Original Article

Trabecular Bone Score in Thais with or without Type 2 Diabetes

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Background: When compared to people without type 2 diabetes mellitus (T2DM), people with T2DM have an increase in fracture risk despite having higher bone mineral density (BMD). Many studies in Caucasians demonstrated that trabecular bone score (TBS) is lower in people with T2DM than those without. The utility of TBS as a fracture risk assessment tool in Asians with T2DM is currently unclear.

Objective: To compared lumbar spine (LS) BMD and TBS in Thais with or without T2DM and investigate the correlation between TBS and hemoglobin A1c (HbA1c) and diabetes duration in participants with T2DM.

Materials and Methods: The present study was a cross-sectional study that included 97 participants with T2DM (37 men and 60 women) and 342 participants without T2DM (174 men and 168 women). LS-BMD and TBS were obtained.

Results: Men and women with T2DM were older and had higher body mass index (BMI). Men with T2DM had significant higher LS-BMD (1.051±0.166 versus 0.972±0.125, p=0.009) and non-significant lower TBS (1.333±0.084 versus 1.365±0.096, p=0.055) than those without. Similarly, women with T2DM had significant higher LS-BMD (0.995±0.155 versus 0.949±0.124, p=0.021) and lower TBS (1.292±0.105 versus 1.382±0.096, p<0.001). After adjusting for age and BMI, T2DM predicted higher BMD in men (p<0.001), but not in women (p=0.143). T2DM was not associated with TBS after adjusting for age and BMI in both genders (p=0.403 and p=0.151 in men and women, respectively). TBS did not correlate with HbA1c in both genders. However, TBS was non-significantly associated with diabetes duration in women (p=0.073), but not in men (p=0.639).

Conclusion: T2DM significantly predicted higher LS-BMD only in men and was not independently associated with TBS in both genders. These data highlighted that, in T2DM, there was some variation in the clinical usefulness of BMD and TBS in predicting osteoporotic fractures with regard to clinical characteristic of participants.

Keywords: Bone mineral density, Type 2 diabetes mellitus, Trabecular bone score

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People with type 2 diabetes mellitus (T2DM) have an increase in fracture risk at most skeletal sites[1-4]. Important risk factors for fractures are diabetes duration, treatment regimens, glycemic control, vitamin D status, and systemic inflammations[5,6]. Impaired osteoblast function is responsible for reduced bone formation leading to osteoporosis in diabetes mellitus[7]. Hyperglycemia stimulates the expression of several proinflammatory cytokines such as tumor necrosis factor, interleukin (IL)-1, and IL-6, which further activate the maturation of osteoclast[7]. The accumulation of advanced glycation end-products in cortical and trabecular bone also alters biomechanical properties of the bone, which lead to increase fragility[8].

Bone mineral density (BMD) has been used as a major determinant of bone mass and fracture

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risk[9]. Despite the fact that individuals with T2DM have greater risk of fracture than those without, normal to high BMD was observed in this group of people[10]. It implies that, in T2DM people, BMD is not a straightforward predictor for fracture risk as in general populations, and thus, might limit its use in people with diabetes[6]. The fracture risk assessment tool (FRAX) also underestimates fracture risk in people with diabetes[11]. Bone turnover markers, such as serum collagen type 1 cross-linked C-telopeptide (βCTX), serum procollagen type 1 N-terminal propeptide (P1NP), and osteocalcin, have not been found to correlate with fracture risk in T2DM[12-14].

Trabecular bone score (TBS) was recently developed for assessing skeletal microarchitecture non-invasively from the spine dual energy X-ray absorptiometry (DXA) images. It provides skeletal microarchitecture information not captured by BMD measurement, and is associated with fracture risk in general population[15]. In addition, TBS is an independent predictor for fractures in Caucasians with T2DM[16]. Few studies in Asians demonstrated the relationship between TBS and skeletal health in people with T2DM. Kim et al reported that men and women younger than 65 years with T2DM had lower TBS when compared to those without[17]. In addition, TBS was negatively correlated to glycemic control and insulin resistance[17]. On the other hand, a study of Japanese men aged 65 years or older demonstrated a similar TBS in T2DM and non-T2DM group[18]. It is possible that, as in people without T2DM, racial differences such as Caucasian versus Asian populations, age, and gender may have great impacts on skeletal health in people with T2DM as seen from previous BMD studies[19-22].

Therefore, the present study aimed to compare lumbar spine (LS) BMD and TBS between Thai participants with or without T2DM. The secondary objective is to assess the association between TBS and hemoglobin A1c (HbA1c) and diabetes duration among participants with T2DM.

Materials and Methods

Study population

The present study was a cross sectional study of two cohorts. Participants without T2DM (n=342) were a subset of the current and ex-employees at the headquarters of the Electricity Generating Authority of Thailand cohort (EGAT)[23]. In addition to the initial aim of studying cardiovascular risk factors in the EGAT cohort in 1985, the survey was extended to collect data on other metabolic disorders as well as bone health. For T2DM cohort (n=97), the participants were recruited from patients being followed in the endocrinology or general medicine clinic at the Faculty of Medicine Ramathibodi Hospital, Mahidol University. Exclusion criteria were diseases that affect bone metabolism, such as hyperthyroidism, primary hyperparathyroidism, Cushing syndrome, hypogonadism, and malignancy. Patients on glucocorticoids, parathyroid hormone, bisphosphonates, strontium ranelate, or hormone replacement therapy were also excluded. Since TBS is recommended to be performed in people with a body mass index (BMI) in the range of 15 to 37 kg/m² to mitigate the effects of extreme variations in tissue thickness[24], the authors excluded participants with BMI of less than 15 and more than 37 kg/m². All participants gave written informed consent. The protocol was approved by the Institutional Review Board and by the Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (ID 03-61-61).

Bone mineral density and trabecular bone score

Each participant changed into light clothing before undergoing BMD assessment by DXA at the LS (L1 to L4 vertebrae). Using a fast array mode, all measurement procedures were performed according to the International Society for Clinical Densitometry recommendations by International Society for Clinical densitometry-certified technologists[25]. The same Hologic Discovery W DXA scanner (Hologic, Bedford, MA) was used in all participants. Quality assurance procedures using a spine phantom were performed daily. The LS-BMD root mean square (RMS) coefficient of variation and RMS standard deviation (SD) were 0.69% and 0.006 g/cm², respectively.

TBS was calculated using TBS iNsight software version 2.1 (medimaps, Mérignac, France) as the mean value of each lumbar vertebra, and for combination from L1 through L4 vertebra. The TBS RMS SD and RMS coefficient of variation were 0.026 and 2.05%, respectively.

Diabetes and other parameters

Diabetes was defined according to the American Diabetes Association criteria[26]. HbA1c was measured using the National Glycohemoglobin Standardization Program (NGSP)-certified methods. The diabetes duration was obtained using a face-to-face interview. Weight and height were measured with standard

Table 1. Characteristics of participants with or without type 2 diabetes

Parameters	All participant (n=439); mean±SD			Men (n=211); mean±SD			Women (n=228); mean±SD		
	With T2DM	Without T2DM	p-value	With T2DM	Without T2DM	p-value	With T2DM	Without T2DM	p-value
Number	97	342		37	174		60	168	
Age (years)	54±10	45.4±7.9	<0.001	55.5±9.4	45.4±8.0	<0.001	54.7±10.4	45.5±7.9	<0.001
Female; n (%)	60 (61.9)	168 (49.1)	0.027	-	-	-	-	-	-
BMI (kg/m2)	27.8±4.3	24.0±3.8	<0.001	26.5±4.5	25.3±3.8	0.078	28.7±4.0	22.8±3.3	<0.001
LS-BMD (g/cm^2)	1.016±0.161	0.961±0.125	0.002	1.051±0.166	0.972±0.125	0.009	0.995±0.155	0.949±0.124	0.021
TBS	1.307±0.099	1.373±0.096	<0.001	1.333±0.084	1.365±0.096	0.055	1.292±0.105	1.382±0.096	<0.001

T2DM=type 2 diabetes mellitus; LS=lumbar spine; BMI=body mass index; BMD=bone mineral density; TBS=trabecular bone score; SD=standard deviation

method and barefoot. The BMI was calculated as weight (in kilograms) divided by height (in meter) squared.

Statistical analysis

Continuous variables were expressed as mean ± SD or mean ± standard error (SE) as indicated. Categorical data were expressed as frequencies or percentages. Comparisons of characteristics between participants with or without T2DM were performed by independent samples t-test and Pearson's chi-squared. Analyses were performed separately in men and women. The association between LS-BMD or TBS (dependent variables) and age, BMI, and T2DM were assessed by multiple linear regression analysis. Comparisons of HbA1c and diabetes duration between men and women were performed by independent samples t-test and Mann-Whitney U test, respectively. The relationship between TBS and HbA1c and diabetes duration were investigated using Pearson and Spearman correlation as appropriate. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

There were 97 participants with T2DM and 342 participants without T2DM included in the present study. Table 1 summarizes the characteristics of the participants based on diabetic status and gender. Those with T2DM were older (54±10 versus 45.4±7.9 years, p<0.001) and had higher BMI (27.8±4.3 versus 24.0±3.8 kg/m², p<0.001) than those without T2DM. More females were included in T2DM group (61.9% versus 49.1%, p=0.027). Mean LS-BMD was higher whereas mean TBS was lower in the T2DM group (Table 1). In participants with T2DM, the average diabetes duration was 11.4±8.5 years (range 0 to 35 years) and mean HbA1c was 7.8±1.4%.

Because gender is a well-known factor influencing bone health, the authors performed analyses separately in men and women. For men, there were 37 participants with T2DM and 174 without. Men with T2DM were older (55.5±9.4 versus 45.4±8.0 years, p<0.001) and had a non-significant higher BMI (26.5±4.5 versus 25.3±3.8 kg/m², p=0.078) than those without. When compared with those without T2DM, men with T2DM had higher LS-BMD (1.051±0.166 versus 0.972±0.125, p=0.009) but tended to have lower TBS (1.333±0.084 versus 1.365±0.096, p=0.055).

For women, there were 60 participants with T2DM and 168 without. When compared to women without T2DM, women with T2DM were older (54.7±10.4 versus 45.5±7.9 years, p<0.001) and had higher BMI (28.7±4.0 versus 22.8±3.3 kg/m², p<0.001). Women with T2DM had higher LS-BMD (0.995±0.155 versus 0.949±0.124, p=0.021) but lower TBS (1.292±0.105 versus 1.382±0.096, p<0.001) than those without.

Multiple linear regression analysis with LS-BMD and TBS as an outcome in men and women

Multiple linear regression analyses adjusting for age and BMI was performed to investigate the effect of T2DM on BMD and TBS in men and women separately (Table 2). In men, younger age (b=–0.003, p=0.018), higher BMI (b=0.006, p=0.010), and T2DM (b=0.097, p<0.001) predicted higher LS-BMD. When considering TBS as an outcome, younger age (b=–0.004, p<0.001) and lower BMI (b=–0.008, p<0.001) predicted higher TBS while T2DM (b=0.014, p=0.403) did not.

For women, younger age (b=–0.006, p<0.001), higher BMI (b=0.011, p<0.001), but not T2DM

Table 2. Multiple linear regression analysis between LS-BMD or TBS and age, BMI, diabetes in men and women

Parameters	Men (n=211)		Women (n=228)	
	b	p-value	b	p-value
LS-BMD as an independent variable				
Age	–0.003	0.018	–0.006	<0.001
BMI	0.006	0.010	0.011	<0.001
T2DM	0.097	<0.001	0.034	0.143
TBS as an independent variable				
Age	–0.004	<0.001	–0.005	<0.001
BMI	–0.008	<0.001	–0.003	0.111
T2DM	0.014	0.403	–0.025	0.151

T2DM=type 2 diabetes mellitus; LS=lumbar spine; BMD=bone mineral density; BMI=body mass index; TBS=trabecular bone score

Table 3. The association between TBS and HbA1c and diabetes duration in men and women with T2DM

Parameters	Men (n=37)		Women (n=60)	
	r	p-value	r	p-value
HbA1c[a]	–0.046	0.785	0.042	0.750
Diabetes duration[b]	–0.080	0.639	–0.233	0.073

T2DM=type 2 diabetes mellitus, TBS=trabecular bone score

[a] Pearson correlation, [b] Spearman correlation

(b=0.034, p=0.143) were significantly associated with higher LS-BMD. For TBS, only younger age (b=–0.005, p<0.001) predicted higher TBS whereas both BMI (b=–0.003, p=0.111) and T2DM (b=–0.25, p=0.151) did not.

The association between LS-BMD or TBS and HbA1c and diabetes duration

Further analyses in T2DM revealed that there was no difference in HbA1c between men and women (7.8±1.4 versus 7.8±1.4%, p=0.989). However, men had longer diabetes duration than women [10 (7 to 20) versus 9 (4 to 15), p=0.031]. There was no correlation between TBS and HbA1c in both men and women (Table 3). TBS was not associated with diabetes duration in men (r=–0.080, p=0.639). However, women with lower TBS tended to have longer diabetes duration (r=–0.233, p=0.073).

Discussion

The present study investigated the difference in LS-BMD and TBS among Thais with or without T2DM. In all participants, mean LS-BMD was higher whereas mean TBS was lower in T2DM group. When considered in men and women separately, LS-BMD was significantly higher in men and women with T2DM when compared to those without. Men with T2DM tended to have lower TBS and women with T2DM had significant lower TBS. When confounding factors including age and BMI were considered, T2DM was independently associated with higher LS-BMD only in men but did not predict LS-BMD in women or TBS in both genders. In addition, TBS was not correlated to HbA1c in participants with T2DM. However, lower TBS was non-significantly associated with longer duration diabetes duration in women. Collectively, there was some variation in the clinical usefulness of BMD and TBS in predicting osteoporotic fractures with regard to clinical characteristic of participants.

Corresponding to other studies[10,22,27,28], both men and women with T2DM had higher unadjusted LS-BMD than those without. It has been established that despite having similar or higher BMD, people with T2DM had a higher risk for osteoporotic fracture than those without T2DM, possibly due to poor bone quality[29]. Obesity is known to be one of the contributed factors for higher BMD in this population as demonstrated in the present study, that participants with T2DM had higher BMI than those without. After adjusting for BMI, LS-BMD was still higher in T2DM in many studies[4,30], but not all[31,32]. Corresponding with the results of the present study, T2DM was associated with higher LS-BMD after adjusted for BMI only in men, but not women. Because of the higher LS-BMD in people with T2DM than those without despite higher osteoporotic fracture rates, LS-BMD could not be used as an effective tool in fracture risk prediction in T2DM. Additional tools are warranted to assess abnormal bone quality. For example, high resolution peripheral quantitative computed tomography (HRpQCT) was used to demonstrate an increased cortical porosity in postmenopausal women with T2DM[33,34].

In addition to areal BMD, TBS has been recognized as a more accurate predictor of incident fracture in T2DM[16]. However, the results of studies investigated TBS as an indicator for skeletal deterioration in T2DM included heterogeneous groups of participants such as age, gender, BMI, and diabetes characters[35]. In the present study, unadjusted TBS tended to be lower in men and was significantly lower in women with T2DM than those without. Nevertheless, the association between T2DM and lower TBS disappeared after adjusting for age and BMI. These results were similar to the studies of

Zhukouskaya et al[36] and Iki et al[18]. The first study (n=206) reported that TBS of participants with well-controlled T2DM with a mean age of 66 years and mean HbA1c of 6.8%, was not different from those of participants without T2DM and a mean age of 65 years[36]. The second study, which had 1,683 participants, reported that there was no difference in TBS among Japanese men with T2DM or without T2DM with a mean HbA1c 6.5% of similar age[18]. In contrary, the study Canadian women with a mean age between 65 and 68 years, revealed that TBS of 2,356 women with diabetes was significantly lower than that of 27,051women without diabetes after controlling for multiple covariates[16]. Lower TBS was also reported in participants with diabetes compared to those with normoglycemia in a study of 555 Australian men with a mean age of 69 years and 514 women with a mean age of 62 years, after adjusting for age, height, and weight or waist circumference[37]. Similarly, TBS in a Korean study of 2,758 men and women with a mean age between 63 and 67 years, was lower in men with diabetes than those without diabetes after controlling for covariates, but the association between lower TBS and diabetes status in women was found only in an unadjusted model[17]. However, a subgroup analysis in women younger than 65 years revealed that they had significantly lower TBS after controlling for covariates[17]. Collectively, there have been only few studies exploring TBS and T2DM in Asian population and different results among cohorts may indicate that low TBS in people with diabetes may not be universal in all population. Effect of races, genetics, age, body composition, diabetic status, on skeletal health and adjusted variables may be of great importance and could explain differences in results between the present study and others. Compare to others, the present study participants were the youngest with a mean age between 45 and 56 years and had good glycemic control. These could possibly explain the lack of association between TBS and diabetes status in the present study participants.

It is well established that many factors affect TBS values. For example, there was a significant decrease in TBS with increasing age. In the present study, older age was correlated to lower TBS in both genders. The rate of loss in TBS is exaggerated after the age of 65 years[38-40]. Few studies reported that, to predict fracture risk in people with diabetes, TBS may be useful for women younger than 65 years[17,37]. Correspondingly, a subgroup analysis of the present study in women younger than 65 years demonstrated that T2DM was non-significantly associated with lower TBS (b=–0.034, p=0.062) after adjusting for both age and BMI. A previous study reported TBS values also showed weakly negative correlation with BMI[38], which was similar to the finding in the present study (data not shown). In T2DM, several studies reported the inverse association between TBS and HbA1c, fasting plasma glucose, fasting insulin, and homeostasis model assessment for insulin resistance (HOMA-IR)[17,18]. However, in the present study, there was no association between TBS and HbA1c in participants with T2DM. The explanation could be relatively good glycemic control (mean HbA1c 7.8%) in the present study participants. In addition, previous study suggested that long standing of hyperglycemia was related to lower TBS[18]. Correspondingly, longer diabetes duration tended to be associated with lower TBS in women, but not in men. Differences in characteristics of participant including age, diabetes duration, glycemic parameters, and metabolic phenotype could explain these contrasting finding between the present study and others.

The strength of the present study is both men and women were included in the study, where many other studies examined only men or women. However, the number of participants was relatively small. The authors did not assess other parameters of hyperglycemia such as HOMA-IR. The participants had relatively well-controlled diabetes, which may not be a true representation of the whole population of T2DM. In addition, fracture outcomes were not assessed. Participants in the present study were originally included from two cohorts. Therefore, this limited the possibility to have well-matched clinical characteristics, including age and BMI, among participants with or without T2DM. Adjusting by statistical analysis could eliminate this confounder, but not all. The authors did not analyze several confounding factors due to lack of data. Factors known to affect bone health included smoking, alcohol drinking, vitamin D status, menopausal status, medications that affect bone metabolism such as steroid or pioglitazone, and FRAX scores are lacking. Future studies that include more participants with well-matched clinical characteristics are warranted to clarify the benefit of TBS in prediction of skeletal deterioration in Thai T2DM.

Conclusion

Men and women with T2DM have higher LS-BMD than those without. TBS was non-significantly lower in men with T2DM, and significantly lower in women with T2DM. T2DM independently predicted

higher LS-BMD only in men after adjusting in age and BMI. The association between T2DM and lower TBS disappeared after adjustment for age and BMI. These data highlighted that, in T2DM, there were some variation in the clinical usefulness of BMD and TBS in predicting osteoporotic fractures with regard to clinical characteristic of participants.

What is already known on this topic?

Many studies, mostly in Caucasians, demonstrated that TBS is lower in people with T2DM than those without, and could be used as a predictor of osteoporotic fracture in people with T2DM. The utility of TBS as a fracture risk assessment tool in Asians with T2DM is currently unclear.

What this study adds?

Men with T2DM had non-significant lower TBS, and women with T2DM had significant lower TBS. When confounding factors including age and BMI were considered, T2DM did not further predict TBS in both genders. In T2DM, there was some variation in the clinical usefulness of BMD and TBS in predicting osteoporotic fractures with regard to clinical characteristic of participants.

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Conflicts of interest

Hataikarn Nimitphong received speaker honoraria from Novo Nordisk, Takeda, MSD, Sanofi Aventis, Amgen, Eli lily, Boehringer Ingelheim Pharmaceuticals and Novartis. Sirimon Reutrakul received speaker honoraria from Novo Nordisk, Sanofi Aventis, Medtronic, and BD, a research grants from Merck Sharp and Dohme, non-financial support from ResMed, Thailand. Sasima Srisukh, Jintanan Jangsiripornpakorn, Nantaporn Siwarasanond, Sunee Saetung, Suchawadee Musikarat, Chanika Sritara, Piyamitr Sritara, and Boonsong Ongphiphadhanakul have nothing to disclose.

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