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Original Article

Assessment of fracture risk by FRAX model in older adults with type 2 diabetes: a cross-sectional study in China

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Abstract: Background: The FRAX model is an effective tool to assess fracture risk, but its application has not been assessed in patients with type 2 diabetes in Chinese mainland. We investigated FRAX-estimated fracture risk in older patients with type 2 diabetes mellitus (T2D) compared with control subjects. Methods: In our study, we assessed the FRAX scores of 267 T2D and 359 non-diabetic subjects from Tongji Hospital, Tongji University School of Medicine. We tested bone mineral density (BMD) and calculated FRAX scores. Binary regression analysis was used to evaluate the risk factors for high risk fracture prediction by FRAX model. Results: The BMI (Body Mass index), WHR (Waist-hip ratio), frequency of smoking, and alcohol consumption were significantly higher in T2D. T2D had significantly elevated BMC (Bone mineral content), T scores, Z scores in FN (Femoral neck) and in LS (lumber spine) (T score: -1.4±1.6 vs. -2.1±1.4, -1.7±1.1 vs. -2.0±1.0, *P*<0.001; Z score: -0.1±1.5 vs. -0.6±1.3; -0.4±1.0 vs. -0.7±1.0, *P*<0.001). T2D had lower FRAX-estimated probability of both major osteoporotic fracture (MOF) and hip fracture (HF) by FRAX-BMI model (4.27±2.84% vs. 5.14±2.92%, *P*<0.001, and 1.42±1.54% vs. 1.83±2.23%, *P*<0.001, respectively). T2D had lower FRAX-estimated probability of MOF by FRAX-BMD model (5.28±4.41% vs. 6.30±5.10%, *P*<0.001). When grouping by BMI, T2D had lower FRAX scores of MOF by FRAX-BMI. Binary regression analysis showed FN T score (B-4.58, P<0.001), smoking (B1.489, P<0.001), family history of hip fracture (B1.993, P<0.001) and corticosteroids use (B2.886, P<0.001) contributed to high risk of HF. FN T score (B-5.313, P<0.001), smoking (B3.753, P<0.01), family history of hip fracture (B2.521, P<0.001) and previous history of fracture (B3.239, P<0.05) contributed to high risk of MOF. Presence of T2D was not a contributing factor to high risk of fracture. Conclusions: Older Chinese patients with T2D had lower mean FRAX scores than non-diabetic subjects. T2D was not a risk contributor to high risk fracture prediction by FRAX. FRAX tool underestimated fracture risk in T2D population. Patients with T2D may be considered treatment when FRAX score was below FRAX-based intervention threshold.

Keywords: FRAX, fracture risk, type 2 diabetes, bone mineral density, osteoporosis

Introduction

Osteoporotic fractures have been a source of significant morbidity and mortality, especially for older adults [1]. Type 2 Diabetes mellitus (T2D) is chronic metabolic disorder which is more frequent in the elderly. The overall prevalence of diabetes was estimated to be 11.6% in the Chinese adult population and was higher in older age groups [2]. Several studies have found an increased risk of fracture in older patients with T2D [3-5]. A recent meta-analysis of 12 studies reported a relative risk of 1.7 (95% CI: 1.3 to 2.2) for hip fracture in patients with T2D [4]. The risk of all clinical fractures also appears to be increased with T2D. The most recent meta-analysis reported a summary RR of 1.2 (95% CI: 1.0 to 1.5) [4]. These findings suggest T2D may be an independent risk factor for fracture [6, 7].

Bone mineral density (BMD) has been shown to correlate with bone strength and is a good predictor of future fracture risk in non-DM osteoporosis [8]. However, T2D is associated with higher BMD in many studies [9, 10]. Cumulative evidence shows that T2D patients have high fracture rate in spite of the absence of BMD

reduction. How to assess the fracture risk of T2D has been a problem in clinical practice.

It is now widely accepted that except for BMD, other clinical factors, including age, body weight, history of a prior fragility fracture and corticosteroids use, are all independent contributors to fracture risk and improve the identification of patients at high risk [11]. FRAX, the World Health Organization's absolute fracture risk assessment tool, has become a standard for fracture prediction in recent years. It can provide a model for assessment of the 10-year probability of a major osteoporotic fracture (MOF) and of a hip fracture (HF), by using easily obtainable clinical risk factors with or without femoral neck (FN) BMD. The FRAX tool is able to capture the independent contribution of multiple different risk factors and combine these with BMD. FRAX model has been shown to improve fracture prediction over T-score alone [12, 13].

Until now, there are few data of FRAX from T2D patients in Chinese older adults [14, 15]. FRAX might be useful for the case-finding strategy picking up T2D patients at high risk for fracture. The aim of our study was to test the FRAX score and BMD in Chinese older adults with T2D in order to evaluate the usefulness of FRAX model in predicting the risk for osteoporotic fractures in older patients with T2D.

Materials and methods

Study design

Patients with type 2 diabetes (T2D) and non-diabetic subjects aged 50 to 80 years were recruited from clinic of Endocrinological department of Tongji Hospital, Tongji University School of Medicine from July, 2013 to June, 2014. Baseline demographic data and information on clinical risk factors were collected including anthropometric measurements, low-trauma fracture history (both personal and family), medical history including current medication, prior use of corticosteroids and secondary causes of osteoporosis. Information on lifestyle habits including smoking, alcohol consumption, physical activity were also obtained. These data were collected by a trained research assistant using a structured questionnaire.

BMD evaluation

BMD was assessed at the L1-4 lumbar spine (LS), femoral neck (FN), and total hip using the same dual-energy X-ray absorptiometry (DEXA) machine (Hologic QDR 4500, Waltham, Mass., USA). BMD T-scores were determined according to the Chinese normative database. All DEXA measurements were performed by one licensed technologist who had completed training by the equipment manufacturers. BMD was expressed both as an absolute value in gram per square centimeter (BMC), T-score and Z-score.

WHO 10-year absolute fracture risk (FRAX score)

The WHO 10-yr absolute risks of hip and osteoporotic fracture (FRAX scores) were calculated by the WHO Collaborating Center for Metabolic Bone Disease, using the FRAX algorithm through www.sheffield. ac.uk/FRAX/(version 3.8). The FRAX algorithm includes FN BMD T-score, age, sex, body mass index (BMI), previous history of fracture (PHF), family history of hip fracture (FHF), current smoking, recent use of corticosteroids, presence of rheumatoid arthritis (RA), and ≥3 alcoholic beverages per day. The clinical information and with (FRAX-BMD model) or without T score of FN BMD (FRAX-BMI model) for each subject are entered manually into the FRAX web calculator. 10-yr probabilities of a major osteoporotic fracture (MOF) or hip fracture (HF) were calculated.

Statistical analysis

Data were expressed as mean values with standard deviations (mean ± SD). All the data sets were normally distributed, except the FRAX score which was skewed. Categorical data were presented by absolute numbers with percentages and analyzed using a chi-square test and Fisher's exact test. For continuous variables, the Student's t-test or the Mann-Whitney U-test (for skewed data) was used. Binary logistic regression analysis was performed to evaluate factors contributing to high fracture risk. Differences were considered significant at a value of $P<0.05$.

The study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the institutional Ethics Board of Tongji Hospital, Tongji University School of Medicine.

Results

The study consisted of 267 patients with type 2 diabetes and 359 non-diabetic subjects.

Table 1. Baseline Demographic characteristics of patients with T2D and non-diabetes

Variable	T2D n=267	Non-DM n=359	t/X^2	*P* value
Age (y)	63.42±6.98	63.16±7.05	0.456	0.649
Sex				
Female	166 (62.2)	325 (90.5)	72.79	<0.001
Male	101 (37.8)	34 (905)		
BMI (kg/m^2)	24.14±3.38**	23.06±3.19	4.09	<0.001
Weight (kg)	64.07±10.46**	58.72±10.11	6.46	<0.001
Height (cm)	162.8±7.86**	159.33±6.49	5.88	<0.001
Waist (cm)	88.99±9.46**	84.84±9.55	5.407	<0.001
Hip (cm)	94.95±7.05	94.49±7.32	0.797	0.426
WHR	0.94±0.63**	0.90±0.62	7.826	<0.001
Menopause age	49.69±4.22	48.71±7.16	1.864	0.063
Previous fracture	69 (25.8)	108 (30.1)	1.543	0.242
Parental fracture	2 (0.7)	5 (1.4)	0.574	0.705
Smoking	58 (21.7)**	21 (5.8)	34.148	<0.001
Alcohol consumption	40 (15.0)**	20 (5.6)	15.646	<0.001
Corticosteroid use	5 (1.9)**	24 (6.7)	14.649	<0.001
RA	2 (0.7)**	16 (4.5)	7.538	0.006
Secondary OP	7 (2.6)	22 (6.1)	4.261	0.053

BMI = Body Mass Index, WHR = Waist Hip Ratio, RA = Rheumatoid Arthritis, OP = Osteoporosis. **: *P*<0.01.

Baseline characteristics are presented in **Table 1**. The items include age, sex, BMI, weight, height, waist circumference, hip circumference, waist-to-hip ratio, menopausal age, current smoking, alcohol consumption, use of corticosteroids, presence of RA and secondary osteoporosis, previous fracture history, parental hip fractures. BMI, WHR, smoking, alcohol consumption were significantly higher in patients with T2D (24.14±3.38 kg/m^2 vs. 23.06±3.19 kg/m^2, *P*<0.001; 0.94±0.63 vs. 0.90±0.62, *P*<0.001; 21.7% vs. 5.8%, *P*<0.001; 15% vs. 5.6%, *P*<0.001). Frequency of treatment with corticosteroids, and presence of RA were significantly lower in patients with T2D (1.9% vs. 6.7%, *P*<0.001; 0.7% vs. 4.5%, *P*<0.05). There were no significant differences in mean values of the evaluated descriptive parameters as regards parental fractures history, smoking and menopausal age.

The results of BMD evaluation were showed in **Table 2**. BMC, T scores of LS and FN, femoral troch and total femur were higher in T2D group. Z scores at LS and FN, femoral troch and total femur were also higher in T2D group.

In our study, calculated by FRAX-BMD model, FRAX scores for MOF were lower for patients with T2D than non-diabetic group (5.28±4.41% vs. 6.30±5.10%, *P*<0.001). FRAX scores for HF were also lower in T2D, although there was no significant difference (2.18±3.13% vs. 2.44±3.52%, *p*=0.067). When using FRAX-BMI model, FRAX scores for MOF and HF were both lower in T2D group (4.27±2.84% vs. 5.14±2.92%, *P*<0.001; 1.42±1.54% vs. 1.83±2.33%, *P*<0.005). The results were showed in **Table 3**.

We further grouped subjects into normal weight, overweight and obese group by BMI, there was no difference between T2D and non-diabetic group in FRAX score calculated by FRAX-BMD model. When using FRAX-BMI model, the probabilities for MOF were lower in T2D group when 24<BMI<28 kg/m^2 (4.18±2.72 vs. 4.98±2.53, *P*=0.037) and BMI<24 kg/m^2 (4.47±2.74 vs. 5.33±3.1, *P*=0.007). The results were showed in **Table 4**.

Binary logistic regression

According to the National Osteoporosis Foundation (NOF) criteria, the 10-yr probability of a major osteoporostic fracture (MOF) ≥20% and/or a 10-yr probability of hip fracture (HF) ≥3% are defined as high fracture risk and should be considered for treatment. In our study, there is no one whose 10-yr probility of MOF was above 20%, and we regard 10% as the threshold for high fracture risk. FRAX score of MOF ≥10% and of HF ≥3% were defined as dependent variable, risk factors including age, sex, BMI (changed into binary variable at 24 kg/m^2), smoking, alcohol consumption, corticosteroids use, previous history of fracture, family history of hip fracture, presence of RA, SOP, presence of T2D, FN T score, LS T score (changed into binary variable at -2.5) were independent variables. The results showed FN T score (B-4.58, P<0.001), smoking (B1.489, P<0.001), family history of hip fracture (B1.993,

Table 2. BMD of patients with T2D and non-diabetes

Variable	T2D (n=267)	Non-DM (n=359)	t	*P* value
BMC				
L1-4	0.910±0.186**	0.824±0.156	6.188	<0.001
Femoral				
Neck	0.675±0.135**	0.629±0.117	4.472	<0.001
Troch	0.632±0.118**	0.584±0.102	5.367	<0.001
Intro	0.973±0.181**	0.894±0.160	5.650	<0.001
Wards	0.495±0.160	0.471±0.149	1.868	0.062
Total	0.820±0.151**	0.751±0.150	5.720	<0.001
T score				
L1-4	-1.4±1.6**	-2.1±1.4	5.438	<0.001
Femoral				
Neck	-1.7±1.1**	-2.0±1.0	3.650	<0.001
Troch	-0.9±1.0**	-1.2±0.9	4.389	<0.001
Intro	-1.0±1.0**	-1.4±1.0	4.473	<0.001
Wards	-2.1±1.3	-2.2±1.1	1.498	0.135
Total	-1.1±1.1**	-1.6±1.0	4.752	<0.001
Z score				
L1-4	-0.1±1.5**	-0.6±1.3	3.708	<0.001
Femoral				
Neck	-0.4±1.0**	-0.7±1.0	2.913	0.004
Troch	-0.2±1.0**	-0.3±0.9	2.15	0.032
Intro	-0.3±1.0**	-0.6±0.9	3.343	0.001
Wards	-0.1±1.2	-0.1±1.1	0.488	0.626
Total	-0.3±1.0**	-0.5±1.0	3.110	0.002

BMC = Bone Mineral Content; **P<0.01.

Table 3. FRAX score of patients with T2D and non-diabetes

Variable	T2D (n=267)	Non-DM (n=359)	Z	*P* value
MOF (with BMD)	5.28±4.41**	6.30±5.10	-4.104	<0.001
HF (with BMD)	2.18±3.13	2.44±3.52	-1.830	0.067
MOF (without BMD)	4.27±2.84**	5.14±2.92	-5.135	<0.001
HF (without BMD)	1.42±1.54**	1.83±2.23	-3.154	0.002

MOF = Major Osteoporotic-Fracture, HF = Hip Fracture. **P<0.01.

P<0.001) and corticosteroids use (B2.886, P<0.001) contributed to high risk of HF. FN T score (B-5.313, P<0.001), smoking (B3.753, P<0.01), family history of HF (B2.521, P<0.001) and previous history of fracture (B3.239, P<0.05) contributed to high risk of MOF. Presence of T2D was not included in either of regression model.

Discussion

Both type 2 diabetes and osteoporosis predispose the elderly people to disabled conditions by causing vascular complications and fractures. Mounting evidence has suggested that diabetic patients have increased fracture risk. The current study provides some evidence that BMD and FRAX model application in elder diabetic patients in Chinese mainland.

Although Smith et al showed that BMD, which accounted for approximately 75-80% of the variance in bone strength [16], studies carried out in patients with type 2 diabetes seems different [4-6]. In our study, BMC, T-score and Z-score of L1-4, FN, femoral troch and total femur were all higher in T2D group than non-diabetic group. Increased fracture risk in T2D despite elevated or normal BMD has led to the hypothesis that there are diabetes-associated alterations in skeletal properties. Bone quality, but not bone mass may affect bone fragility causing hip and vertebral fractures in T2D. High glucose levels in T2D lead to accumulation of advanced glycosylation end-products (AGEs) in the organic bone matrix [17]. The best studied AGE, pentosidine, was found associated with a 42% increase in clinical fracture incidence in T2D [18]. AGE cross- links lead to biomechanically more brittle bone [19]. AGEs have been identified as a biomarker for the increased risk of fractures because it decreases the synthesis of type I collagen and decreases the bone strength [20]. Numerous data suggest that skeletal dynamics are reduced in T2D, with a disproportionate reduction in bone formation [21]. Diabetes mellitus (DM) not only induces the overexpression of DKK-1, Sclerostin, Gremlin, PTH, angiotensin II (Ang-II), IL-6 and TNFs, but also sequesters the over expression of Vitamin D and neurotransmitters required for the normal growth of osteoblast [22]. Studies suggest that in patients with T2D, trabecular bone mass and structure are intact, whereas the cortical compartment is compromised [23]. Increaseed cortical porosity may be an important cause of increased fracture risk in T2D because of reduced bone strength yet it is undetectable by DEXA [24].

Table 4. FRAX score of patients with T2D and non-diabetes grouped by BMI

Variable	T2D	Non-DM	Z	*P* value
BMI<24	n=140	n=234		
MOF (with BMD)	5.80±4.66	6.69±5.80	-1.542	0.124
HF (with BMD)	2.77±3.61	2.85±4.12	-0.194	0.846
MOF (without BMD)	4.47±2.74**	5.33±3.10	-2.722	0.007
HF (without BMD)	1.64±1.56	2.06±2.34	-1.889	0.060
24<BMI<28	n=90	n=102		
MOF (with BMD)	4.82±3.91	5.82±3.45	-1.868	0.063
HF (with BMD)	1.66±2.47	1.81±1.83	0.991	0.643
MOF (without BMD)	4.18±2.72*	4.98±2.53	0.366	0.037
HF (without BMD)	1.22±1.47	1.49±2.12	0.265	0.311
BMI>28	n=35	n=23		
MOF (with BMD)	4.33±4.38	4.40±2.41	-0.071	0.943
HF (with BMD)	1.15±1.94	1.07±1.02	0.176	0.861
MOF (without BMD)	3.71±3.49	4.00±2.26	-0.359	0.721
HF(without BMD)	1.02±1.55	1.00±0.97	0.059	0.953

MOF = Major Osteoporotic Fracture, HF = Hip Fracture. **P<0.01; *P<0.05.

Furthermore, there are some evidences showed that, patients with T2D have muscle weakness which is associated with diabetic neuropathy mediated muscle atrophy [25].

In clinical practice, BMD is not a sensitive index to assess the risk of osteoporotic fractures. The WHO FRAX algorithm integrates the influence of several well validated risk factors for fracture that are independent of BMD. When BMD measurements are not available, WHO proposes to use BMI to replace BMD as it provides a similar risk profile for fracture prediction. FRAX is now widely used clinically in western countries, but the osteoporosis research community still continues to evaluate FRAX'S applicability to predict fractures in various subpopulations. Type 1 diabetes is considered in FRAX model as one of the secondary causes of osteoporosis. T2D is not included as a risk factor in the FRAX model, and this may reduce its ability to predict fractures in T2D.

Our study shows patients with T2D have lower FRAX score of MOF calculated by FRAX model with or without BMD, which means they have less estimated probability of MOF in the following ten years. When subjects were divided into different groups by BMI, risk of MOF calculated by FRAX-BMI was lower in T2D group when BMI<28 kg/m^2. As for HF, patients with T2D also have much lower FRAX score calculated by FRAX-BMI. Further binary logistic regression analysis showed presence of T2D was not a significantly contributing factor to high risk of fracture assessed by FRAX Model. Considering increased risk of low trauma fracture of T2D in clinical practice, FRAX tool may underestimate the fracture risk in patients with T2D in China mainland. Compared with FRAX-BMI, FRAX-BMD model may be more appropriate when used to assess hip fracture risk of patients with T2D.

Schwartz et al recently analyzed data from three major prospective observational studies [6]. The results indicated that FN BMD T score and FRAX score were associated with hip and nonspine fracture risk among older adults with T2D. And for a given FRAX score or for a given T score, the fracture risk of these patients was higher than participants without DM. They also found in type 2 diabetes populations, a 1% increase in baseline FRAX score (predicted risk) was associated with a 5% increased risk of observed hip fractures in women and a 16% observed fracture increase in men. Another clinical study in Canada demonstrated that diabetes is predictive of future hip and major osteoporotic fractures independent of FRAX probability and its associated risk factors including BMD. Researchers suggested future fracture prediction algorithms should consider including diabetes as an independent risk factor [7, 26].

Chen et al found that in a selected population with osteoporotic fracture in Chinese mainland, 1.0% patients had a 10-year MOF ≥20%, and 42.4% had a 10-year HF probability ≥3%. The NOF thresholds could only identify fewer than half of patients with osteoporotic fracture in China. The mean 10-year MOF probability and 10-year HF probability were 6.6% and 3.0% respectively [26]. Based on a study involved 778 urban postmenopausal women in central south China, Zhang et al recommended 10-year probabilities of MOF and HF of above 4.0% and 1.3% may be currently acceptable as the intervention thresholds in China [15], which is obviously lower than the NOF suggested thresholds. Results of our study showed for patients

with T2D in Chinese mainland, 10-year probabilities for MOF and HF were lower than those without T2D. For T2D population in Chinese mainland, FRAX model may be not a desirable tool to predict fracture risk. Patients with T2D should be treated at lower FRAX score than recommended by Zhang et al.

Our study has several limitations. First, this study is a cross-sectional study, a prospective longitudinal trial is more desirable to find the actual incidence of fracture. Secondly, subjects are all from Shanghai, conclusions are theoretically limited to this urban area. Next, there is a possibility that some data for FRAX calculation might be limited as the data source was from patients. Finally, confounding complicated risk factors of fracture in patients of diabetes such as fall, eyesight, and muscle weakness may also increase fracture risk in patients of T2D.

In conclusion, our study provide the data of risk assessment of major osteoporotic fracture and hip fracture calculated by FRAX model in older patients of type 2 diabetes in Chinese mainland. FRAX model underestimated the fracture probability in older T2D population. Patients with T2D should be considered treatment even though FRAX score was below but close to recommended FRAX-based intervention threshold in China.

Disclosure of conflict of interest

None.

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