.0)	65.0 (12.0)	<0.001
YSM (years), median (IQR)	12.0 (16.0)	1.0–40.0	11.0 (16.0)	16.0 (14.0)	<0.001
BMI (kg/m <sup>2</sup> ), mean (SD)	26.00 (3.52)	17.26–39.82	25.89 (3.53)	26.45 (3.47)	0.050
BMI $\geq 24$ kg/m <sup>2</sup> , <i>n/N</i> (%)	687/982 (70.0%)	–	549/796 (69.0%)	138/186 (74.2%)	0.183
Any previous fracture, <i>n/N</i> (%)	371/982 (37.8%)	–	297/796 (37.3%)	74/186 (39.8%)	0.531
Previous clinical fracture, <i>n/N</i> (%)	214/982 (21.8%)	–	174/796 (21.9%)	40/186 (21.5%)	0.916
Previous VF, <i>n/N</i> (%) <sup>c</sup>	214/886 (24.2%)	–	168/717 (23.4%)	46/169 (27.2%)	0.301
Any incident fracture, <i>n/N</i> (%)	93/982 (9.5%)	–	69/796 (8.7%)	24/186 (12.9%)	0.076
Incident clinical non-VF, <i>n/N</i> (%)	59/982 (6.0%)	–	41/796 (5.2%)	18/186 (9.7%)	0.019
Incident VF, <i>n/N</i> (%) <sup>d</sup>	43/868 (5.0%)	–	35/700 (5.0%)	8/168 (4.8%)	0.898
LS BMD (g/cm <sup>2</sup> ), mean (SD) <sup>c</sup>	1.006 (0.184)	0.517–2.120	1.008 (0.187)	0.999 (0.174)	0.541
LS <i>T</i> -score, median (IQR)	– 1.045 (2.070)	– 4.640–8.720	– 1.000 (2.088)	– 1.100 (1.925)	0.442
FN BMD (g/cm <sup>2</sup> ), median (IQR) <sup>c</sup>	0.783 (0.180)	0.464–1.264	0.783 (0.184)	0.778 (0.169)	0.753
FN <i>T</i> -score, median (IQR)	– 1.010 (1.410)	– 3.640–3.000	– 1.010 (1.470)	– 1.030 (1.300)	0.739
Osteoporosis, <i>n/N</i> (%) <sup>b</sup>	256/954 (26.9%)	–	210/770 (27.3%)	46/184 (25.0%)	0.532
LS osteoporosis, <i>n/N</i> (%)	144/954 (15.1%)	–	120/770 (15.6%)	24/184 (13.0%)	0.387
FN osteoporosis, <i>n/N</i> (%)	54/953 (5.7%)	–	48/769 (6.2%)	6/184 (3.3%)	0.116
FPG (mmol/L), median (IQR)	5.30 (1.00)	2.68–18.9	5.17 (0.79)	7.06 (2.53)	<0.001
$\beta$ -CTX (ng/mL), median (IQR)	0.409 (0.252)	0.036–1.670	0.417 (0.256)	0.385 (0.234)	<0.001
P1NP (ng/mL), median (IQR)	52.30 (27.11)	10.45–151.4	54.57 (27.35)	45.16 (21.78)	<0.001

Reference ranges of all the biochemical parameters were obtained from the central laboratory of Peking Union Medical College Hospital and were all age/sex/ethnically appropriate. Reference interval of each biochemical parameter: ALT 5–40 U/L, ALP 27–107 U/L, Calcium 2.13–2.70 mmol/L, Phosphate 0.81–1.45 mmol/L, Cr 59–104  $\mu$ mol/L,  $\beta$ -CTX 0.260–0.512 ng/mL, P1NP 15–75 ng/mL, 25(OH)D 8–50 ng/mL

*DM* diabetes mellitus, *T2DM* type 2 diabetes mellitus, *VF* vertebral fracture, *LS* lumbar spine, *FN* femoral neck, *OP* osteoporosis, *IQR* interquartile range, *YSM* years since menopause, *SD* standard deviation, *BMI* body mass index, *FPG* fasting plasma glucose,  *$\beta$ -CTX* C-terminal telopeptide of type I collagen, *P1NP* N-terminal propeptide of type I procollagen

<sup>a</sup>Without any adjustment. Normally distributed continuous variables, expressed as mean (SD), were compared by Student's *t* test. Non-parametric continuous variables, expressed as median (IQR), were compared by Mann-Whitey *U* test. Categorical variables, expressed as frequencies (percentages), were compared by Pearson's  $\chi^2$  test

<sup>b</sup>Only 954 women (non-DM group: T2DM group = 770:184) had baseline BMDs measured

<sup>c</sup>Only 886 women (non-DM group: T2DM group = 717:169) took the lateral radiographs of the thoracolumbar spine (T4–L5)

<sup>d</sup>Only 868 women (non-DM group: T2DM group = 700:165) took the lateral radiographs of the thoracolumbar spine (T4–L5) at both visits



## Ascertainment of Fractures

Morphometric VFs were assessed by the lateral radiographs of the thoracolumbar spine (T4–L5) in 886 (90.2%) women at first visit and in 868 (88.4%) women at both visits. Using Genant's semiquantitative (SQ) visual criteria [39], two experienced radiologists independently evaluated the radiographs to diagnose VF. Previous VF with  $SQ \geq 1$  was confirmed by baseline X-ray. Incident VF was defined as an increase of at least 1 SQ score from baseline.

Self-reports of previous fractures before the first visit and self-reports of incident fractures from 2008 through 2014 were obtained using the aforementioned questionnaire. Fractures at the spine, rib, proximal humerus, distal forearm, hand, pelvis, hip, distal femur, tibia, fibula, and foot were recorded. The specific time and cause of each fracture were inquired. Only fractures occurring during routine activities or due to mild trauma were analyzed in our study. If a woman had multiple incident fractures, only the first one was used for our analysis. If a woman had a self-reported VF that was not verified by lateral radiographs of spine, we did not consider that she really had a clinically diagnosed VF. As a consequence, 23 women with self-reported previous VFs and 12 women with self-reported incident VFs were identified; meanwhile, 214 women with previous morphometric VFs and 43 women with incident morphometric VFs were identified. Only 11 (47.8%) self-reported previous VFs and 5 (41.7%) self-reported incident VFs were confirmed by X-rays. In summary, previous and incident clinical fractures were defined as self-reported fractures occurring during routine activities or due to mild trauma before the first visit and during the 2008–2014 period, respectively, with vertebral fractures confirmed by the lateral radiographs of the spine. A woman was then defined with any incident fracture if she had an incident VF or an incident clinical non-VF. A similar definition was also applied to any previous fracture.

## Statistical Analysis

All of the statistical analyses were conducted using SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL) or Stata (version 14.2; Stata Corporation, Inc., College Station, TX, USA). Data were presented as frequencies (percentages), mean (standard deviation [SD]), median (interquartile ranges [IQR]), correlation coefficient ( $r$ ), hazard ratio (HR), odds ratio (OR), and 95% confidence interval (95% CI). Kolmogorov–Smirnov tests were used to verify the normal or skewed distributions of baseline continuous variables. Student's  $t$  test was conducted to compare normally distributed continuous variables between the T2DM group and non-DM group, while Mann-Whitney  $U$  tests were conducted to compare non-parametric continuous variables between groups. Comparisons of categorical variables were performed by

Pearson's  $\chi^2$  test. General linear model analysis of variance (GLM-ANOVA) was performed to further compare the BTMs and BMDs between groups, adjusting for age, YSM, and BMI. Because BTMs and FN BMD were normally distributed only after logarithmic transformation with base 10, transformed values were used in GLM-ANOVA. Logistic regression analyses were performed to compare the odds ratio for any incident fractures and incident VFs between groups, while Cox proportional hazards regression analyses were used to compare the hazard ratio for incident clinical non-VFs between groups, with or without adjustment for age, YSM, BMI, BMDs, and any previous fractures. All the ratios were further calculated among population stratified by BMI status ( $BMI \geq 24 \text{ kg/m}^2$  and  $BMI < 24 \text{ kg/m}^2$ ) with adjustment for age, YSM, BMI, FN BMD, and any previous fractures. The association was tested for interactions between T2DM and BMI status. The effects of baseline BMD  $T$ -scores and BTMs on the fracture incidence in women with and without T2DM were examined by logistic regression analysis for incident VFs and by Cox proportional hazards regression analysis for incident clinical non-VFs. Those associations were tested for interactions between BMD  $T$ -scores and diabetes status, and between BTMs and diabetes status. To calculate the average difference in  $T$ -score between T2DM and non-DM women with the same risk of incident fractures, we used logistic models to estimate the associations of LS  $T$ -score and T2DM with the outcomes of incident VFs, and used Cox proportional hazards models to estimate the associations of FN  $T$ -score and T2DM with the outcomes of incident non-VFs, with adjustment for age, BMI, YSM and any previous fractures. The difference in  $T$ -score for those with and without T2DM but with the same incident fracture risk was calculated as the ratio of the regression coefficient for T2DM to the coefficient for  $T$ -score as previously published [40], with a 95% CI obtained by the delta method.  $p$  values of less than 0.05 were considered to be significant.

## Results

### Difference in the Risk of Incident Fractures Between T2DM and Non-DM Women

Baseline characteristics of all of the participants according to diabetes status are summarized in Table 1. 43 (5.0%) incident VFs and 59 (6.0%) incident clinical non-VFs were reported during the follow-up, with 8 (0.9%) VFs and 18 (1.8%) clinical non-VFs associated with type 2 diabetic women (Table 1). Type 2 diabetic women had mildly lower risk for VFs than women without diabetes (OR 0.95, 95% CI 0.43–2.09). However, this difference did not reach statistical significance in any analyzed model (Table 3), and 95%

CI for these estimates were wide and the power to detect modest associations was limited. The incidence and hazard ratio for clinical non-VFs among women with T2DM were nearly twice those among women without diabetes (incidence: 9.7% vs. 5.2%; HR 1.95, 95% CI 1.11–3.35). This hazard ratio became even higher after adjusting for age, YSM, BMI, BMD, and previous fractures (Table 2). When fractures by anatomic site were compared (data not shown), only the difference in incident foot fractures remained statistically significant (HR 3.56, 95% CI 1.24–10.22), but the limited number of fractures at other sites did not allow us to make a definite conclusion.

### The Modifying Effect of BMI on the Association Between T2DM and Incident Fractures

When stratifying the population by BMI status, we performed the same regression models in individuals with BMI  $\geq 24$  kg/m<sup>2</sup> and in individuals with BMI  $< 24$  kg/m<sup>2</sup> (Table 3). The risk of VFs remained similar between diabetics and non-diabetics despite their BMI status. However, the increased risk of non-VFs was only associated with T2DM in women BMI  $\geq 24$  kg/m<sup>2</sup> (HR 2.80, 95% CI 1.41–5.57, *p* for interaction = 0.002).

### The Association Between BMD T-Scores and Incident Fractures in Either T2DM Women or Non-DM Women

Higher BMD *T*-scores at the lumbar spine were similarly and negatively associated with incident VFs both in women with T2DM (OR 0.34, 95% CI 0.12–0.88) and in women without diabetes (OR 0.60, 95% CI 0.44–0.82, *p* for interaction = 0.430). However, no significant associations were found between LS *T*-scores and incident non-VFs in either T2DM women or non-DM women (Table 4). Therefore, the LS *T*-score predicts VF risks similarly in T2DM and non-DM, but does not predict non-VF in either group. Although BMD *T*-scores at the femoral neck were found to be negatively associated with incident non-VFs (HR 0.55, 95% CI 0.37–0.81) and incident VFs (OR 0.54, 95% CI 0.34–0.84) only in non-DM women, no evidence of interaction by diabetes status indicated that the FN *T*-score predicts fracture risks similarly in T2DM as in non-DM (Table 4). Neither BTM was found to be significantly associated with incident fractures (Table 4).

Considering the challenge of interpreting BMD *T*-scores in type 2 diabetic patients, we analyzed mean differences in *T*-scores, comparing women with and without diabetes at a similar fracture risk. The difference in LS *T*-score comparing

**Table 2** Risk of incident fractures in type 2 diabetic women

Model	Any incident fractures		Incident clinical non-VFs		Incident VFs	
	OR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Model 1: no adjustment	1.56 (0.95–2.56)	0.078	1.93 (1.11–3.35)	0.021	0.95 (0.43–2.09)	0.898
Model 2: age, YSM, BMI and any previous fractures	1.55 (0.93–2.58)	0.089	2.15 (1.22–3.81)	0.009	0.83(0.37–1.84)	0.639
Model 3: Model 2, FN BMD	1.54 (0.92–2.60)	0.102	2.25 (1.27–3.98)	0.006	0.77 (0.33–1.80)	0.545
Model 4: Model 2, LS BMD	1.51 (0.90–2.54)	0.122	2.144 (1.21–3.80)	0.009	0.74 (0.32–1.74)	0.489

HR hazard ratio, OR odds ratio, 95% CI 95% confidence interval, VF vertebral fracture, YSM years since menopause, BMI body mass index, FN BMD bone mineral density at femoral neck, LS BMD bone mineral density at lumbar spine

Model 1: without any adjustment; Model 2: adjusted for age, YSM, BMI, and any previous fractures; Model 3: adjusted for age, YSM, BMI, FN BMD, and any previous fractures; Model 4: adjusted for age, YSM, BMI, LS BMD, and any previous fractures

**Table 3** Risk of incident fractures in type 2 diabetic women stratifying by BMI status

BMI status <sup>a</sup>	Any incident fractures			Incident clinical non-VFs			Incident VFs		
	OR (95% CI)	<i>p</i>	<i>p</i> for interaction <sup>b</sup>	HR (95% CI)	<i>p</i>	<i>p</i> for interaction	OR (95% CI)	<i>p</i>	<i>p</i> for interaction
BMI $\geq 24$ kg/m <sup>2</sup>	2.25 (1.22–4.15)	0.009	0.016	2.80 (1.41–5.57)	0.003	0.002	1.09 (0.42–2.85)	0.861	0.902
BMI $< 24$ kg/m <sup>2</sup>	0.59 (0.19–1.80)	0.354	1.32 (0.43–4.06)	0.634	0.30 (0.04–2.34)	0.248			

HR hazard ratio, OR odds ratio, 95% CI 95% confidence interval, VF vertebral fracture, BMI body mass index

<sup>a</sup>Adjusted for age, years since menopause, BMI, bone mineral density at femoral neck and any previous fractures

<sup>b</sup>Interaction between diabetes status and BMI status

**Table 4** Effects of BMD T-scores and BTMs on incident fractures in women with and without T2DM

	Incident clinical non-VFs					Incident VFs				
	T2DM group		Non-DM group		$p^b$	T2DM group		Non-DM group		$p^b$
	HR (95%CI)	$p^a$	HR (95%CI)	$p^a$		OR (95%CI)	$p^a$	OR (95%CI)	$p^a$	
FN <i>T</i> -score	0.76 (0.43–1.34)	0.337	0.55 (0.37–0.81)	0.003	0.286	0.63 (0.24–1.67)	0.350	0.54 (0.34–0.84)	0.006	0.593
LS <i>T</i> -score	0.91 (0.61–1.35)	0.624	0.85 (0.66–1.09)	0.201	0.568	0.34 (0.12–0.88)	0.026	0.60 (0.44–0.82)	0.001	0.430
$\beta$ -CTX	1.13 (0.08–16.80)	0.927	1.41 (2.61–7.65)	0.689	0.653	5.22 (0.15–185.34)	0.364	2.14 (0.40–11.35)	0.373	0.811
P1NP	0.99 (0.97–1.02)	0.627	1.00 (0.99–1.02)	0.849	0.521	1.02 (0.99–1.05)	0.178	1.01 (0.99–1.02)	0.410	0.612

HR or OR is per 1 SD increase in *T*-score or in the value of BTM

*BMD* bone mineral density, *BTM* bone turnover markers, *T2DM* type 2 diabetes mellitus; *HR* hazard ratio, *OR* odds ratio, *95% CI* 95% confidence interval, *FN T* BMD *T*-score at femoral neck, *LS T* BMD *T*-score at lumbar spine,  $\beta$ -*CTX* C-terminal telopeptide of type I collagen, *P1NP* N-terminal prepeptide of type I procollagen

<sup>a</sup>Adjustment for age, YSM, BMI and previous fractures

<sup>b</sup> $p$  for interaction between diabetes status and different BMD *T*-scores, and between diabetes status and different BTMs

T2DM and non-DM women with similar VF risk was  $-0.36$  (95% CI  $-1.77$  to  $1.04$ ). The difference in FN *T*-score comparing T2DM and non-DM women with similar non-VF risk was  $1.61$  (95% CI  $-0.11$  to  $3.34$ ). It seemed that LS *T*-score would slightly overestimate the risk of VFs in T2DM, while the FN *T*-score would possibly underestimate the risk of non-VFs in T2DM. However, none of the results were statistically significant.

## Discussion

In this longitudinal cohort study based on data from PK-VF, we first demonstrated that the odds ratio for osteoporotic fracture in patients with type 2 diabetes is about 1.5, which is same as reported by Ferrari et al. [29] Nevertheless, no significant association existed between incident VFs and T2DM, even after BMDs and previous fracture history were taken into account. This finding is consistent with some studies [9, 13, 23, 24] while inconsistent with others [5, 9, 11, 12]. Most studies reporting an increased risk of incident VFs used clinical VFs as the outcome, not morphometric VFs [5, 11]. Our study and the MrOS study [21] respectively showed that only 11.6% and 13.5% of morphometric VFs could be recognized as clinical VFs, most of which had a SQ score change  $\geq 2$ , indicating more severe VFs. Other studies [12, 13, 23, 24] based on spine radiographs, including our previous study [6], mainly investigated prevalent VFs and yielded conflicting results. In agreement with our data, the CaMos study also found an insignificantly lower prevalence of VFs in men with T2DM (OR 0.77, 95% CI 0.49–1.22) [23]. However, slightly higher risks of incident VFs were detected in the MrOS study (OR 1.28, 95% CI 0.81–2.00) [24] and SOF study (OR 1.06–1.09, 95% CI 0.33–3.55) [13], but none of those differences were statistically significant. Meanwhile, the risk of incident non-VFs was substantially

increased in women with T2DM compared to women without diabetes. This difference was mainly caused by foot fractures in our study. These results are compatible with some previous research also reporting an increased risk of non-VFs in patients with T2DM [4, 5, 7, 9, 13, 14], and among these studies, those of Luetters et al. [4] and Schwartz [13] respectively described positive associations between T2DM and prevalent foot fractures (OR 1.45, 95% CI 1.07–1.83) and incident foot fractures (HR 2.68, 95% CI 1.18–6.06).

Taken together, our results suggest that the risk of incident fractures associated with T2DM differed according to fracture site. The difference in the cortical to trabecular bone ratio between vertebral and non-vertebral bones may be a reasonable explanation for this discrepancy [41]. Increased cortical porosity in populations with T2DM has been proven to be related to elevated fracture risk at the hip and other non-vertebral sites [30, 42–44] that have a higher proportion of cortical bone. Another possible explanation for the increased incidence of non-VFs, especially of foot fractures, is that diabetic individuals have an elevated risk of falling, which is probably due to some disease-related chronic complications (peripheral neuropathy and retinopathy) [30, 45]. Previous studies have described an association of peripheral neuropathy with metatarsal fracture [46] and calcaneal fracture [47].

High BMI is a known protective factor for fractures, most evidence for which comes from studies of hip fractures [9, 17, 34]. However, our study found that the modifying effect of BMI on diabetes-related fractures also differed according to the site. Compared to non-diabetic women, women with T2DM always had a similar risk of incident VFs despite the different BMI status, but had a significantly higher risk of incident non-VFs only in individuals with BMI  $\geq 24$  kg/m<sup>2</sup>. These results suggest that higher BMI increased the association between T2DM and risk of non-VFs, but did not modify the effect of T2DM on the risk of VFs. In agreement with

our findings, Holmberg et al. [9] reported that high BMI increases the risk of ankle fractures; while decreasing the risk of hip fractures and maintaining the risk of vertebral fractures. One hypothesis for this discrepancy is that different risk factors predominate in different types of fractures, such as poor bone quality in hip fractures and a tendency to fall in foot fractures [9].

Finally, we characterized the relationship between BTMs, BMDs, and incident fractures in T2DM and non-DM women. Unlike previous studies [25, 31–33], we did not find any significant association between BTMs and fractures either in T2DM women or in non-DM women, indicating that BTMs might not be reliable predictors for incident fractures. In line with the results for VFs in T2DM men reported by Napoli et al. [24] our results also described a similar and negative association between LS *T*-score and incident VFs both in T2DM women and non-DM women, suggesting that a lower LS *T*-score is a possible risk factor for VFs in T2DM women. Similar with the results of Schwartz et al. [40] the lack of interaction between FN *T*-score and diabetes status indicates that the FN *T*-score predicts the risks of VF and non-VF in those with T2DM just as it does in those without diabetes. There might be a difference in the association between FN *T*-score and fracture risk by diabetes status, but only a larger study would be able to determine if there is a real difference or if this is just a chance finding. In order to address how well the *T*-score predicts incident fractures in T2DM and non-DM women, we estimated the reduction in *T*-score equivalent to having T2DM. For incident non-VFs, we found an insignificant trend suggesting that having T2DM equates to having a FN *T*-score 1.61 units lower as compared with not having DM, indicating that the FN *T*-score would possibly underestimate the incident non-VF risk, although the degree of underestimation is difficult to determine with the small number of fractures in T2DM. Although the point estimate (1.61) reported by our study appears quite different from the value reported by Schwartz et al. (0.59) [40], there is no good evidence that they are really different, given the wide 95% CI (−0.11 to 3.34), which also includes the point estimate for the study by Schwartz et al. Similarly, for LS *T*-score and incident VFs, comparing these results with those of Napoli et al. [24] which reported a difference in LS *T*-score of 0.64 (95% CI −0.43 to 1.71) with a similar VF risk, the point estimates are in opposite directions, the 95% CI values are wide for both studies, and the point estimate for our study is within the 95% CI for that of Napoli et al. Thus, it is not clear whether LS *T*-score would under- or over-estimates VF risk in T2DM.

To our knowledge, this is the first and largest longitudinal cohort study investigating the risk of incident fractures associated with T2DM in a mainland Chinese population. We analyzed a well-characterized cohort of postmenopausal

women with a long follow-up, for whom both self-reported fractures and morphometric VFs were available. We also examined the modifying effect of BMI on the diabetes-fracture association. For the first time in a Chinese population, we analyzed the value of BMD *T*-scores in predicting incident fracture risk and calculated the point estimate and 95% CI for their relationship.

However, our study has some inevitable limitations. The sample size was not large enough and the incidence of VFs or hip fractures in the T2DM group was relatively low as aforementioned, both of which limited the power to make definitive conclusions. Selection bias existed in our study due to the high ratio of loss to follow-up (46, 86%) and relatively low response rate (53.14%). Study participants were volunteers, community dwelling, and ambulatory, and therefore women with or without diabetes in PK-VF may be healthier than the general population, which limited the application of our results to the broader population of older women and women with T2DM. Since the original study was not designed to investigate diabetes, essential data needed to diagnose diabetes or assess diabetic severity were lacking, such as HbA1c, advanced glycation end-products (AGEs), and diabetic complications, and information on the specific anti-diabetic medications used by each participant was incomplete. Thus, it is possible that some undiagnosed diabetics existed in our study, but the adoption of FPG to ascertain diabetes almost eliminated this possibility. Similarly, since we did not confirm non-VFs by radiologic methods, there may be under- or over-reporting of non-VFs. Therefore, a large-scale prospective study is required in the future, with a higher incidence of radiologically confirmed fractures in diabetics, and considering falls, diabetic complications, and anti-diabetic drugs as confounders, and while measuring the levels of HbA<sub>1c</sub> and AGEs.

In conclusion, in this analysis of PK-VF, not only the association between T2DM and incident fractures, but also the modifying effect of BMI on this association differed according to the fracture site. Type 2 diabetic women had a similar risk of VFs, but a significantly higher risk of incident non-VF, compared to non-diabetic women, even after adjustment for age, BMI, BMD, and previous fractures. Higher BMI increased the association between diabetes and the risk of non-VFs, but it did not modify the effect of diabetes on risk of VFs. LS BMD *T*-score was similarly and negatively associated with VF risk in T2DM and non-DM women, and appears to be useful for clinical evaluation of VF risk. However, FN BMD *T*-score seemed to underestimate the non-VF risk in T2DM women despite the increased non-VF risk in this population.

**Acknowledgements** Our deepest gratitude to all the study participants and to the participating centers of the original parent study: Department of Endocrinology, China Rehabilitation Research Center; Department



of Endocrinology, Beijing Liangxiang Hospital; Department of Cadre Unit, General Hospital of the Second Artillery Force; Department of Endocrinology, Peking University Shougang Hospital; Department of Endocrinology, Beijing Chaoyang Hospital, Capital University of Medical Science; Department of Endocrinology, Beijing Haidian Hospital; Department of Geriatric Endocrinology, Chinese People's Liberation Army, General Hospital. We would also like to thank Ms. Yingying Hu for her valuable work in testing biomarker. The Peking Vertebral Fracture Study (PK-VF) was funded by the National Natural Science Foundation of China (No.81070687 and 81170805), National Science and Technology Pillar Program (2006BAI02B03), National Science and Technology Major Projects for "Major New Drugs Innovation and Development" (Grant2008ZX09312-016), Beijing Natural Science Foundation (No. 7121012), Scientific Research Foundation of Beijing Medical Development (No. 2007-3029), and National Key Program of Clinical Science (WBYZ2011-873).

## Compliance with Ethical Standards

**Conflict of interest** Ruizhi Jiajue, Xuan Qi, Yan Jiang, Qiuping Wang, Wenbo Wang, Yu Pei, Xiran Wang, Wei Huang, Xin Zheng, Zhiwei Ning, Ou Wang, Mei Li, Xiaoping Xing, Wei Yu, Ling Xu, and Weibo Xia declare that they don't have any conflicts of interest in this work.

**Human and Animal Rights and Informed Consent** All of the subjects agreed to participate in this study and signed informed consent forms.


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## Affiliations

Ruizhi Jiajue<sup>1</sup> · Xuan Qi<sup>1</sup> · Yan Jiang<sup>1</sup> · Qiuping Wang<sup>2</sup> · Wenbo Wang<sup>3</sup> · Yu Pei<sup>4</sup> · Xiran Wang<sup>5</sup> · Wei Huang<sup>6</sup> · Xin Zheng<sup>7</sup> · Zhiwei Ning<sup>8</sup> · Ou Wang<sup>1</sup> · Mei Li<sup>1</sup> · Xiaoping Xing<sup>1</sup> · Wei Yu<sup>9</sup> · Ling Xu<sup>10</sup> · Weibo Xia<sup>1</sup> 

<sup>1</sup> Department of Endocrinology, Key Laboratory of Endocrinology, National Commission of Health, Ministry of Health, Peking Union Medical College Hospital, Chinese Academy of Medical Science, No. 1 Shuaifuyuan, Wangfujing Street, Dongcheng District, Beijing 100730, China

<sup>2</sup> Department of Endocrinology, Beijing Liangxiang Hospital, Beijing 102401, China

<sup>3</sup> Department Endocrinology, Peking University Shougang Hospital, Beijing 100144, China

<sup>4</sup> Department of Geriatric Endocrinology, Chinese PLA General Hospital, Beijing 100853, China

<sup>5</sup> Department of Cadre Unit, General Hospital of the Second Artillery Force, Beijing 100088, China

<sup>6</sup> Department of Endocrinology, Beijing Haidian Hospital, Beijing 100080, China

<sup>7</sup> Department of Endocrinology, China Rehabilitation Research Center, Beijing 100068, China

<sup>8</sup> Department of Endocrinology, Beijing Chaoyang Hospital, Beijing 100020, China

<sup>9</sup> Department of Radiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Shuaifuyuan No. 1, Wangfujing, Dongcheng District, Beijing 10, China

<sup>10</sup> Department of Gynaecology and Obstetrics, Peking Union Medical College Hospital, Chinese Academy of Medical Science, Beijing 100730, China