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Age-related trends in trabecular bone scores and bone mineral density in Chinese men with type 2 diabetes mellitus: a cross-sectional study

Yunyun Lin[1], Juanjuan Tang[2], Cheng Xue[3], Wenjuan Di[3] & Peng Cheng[3]✉

Patients with Type 2 diabetes mellitus(T2DM) typically have an average or higher bone mineral density (BMD) but are at a significantly higher risk of fracture than patients without diabetes. Trabecular bone score (TBS) is a textural index derived from pixel gray-level variations in lumbar spine DXA image, which has been introduced as an indirect measure of bone quality. This study aimed to discuss the trends and annual rates of change in BMD and TBS with age in Chinese men with T2DM and men without diabetes mellitus. Lumbar spine(LS) TBS was significantly lower in males with T2DM compared to men without diabetes(1.279 ± 0.117 vs. 1.299 ± 0.090, *P* = 0.005). However, TBS in men with T2DM peaked around age 60, which occurred later and was lower than the peak observed in men without diabetes, who reached their peak TBS around age 50 (1.294 ± 0.126 vs. 1.328 ± 0.088). Femoral neck, total hip, and lumbar spine BMD in men with T2DM were not significantly different from those in men without diabetes. The results showed that both men with or without T2DM exhibited the lowest annual rates of change in TBS at 66–75 years of age, with values of -1.05%(*P* < 0.001) and − 0.90%(*P* < 0.001), respectively. Patients with great glycemic control demonstrated higher TBS and BMD. Men with T2DM have later and lower peak TBS and faster bone loss, suggesting that diabetes may negatively impact bone microarchitecture and mineralization.

Keywords Type 2 diabetes, Bone mineral density, Trabecular bone score, Men, Average annual rate of change

Abbreviations

BMI	Body mass index
T2DM	Type 2 diabetes mellitus
DXA	Dual-energy X-ray absorptiometry
BMD	Bone mineral density
TBS	Trabecular bone score
FN	Femoral neck
TH	Total hip
LS	Lumbar spine
TBS	Trabecular bone score
HbA1c	Glycated hemoglobin

Osteoporosis is a systemic skeletal disease characterized by diminished bone mass or defects in bone microarchitecture, which leads to decreased bone strength and an increased risk of fractures[1]. According to the 2018 China Osteoporosis Epidemiology Survey, released by the National Health Commission of China, the prevalence of osteoporosis among individuals aged 50 years or older was 19.2%, and it increased to 32.0%

[1]Department of Gerontology, The Fifth Affiliated Hospital of Wenzhou Medical University, Lishui Municipal Central Hospital, Lishui, People's Republic of China. [2]Department of Gynecology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, People's Republic of China. [3]Department of Gerontology, The First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Road, Gulou District, Nanjing, Jiangsu Province, People's Republic of China. ✉email: cphh@sohu.com

among those aged 65 years or older. Given the agingm population, the prevalence of osteoporosis is expected to rise annually[2]. Type 2 diabetes, another prevalent chronic ailment, poses a substantial global public health burden associated with aging. The global prevalence of diabetes among adults aged 20–79 years is projected to reach 7.7%, affecting approximateky 439 million adults by 2030[3]. Increased bone fragility is acknowledged as a frequent and severe complication in patients with diabetes. The fracture risk is notably higher in individuals with diabetes in comparison to those without the condition. Moreover, a substantial number of individuals at risk of osteoporosis may also have diabetes, impacting their quality of life and potentially leading to severe health consequences such as immobility. Prolonged immobilization and hospitalization, as a result, can contribute to significant morbidity and mortality. Consequently, there is a critical need for early identification of patients with diabetes at high risk of fractures, a comprehensive understanding of the connection between these two conditions, and the development of effective assessment and management strategies to mitigate their impact on patients' health.

Bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) is the gold standard for assessing osteoporosis. Nevertheless, prevailing research indicates that individuals with T2DM often exhibit average or higher BMD levels compared to patients without T2DM. Additionally, individuals with T2DM often have a higher rate of obesity, which is also linked to elevated BMD levels[4–7]. A meta-analysis demonstrated an elevated risk of hip and non-spine fractures among individuals with T2DM[8]. Interestingly, there tends to be an underestimation of the fracture risk in patients with diabetes. The Trabecular Bone Score (TBS) is a non-invasive tool utilizing DXA pixel gray level analysis to assess bone microstructure indirectly by analyzing trabecular bone texture sparseness. TBS can be applied retrospectively to existing DXA images, eliminating the need for additional X-ray exposure, time, or cost. It is widely accessible, as it requires no new equipment, provided proper calibration is ensured[9]. The TBS estimate is usually robust and helpful in collecting empirical data. TBS has been associated with various conditions, including diabetes, primary hyperthyroidism, rheumatoid arthritis, adrenal gland disease, chronic kidney disease, and fractures in individuals undergoing long-term glucocorticoid therapy[10,11]. In patients with similar BMD levels, TBS provides additional information about bone microstructure and quality, offering information independent of BMD. The combined use of TBS and BMD significantly enhances fracture risk prediction[12]. Specifically, lumbar spine(LS) TBS emerges as a predictor of osteoporotic fractures in individuals with diabetes, capturing a more significant portion of the diabetes-associated fracture risk compared to BMD[13–16]. While the majority of TBS studies in T2DM populations have focused on women, limited research has explored the impact of TBS in Asian men with type 2 diabetes.

This study aims to investigate the differences in TBS and BMD between Chinese men with T2DM and those without T2DM, exploring the correlation with age through cross-sectional studies.

Materials and methods

Study population

Subjects were recruited from Nanjing (China) and its surrounding areas and underwent a detailed medical history review and physical examination. All participants had undergone regular physical examinations at our Geriatric Endocrinology Department between 2013 and 2023. To ensure an adequate sample size and minimize age-related bias, patients younger than 36 and older than 96 were excluded, as most of the participants were older adults. Our study included 446 male patients with T2DM and 322 men without diabetes. Age, height, weight, BMI, BMD by site, TBS, and HbA1c of T2DM patients were recorded for each subject. The exclusion criteria included a BMI greater than 35 kg/m2 or less than 15 kg/m2, as well as common chronic diseases affecting bone metabolism, such as endocrine disorders (hypogonadism, hyperthyroidism), rheumatic immune disorders, tumors, blood system diseases, chronic liver disease and chronic kidney disease. Additionally, individuals taking medications that influence bone metabolism, such as glucocorticoids, proton pump inhibitors, antiepileptic drugs, aromatase inhibitors, gonadotropin-releasing hormone analogs, antivirals, thiazolidinediones, or excess thyroid hormones, were excluded. Patients with type 1 diabetes mellitus and those with macrovascular or microvascular comlications were also excluded based on the medical history review.

Bone mineral density and trabecular bone score

Bone density DXA scans and TBS analyses were performed at the Department of Geriatric Endocrinology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China. All patients underwent scans using the same machine. Measurements were performed using a Hologic DEXA (USA), with a precision (CV value) of $<0.5\%$. BMD measurements were conducted by trained professionals, and a lumbar spine model was used for daily quality control test to ensure instrument's precision after the machine's start-up. Scans were performed using the standard scanning mode, and the results were processed by using the same software (Hologic Discovery W) to generate BMD values. TBS was calculated by uploading the raw DXA lumbar spine images to the TBS iNsight software (version 2.0.0.1, Med-Imaps, Bordeaux, France), which then calculated the LS TBS within the same region as the LS BMD. A proprietary algorithm was used to calculate the LS TBS within the same measurement area as the LS BMD, and the equipment was accurately calibrated for this study. The TBS index measures bone microstructure by analyzing the texture of anterior and posterior lumbar spine DXA scans.

Diabetes and other parameters

Standardized methods were employed to collect basic information, including age, gender, and medical history. Participants were instructed to wear lightweight clothing during height, weight, and DXA measurements. BMI was calculated as weight(kg) divided by the square of height (m^2). The diagnosis of diabetes mellitus was based on a fasting plasma glucose (FPG) level of ≥ 7.0 mmol/L, a 2-hour oral glucose tolerance test (OGTT) result of ≥ 11.1 mmol/L, a glycated hemoglobin (HbA1c) level of $\geq 6.5\%$, or a random blood glucose level of ≥ 11.1 mmol/L, in the presence of typical symptoms of hyperglycemia or hyperglycemic crisis[17]. HbA1c was measured

using high performance liquid chromatography(HPLC) with the Beckman Coulter AU5800 fully automatic biochemical analyzer at our hospital.

Statistical analysis

Participants were organized into age groups, with each age subgroup spanning a decade. After assessing the normality of the data, results are presented as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) and independent samples t-tests were used to compare differences in BMD and TBS between age groups and between populations(T2DM vs. non-T2DM). A linear trend test was used to assess trends in TBS and BMD across different age subgroups of males with and without T2DM. Pearson's correlation analysis was used to assess the relationship between TBS and biochemical parameters. The average annual change rate reflects the changes in TBS and BMD over time. SPSS V27.0 statistical software was utilized in this study, and a significance level of $P<0.05$ was considered statistically significant.

Results

Table 1 summarizes the baseline characteristics of men with T2DM, including height, weight, BMI, and HbA1c. A total of 446 male patients with diabetes aged 36 to 95 were enrolled. A visual comparison between T2DM males and normal male controls is shown in Fig. 1. TBS was significantly lower in males with T2DM compared to normal males (1.279 ± 0.117 vs. 1.299 ± 0.090, $P=0.005$). After multivariate analysis of variance, TBS was not affected by age distribution ($P=0.55$). The relationship between TBS levels and age subgroups is depicted in Fig. 2. In males with T2DM, TBS exhibited an increasing trend until the age of 60, followed by a decline after 60, peaking at 1.294 in the 56–65 age range. TBS showed a negative correlating with age ($r=-0.102$, $P=0.031$), and this trend was statistically significan($P=0.031$). Lumbar spine TBS in men without diabetes displayed significant variation with age, as analyzed by a linear trend test ($P<0.001$). In contrast to men with diabetes, LS TBS reached its highest value at 46–55 years of age, 1.328, followed by a decreasing trend. LS TBS in T2DM men peaked later than normal males and exhibited a significantly lower peak than normal males.

Figure 3 illustrates the relationship between BMD and age subgroups in men with T2DM. Independent samples t-test revealed no significant differences in BMD between non-T2DM men and men with T2DM by site(Fig. 4). Specifically, LS BMD (1.041 ± 0.169 g/cm2vs.1.033 ± 0.162, $P=0.500$), FN BMD (0.790 ± 0.121 g/cm2vs.0.783 ± 0.121, $P=0.418$), and TH BMD (0.941 ± 0.125 g/cm2vs.0.939 ± 0.127, $P=0.810$) showed no significant differences. In T2DM patients, FN BMD and TH BMD exhibited a decrease after 40 years ($P=0.002$ and $P=0.004$, respectively), while LS BMD demonstrated a progressive increase ($P=0.003$). LS BMD was positively correlated with age ($r=0.147$, $P=0.002$) in T2DM men. The relationship between the respective LS BMD and TBS in the two populations is shown in Fig. 5, and both were positively correlated, T2DM ($r=0.302$, $P<0.001$) and non-T2DM ($r=0.449$, $P<0.001$).

Our study included 446 male patients with T2DM and 322 normal adult males. Among them, 165 patients with T2DM and 310 males without T2DM underwent two TBS and BMD examinations. The interval between examinations ranged from 2 to 7 years, with an average interval of 3.6 years and 3.0 years, respectively. Upon data analysis, the mean annual rate of change was calculated for LSTBS, LSBMD, FNBMD, and THBMD. A negative mean annual rate of change indicates bone loss, while a positive rate indicates bone gain. Table 2 shows the annual rate of change in men with T2DM and normal men in different age subgroups, grouped by the mean age at the two tests.The mean annual rates of change in LS, FN, and TH BMD in T2DM men were 0.33%, 0.06%, and 0.15%, respectively, while the mean annual rate of change in LS TBS was −0.10%. In contrast, the mean annual rate of change in LS TBS in men without diabetes was −0.19%. Both men with and without T2DM exhibited the lowest annual rates of change at 66–75 years of age, with values of −1.05% and −0.90%, respectively.

The glycated hemoglobin (HbA1c) level, reflecting the average blood glucose level over a 2–3 month period, plays a critical role in clinically managing hyperglycemia. In our study, HbA1c was also recorded in men with T2DM, and patients' glycemic control was assessed based on the HbA1c levels. Conventionally, an HbA1c level

Age groups, years		36–45	46–55	56–65	66–75	76–85	86–95	Total
Number	a	34	70	87	55	35	41	322
	b	31	111	134	75	49	46	446
BMI, kg/m^2	a	26.4(3.4)	25.7(2.6)	25.4(2.4)	24.7(2.9)	24.6(2.6)	23.4(3.8)	25.1(3.0)
	b	26.1(3.8)	26.4(2.8)	25.5(2.4)	24.2(2.5)	23.8(2.7)	23.0(3.5)	25.1(3.0)
LS TBS	a	1.284(0.106)	1.328(0.088)	1.315(0.087)	1.296(0.081)	1.284(0.088)	1.246(0.092)	1.299(0.092)
	b	1.281(0.120)	1.284(0.110)	1.294(0.126)	1.279(0.104)	1.252(0.127)	1.247(0.114)	1.279(0.117)
LS BMD, g/cm^2	a	0.986(0.093)	1.035(0.133)	1.022(0.131)	1.079(0.200)	1.068(0.222)	1.064(0.227)	1.041(0.169)
	b	0.998(0.122)	1.000(0.122)	1.045(0.139)	1.037(0.189)	1.038(0.217)	1.094(0.200)	1.033(0.162)
FN BMD, g/cm^2	a	0.830(0.093)	0.830(0.116)	0.806(0.115)	0.797(0.128)	0.715(0.095)	0.708(0.108)	0.790(0.121)
	b	0.845(0.118)	0.804(0.100)	0.805(1.116)	0.773(0.120)	0.709(0.115)	0.722(0.134)	0.783(0.121)
TH BMD, g/cm^2	a	0.948(0.083)	0.976(0.120)	0.956(0.124)	0.954(0.126)	0.888(0.109)	0.870(0.138)	0.941(0.124)
	b	0.985(0.127)	0.952(0.101)	0.966(0.124)	0.923(0.128)	0.878(0.137)	0.889(0.152)	0.939(0.128)

Table 1. Baseline characteristics of study subjects. Data are presented as mean(SD), a men without T2DM; b men with T2DM.

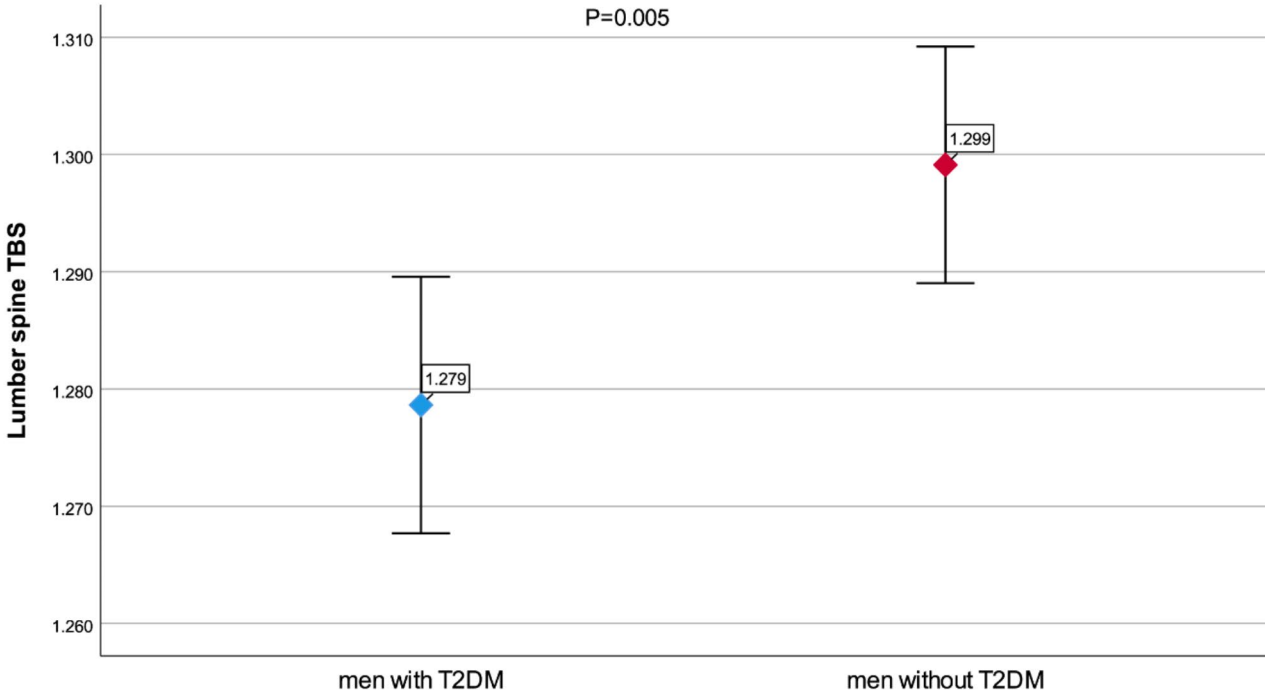

Fig. 1. Comparison of TBS between men with T2DM and controls.

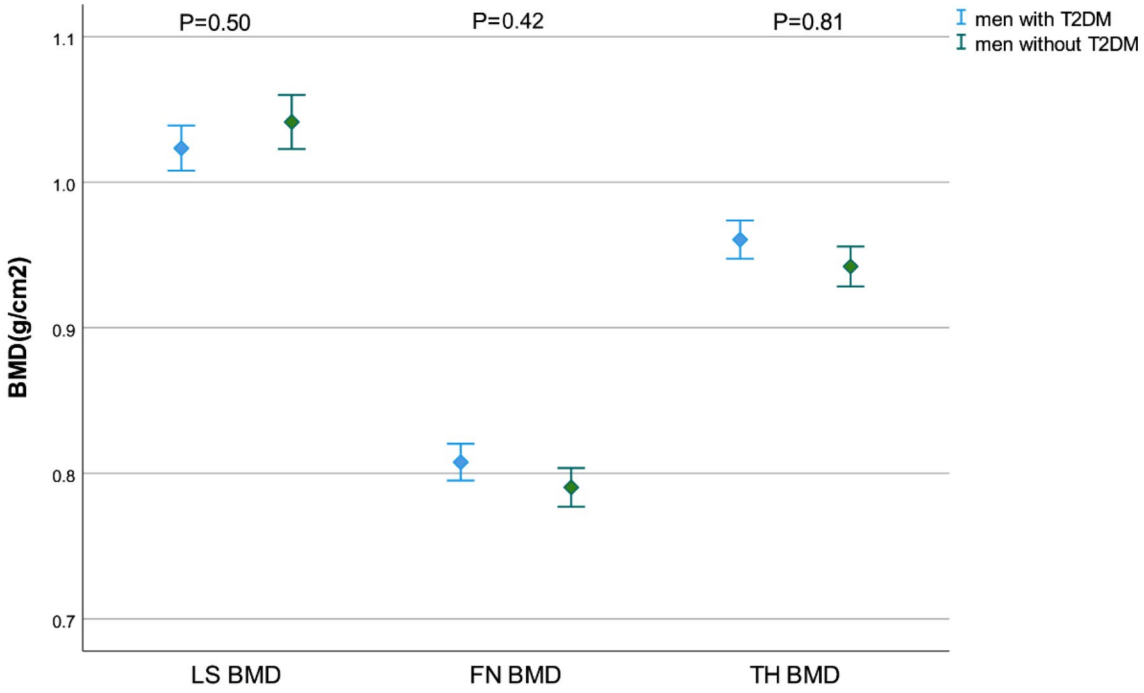

Fig. 2. Average TBS for 10-year age subgroups in men with T2DM and controls. P for trend according to the 10-year age subgroups using linear trend test.

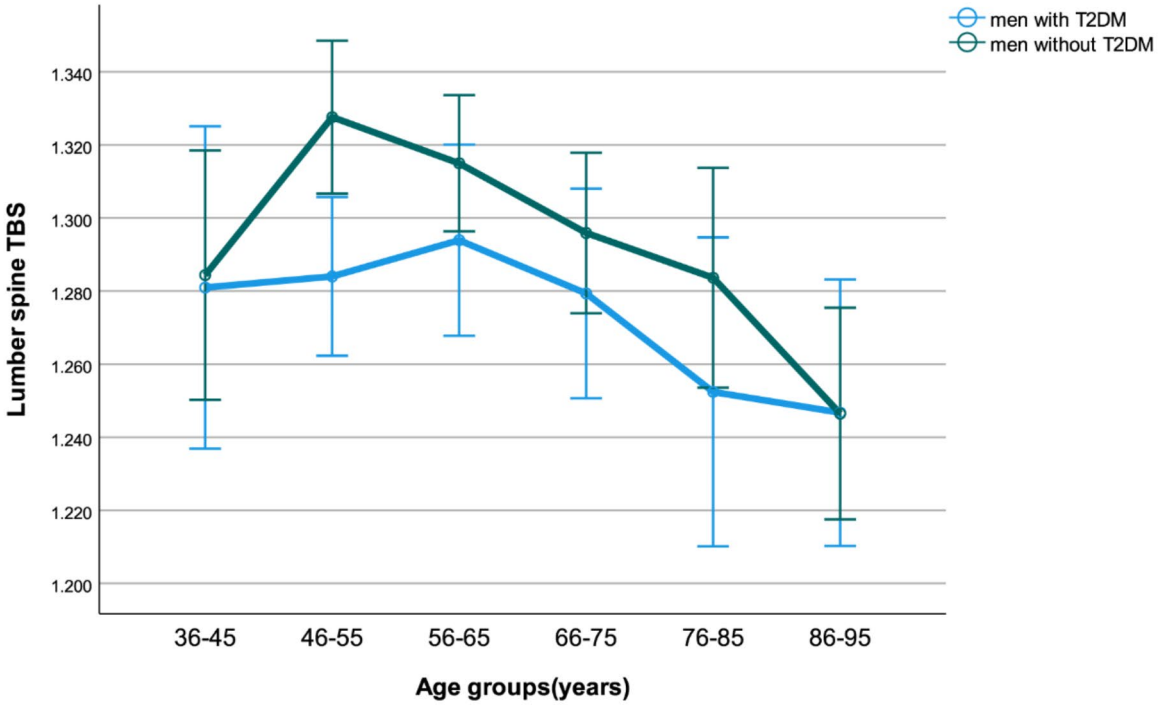

Fig. 3. Average BMD at the total hip, femoral neck, and lumbar spine for 10-year age subgroups in men with T2DM and controls. P for trend according to the 10-year age subgroups using linear trend test.

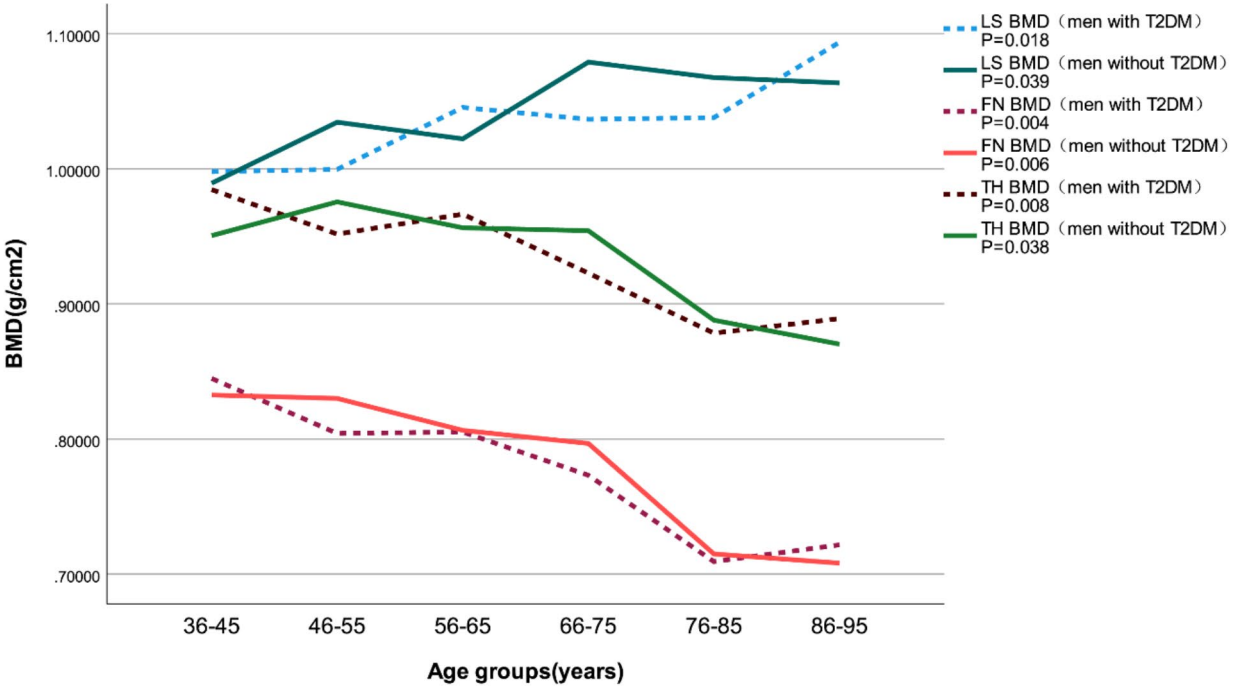

Fig. 4. Comparison of BMD between men with T2DM and controls.

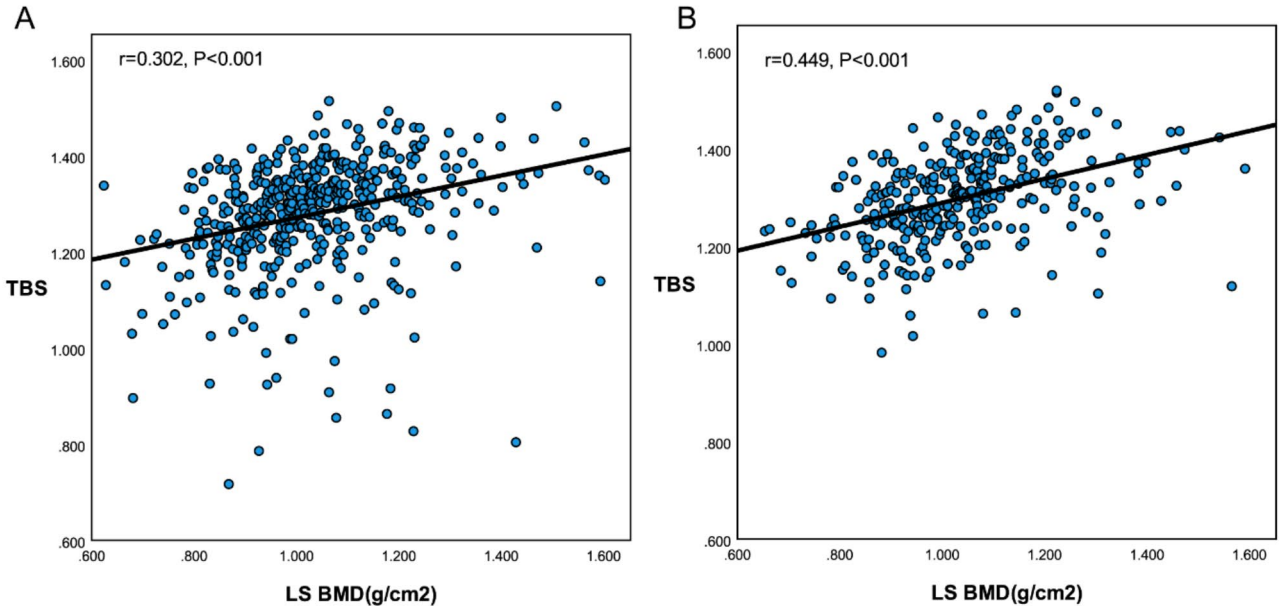

Fig. 5. Scatter plots between TBS and BMD. A, men with T2DM. B, men without T2DM.

Age groups(years)	LS TBS(%/years)		LS BMD(%/years)		FN BMD(%/years)		TH BMD(%/years)	
	a	b	a	b	a	b	a	b
36–45	0.01 ± 2.41	1.22 ± 5.56	0.19 ± 2.29	0.38 ± 3.72	−0.05 ± 2.27	−0.41 ± 1.10	0.24 ± 1.71	−0.48 ± 0.37
46–55	−0.31 ± 2.70	0.46 ± 4.30	0.63 ± 1.66	0.04 ± 1.72	−0.04 ± 2.81	0.07 ± 2.41	−0.04 ± 2.18	0.28 ± 1.80
56–65	−0.02 ± 2.30	0.10 ± 6.57	0.64 ± 1.68	0.29 ± 2.18	−0.32 ± 1.79	−0.49 ± 2.50	0.08 ± 2.20	0.38 ± 1.98
66–75	−0.90 ± 2.48	−1.05 ± 4.41	0.98 ± 1.74	0.27 ± 2.34	0.04 ± 1.91	0.44 ± 4.45	0.25 ± 1.62	−1.09 ± 3.16
76–85	0.24 ± 1.69	−0.81 ± 6.09	1.08 ± 1.72	1.06 ± 1.99	−0.22 ± 2.24	−0.11 ± 2.84	0.19 ± 1.48	1.07 ± 2.19
86–95	0.24 ± 2.95	−0.27 ± 4.99	0.20 ± 2.26	0.54 ± 1.89	0.81 ± 2.13	1.27 ± 4.42	0.38 ± 1.82	0.65 ± 3.18
Total	−0.19 ± 2.46	−0.10 ± 5.39	0.66 ± 1.83	0.33 ± 2.12	−0.08 ± 2.21	0.06 ± 3.18	0.13 ± 1.94	0.15 ± 2.40

Table 2. Average annual change rate (%/Year) of BMD at each site and LS TBS in 10-Year age subgroups. Variables are expressed as mean ± SD, a, men without T2DM; b, men with T2DM.

of < 7% (mmol/mol) is considered an indicator of good glycemic control. Many previous studies have used this as a standard. We examined the differences in TBS and BMD between two groups based on stricter glycemic control. In patients with HbA1c < 6% (mmol/mol), the mean TBS was 1.307, mean LS BMD was 1.045 g/cm^2, mean TH BMD was 0.799 g/cm^2, and mean FN BMD was 0.944 g/cm^2. In contrast, in patients with HbA1c > 6% (mmol/mol), the mean TBS was 1.287, mean LS BMD was 1.017 g/cm^2, mean TH BMD was 0.775 g/cm^2, and mean FN BMD was 0.932 g/cm^2. Patients with better glycemic control demonstrated higher TBS and BMD.

Discussion

Numerous studies have demonstrated that men with diabetes have lower TBS than men without diabetes[18,19]. In a study in Vietnam, it was shown that TBS was lower in women with diabetes than without. In contrast, the difference between men with and without diabetes was not statistically significant[20]. In another cross-sectional observational study based on a Spanish population, LS BMD was significantly higher in patients with T2DM, but TBS was substantially lower[21]. The study from the FRISBEE cohort also indicated that BMD was higher in T2DM than in controls, and TBS was significantly lower in the T2DM group compared to controls[22]. Although there was no significant difference between non-T2DM and T2DM men's BMD values at each site in our study, TBS was significantly lower (1.279 ± 0.117 vs. 1.301 ± 0.090, $P = 0.005$). Furthermore, the peak TBS of men with T2DM occurred at a later age, possibly indicating the impact of diabetes on bone microstructure. The pathophysiological mechanisms of bone fragility in patients with T2DM are complex and multifactorial. Increasing evidence suggests it may be associated with hyperglycemia or insulin resistance[23].

Chronic hyperglycemia, accumulation of advanced glycation endproducts (AGE), insulin resistance, bone marrow fatty changes, inflammatory factors, adipokines from visceral fat, and oxidative stress are the primary mechanisms by which T2DM contributes to bone fragility[24,25]. Chronic hyperglycemic stimulation and insulin resistance may disrupt bone tissue's normal calcium and phosphorus metabolism[9]. In patients with diabetes,

AGE levels are elevated and accumulate due to hyperglycemia and increased levels of oxidative stress. Activating the receptor for AGEs (RAGE) expressed in human bone-derived cells enhances the production of inflammatory cytokines and reactive oxygen species (ROS), activating osteoblastic bone formation and inhibiting osteoclast differentiation, resulting in impaired bone material properties[15,26–30]. In addition, it has been hypothesized that diabetic bone loss may be a microvascular complication of diabetes mellitus. Microangiopathy is suggested to accelerate age-related bone loss, resulting in decreased bone mass, deterioration of bone microarchitecture, and increased skeletal fragility. These interconnected contribute to insufficient peak bone mass accumulation in patients with T2DM[28,31]. A cross-sectional study conducted in Korea suggested a negative correlation between lumbar spine TBS and insulin resistance[3]. In the early stage of type 2 diabetes, the increased insulin levels resulting from insulin resistance may initially have a protective effect on bones. The higher BMI in patients with T2DM may be associated with increased bone mass, indicating a protective mechanism leading to reduced bone turnover. This may result in a delayed peak TBS in patients with T2DM[32,33].

A previous longitudinal study on BMD and TBS changes in Korean adults found a mean annual rate of change of 0.3% for LS BMD and − 0.27% for LS TBS in men[34]. A recent study in a Chinese population of healthy men showed a mean annual rate of change in TBS of −0.17%[35]. However, few studies have assessed the average annual rate of change in TBS and BMD in male patients with T2DM. The results revealed that the lowest annual rate of change in TBS was observed in the 66–75 age group for men with T2DM and men without T2DM, at −1.05% and − 0.90%, respectively. Research has shown that bone loss in adult males begins to accelerate significantly after age 65. Higher rates of cortical and trabecular bone loss have been linked to lower levels of bioactive steroids and elevated levels of follicle-stimulating hormone and bone turnover markers[36]. The significant decline in TBS suggests that men in this age group experience rapid bone loss and are at a greater risk of fracture. A retrospective study of a Chinese population found that the prevalence of vertebral fractures was significantly higher in the 60–69 and 70–79 age group compared to the 50–59 age group ($P< 0.05$) among both T2DM patients and those without diabetes. Therefore, it is essential to prevent bone loss and decrease the risk of fractures in men over 65. A meta-analysis revealed that BMD was significantly higher in the femoral neck, total hip, and lumbar spine in patients with T2DM[37]. There was no significant difference in BMD at each site in our study population between men without non-T2DM and patients with T2DM. Therefore, conventional diagnostic tools that use BMD for fracture risk assessment may underestimate fracture risk in patients with T2DM. In patients with T2DM, combined evaluation of TBS and BMD ican more accurately reflects bone-strength changes and predicts osteoporotic fractures[38–40].

In our study, TBS and BMD were higher in patients with well-controlled glycemic levels. This is similar to numerous previous studies. For example, a study in Rotterdam reported that patients with T2DM and HbA1c ≥ 7.5% (mmol/mol) had a 62% higher fracture risk than patients with HbA1c ≤ 7.5% (mmol/mol)[26]. Another cross-sectional analysis of 493 women aged 65 years and older concluded that longer duration of T2DM and higher HbA1c levels were associated with higher hip BMD and lower TBS[41]. In addition, several extensive population-based cohort studies have confirmed that poor glycemic control is strongly associated with fracture risk; The risk of fracture is similar in patients without diabetes and those with well-controlled type 2 diabetes[42–44].

Before interpreting our results, we acknowledge specific strengths and limitations. The strengths of our study include analyzing men with T2DM compared to non-T2DM men. This allowed us to capture the variations in BMD and TBS at different sites. Additionally, all participants were scanned using the same DXA equipment, minimizing inter-machine errors. Both populations were also followed up, and data have been collected from participants over the past ten years. In our study, we performed a comparative analysis based on glycemic control status. However, we did not account for the duration of T2DM and its complications. T2DM may often remain undiagnosed for many years, which is a limitation of our study. Ideally, individuals under 36 should have been included in the analysis to determine the age at which our population reached peak BMD and TBS. Regrettably, the analysis of trends across the entire age range was not feasible due to the limited number of individuals under 35 in the population studied at our hospital. Finally, the primary focus of osteoporosis management should be reducing the risk of fractures. However, this study's limited number of fractures made it impossible to establish the relationship between TBS and fracture risk.

Conclusions

Patients with T2DM often present with higher BMD but lower TBS. Since TBS is an effective indicator of bone deterioration, particularly in high-BMD patients with diabetes, it plays a crucial role in identifying diabetes-related fracture risk. Monitoring TBS enables early detection and prevention of osteoporosis, allowing timely intervention with medications to slow down bone loss.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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YL and WD conceived and designed the experiments. YL and CX collected data, performed the data analysis, and wrote the manuscript. PC and JT provided supervision. All authors contributed to the article and approved the submitted version.

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Declarations

Competing interests
The authors declare no competing interests.

Conflict of interest
The authors declare that they have no conflict of interest.

Ethics approval
The study was approved by the Ethics Committee of the First Affiliated Hospital with Nanjing Medical University and conformed to the provisions of the Declaration of Helsinki (revised in Brazil in 2013). The patients' identities were anonymized.

Additional information
Correspondence and requests for materials should be addressed to P.C.