ISSN 1948-9358 (online)

World Journal of *Diabetes*

World J Diabetes 2022 July 15; 13(7): 471-586

Published by Baishideng Publishing Group Inc

World Journal of Diabetes

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Monthly Volume 13 Number 7 July 15, 2022

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World Journal of Diabetes

Monthly Volume 13 Number 7 July 15, 2022

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NAME OF JOURNAL
World Journal of Diabetes

ISSN
ISSN 1948-9358 (online)

LAUNCH DATE
June 15, 2010

FREQUENCY
Monthly

EDITORS-IN-CHIEF
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https://www.wjgnet.com/1948-9358/editorialboard.htm

PUBLICATION DATE
July 15, 2022

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World Journal of Diabetes

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World J Diabetes 2022 July 15; 13(7): 553-565

DOI: 10.4239/wjd.v13.i7.553

ISSN 1948-9358 (online)

ORIGINAL ARTICLE

Observational Study

Factors associated with trabecular bone score in postmenopausal women with type 2 diabetes and normal bone mineral density

Olga N Fazullina, Anton I Korbut, Vadim V Klimontov

Specialty type: Endocrinology and metabolism

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Bhattacharya S, India; Jones AR, Australia; Koo M, Taiwan

Received: February 15, 2022
Peer-review started: February 15, 2022
First decision: April 17, 2022
Revised: May 2, 2022
Accepted: June 24, 2022
Article in press: June 24, 2022
Published online: July 15, 2022

Olga N Fazullina, Anton I Korbut, Vadim V Klimontov, Laboratory of Endocrinology, Research Institute of Clinical and Experimental Lymphology - Branch of the Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences, Novosibirsk 630060, Russia

Corresponding author: Vadim V Klimontov, DSc, MD, PhD, Professor, Laboratory of Endocrinology, Research Institute of Clinical and Experimental Lymphology - Branch of the Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences, Timakov Street 2, Novosibirsk 630060, Russia. klimontov@mail.ru

Abstract

BACKGROUND

Osteoporosis and type 2 diabetes (T2D) have been recognized as a widespread comorbidity leading to excess mortality and an enormous healthcare burden. In T2D, bone mineral density (BMD) may underestimate the risk of low-energy fractures as bone quality is reduced. It was hypothesized that a decrease in the trabecular bone score (TBS), a parameter assessing bone microarchitecture, may be an early marker of impaired bone health in women with T2D.

AIM

To identify clinical and body composition parameters that affect TBS in postmenopausal women with T2D and normal BMD.

METHODS

A non-interventional cross-sectional comparative study was conducted. Potentially eligible subjects were screened at tertiary referral center. Postmenopausal women with T2D, aged 50-75 years, with no established risk factors for secondary osteoporosis, were included. BMD, TBS and body composition parameters were assessed by dual-energy X-ray absorptiometry. In women with normal BMD, a wide range of anthropometric, general and diabetes-related clinical and laboratory parameters were evaluated as risk factors for TBS decrease using univariate and multivariate regression analysis and analysis of receiver operating characteristic (ROC) curves.

RESULTS

Three hundred twelve women were initially screened, 176 of them met the inclusion criteria and underwent dual X-ray absorptiometry. Those with reduced BMD were subsequently excluded; 96 women with normal BMD were included in final analysis. Among them, 43 women (44.8%) showed decreased TBS values (≤

1.31). Women with TBS ≤ 1.31 were taller and had a lower body mass index (BMI) when compared to those with normal TBS (P = 0.008 and P = 0.007 respectively). No significant differences in HbA1c, renal function, calcium, phosphorus, alkaline phosphatase, PTH and 25(OH)D levels were found. In a model of multivariate linear regression analysis, TBS was positively associated with gynoid fat mass, whereas the height and androgen fat mass were associated negatively (all P < 0.001). In a multiple logistic regression, TBS ≤ 1.31 was associated with lower gynoid fat mass (adjusted odd ratio [OR], 0.9, 95% confidence interval [CI], 0.85-0.94, P < 0.001), higher android fat mass (adjusted OR, 1.13, 95%CI, 1.03-1.24, P = 0.008) and height (adjusted OR, 1.13, 95%CI, 1.05-1.20, P < 0.001). In ROC-curve analysis, height ≥ 162.5 cm (P = 0.04), body mass index ≤ 33.85 kg/m^2 (P = 0.002), gynoid fat mass ≤ 5.41 kg (P = 0.03) and android/gynoid fat mass ratio ≥ 1.145 (P < 0.001) were identified as the risk factors for TBS reduction.

CONCLUSION

In postmenopausal women with T2D and normal BMD, greater height and central adiposity are associated with impaired bone microarchitecture.

Key Words: Diabetes; Osteoporosis; Bone mineral density; Trabecular bone score; Obesity; Body composition

Core Tip: In this study, we assessed the impact of a wide range of general and diabetes-related parameters on trabecular bone score (TBS) in postmenopausal women with type 2 diabetes (T2D) and normal bone mineral density (BMD). A decrease in TBS was revealed in 44.8% of study participants. These data indicate that a substantial proportion of postmenopausal women with T2D and normal BMD may have impaired bone microarchitecture. Greater height and central adiposity turned out to be the risk factors for decreased TBS in these women.

Citation: Fazullina ON, Korbut AI, Klimontov VV. Factors associated with trabecular bone score in postmenopausal women with type 2 diabetes and normal bone mineral density. *World J Diabetes* 2022; 13(7): 553-565

URL: https://www.wjgnet.com/1948-9358/full/v13/i7/553.htm

DOI: https://dx.doi.org/10.4239/wjd.v13.i7.553

INTRODUCTION

Type 2 diabetes (T2D) and bone fractures have been recognized as a widespread comorbidity leading to excess mortality and an enormous healthcare burden[1,2]. Recent data from the Continuous National Health and Nutrition Examination Survey (NHANES) indicate an increasing prevalence of osteoporosis and osteopenia in the US among T2D patients[3]. People with T2D have higher risk of vertebral and some non-vertebral fractures than non-diabetic individuals[4,5], regardless of normal or even increased bone mineral density (BMD)[6,7]. This “diabetic paradox” has been attributed to the modified effect of hyperglycemia, obesity and related factors on BMD[8]. As BMD assessment may lead to underestimation of a fracture risk in T2D, additional parameters of bone health should be taken into consideration.

In recent years, the Trabecular Bone Score (TBS) on lumbar spine dual X-ray absorptiometry (DXA) images is increasingly applied for the assessment of bone microarchitecture. It had been demonstrated that low TBS is associated with both prevalent and incident fractures; therefore, TBS was incorporated in the Fracture Risk Assessment tool (FRAX) algorithm[9]. The impaired bone microarchitecture is considered as a major contributor to fracture risk in T2D[10]. Accordingly, the utility of TBS for osteoporotic fracture risk assessment was shown in postmenopausal women with T2D[11,12]. Individuals with diabetes as compared to those without have significantly lower TBS[13,14]; the difference is greater in women[13]. It could be speculated that the reduction of TBS is an earlier event in the deterioration of bone health in T2D than BMD decrease. However, at present, data on TBS in postmenopausal women with T2D and normal BMD is limited, and predictors of the TBS decrease in these women need to be refined.

A growing body of evidence indicates the pivotal role of hyperglycemia-related biochemical abnormalities, as well as obesity and dysregulated adipokine production, in the pathogenesis of increased bone fragility in T2D[15,16]. Nevertheless, the role of diabetes-related factors and fat accumulation at early stages of bone metabolic disease in T2D needs further research.

Therefore, in this study we aimed to identify clinical and body composition parameters that affect TBS in postmenopausal women with T2D and normal BMD.

MATERIALS AND METHODS

Design

A non-interventional cross-sectional comparative study was conducted.

To be included in the study, women had to meet the following criteria: (1) Caucasian origin; (2) Age 50-75 years; (3) Time since menopause ≥ 1 year; (4) Known T2D duration ≥ 1 year; and (5) Normal BMD assessed by DXA.

The following list of exclusion criteria was applied: Endocrine diseases other than T2D (hyperthyroidism, hypothyroidism, hyperparathyroidism, hypopituitarism, acromegaly, and Cushing syndrome); Rheumatic diseases (rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, systemic lupus erythematosus, systemic sclerosis, vasculitis, and crystal-induced arthritis); Inflammatory bowel diseases, celiac disease, malabsorption or bariatric surgery in medical history; Chronic kidney disease with an estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m^2; Ever diagnosed with any kind of malignancy; Immobilization for more than one month in medical history; Treatment with thiazolidinediones, glucocorticoids, anticonvulsants or immunosuppressive drugs, postmenopausal hormonal replacement therapy, anti-osteoporotic therapy at the time of the study or in the past.

Potentially eligible subjects were screened at the clinic of Research Institute of Clinical and Experimental Lymphology - Branch of the Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences (Novosibirsk, Russa), a tertiary referral center. All women underwent a detailed clinical examination, which included the assessment of glycemic control, in-depth screening/monitoring of diabetic complications and associated diseases. Women who met the inclusion criteria (1-4) and did not have the exclusion criteria underwent DXA to determine body composition, BMD and TBS. Those with abnormal BMD (T-score ≤ -1 SD) were excluded. The rest of the participants were divided into 2 groups: 1) women with normal TBS (>1.31); 2) women with TBS reduction (≤1.31). The cut-off TBS value was chosen according to the results of meta-analysis [17]. The risk factors for TBS reduction were estimated by univariate and multivariate regression analysis and analysis of receiver operating characteristic (ROC)-curves.

Ethical issues

The study protocol was approved by the Ethical Committee of the clinic of Research Institute of Clinical and Experimental Lymphology - Branch of the Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences (protocol N. 104 from 20 December 2014). All study participants provided informed written consent prior to study enrollment.

Methods

DXA and fracture risk assessment: The BMD and T-score at the lumbar spine (L1–L4), femur, femoral neck and forearm were assessed by DXA (Lunar Prodigy Advance bone densitometer, GE healthcare, Madison, WI, United States; database NHANES III; the Least significant change is 0.028 g/cm^2 for L1-L4, 0.033 g/cm^2 for femur, and 0.055 g/cm^2 for radius 33%). The TBS was estimated with the use of TBS iNsight software (version 3.0.2.0, GE healthcare). The Body Composition software (GE healthcare) was applied for assessment of body composition parameters, including bone mineral component, fat mass and lean mass, and fat distribution. Fat distribution patterns were differentiated based on the ratio of fat mass in the abdominal and hip areas (android and gynoid fat mass respectively)[18].

The FRAX tool (web version 4.3, country-specific algorithm, https://www.sheffield.ac.uk/FRAX/tool.aspx?country=13) was used to determine the ten-year risk of low-energy fractures. Both TBS-unadjusted and TBS-adjusted FRAX scores were calculated.

Laboratory investigations: The measurements of the levels of glycated hemoglobin A1c (HbA1c), total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, uric acid, creatinine, calcium, phosphorus and alkaline phosphatase were performed with a biochemical analyzer AU480 (Beckman Coulter, Minneapolis, MN, United States). eGFR was calculated using the CKD-EPI formula (2009). Albumin concentrations were determined in the morning urine samples by immunoturbidimetric method with a fully automated chemistry analyzer BS-120 (Mindray, Shenzhen, China); the result was adjusted to excreted creatinine. Serum levels of PTH and 25(OH)D were measured by ELISA with the use of Access 2 Immunoassay System analyzer (Beckman Coulter) and Access Intact PHT, Access 25(OH) Vitamin D Total kits (Beckman Coulter).

Statistical analysis

Dell Statistica 13.0 (Dell Software, Aliso Viejo, CA, United States) was used for most of the applied statistical procedures. The sample size was calculated with a predetermined Type I error rate $\alpha = 0.05$, power goal 1–β = 80% and standardized size effect 0.5 for clinical characteristics (age, duration of diabetes, age and duration of menopause, height, body weight, body mass index [BMI], waist-to-hip circumference), laboratory parameters (HbA1c, eGFR, calcium, phosphorus, 25(OH)D, PTH) and body composition (fat and lean mass, android and gynoid fat mass and percentage, android/gynoid fat mass ratio). The minimal number of participants in each group was defined as 34 persons. Assuming the prevalence of osteoporosis[19,20] and decreased TBS[21,22] in patients with T2D and using principles described previously[23,24], we estimated the minimal number of study participants as 150 individuals.

Quantitative data are presented as medians (lower quartiles; upper quartiles), frequencies are presented as percentages (%). The Kolmogorov–Smirnov (KS) test was applied to test the normality. As the majority of the quantitative parameters were not distributed normally, the non-parametric Mann–Whitney U-test was used for the group comparisons. The differences in discrete parameters were assessed using the χ^2 test. *P* values below 0.05 were considered as significant.

Spearman rank correlation analysis was applied to test associations between variables. Multiple linear regression analysis with backward elimination was used to reveal factors affecting TBS. The description of the model included beta coefficients with standard errors and *P* values, adjusted coefficient of determination (R^2), standard error of estimate and *P* value of the model.

Multiple logistic regression analysis with backward elimination was used to identify predictors of decreased TBS. The models with lower KS statistics p value and higher area under the curve (AUC), selectivity (Se), and specificity (Sp) were selected. Crude and adjusted odd ratio (OR), 95% confidence interval (CI) and *P* value were calculated for parameters included in the models.

To assess the parameters associated with decreased TBS, ROC-curve analysis was performed with IBM SPSS Statistics for Windows, Version 26.0 (International Business Machines Corporation, Armonk, NY, USA). The AUC with 95%CI and *P* value were calculated. The results were considered significant if the AUC with a lower border of 95%CI was above 0.5 and *P* value was below 0.05. The cut-off values were found with both Se and Sp above 0.55.

RESULTS

Study participants

Three hundred twelve women were initially screened, 176 of them met the inclusion criteria (1-4). These subjects underwent DXA with BMD and TBS assessment. According to DXA results, 17 women had osteoporosis and 63 had osteopenia; these individuals were excluded. Ultimately, 96 women with normal BMD were included in the final analysis.

The mean age of women was 64 years (range: 50-75 years) and mean time since menopause was 16 years (range: 1-37 years). Thirteen women were overweight, 79 were obese and four had a normal BMI. The BMI ranged from 19.1 to 50.2 kg/m^2 (median 33.6 kg/m^2). The duration of T2D varied from 1 to 48 years (median 15 years). All patients received antihyperglycemic therapy, including metformin (*n* = 80), sulfonylurea (*n* = 34), sodium glucose cotransporter 2 inhibitors (*n* = 26), dipeptidyl peptidase-4 inhibitors (*n* = 9), and insulin (*n* = 70), mostly in combinations. The mean level of HbA1c was 8.76% (72.2 mmol/mol), ranging from 5.61 to 13.64% (37.7 to 125.6 mmol/mol).

Characteristics of women with T2D depending on TBS values

The clinical characteristics of women with preserved and decreased TBS are presented in Table 1. Women with TBS ≤ 1.31 were taller and had a lower BMI when compared to those with normal TBS (*P* = 0.008 and *P* = 0.007 respectively). There was a trend towards greater age and longer diabetes duration in women with TBS ≤ 1.31 (*P* = 0.09 and *P* = 0.052 respectively). The levels of HbA1c were slightly higher in women with TBS ≤ 1.31, but the difference with women with TBS > 1.31 were not statistically significant (*P* = 0.13). No differences in HbA1c, eGFR, calcium, phosphorus, alkaline phosphatase, PTH and 25(OH)D levels were found between the groups. Most women, including 45 (84.9%) with TBS > 1.31 and 38 women (88.4%) with TBS ≤ 1.31, had 25(OH)D concentrations < 30 ng/mL. The prevalence of diabetic complications and diabetes-associated conditions, as well as antihyperglycemic therapy, did not differ between the groups.

Six women with TBS > 1.31 and 14 women with TBS ≤ 1.31 had at least one fracture in their medical history (χ^2 = 5.64, *P* = 0.02). Two women with TBS > 1.31 had a low-energy fracture (humerus, tibia) in anamnesis. In the group of patients with TBS ≤ 1.31, nine women reported low-energy fractures of spine (*n* = 2), radius (*n* = 4), femur neck (*n* = 1) and humerus (*n* = 2). A difference in the prevalence of low-energy fractures was statistically significant (χ^2=6.05, *P* = 0.01). At the same time, there were no differences in BMD and T-score between two groups (Table 2). The 10-year risk of low-grade hip fractures was higher in those with TBS ≤ 1.31 (all *P* < 0.0001). The inclusion of TBS data in the FRAX algorithm exacerbated the differences between the groups.

Women with reduced TBS had lower gynoid fat mass and higher android/gynoid fat mass ratio (*P* = 0.004 and *P* < 0.0001 respectively). No differences in trunk fat mass, lean mass and BMC were found (Table 3).

Table 1 Clinical characteristics of postmenopausal women with type 2 diabetes depending on trabecular bone score values

Parameter	Women with TBS > 1.31 (n = 53)	Women with TBS ≤ 1.31 (n = 43)	P value
Age (yr)	62 (59; 68)	65 (59; 72)	0.09
Age at menopause (yr)	50 (46; 53)	50 (45; 52.5)	0.6
Time since menopause (yr)	14 (10; 19)	17 (9; 21.5)	0.72
Diabetes duration (yr)	14 (10; 20)	19 (12; 23)	0.052
Height (cm)	160 (156; 165)	164 (160; 167)	0.008
Body weight (kg)	90 (81; 101)	84 (80; 93)	0.2
BMI (kg/m^2)	35.3 (32.5; 37.2)	32 (29.7; 34.9)	0.007
WHR	0.95 (0.93; 1.0)	1.02 (0.9; 1.05)	0.37
HbA1c (%)	8.5 (7.1; 9.3)	8.9 (7.7; 10.1)	0.13
Total cholesterol (mmol/L)	4.4 (4.1; 5.6)	5.1 (3.9; 5.7)	0.44
LDL-cholesterol (mmol/L)	2.9 (2.6; 3.7)	3.4 (2.7; 3.9)	0.21
HDL-cholesterol (mmol/L)	1.3 (1.1; 1.5)	1.2 (1.1; 1.5)	0.67
Triglycerides (mmol/L)	1.8 (1.1; 2.5)	2.1 (1.4; 2.7)	0.31
hsCRP (mmol/L)	3.1 (1.8; 8.3)	3.3 (1.5; 7.3)	0.71
Calcium (mmol/L)	2.4 (2.4; 2.5)	2.4 (2.4; 2.5)	0.96
Phosphorus (mmol/L)	1.2 (1.1; 1.4)	1.3 (1.2; 1.4)	0.11
Alkaline phosphatase (IU/L)	84.6 (67.3; 107.3)	81.1 (64.8; 98.5)	0.66
PTH (pg/mL)	32.4 (24; 45.4)	31.2 (15.3; 39.0)	0.36
25(OH)D (ng/mL)	21.3 (15.8; 26.5)	18.7 (12.4; 24.2)	0.07
eGFR (mL/min/1.73 m^2)	76 (55; 93)	72 (57; 92)	0.7
UACR (mg/mmoL)	0.6 (0.3; 1.1)	0.5 (0.3; 1.0)	0.18
Diabetic retinopathy, n (%)	24 (45.3%)	24 (55.8%)	0.38
CKD, n (%)	22 (41.5%)	20 (46.5%)	0.89
Diabetic neuropathy, n (%)	53 (100%)	43 (100%)	0.76
Peripheral artery disease, n (%)	19 (35.8%)	19 (48.3%)	0.42
Coronary artery disease, n (%)	17 (32.1%)	11 (27.6%)	0.59
Metformin, n (%)	43 (81.1%)	37 (86%)	0.68
Sulfonylurea, n (%)	20 (37.7%)	14 (32.6%)	0.67
DPP4 inhibitor, n (%)	3 (5.7%)	6 (14%)	0.49
SGLT2 inhibitor, n (%)	16 (30.2%)	10 (23.3%)	0.56
Insulin, n (%)	38 (71.7%)	32 (74.4%)	0.82
Fracture in medical history, n (%)	6 (11.3%)	14 (32.6%)	0.02
Low-energy fracture in medical history, n (%)	2 (3.8%)	9 (20.9%)	0.01

Data are presented as medians (25; 75 percentiles). TBS: Trabecular bone score; BMI: Body mass index; WHR: Waist-to-hip ratio; HbA1c: Hemoglobin A1c; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; hsCRP: High-sensitivity C-reactive protein; PTH: Parathyroid hormone; 25(OH)D: 25-hydroxyvitamin D; eGFR: Estimated glomerular filtration rate; UACR: Urinary albumin-to-creatinine ratio; CKD: Chronic kidney disease; DPP4: Dipeptidyl peptidase-4; SGLT2: Sodium glucose cotransporter 2.

Associations of TBS with clinical and laboratory parameters

In observed women, TBS correlated positively with BMI (r = 0.33, P = 0.001), total fat mass (r = 0.26, P = 0.01) and gynoid fat mass (r = 0.39, P = 0.001). Height and android/gynoid fat mass ratio demonstrated inverse correlations with TBS (r = -0.26, P = 0.01 and r = -0.44, P = 0.00001 respectively), meanwhile, all assessed laboratory parameters, with the exception of 25(OH)D, did not show significant relationships.

Table 2 Dual X-ray absorptiometry parameters and Fracture Risk Assessment tool scores in postmenopausal women with type 2 diabetes depending on trabecular bone score values

Parameter	Women with TBS > 1.31 (*n* = 53)	Women with TBS ≤ 1.31 (*n* = 43)	*P* value
TBS	1.465 (1.39; 1.514)	1.206 (1.127; 1.271)	< 0.001
T-score, minimal	0.0 (-0.5; 0.5)	-0.2 (-0.6; 0.3)	0.42
T-score, L1-L4	0.9 (0.1; 1.7)	1.0 (0.1; 1.7)	0.84
T-score, femoral neck	0.1 (-0.2; 0.7)	-0.05 (-0.5; 0.5)	0.42
T-score, total femur	1.3 (0.85; 1.6)	1.3 (0.6; 1.8)	0.97
T-score, radius	0.3 (-0.3; 0.7)	-0.05 (-0.7; 0.7)	0.27
BMD, L1-L4 (g/cm^2)	1.278 (1.197; 1.387)	1.317 (1.205; 1.39)	0.86
BMD, neck (g/cm^2)	1.044 (1.011; 1.129)	1.045 (0.968; 1.105)	0.45
BMD, total femur (g/cm^2)	1.173 (1.099; 1.210)	1.178 (1.088; 1.237)	0.85
BMD, radius, (g/cm^2)	0.897 (0.849; 0.939)	0.873 (0.816; 0.938)	0.27
FRAX major (%)	6.1 (5.7; 6.8)	6.4 (5.7; 7.1)	0.38
FRAX hip (%)	0.1 (0.1; 0.3)	0.3 (0.1; 0.4)	0.08
FRAX major, TBS-adjusted (%)	5.1 (4.6; 6.0)	7.8 (6.9; 9.2)	< 0.001
FRAX hip, TBS-adjusted (%)	0.1 (0.0; 0.2)	0.4 (0.2; 0.6)	< 0.001

Data are presented as medians (25; 75 percentiles). TBS: Trabecular bone score; BMD: Bone mineral density; FRAX: The Fracture Risk Assessment Tool; FRAX hip: 10-year risk of hip low-energy fractures; FRAX major: 10-year risk of major low-energy fractures.

Table 3 Body composition parameters in postmenopausal women with type 2 diabetes depending on trabecular bone score values

Parameter	Women with TBS > 1.31 (*n* = 53)	Women with TBS ≤ 1.31 (*n* = 43)	*P* value
Total fat mass (%)	45.1 (41.7; 48.3)	43.7 (40.2; 46.2)	0.1
Total fat mass (kg)	40.4 (33.0; 40.4)	36.8 (32.4; 39.5)	0.12
Trunk fat mass (kg)	23.0 (18.8; 25.9)	21.9 (20.2; 25.1)	0.89
Android fat mass (kg)	4.0 (2.9; 4.6)	3.9 (3.5; 4.7)	0.47
Gynoid fat mass (kg)	5.8 (4.9; 6.9)	4.9 (4.3; 5.9)	0.004
Android/gynoid fat mass ratio	1.07 (0.99; 1.17)	1.18 (1.12; 1.29)	< 0.001
Lean mass (kg)	48.2 (44.4; 52.0)	47.7 (44.0; 52.1)	0.83
Bone mineral component (kg)	2.5 (2.4; 2.6)	2.5 (2.3; 2.7)	0.8

Data are presented as medians (25; 75 percentiles). TBS: trabecular bone score.

The levels of 25(OH)D demonstrated weak positive correlation with TBS (*r* = 0.21, *P* = 0.042). In addition, 25(OH)D correlated negatively with android fat mass (*r* = -0.20, *P* = 0.048), waist circumference (*r* = -0.24, *P* = 0.024), PTH (*r* = -0.34, *P* = 0.006), and alkaline phosphatase (*r* = -0.28, *P* = 0.007).

In a model of multivariate linear regression analysis, TBS was positively associated with gynoid fat mass (+0.007 per each 100 g), whereas the influence of height and androgen fat mass was negative (-0.008 per each cm and and -0.007 per each 100 g, respectively, Table 4). The same factors were identified in a multiple logistic regression model (Table 5). Thus, gynoid fat mass turned out to be a protective factor for TBS (-10% per each 100 g), while height and android fat mass were the risk factors for TBS reduction (+13% per each cm and each 100 g). However, the influence of android fat mass became significant only after being adjusted on height and gynoid fat mass. Moreover, the influence of all factors included in the logistic regression model increased after adjustment.

We have used ROC-analysis to estimate the cut-off values of the factors associated with TBS (Table 6). The height ≥ 162.5 cm, BMI ≤ 33.85 kg/m^2, gynoid fat mass ≤ 5.4 kg (≤ 43.2%), and android/gynoid fat mass ratio ≥ 1.15 were identified as the risk factors of decreased TBS.

Table 4 Factors associated with trabecular bone score in postmenopausal women with type 2 diabetes

Parameter	Coefficient β ± SE	*P* value
Height (cm)	-0.008 ± 0.002	< 0.001
Android fat (100 g)	-0.007 ± 0.002	< 0.001
Gynoid fat (100 g)	0.007 ± 0.002	< 0.001

The linear regression models with backward stepwise selection. Parameters of the model: Intercept 2.54 ± 0.39, adjusted R2 0.31, SE of estimate 0.14, *P* value < 0.001.

Table 5 Factors associated with decreased trabecular bone score in postmenopausal women with type 2 diabetes

Parameter	Crude OR, 95%CI, *P* value	Adjusted OR, 95%CI, *P* value
Height, cm	1.10 (1.02-1.19), *P* = 0.01	1.13 (1.03-1.24), *P* = 0.008
Android fat, 100 g	1.02 (0.98-1.05), *P* = 0.38	1.13 (1.05-1.20), *P* < 0.001
Gynoid fat, 100 g	0.96 (0.93-0.99), *P* = 0.01	0.90 (0.85-0.94), *P* < 0.001

The logistic regression models with forward stepwise selection. Parameters of the model: Intercept 19.0, Kolmogorov–Smirnov test *P* value < 0.001, area under the curve 0.82, Selectivity 0.74, Specificity 0.77, OR 7.69, 95%CI (3.08-19.2), *P* < 0.001 for cut-off value of logistic function = 0.47. 95%CI: 95% confidence interval; OR: Odd ratio.

Table 6 Risk factors of decreased trabecular bone score in postmenopausal women with type 2 diabetes estimated by receiver operating characteristic-analysis

Parameter	Cut-off points	Se	Sp	AUC ± SE (95%CI), *P* value	OR (95%CI), *P* value
Height (cm)	≥ 162.5	0.605	0.604	0.66 ± 0.06 (0.55-0.77), *P* = 0.009	2.33 (1.02-5.31), *P* = 0.04
BMI (kg/m^2)	≤ 33.85	0.70	0.62	0.66 ± 0.06 (0.55-0.77), *P* = 0.008	3.81 (1.62-8.96), *P* = 0.002
Gynoid fat (kg)	≤ 5.41	0.63	0.60	0.67 ± 0.06 (0.56-0.78), *P* = 0.004	2.49 (1.09-5.71), *P* = 0.03
Android fat mass (kg)	≥ 3.95	0.49	0.48	0.54 ± 0.06 (0.43-0.66), *P* = 0.46	0.88 (0.39-1.98), *P* = 0.76
Android/gynoid fat	≥ 1.145	0.70	0.71	0.75 ± 0.05 (0.66-0.85), *P* < 0.001	5.69 (2.35-13.79), *P* < 0.001

Sp: Specificity; Se: Sensitivity; AUC: Area under the curve; SE: Standard error; OR: Odd ratio; 95%CI: 95% Confidence interval; BMI: Body mass index.

DISCUSSION

In this study, we investigated the effects of a number of anthropometric parameters, general and diabetes-related clinical characteristics and body composition on bone microarchitecture, assessed by TBS, in postmenopausal women with T2D and normal BMD.

To date, several imaging modalities, including DXA, radiography, micro-computed tomography, high-resolution peripheral quantitative computed tomography (HR-pQCT), and high-resolution magnetic resonance imaging, have been proposed for bone quality assessment[25]. Among these methods, HR-pQCT and TBS are the most used tools to study the bone microarchitecture in diabetes [26]. HR-pQCT is a non-invasive three-dimensional imaging modality for assessment of bone microarchitecture and bone strength in the appendicular skeleton (*i.e.*, distal radius and tibia)[27]. In the Framingham-HR-pQCT study a modest deterioration in cortical bone and reductions in bone area in patients with T2D were revealed[28]. At the same time, in another population-based study by Nilsson *et al*[29] more favorable bone microarchitecture was observed in elderly women with T2D compared to non-diabetic subjects. TBS is a gray-level textural metric that can be extracted from the two-dimensional lumbar spine DXA image[30]. This analytical method for bone microarchitecture assessment is more available and less expensive than HRpQCT.

The normal range for TBS remains a matter of debate. In 2012, an international working group of TBS users proposed the following criteria: TBS ≥ 1.35 is considered to be normal; TBS between 1.20 and 1.35 indicates partially degraded microarchitecture; finally, TBS ≤ 1.20 defines degraded microarchitecture [31]. Later, based on the results of meta-analysis of 14 population cohort studies from North America, Asia, Australia, and Europe (*n* = 17809) estimated relationship between TBS and fracture risk, slightly different criteria for assessing TBS have been proposed[17]. TBS > 1.31 was attributed to normal microarchitecture, TBS values between 1.23 and 1.31 were associated with partially degraded microarchitecture, and TBS < 1.23 was considered as an indicator of degraded microarchitecture. Taken into account that fractures are the most important clinical events related to the bone health, in this study we also used the cut-off value 1.31 to differentiate women with normal and degrade microarchitecture. This cut-off point has been also applied in recent osteoporosis studies[32,33]. Given the relatively small sample size, we did not distinguish a subgroup of patients with borderline TBS (1.23–1.31).

A significant proportion (44.8%) of women in our study showed TBS values less than 1.31. Earlier it was found that T2D women 50 years old and over had lower TBS but higher BMD when compared to non-diabetic women[11]. Postmenopausal women with newly diagnosed T2D showed a decrease in TBS and bone formation markers[34]. A recent study has demonstrated a negative association between TBS and pre-diabetes in subjects aged over 60 years and discordance between TBS and BMD in these subjects [35]. Therefore, the reduction of TBS may reflect an early stage of the impairment of bone health in diabetes. Previously an inverse association between age and TBS was observed in population studies in French and non-Hispanic white US women[36,37]. In this study we were unable to identify age as an independent risk factor for TBS reduction. This can be explained by the relatively small sample size, the upper age limit of 75 years, and the greater influence of other risk factors.

Our results indicate that greater height, lower BMI and gynoid fat mass, but higher android fat mass and android/gynoid fat mass ratio contribute to TBS decrease in women with T2D. A favorable effect of BMI and fat mass on BMD in postmenopausal women with T2D was documented in previous studies [38,39]. However, data on the effect of obesity on the bone metabolism, TBS and fracture risk are not so optimistic[40-42]. In disagreement with previously reported data[43], we observed a positive association between BMI and TBS. At the same time, we found negative association between android/gynoid fat mass ratio and TBS. Moreover, gynoid fat turned out to be a protective factor and android fat was a risk factor for TBS reduction. These findings provide further support to notion that not only fat mass, but also fat distribution, is important for bone health. Previously, inverse association between android fat and TBS was found in Chinese men[44]. Moon *et al*[40] have shown that TBS increase as visceral fat mass decrease in men and women with T2D. In the Newcastle Thousand Families Study an increase in total and, especially, visceral fat mass was associated with prevalent vertebral fracture irrespective of BMD in women aged about 62 years[41]. It was shown that abdominal fat is related to retarded bone formation and impaired bone quality in premenopausal women[42]. Therefore, central adiposity can be considered as a risk factor of bone fragility in T2D.

The association between abdominal obesity and impaired bone microarchitecture can be mediated *via* insulin resistance[43]. Increased bone marrow adiposity, the changes in adipokine production and low-grade inflammation are considered as the relevant mechanisms also[45]. In addition, vitamin D deficiency can worsen bone microarchitecture in women with T2D and abdominal obesity. In our cohort, 25(OH)D demonstrated negative correlation with waist circumference and abdominal fat mass. This data is in agreement with findings from recent meta-analysis of epidemiologic studies indicating an association between vitamin D deficiency and abdominal obesity[46]. Vitamin D deficiency in obese people is attributed to lower dietary intake of vitamin D, lesser skin exposure to sunlight, decreased vitamin absorption, impaired hydroxylation in adipose tissue and 25(OH)D accumulation in fat[47]. At the same time, it is believed that vitamin D deficiency can be associated with insulin resistance and related disorders[48,49].

The role of hyperglycemia as a factor contributing to the degradation of bone microarchitecture is widely discussed. The mechanisms of bone fragility in hyperglycemia include the accumulation of advanced glycation end products and collagen cross-linking, suppressed osteoid mineralization, reduced osteoblastogenesis, and retarded bone turnover[50]. Ho-Pham *et al*[13] reported that subjects with pre-diabetes have a decrease in TBS when compared with normal individuals. At the same time, Holloway *et al*[14] found no difference in TBS between subjects with normoglycaemia and impaired fasting glucose. A negative association between TBS and HbA1c has been reported in subjects with diabetes[51]. In the Maasticht study a negative association was found between HbA1c and parameters of bone health estimated by HR-pQCT in individuals with well-controlled T2D[52]. In our study, HbA1c was only slightly higher in patients with TBS ≤ 1.31. Even though we did not identify HbA1c as a risk factor for a decrease TBS, we cannot exclude the role of hyperglycemia in the deterioration of bone microarchitecture. Most of the patients had long-term diabetes and non-target glycemic control parameters on combined antidiabetic therapy. These factors could modify the effect of hyperglycemia on TBS. Besides, single HbA1c measurements were included in the analysis. Therefore, the effect of metabolic memory on bone structure cannot be ruled out.

The value of TBS as a predictor of low-energy fractures is a matter of increasing interest. It was demonstrated that in postmenopausal women with T2D TBS rather than BMD is associated with vertebral[53] and major osteoporotic fractures[11]. The FRAX score, being unadjusted to TBS, underestimates fracture risk in these women[54]. In our study, women with normal and reduced TBS demonstrated no differences in the unadjusted FRAX scores, although they were different in the prevalent fractures. As expected, incorporation of TBS values into the FRAX algorithm increased probability of the fractures in women with lower TBS. Therefore, TBS can help to improve the assessment of the risk of fractures in women with T2D and normal BMD. However, even after TBS adjustment the risk of fractures may be underestimated. A recent population-based prospective study by Leslie *et al*[55] (the Manitoba BMD Registry) showed that a residual effect of diabetes on major osteoporotic fractures estimated with FRAX persists even after TBS adjustment, though the adjustment attenuated the effect of the disease. Adjustment for diabetes further improves the quality of fracture prediction.

The cross-sectional design and relatively small sample size are the limitations of our study. The recruitment of patients in one clinical center could lead to some sample bias. We could not differentiate visceral and subcutaneous adipose tissue with the applied DXA technique. As the used version of TBS iNsight software does not correct for extremes of BMI, we cannot exclude some underestimation of TBS in patients with obesity class 2 and 3[56].

At the same time, as far as we know, this is the first study estimating the risk factors for impaired bone microarchitecture assessed by TBS in postmenopausal women with T2D and normal BMD. Further studies of a larger size and prospective design are needed to establish the role of the identified factors as predictors of TBS reduction in these women. The value of TBS in the prediction of osteoporosis-related fractures in postmenopausal women with T2D and normal BMD is another challenge for future research.

CONCLUSION

In this study, we have revealed a decrease in the TBS values in 44.8% of postmenopausal women with T2D and normal BMD. These data indicate that a substantial proportion of postmenopausal women with T2D have impaired bone microarchitecture despite the normal BMD parameters. Greater height and central adiposity turned out to be the risk factors for impaired bone microarchitecture in these women. The results give further support to notion that estimation of TBS should be an essential element of DXA protocol in postmenopausal women with T2D.

ARTICLE HIGHLIGHTS

Research background

People with type 2 diabetes (T2D) have higher risk of vertebral and some non-vertebral fractures than non-diabetic individuals, regardless of normal or even increased bone mineral density (BMD). As BMD assessment may lead to underestimation of a fracture risk in T2D, additional parameters of bone health should be taken into consideration. The impaired bone microarchitecture is considered as a major contributor to fracture risk in T2D. Trabecular Bone Score (TBS) on lumbar spine dual X-ray absorptiometry (DXA) images is increasingly applied for the assessment of bone microarchitecture. Individuals with diabetes as compared to those without have significantly lower TBS.

Research motivation

At present, data on TBS in postmenopausal women with T2D and normal BMD is limited, and predictors of TBS decrease in these women need to be refined. In particular, the role of body composition and diabetes-related parameters as risk factors for deterioration of bone microarchitecture needs further research.

Research objectives

To identify clinical and body composition parameters that affect TBS in postmenopausal women with T2D and normal BMD.

Research methods

A non-interventional cross-sectional comparative study was conducted. Postmenopausal women with T2D, aged 50-75 years, with no established risk factors for secondary osteoporosis, were included. BMD, TBS and body composition parameters were assessed by DXA. In women with normal BMD, a wide range of anthropometric, general and diabetes-related clinical and laboratory parameters were evaluated as risk factors for TBS decrease using univariate and multivariate regression analysis and analysis of receiver operating characteristic (ROC) curves.

Research results

Among women with normal BMD, 44.8% showed decreased TBS values (≤ 1.31). Women with decreased TBS were taller and had a lower BMI when compared to those with normal TBS. No significant differences in HbA1c, renal function, calcium, phosphorus, alkaline phosphatase, PTH and 25(OH)D levels were found. In the models of multivariate regression analysis, TBS was positively associated with gynoid fat mass, whereas the height and androgen fat mass were associated negatively.

In the ROC-curve analysis, height ≥ 162.5 cm, body mass index < 33.85 kg/m^2, gynoid fat mass ≤ 5.41 kg and android/gynoid fat mass ratio ≥ 1.145 were identified as the risk factors for TBS reduction.

Research conclusions

The obtained results indicate that a substantial proportion of postmenopausal women with T2D and normal BMD may have impaired bone microarchitecture. Greater height and central adiposity turned out to be the risk factors for decreased TBS in these women. The results give further support to notion that estimation of TBS should be an essential element of DXA protocol in postmenopausal women with T2D.

Research perspectives

The prognostic value of TBS as a risk factor for fractures in patients with T2D and normal BMD needs further research. Prospective studies should determine the effect of changes in body weight and body composition on bone microarchitecture in these patients. The impact of hyperglycemia, glucose variability and metabolic memory, as well as various antihyperglycemic drugs, also needs to be clarified.

FOOTNOTES

Author contributions: Klimontov VV contributed to study conception and design, data analysis and interpretation; Fazullina ON and Korbut AI collected the data and performed data analysis and interpretation; Fazullina ON and Klimontov VV wrote the article; all authors approved the final version of the manuscript.

Institutional review board statement: The study protocol was approved by the Ethical Committee of the RICEL - Branch of IC&G SB RAS (protocol N. 104 from 20 December 2014).

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: Russia

ORCID number: Olga N Fazullina 0000-0002-5868-579X; Anton I Korbut 0000-0003-3502-5892; Vadim V Klimontov 0000-0002-5407-8722.

S-Editor: Chang KL
L-Editor: A
P-Editor: Chang KL

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