Archives of Osteoporosis (2023) 18:98
https://doi.org/10.1007/s11657-023-01310-1

ORIGINAL ARTICLE

Hip structural analysis, trabecular bone score, and bone mineral density in post-menopausal women with type-2 diabetes mellitus: a multi-center cross-sectional study in the south of Iran

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Received: 5 March 2023 / Accepted: 6 July 2023 / Published online: 16 July 2023

Abstract

Summary This study aimed to evaluate bone mineral density (BMD), trabecular microarchitecture, and proximal hip geometry in diabetic postmenopausal women, where BMD alone cannot reflect bone strength adequately. We found significantly lower trabecular bone score and BMD at the distal radius and total forearm in diabetic subjects compared to controls.

Purpose The limitations resulting from the exclusive assessment of bone mineral density (BMD) in people with diabetes can lead to underestimation of microarchitectural and geometric changes, both of which play an essential role in the fracture risk. Therefore, we aimed to evaluate BMD, trabecular bone score (TBS), and hip structural analysis (HSA) in diabetic type-2 post-menopausal women and compare them with healthy postmenopausal subjects.

Methods BMD was assessed at the lumbar spine, femoral sites, distal radius, and total forearm using dual-energy X-ray absorptiometry (DXA); TBS was measured based on DXA images using the software at the same region of interest as the BMD measurements; geometric assessment at the proximal femur was performed by the HSA program.

Results A total of 348 ambulatory type-2 diabetic postmenopausal women and 539 healthy postmenopausal women were enrolled. TBS and BMD at the distal radius and total forearm were significantly (P value < 0.05) lower in cases compared to controls after age and body mass index (BMI) adjustment. In addition, degraded bone microarchitecture was significantly (P value < 0.05) more prevalent in diabetic subjects than in non-diabetic controls after adjusting for age and BMI. A number of geometric indices of the proximal hip were significantly lower in the controls than in those with diabetes (P-value < 0.05).

Conclusion This study may highlight the utility of the TBS and BMD at the distal radius and total forearm in subjects with type-2 diabetes mellitus, where the BMD at central sites may not adequately predict fracture risk.

Keywords Bone mineral density · Trabecular bone score · Hip structural analysis · Post-menopausal osteoporosis · Diabetes mellitus type 2 · Fracture risk

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Introduction

The prevalence of diabetes mellitus, as one of the four major non-communicable diseases, has grown in many countries in recent decades, and this trend is expected to continue [1–3]. It is estimated that the total number of people with diabetes will rise from 171 million in 2000 to 366 million in 2030 [4]. Diabetes and bone disease have a complex relationship. There are several pathways in which diabetes can affect bones, including obesity, insulin level changes, decreased calcium absorption in the intestine in addition to its increased urinary excretion, higher levels of advanced glycation end products in collagen, complex physiological changes in vitamin D regulation, decrease in renal function, reduced insulin-like growth factor-I, secretion of parathyroid hormone by an inappropriate hemostatic response, inflammation, and microangiopathy [5].

Almost 9 out of 10 people with diabetes mellitus have type 2 diabetes mellitus (T2DM) [6]. Diabetes mellitus type-2 is associated with an increased risk of fracture and impaired fracture healing, but paradoxically higher levels of BMD. Therefore, measurement of BMD alone is not a good tool to indicate the bone strength in patients with diabetes mellitus type-2 [7–9]. This could be explained by the fact that BMD does not include all bone strength components, such as trabecular architecture, cortical geometry, and tissue mineralization or turnover [10–12]. Therefore, considering all bone strength influencing factors, including bone quality, bone density, and total content of both mineral and organic matrix, rather than BMD alone, can compensate for the inability of bone density to predict the fracture risk in patients with type-2 diabetes mellitus [13, 14].

As a result of menopause, obesity, dyslipidemia, and impaired fasting glucose become more prevalent as risk factors for type 2 diabetes mellitus, and it is known that menopause can increase the risk of diabetes and osteoporosis and, subsequently, the risk of fractures [4, 15–21]. Given that identifying postmenopausal women at risk of fracture is based on the T score, which is calculated based on BMD [22], and that patients with type-2 diabetes mellitus, despite the high chance of fracture, have a high bone mineral density [15–17], other tools should be used to assess the bone strength in post-menopausal women with type-2 diabetes mellitus.

The trabecular bone score is a recently developed densitometric tool that performs novel gray-level texture measurements on the lumbar spine dual X-ray absorptiometry (DXA) images and is related to bone microarchitecture and fracture risk independent of BMD [23]; therefore, it can be a valuable measurement for the assessment of fracture risk in a patient with type-2 diabetes mellitus [24–28].

Due to the limitations of conventional DXA measures for interpreting dimensional properties (i.e., geometry) to evaluate the mechanical strength, the hip structural analysis (HSA) method was developed to analyze archived hip DXA scans to extract geometric strength information. Hip structural analysis (HSA) derives proximal hip geometry variables, including cross-sectional area (CSA), cross-sectional moment of inertia (CSMI), section modulus (Z), and buckling ratio at the narrow neck (NN), intertrochanter (IT), and femoral shaft (FS) separately from DXA scans [29, 30]. There are few studies with controversial results that have investigated the role of TBS and HSA in the assessment of skeletal integrity in postmenopausal women with type-2 diabetes mellitus.

To the best of our knowledge, it is the first study conducted on the usefulness of TBS and HSA in assessing the bone strength in postmenopausal Iranian women with type-2 diabetes mellitus.

We aimed to evaluate the BMD, TBS, and HSA as variables derived from DXA in postmenopausal Iranian women with type-2 diabetes mellitus and compare them with age- and BMI-adjusted nondiabetic postmenopausal Iranian women as the control group.

Material and methods

Patient population and study design

This cross-sectional study was conducted over 3 years in the southern region of Iran.

The study included ambulatory post-menopausal women with type-2 diabetes mellitus referred by endocrinology and metabolism clinics of the Shiraz University of Medical Sciences to its bone densitometry units between 2018 and 2021. Additionally, 539 healthy postmenopausal women were enrolled as the controls.

Postmenopausal women aged less than 45 years old, those with a history of taking medications or supplements affecting the bone metabolism, those with all secondary causes of osteoporosis except for T2DM, and those who were on treatment for osteoporosis were excluded.

Clinical assessment

Demographic characteristics and detailed clinical information, including the history of past illness, age of menopause, osteoporosis risk factors, supplements, medications, and duration and treatment of diabetes, were obtained by a qualified medical doctor and recorded in a questionnaire. Anthropometric parameters such as height and weight were assessed by an electronic portable, wall-mounted

stadiometer. Body mass index (BMI) was measured as the weight in kilograms divided by height squared in meters (kg/m2). The glycated hemoglobin level (HbA1C) was used to assess glycemic control.

BMD, TBS, and HSA measurements

Bone mineral density (BMD)

Areal BMD (g/cm^2) was assessed at the lumbar spine (L1-L4), femoral sites (femoral neck and total hip), distal radius, and total forearm using DXA Hologic Horizon (Hologic Corp, Bedford, MA, USA) by a qualified technologist according to the manufacturer and International Society for Clinical Densitometry (ISCD) protocols. Vertebrae with fractures or degenerative changes that result in over 1 SD higher aBMD from immediate adjacent vertebra were excluded in accordance with the ISCD guidelines [31]. Unlike the lumbar spine and femoral sites, which have been assessed in terms of bone mineral density in all participants, according to the 2019 ISCD Official Positions, the distal one-third (33% radius) of the nondominant forearm and total forearm were assessed in some individuals, when the hip or spine could not be accurately measured, or their measurement data could not be interpreted [31]. Normal reference values of the age- and gender-matched group provided by the DXA system manufacturer were used to calculate *T* and *Z* scores [31, 32]. Osteoporosis, osteopenia, and normal BMD were defined as *T* scores − 2.5 or less, between − 1 and − 2.5, and − 1 or more, respectively, based on ISCD guidelines [33]. In our laboratory, The coefficient of variation was 1.8% for the femoral neck and less than 1% for the lumbar spine, total hip, distal radius, and total forearm based on measurements in 10 adults.

Trabecular bone score (TBS)

TBS is a non-BMD DXA measure derived from the lumbar spine DXA image and helps assess bone microarchitecture [34]. TBS was measured based on DXA images using software (TBS iNsight, version 2.1.2.0, Medimaps, Mérignac, France) in the same region of interest as the BMD measurement.

TBS values of > 1.350, 1.200–1.350, and < 1.250 indicate normal microarchitecture, partially degraded microarchitecture, and degraded bone microarchitecture, respectively [35].

Hip structural analysis (HSA)

Geometric assessment at the proximal femur was performed by the HSA program, a simple tool designed to assess the bone strength in this area [36]. The HSA program included in APEX software (v3.2, Hologic Inc.Waltham, MA, USA) performed the analysis at three regions of interest, including the Narrow Neck (NN) region, which is the narrowest width of the femoral neck, the inter-trochanteric region that crosses along the bisector of the angle between the axes of the neck and femoral shaft, and the femoral shaft (FS) region at a distance of 2 cm distal to the midpoint of the lesser trochanter.

In all three regions described above, the following HSA geometric indices were assessed:

Sub-periosteal diameter (cm), endo cortical diameter (cm), cross-sectional area (CSA) excluding soft spaces in the marrow and pores which reflects resistance to forces along the long axis (cm2), cross-sectional moment of inertia (CSMI) that represents resistance to bending forces in a cross-section(cm4), section modulus (Z) which is an index of maximal stress with bending forces(cm3), cortical thickness (cm), buckling ratio (BR) which is the ratio of outer radius to wall thickness which indicates the susceptibility of fracture by buckling under compressive load, and the neck shaft angle which is the angle of the lang axes of the femoral shaft and the femoral neck.

Statistical analysis

Quantitative variables were expressed as means with standard deviation (mean ± SD), and qualitative variables were presented as frequency (N) and percentages (%). To compare the mean scores of quantitative variables in the cases and controls, we performed Student's *t* test for parameters. Moreover, covariance analysis was performed to adjust age and BMI to compare the two groups BMD, TBS, and HSA values. Pearson's chi-square test was used to compare the categorical variables. SPSS 19.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. A *P* value less than 0.05 was considered statistically significant.

Result

Of the 887 postmenopausal women who participated in our study, 348 had type-2 diabetes mellitus, and 539 were selected as a control group from healthy community individuals. The mean (SD) age of the women with T2DM and controls was 61.40 (7.93) and 55.13 (6.61), respectively, which was significantly higher in diabetic subjects, similar to the years since menopause ($P < 0.001$). There was no significant difference between the cases and controls in BMI and age at menopause, as shown in Table 1. Among diabetics, the mean (SD) duration of diabetes was 11.67 (6.05) years, and the mean (SD) HbA1C was 7.48 (1.97) %. The number (percent) of cases who used oral antidiabetic agents, insulin, or a combination of both was 264 (75.9%), 63 (18.1%), and 21 (6%), respectively. Overall, the women with diabetes had lower BMD at the lumbar spine, femoral

neck, and hip compared with the control; however, there were no significant differences between the two groups after age and BMI adjustment. ($P > 05$). A total of 114 subjects in the control group and 83 in the case group were also assessed in terms of the total forearm and distal radius BMD, which were significantly lower in cases compared to controls before and after age and BMI adjustment. Another highly significant ($P < 0.001$) difference between the groups was that the TBS score was lower in diabetic women than in non-diabetic ones (1.280 vs. 1.343) (Table 2). Before adjusting for age and BMI, osteoporosis at the lumbar spine, femoral neck, hip, total forearm, and distal radius was significantly more prevalent in the diabetic group than in non-diabetics; however, after age and BMI adjustment, there were no significant differences between the two groups. Also, the prevalence of degraded bone microarchitecture (TBS < 1.200) was significantly higher in cases than in controls (8.2% vs 4.5%, $P < 0.001$) (Table 3). No significant difference was found in most hip geometry indices after age and BMI adjustment, but femoral shaft CSA, CSMI, Z, and subperiosteal diameter significantly tended to be lower in controls than diabetics (Table 4).

Table 1 Demographic data of subjects with or without type-2 diabetes mellitus

Variable	Non-T2DM patients ($N = 539$) Mean (SD)	T2DM patients ($N = 348$) Mean (SD)	*P*-value
Age	55.13 (6.61)	61.40 (7.93)	< 0.001
Weight	69.5 (11.12)	69.78 (11.83)	0.719
Height	154.91 (5.64)	153.82 (5.90)	0.006
Body mass index	28.941 (4.26)	29.48 (4.69)	0.076
Age at menopause	49.20 (4.97)	48.76 (5.03)	0.217
Years since menopause	7.26 (7.43)	12.72 (9.22)	< 0.001

T2DM, type 2 diabetes mellitus

Table 2 Bone mineral density and trabecular bone score in the cases and controls

Variable	Number	Non-T2DM patients Mean (SD)	Number	T2DM patients Mean (SD)	*P*-value	*P*-value*
Lumbar spine BMD (g/cm^2)	539	0.887 (0.142)	348	0.856 (0.141)	0.002	0.904
Femoral neck BMD (g/cm^2)	539	0.731 (0.116)	348	0.704 (0.132)	0.002	0.402
Hip BMD (g/cm^2)	539	0.869 (0.119)	348	0.847 (0.141)	0.018	0.108
TBS	539	1.343 (0.101)	348	1.280 (0.111)	< 0.001	0.001
Total forearm BMD (g/cm^2)	114	0.551 (0.075)	83	0.448 (0.089)	< 0.001	0.005
Distal Radius BMD (g/cm^2)	114	0.637 (0.073)	83	0.540 (0.081)	< 0.001	0.021

*Adjusted based on age and BMI

BMD, bone mineral density; *TBS*, trabecular bone score; *T2DM*, type 2 diabetes mellitus

Table 3 Frequency and prevalence of osteoporosis and low trabecular bone score in cases and controls

Variable	Non-T2DM patients *N* (%)	T2DM patients *N* (%)	*P* value	*P*-value*
Osteoporosis at lumbar spine	130 (24.1)	106 (30.5)	0.035	0.885
Osteoporosis at femoral neck	41 (7.6)	51 (14.7)	0.001	0.454
Osteoporosis at hip	15 (2.8)	26 (7.5)	0.001	0.250
Osteoporosis at total forearm	13 (6.6)	20 (10.2)	0.018	0.589
Osteoporosis at radius	13 (6.6)	22 (11.2)	0.006	0.892
TBS < 1.200	40 (4.5)	73 (8.2)	< 0.001	0.016

*Adjusted based on age and BMI

TBS, trabecular bone score; *T2DM*, type 2 diabetes mellitus

Table 4 Hip structural analysis variables of diabetic and non-diabetic postmenopausal women

HAS variable	Non-T2DM patients ($n=539$) Mean (SD)	T2DM patients ($n=348$) Mean (SD)	*P* value	*P* value*
NN (CSA) cm^2	2.715 (0.428)	2.639 (0.442)	0.011	0.394
NN (CSMI) cm^4	2.083 (0.500)	2.108 (0.467)	0.463	0.060
NN (Z) cm^3	1.186 (0.250)	1.170 (0.237)	0.348	0.149
NN (BR)	10.878 (3.229)	11.928 (4.023)	< 0.001	0.332
NN (subperiosteal diameter) cm	3.220 (0.327)	3.295 (0.360)	0.001	0.147
NN (endocortical diameter) cm	2.874 (0.362)	2.967 (0.405)	0.001	0.188
NN (cortical thickness) cm	0.173 (0.032)	0.164 (0.036)	< 0.001	0.985
IT (CSA) cm^2	4.442 (0.788)	4.324 (0.934)	0.042	0.068
IT (CSMI) cm^4	10.328 (2.945)	10.177 (3.018)	0.460	0.166
IT (Z) cm^3	3.553 (0.818)	3.458 (0.894)	0.103	0.266
IT (BR)	8.150 (1.918)	8.846 (2.402)	< 0.001	0.302
IT (subperiosteal diameter) cm	5.001 (0.436)	5.041 (0.393)	0.166	0.149
IT (endocortical diameter) cm	4.270 (0.448)	4.340 (0.423)	0.02	0.292
IT (cortical thickness) cm	0.368 (0.070)	0.351 (0.081)	0.001	0.674
FS (CSA) cm^2	3.917 (0.556)	3.955 (0.640)	0.350	< 0.001
FS (CSMI) cm^4	3.005 (0.756)	3.144 (0.742)	0.007	0.001
FS (Z) cm^3	1.987 (0.371)	2.059 (0.398)	0.002	< 0.001
FS (BR)	2.977 (0.765)	3.060 (0.772)	0.115	0.474
FS (subperiosteal diameter) cm	2.925 (0.260)	2.972 (0.218)	0.004	0.012
FS (endocortical diameter) cm	1.866 (0.388)	1.927 (0.340)	0.014	0.373
FS (cortical thickness) cm	0.529 (0.101)	0.522 (0.107)	0.367	0.139
Neck-shaft angle°	124.040 (5.830)	123.430 (5.829)	0.131	0.401

*Adjusted based on age and BMI

CSA, cross-sectional area; *CSMI*, cross-sectional moment of inertia; *Z*, section modulus; *BR*, buckling ratio; *NN*, narrow neck; *IT*, inter-trochanteric; *FS*, femoral shaft; *T2DM*, type 2 diabetes mellitus

Discussion

This is the first paper from Iran that investigated the determinants of bone health, including HSA (hip structural analysis), TBS (Trabecular bone score), and BMD (bone mineral density) in ambulatory postmenopausal women with type-2 diabetes mellitus in comparison with age- and BMI-adjusted healthy nondiabetic controls.

The current study found that BMD at the distal radius and total forearm was significantly lower in post-menopausal women with diabetes mellitus type-2 compared to the control group. This finding is in the same line with that of Majima et al. [37], who showed BMD was significantly lower at the distal radius in both male and female Japanese type-2 diabetic patients than in control subjects; however, there were no significant differences at the lumbar spine or the femoral neck between these two groups. Also, the results of some other studies demonstrated that, despite higher BMD levels at the lumbar spine and femoral neck, diabetic postmenopausal women had lower BMD levels at the distal and total radius as compared to controls. However, these differences were not significant except for the lumbar spine BMD in Sharifi et al.'s study [38, 39]. It seems that type-2 diabetes mellitus negatively affects the cortical bone structure, causing higher cortical porosity and lower cortical BMD while associated with greater trabecular BMD or not adversely affecting it [40–43]. The distal radius has a higher cortical-to-cancellous bone ratio rather than the lumbar spine and femoral neck [37]. Thus, it can be explained why the radius had a lower BMD in type-2 diabetic patients whose BMD at central sites is higher or not different compared to healthy subjects [44, 45]. On the other hand, it has been demonstrated that BMD assessment at the forearm can be used as a predictor of trabecular microarchitecture and also for central site osteoporosis prediction at the femoral neck and lumbar spine in postmenopausal women [32]. In addition, it has been shown that the assessment of BMD at the distal radius may improve fracture risk estimation [46]. Thus, we suggest that distal radius or forearm BMD could be a good indicator of bone strength in postmenopausal type 2 diabetic women whose BMD values at central sites have the inability to explain their lower bone strength and higher elevated fracture incidence. In addition, due to the association of menopausal status and type 2 diabetes mellitus with obesity and spinal degenerative changes, assessment of forearm BMD is beneficial for type 2 diabetic postmenopausal

women with morbid obesity who weigh more than the DXA table weight limit, as well as for those with degenerative disease affecting the spine [31, 47, 48].

In line with previous studies [45, 49, 50], we showed a significantly lower TBS in post-menopausal type-2 diabetic patients; therefore, given that BMD is not an optimal indicator for assessment of bone health in diabetic patients, TBS can be used for prediction of skeletal deterioration in this population [51].

We found no statistically significant differences in most indices of the proximal hip geometry except femoral shaft CSA, CSMI, Z, and subperiosteal diameter, which were stronger in diabetic subjects. This finding is in contrast with those of previous studies [49, 52] that showed weaker skeletal geometry in women with T2DM; however, it supports Garg et al.'s [44] report that found higher geometry variables in diabetic women. Also, it differs from the findings of the Bonaccorsi et al. study that showed no significant difference in HSA values between diabetic women and controls [53]. Therefore, there is a controversy between studies on the hip structural analysis results in women with type-2 diabetes.

There are some limitations in the hip structural analysis method for the assessment of bone strength, including a lack of DXA device design due to its 2-dimensional nature to assess hip geometry, difficulty in accurate positioning of the femur by technologists so that the plane of the neck-shaft angle be parallel to the scan table, and difficulty in locating precise edge margins of noisy and blurred DXA scan images. Also, body composition parameters, especially total body lean mass scaling, are important in the interpretation of HSA results [11, 29, 30]. Therefore, these limitations can lead to misinterpretation of HSA values and controversies in the results of studies. Further studies attempting to reduce the effects of limitations and adjustment of HSA values with body composition parameters, especially body lean mass, are recommended to resolve these controversies.

The strength of this study is that it is the first study in the Middle East investigating BMD, TBS, and HSA in diabetic and non-diabetic postmenopausal women and comparing them with each other. Also, unlike previous similar studies, the distal radius and total forearm BMD were assessed in our research work. The limitations of this study should be considered when interpreting its results. Most of these limitations are due to the cross-sectional nature of the study. There was a significant difference in age between the cases and controls due to restrictions on recruiting the patient population and healthy volunteers. However, a logistic regression model was used for age adjustment to circumvent this limitation. In addition, Healthy adults without a history of diabetes, who were considered the control group, were not confirmed by laboratory tests. Furthermore, based on ISCD guidelines, BMD at the distal radius and total forearm were assessed only in some patients. Therefore, further multi-center longitudinal prospective studies are needed to verify these findings.

Conclusion

In conclusion, we found that TBS and BMD in the distal radius and total forearm were significantly lower in postmenopausal women with type-2 diabetes compared to healthy postmenopausal women before and after age and BMI adjustment. However, the similar difference between the two groups in BMD at the central sites was insignificant after adjusting age and BMI. This study may highlight the utility of the trabecular bone score and BMD at the distal radius and total forearm in subjects with diabetes where the bone mineral density at central sites may not adequately predict fracture risk; however, further studies are needed to validate these findings.

Acknowledgements The authors would like to thank Dr. Nasrin Shokrpour for editorial assistance.

Data availability The authors confirm that the data supporting the findings of this study are available and can be requested from the corresponding author upon reasonable request.

Declarations

Consent to participate All participants in the study were fully informed about the goals, cooperation, benefits, and potential harms of the study and completed the ethical consent forms.

Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of The Human Ethics Committee of Shiraz University of Medical Sciences with the approval code of IR.SUMS.REC.1401.281 and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflicts of interest None.

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