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Association between pre-diabetes, type 2 diabetes and trabecular bone score: The Vietnam Osteoporosis Study

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ABSTRACT

Aims: Trabecular bone score (TBS) is a surrogate indicator of bone microarchitecture. The present study sought to examine the association between type 2 diabetes (T2D) and trabecular bone score (TBS) in adult Vietnamese men and women.

Methods: The study was part of the Vietnam Osteoporosis Study, in which 2702 women and 1398 men aged ≥30 years were recruited from the general community in Ho Chi Minh City. HbA_{1c} levels were measured by the ADAMS™ A_{1c} HA-8160 (Arkray, Kyoto, Japan), and classified into 3 groups: normal if $HbA_{1c} < 5.7\%$; pre-diabetes (5.7–6.4%); and diabetes (>6.4%). TBS was evaluated by iNsight Software, version 2.1 (Medimaps, Merignac, France) on lumbar spine BMD scan (Hologic Horizon). Differences in TBS between diabetic status were analyzed by the multivariable regression model with adjustment for age and body mass index.

Results: The prevalence of pre-diabetes and diabetes in men and women was 30.2% and 8.3%, respectively. In women, TBS was lower in pre-diabetes (−0.02; $P < 0.001$) and diabetes (−0.02; $P < 0.001$) compared with normal individuals. In men, there was no statistically significant difference in TBS between diabetic status. Moreover, TBS was significantly inversely correlated with HbA_{1c} levels in women ($P = 0.01$), but not in men ($P = 0.89$).

Conclusion: Women, but not men, with type 2 diabetes and pre-diabetes have lower TBS than individuals without diabetes. These data suggest that diabetes and prediabetes are associated with deterioration of bone microarchitecture.

1. Introduction

Type 2 diabetes (T2D) is associated with higher bone mineral density (BMD) [1], which is supposed to be associated with lower risk of fracture in the general population. However, individuals with T2D actually have higher risk of fracture, particularly hip fracture [2] and vertebral fracture [3]. Our previous study showed that approximately half of all fractures

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occurred in those do not have low BMD [4]. This suggested that fractures in patients with diabetes may result from alterations in skeletal properties or bone quality not captured by dual-energy X-ray absorptiometry (DXA)-derived BMD [5].

Recent developments in image analysis allow the evaluation of trabecular bone in dual-energy X-ray absorptiometry lumbar spine BMD scan in the form of trabecular bone score (TBS) [6]. TBS is a measure of variance of grey-level texture from 2-dimension images, with low values representing fracture-prone bone structure, while high values reflect fracture-resistant bone. In observational studies, higher TBS is associated with stronger bone and lower risk of fracture [7,8], and the association is independently of lumbar spine BMD [9–11]. Furthermore, TBS has been shown to be useful for predicting fracture risk in patients with diabetes [12,13].

It has been suggested that TBS may explain the increased fracture risk in patients with diabetes. Nevertheless, findings on the relationship between diabetes and TBS are mixed: cohort studies in Caucasian populations showed that patients with diabetes had lower TBS than individuals without diabetes [13,14], but a study in Italians [15] found no significant difference in TBS between the two groups. A study in Japan found that men with hyperglycemia had lower TBS than those without diabetes [16]. Another study in Koreans [17] found that TBS was lower in men with diabetes than men without diabetes; but in women, the same observation only observed in an unadjusted model. The discrepancy in findings could be attributable to differences in population characteristics, sampling methods, duration of disease and HbA1c levels. Taken together, the association between TBS and type 2 diabetes is still uncertain, and a larger study may help refine the magnitude of association.

We hypothesize that patients with diabetes have greater BMD but poor bone microarchitecture associated with reduced bone strength. This study sought to test the hypothesis by assessing the association between type 2 diabetes and TBS in adult Vietnamese men and women. We also wanted to define the relationship between HbA1c levels and TBS in men and women.

2. Material and methods

2.1. Study design

This study was part of the Vietnam Osteoporosis Study (VOS) which was described previously [18]. Briefly, VOS is designed as a population-based prospective study initiated in 2015, with the setting being Ho Chi Minh City (formerly Saigon). Data collection had been conducted between 2015 and 2017. The overall goal of VOS is to investigate risk factors for non-communicable diseases. The Study involved 4157 men and women aged 20 years and older (average age being 51). The study's procedure and protocol were approved by the research and ethics committee of the People's Hospital 115. The study was conducted according to the ethical principles of the Declaration of Helsinki, and all participants gave written informed consent.

In this study, we included people aged 30 years and above, because there is a significant number of young people diagnosed with diabetes in Asian countries [19]; furthermore, type 2 diabetes is usually diagnosed in over 30 years old, whereas type 1 diabetes is often diagnosed in childhood. We excluded individuals with type 1 diabetes based on self-report. We also excluded individuals with impaired cognitive function or not willing to give informed consent or unable to complete required clinical examinations.

2.2. Data collection and measurements

Demographic characteristics including lifestyle factor and clinical information were ascertained by a structured questionnaire. Height and weight were measured by an electronic portable, wall-mounted stadiometer (Seca Model 769; Seca Corp, CA, USA) without shoes, ornaments, hats or heavy layers of clothing. Body mass index (BMI) was derived as the weight in kilograms divided by the square of the height in meters (kg/m^2), and categorized into 4 groups: underweight (<18.5); normal (18.5 to <23.0); overweight (23.0 to <27.5) and obese (≥27.5) [20].

Participants were asked to provide information on current and past smoking habits. Alcohol consumption (numbers of standard drinks per day) at present and in the last 5 years, was obtained. Clinical data including blood pressure, pulse, and reproductive history (i.e. parity, age of menarche and age of menopause), medical history (i.e. previous fracture, previous and current use of pharmacological therapies) were also obtained; drug history was obtained specifically antidiabetic medicines. Two blood pressure measurements were taken (5 min apart) in seated position, and the average value was recorded and classified as hypertension if their average systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.

2.3. Ascertainment of type 2 diabetes

Overnight fasting blood sample (12 ml) was taken between 7:00 AM and 11:00 AM by venepuncture. The serum was immediately frozen to −20 °C prior to biochemical analysis which was done within 24 h after the collection. HbA1c levels were determined using the high-pressure liquid chromatography (HPLC) analyzers ADAMS™A_{1c} HA-8160 (Arkray, Kyoto, Japan); the intra- and inter-assay coefficient of variation of the technique was less than 1%. Fasting plasma glucose (FPG) levels were determined using hexokinase method (Advia 1800 Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany) with an intra-measurement coefficient of variance of 0.98–1.34%. All biochemical analyses were performed at MEDIC's Department of Biochemistry and Paraclinical Services (Ho Chi Minh City, Vietnam). An individual was diagnosed with diabetes if their HbA1c level was ≥6.5% (48 mmol/mol) [21] or pre-diabetes if HbA1c between 5.7% and 6.4% (39–46 mmol/mol) [22]. The diagnosis of diabetes was also verified by an ascertainment of medication use, but most patients with type 2 diabetes (~90%) was undertreated.

2.4. *Trabecular bone score*

Areal BMD was measured at the lumbar spine, femoral neck, total hip and whole body using a Hologic Horizon (Hologic Corp, Bedford, MA, USA) by a qualified radiology technologist. For the lumbar spine, we measured BMD from L2 to L4. The densitometer was standardized by phantom before each measurement. The coefficient of variation in BMD measurement at our lab was 1.5% for the lumbar spine and 1.7% for the hip.

TBS measurements were performed in the Department of Medicine, Khon Kaen University (Thailand) using the iNsight Software, version 2.1 (Medimaps, Merignac, France). These analyses were performed blind to diabetic status and other clinical information. The software uses the antero-posterior spine raw image(s) from the densitometer (Hologic Corp, Bedford, MA, USA), including the BMD region of interest and edge detection so that the TBS calculation is performed over exactly the same region of interest as the BMD measurement. In this analysis, we used a research version of the commercialized TBS iNsight software. The analysis was performed by a doctor using the same densitometer. The reproducibility of TBS determinations in several mono-center studies was reported between 1.1% and 1.9% CV [9].

2.5. *Data analysis*

In order to address our primary aim (i.e., examining the association between diabetes and TBS), we used the analysis of covariance (ANCOVA) and multiple linear regression analysis to model the data. In the ANCOVA, TBS was treated as the outcome, and diabetic status (eg normal, pre-diabetes and diabetes) was the independent variable. In this ANCOVA model, age and BMI were considered covariates, because the two factors are known to be associated with TBS. The least-squares (adjusted) mean of TBS was estimated from the ANCOVA parameters for normal, pre-diabetes and diabetes groups, and was visualized by the "visreg" program [23]. In the second analysis, we used the multiple linear regression model to examine the relationship between TBS (dependent variable) and HbA1c levels (independent variable), with adjustment for age and BMI. Because the distribution of HbA1c levels was skewed, we applied the natural logarithmic transformation to the data prior to the analysis. The linear regression model satisfied all assumptions of normality, homoscedasticity, and independence. All analyses were conducted using the R statistical environment [24].

3. Results

The study included 2702 women and 1398 men aged 30 years and older, whose baseline characteristics stratified by gender are shown in Table 1. The average age of participants was 47.4 years, and women appeared to be older than men ($P < 0.001$). Approximately 53% (n = 1430) women were post-menopausal, and the average age at menopause was ~50 years. The mean BMI of the participants was 22.9 (SD 3.3) kg/m^2. Overall, 209 women (7.7%) and 142 men (10.2%) had BMI $\geq$ 27.5 kg/m^2, the level considered "obese" by Asian

Table 1 – Baseline characteristics of participants stratified by sex.

Parameter	Men	Women	P-value
N	1398	2702	
Age	45.7 (14.9)	48.4 (14.2)	<0.001
Age at menopause		49.6 (4.4)	
Number of post-menopausal women (n; %)[1]		1430 (52.9)	
Body mass index	23.3 (3.3)	22.8 (3.3)	<0.01
Hypertension (n; %)	359 (25.7)	513 (19.0)	<0.01
Diabetes mellitus (n; %)	105 (7.6)	234 (8.7)	0.23
Number on oral antidiabetes medication (n; %)[2]	10 (9.5%)	24 (10.25%)	0.73
Duration of antidiabetes medication (yr)	4.0 (0.17–5.0)	3.5 (0.1–7.7)	0.95
Current smoking (n; %)	579 (41.3)	40 (1.5)	<0.001
HbA1c	5.7 (0.9)	5.6 (0.8)	0.25
Total cholesterol	4.8 (0.97)	5.0 (1.02)	<0.01
LDL cholesterol	3.0 (0.86)	3.16 (0.93)	<0.01
Femoral neck BMD	0.78 (0.15)	0.68 (0.13)	<0.001
Lumbar spine BMD	1.03 (0.16)	0.99 (0.17)	<0.001
Prevalence of osteoporosis (n; %)[3]	53 (5.2)	508 (18.8)	<0.001
Trabecular bone score	1.39 (0.09)	1.34 (0.12)	<0.001
Obesity (n; %)			<0.01
Underweight	81 (5.8)	205(7.6)	
Normal	606 (43.3)	1335 (49.4)	
Overweight	569 (40.7)	953 (35.3)	
Obese	142 (10.2)	209 (7.7)	

Values are mean and standard deviation (in parentheses) for continuous variables, and n (%) for categorical variables. P-values for testing difference between men and women were derived from the t-test (for continuous data) or Chi-squared test (for categorical data).

[1] Percent of total.

[2] Percent of the individuals with diabetes.

[3] For individuals aged 50 years and older.

Table 2 – Baseline characteristics of participants stratified by sex and diabetic status.

Parameter	Non-diabetes	Pre-diabetes	Diabetes	P-value
Men				
N	887 (63.4)	406 (29.0)	105 (7.6)	
Age	41.5 (14.5)	52.3 (12.9)	56.2 (11.2)	<0.001
BMI	22.8 (3.1)	23.8 (3.3)	25.7 (3.5)	0.26
Hypertension	199 (22.4)	120 (29.6)	40 (38.1)	<0.001
Current smoking	343 (38.7)	189 (46.6)	47 (44.8)	0.02
Total cholesterol	4.74 (0.90)	4.95 (0.99)	5.04 (1.27)	<0.001
LDL cholesterol	2.94 (0.81)	3.11 (0.90)	3.04 (1.02)	0.06
Femoral neck BMD	0.8 (0.16)	0.75 (0.13)	0.78 (0.14)	0.49
Lumbar spine BMD	1.03 (0.15)	1.01 (0.16)	1.05 (0.16)	0.48
Trabecular bone score	1.41 (0.08)	1.37 (0.09)	1.37 (0.09)	0.015
Obesity				<0.001
Underweight	60 (6.8)	21 (5.2)	0 (0)	
Normal	442 (49.8)	139 (39.2)	24 (22.9)	
Overweight	319 (36.0)	194 (47.8)	56 (53.3)	
Obese	66 (7.4)	52 (12.8)	25 (23.8)	
Women				
N	1635 (60.5)	833 (30.8)	234 (8.7)	
Age	43 (13.6)	55.7 (10.3)	60.3 (10.8)	<0.001
BMI	22.0 (2.98)	23.6 (3.26)	25.0 (3.9)	0.04
Hypertension	244 (14.9)	205 (24.6)	64 (27.4)	<0.001
Current smoking	21 (1.3)	12 (1.4)	7 (3.0)	0.12
Total cholesterol	4.83 (0.92)	5.32 (1.1)	5.03 (1.16)	<0.01
LDL cholesterol	3.03 (0.84)	3.41 (0.98)	3.15 (1.09)	<0.001
Femoral neck BMD	0.70 (0.12)	0.65 (0.13)	0.65 (0.13)	0.49
Lumbar spine BMD	1.02 (0.16)	0.93 (0.17)	0.94 (0.17)	0.49
Trabecular bone score	1.38 (0.11)	1.29 (0.10)	1.27 (0.11)	<0.001
Obesity				<0.001
Underweight	168 (10.3)	31 (3.7)	6 (2.6)	
Normal	931 (56.9)	341 (40.9)	64 (27.4)	
Overweight	467 (36.0)	368 (47.8)	117 (53.3)	
Obese	69 (4.2)	93 (11.2)	47 (20.1)	

Values are mean and standard deviation (in parentheses) for continuous variables, and n (%) for categorical variables. P-values for testing difference between men and women were derived from the analysis of variance (for continuous data) or Chi-squared test (for categorical data).

criteria [20]. The men also had significantly higher proportion of hypertension, current smoking or regular alcohol use than women. About half of men and 3% of women reported that they were current smokers.

However, the proportion of diabetes was not significantly different between genders. About 9.5% (n = 10) of men and 10.25% (n = 24) women with diabetes were on oral anti-diabetes medications. As expected, the average lumbar spine BMD and trabecular bone score (TBS) were higher in men than in women. Among individuals aged 50 years and older, the prevalence of osteoporosis (T-scores < −2.5) was 5.2% in men and ~19% in women. However, only 2 men and 29 women were on bisphosphonates.

Using the criteria of HbA1c ≥6.5%, the prevalence of diabetes was 8.7% (n = 234) of women, and 7.6% (n = 105) of men (Table 2). The prevalence of pre-diabetes was 30.8% in women and 29% in men. On average, patients with diabetes were older than individuals without diabetes. Women and men with diabetes also had significantly greater proportion of overweight and obese than individuals without diabetes. In fact, the prevalence of overweight and obesity among patients with diabetes was nearly two-fold higher than that among individuals without diabetes.

3.1. *TBS and diabetes*

In unadjusted analysis, TBS was significantly ($P < 0.001$) lower in those with diabetes and pre-diabetes compared to people without diabetes, and this was observed in men and women (Table 3). However, after adjusting for age and BMI, women with pre-diabetes (difference: −0.02, P < 0.001) and diabetes (difference −0.02, P = 0.004) had significantly lower TBS than those with 'Normal' status. However, in men, the difference in TBS between pre-diabetes (P = 0.44), diabetes (P = 0.67) and non-diabetes group was not statistically significant. The adjusted means of TBS for the 3 groups (non-diabetes, pre-diabetes and diabetes) are shown Fig. 1.

3.2. *TBS and HbA1c*

In a further analysis, we examined the association between HbA1c and TBS (Table 4). There was a significant inverse association between HbA1c and TBS (Fig. 2), but this was observed in women, not in men. In women, after adjusting for age and BMI, each log percentage increase in HbA1c was associated with ~0.4% decrease in TBS ($P = 0.016$). The three factors –

Table 3 – Association between TBS (outcome) and diabetic status: analysis of covariance.

Predictor	Women	Men
Age (+1 year)	−0.0035 (0.00017)**	−0.0026 (0.00015)**
Post-menopause (yes)	0.0704 (0.0048)**	
BMI (+1 kg/m^2)	0.0012 (0.0005)**	−0.0016 (0.00064)*
Pre-diabetes vs Non-diabetes	−0.0110 (0.0039)**	−0.0037 (0.0048)
Diabetes vs Non-diabetes	−0.0121 (0.0063)**	0.0035 (0.008)

Note: Values are regression coefficient and standard error (in parenthesis). Statistical significance is indicated by **P < 0.0001 and *P = 0.01.

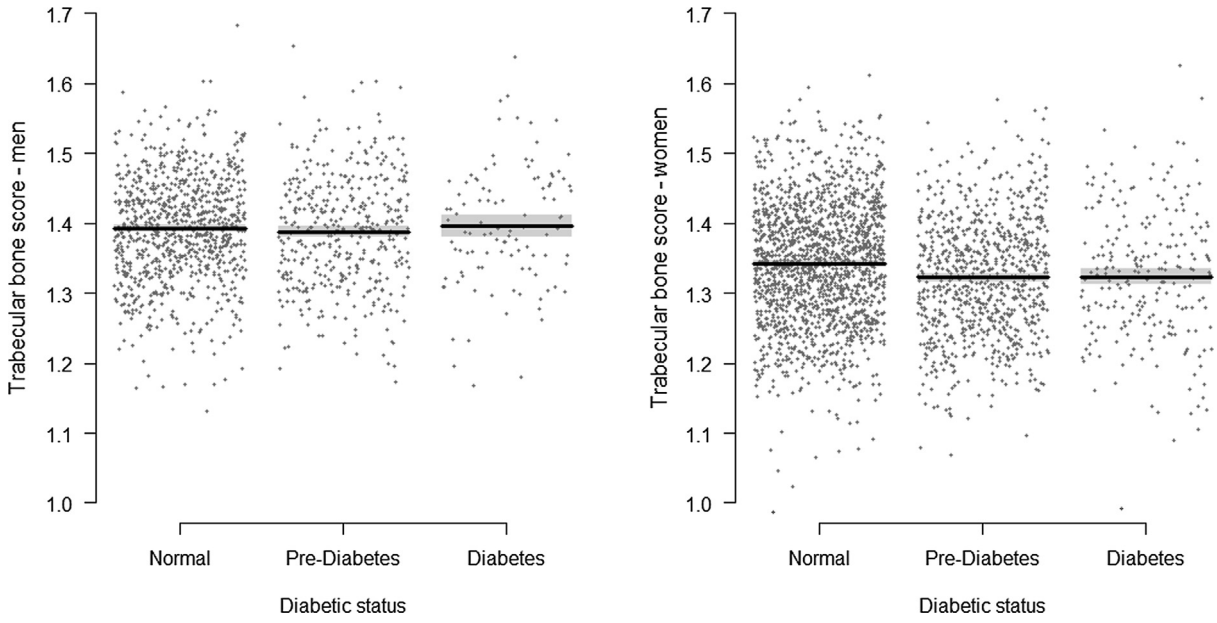

Fig. 1 – Adjusted (least squares) mean of TBS by diabetic status for men (left panel) and women (right panel). The adjusted values were estimated from the analysis of covariance model with age and BMI being covariates. The difference in TBS between diabetic status was statistically significant (P < 0.001) in women, but not in men.

Table 4 – Association between TBS (outcome) and HbA1c: multiple linear regression analysis in women.

Predictor	Women	Men
Age	−0.0053 (0.0001)**	−0.0027 (0.0001)**
BMI	0.0015 (0.0005)**	−0.0016 (0.0006)**
HbA1c	−0.3973 (0.165)*	0.0026 (0.0183)
HbA1c squared	0.0951 (0.042)*	
R squared value	0.452	0.222

Note: Values are regression coefficient and standard error (in parenthesis). Statistical significance is indicated by **P < 0.0001 and *P = 0.01.

age, BMI and HbA1c – collectively explained 45% of the variance in TBS.

When type 2 diabetes was treated as the outcome, each 0.1 unit decrease in TBS was associated with an odds ratio of 1.69 (95% CI, 1.51–1.85) after adjusting for age and body mass index.

4. Discussion

In recent years, TBS has emerged as an important risk factor for fracture and may explain why patients with T2D have higher risk of fracture despite they have higher BMD than non-diabetic individuals. However, the association between TBS and diabetes has been controversial, with conflicting results being reported in the literature. In this study, based on a well characterized cohort of large sample size, we found that there was an inverse association between TBS and HbA1c levels, but the association was observed in women, not in men. More importantly, we found that women with pre-diabetes had significantly lower TBS than those with normal glycemia. Consequently, women with diabetes (or pre-diabetes) had significantly lower TBS than those normal HbA1c levels. These findings deserve further elaboration.

Patients with T2D have normal or higher areal BMD but increased fracture risk [25,26], and this is considered a paradox. This paradox has led to the suggestion that fragility fracture in T2D may result from diabetes-induced alteration in bone properties [27], and TBS may serve as an indicator of vertebral deterioration in patients with diabetes. Our finding

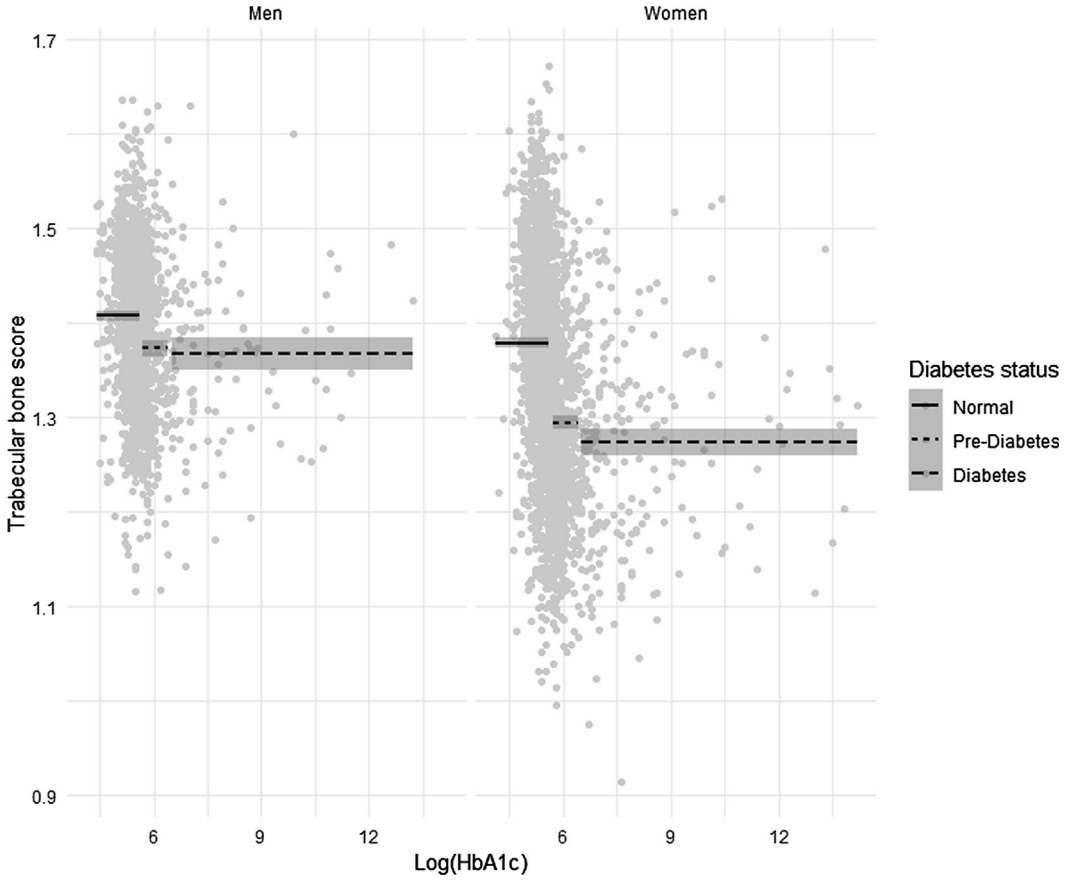

Fig. 2 – Relationship between trabecular bone score and HbA1c (in natural log scale) grouped by diabetic status for men (left panel) and women (right panel). Higher values of HbA1c were associated with lower values of trabecular bone score, but this correlation was observed in women, not in men.

supports this hypothesis. Indeed, our result is consistent with previous studies [13,14,17,28] which also found that TBS was significantly lower in patients with T2D compared with normal individuals. However, our finding is not agreeable with other studies that found no significant association between TBS and diabetes [15,16]. It is not apparently clear why there were difference in findings between studies, but it may be due to the differences in sample sizes, characteristics of participants (ethnicity, age, obesity status) and statistical analysis. In this study, we have been carefully adjusted for covariates that are known to relate to TBS, and we have shown that TBS was statistically significantly associated with HbA1c as a continuous variable or with diabetic status as a categorical variable.

It should be noted that the observed effect size in this study and other studies is reasonable large. Indeed, the average difference in TBS between patients with T2D and normal individuals is ~0.1, approximately 1 standard deviation. Each standard deviation decrease/lower in TBS is associated with 1.4-fold increase in fracture risk in the general population [29] and 1.27-fold (95% confidence interval, 1.10–1.46) in women with type 2 diabetes [13]. Thus, while it seems that areal BMD is not a useful measurement in the assessment of fracture risk in patients with T2D, TBS can be a useful marker [13]. Moreover, we and others [30–32] have shown that patients with T2D have lower cortical volumetric BMD (and hence lower bone strength) which might explain why they have a greater risk of fracture at cortical rich bone sites. Furthermore, in a recent cross-sectional study using HRpQCT [33], it was shown that patients with type 2 diabetes were associated with significantly lower cortical bone mineral density, lower cortical thickness, higher cortical porosity and lower trabecular thickness which all contribute to reduced bone strength. Taken together, the higher fracture risk in patients with T2D is due to multifactorial factors, including deterioration of trabecular bone and reduced bone strength.

A novel finding from our study was the association between pre-diabetes and lower TBS values. The mechanism of association between TBS and type 2 diabetes or pre-diabetes is not clear. However, it can be hypothesized that the association may be mediated by advanced glycation end (AGE) product. Advancing age is associated with the accumulation of AGE in bone matrix, leading to increased bone fragility [34]. Patients with type 2 diabetes have higher accumulation of pentosidine, a product of AGE [35]. Moreover, in a recent study on patients with type 2 diabetes, a correlation between TBS and pentosidine was observed [36]. Thus, AGE may explain why individuals with pre-diabetes had lower

TBS than those with normal glycemia, but this hypothesis needs to be tested in a well characterized prospective study.

In this study, the association between TBS and diabetic status was observed in women, not in men. The mechanism for this differential association is unknown, but a hypothesis can be put forward. We postulate that the difference could be due to the effect of degenerative changes on the DXA measurement of bone density in the lumbar spine [37]. Degenerative changes in the lumbar spine obscures the age-related change in lumbar spine BMD in men. Because TBS is derived from DXA spinal scan, its measured value is also likely to be affected by degenerative changes, and this could explain why the association between TBS and diabetes in men is not apparent.

The present findings should be put in context of strengths and weaknesses. The study was based on a large and well characterized cohort that was sampled from the general population. A small proportion (~10%) of the patients with T2D was on anti-diabetic medications which largely preclude the confounding effect of medication use. However, in this study participants were sampled from an East Asian population in urban setting, and the finding may not be generalizable to other populations or the rural setting where the prevalence of diabetes is generally lower than that in the urban populations. Since participants of the present study were volunteers, patients with severe or symptomatic diabetes may have been less likely to participate in the study; this potential bias may have resulted in an underestimation of the association of interest. Another weakness is that we could not ascertain the duration of diabetes. Moreover, we did not use autoantibody tests to identify patients with type 1 diabetes. Nevertheless, previous studies suggested that LADA may account for only 2–12% of all cases of diabetes in adult population [38]. We did not have fracture incidence data, and as a result, no inference on the relationship between bone strength, diabetes and fracture could be made. The data were obtained from a cross-sectional study, and no causal inference could be made on the association between bone architecture and diabetes.

In conclusion, our data suggest that there was a statistically significant association between trabecular bone score and type 2 diabetes or HbA1c in women, but not in men. These data suggest that in women diabetes and prediabetes are associated with deterioration of bone microarchitecture.

Declaration of Competing Interest

None

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Author Contributions

Conceived and designed the experiments: LHP, TVN. Performed the experiments and data collection: LHP, BT, ATD. Analyzed the data: TVN, BT, LHP. Wrote the paper and interpretation of data: LHP, TVN.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107790.

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