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ARTÍCULOS ORIGINALES / *Originals*

VERTEBRAL FRACTURES IN ADULT WOMEN WITH TYPE 2 DIABETES MELLITUS

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Abstract

Introduction. Diabetes is a chronic disease associated with important comorbidities. Type 2 diabetes (T2DM) is associated with a three times increased risk of hip fracture but reports describing potential associations with vertebral fractures (VF) are contradictory. Our objective was to evaluate the factors involved in the prevalent VF in women with and without T2DM.

Materials and methods. A cross-sectional design was used and the relationship between morphometric VF and T2DM in adult women was evaluated. The cases were adult women with morphometric VF and the controls were adult women without VF. Thoracic and spinal radiographs in lateral and antero-posterior projections were obtained. Bone mineral density (BMD) values of the lumbar spine (L-BMD) were measured by DXA.

Results. A greater number of women with T2DM were found in the VF group (61% vs 31.5%). Non-T2DM women with VF were significantly older and with lower L-BMD than non-T2DM without VF. We observed a negative correlation between age and L-BMD (r=-0.463) in non-T2DM women, but not in the T2DM with FV group. T2DM was a risk factor for prevalent VF with OR of 3.540 (IC95% 1.750-7.160).

Conclusion. Our study showed a higher prevalence of T2DM in the VF group. T2DM women with VF were younger and had higher L-BMD than non-T2DM women, L-BMD did not correlate with age and VF were not distributed according to BMD-L and age.

Keywords: diabetes mellitus, osteoporosis, vertebral fractures.

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Resumen

FRACTURAS VERTEBRALES EN MUJERES ADULTAS CON DIABETES MELLITUS TIPO 2

Introducción. La diabetes es una enfermedad crónica asociada con comorbilidades importantes. La diabetes tipo 2 (DM2) se asocia con un riesgo tres veces mayor de fractura de cadera pero la asociación con fracturas vertebrales (FV) es contradictoria. Nuestro objetivo fue evaluar los factores involucrados en las FV prevalentes en mujeres adultas con y sin DM2. Materiales y métodos. Se realizó un diseño transversal y se evaluó la relación entre FV morfométrica y DM2 en mujeres adultas. Los casos fueron mujeres adultas con FV morfométricas y los controles fueron mujeres adultas sin FV. Se obtuvieron radiografías torácicas y espinales en proyecciones lateral y anteroposterior. Los valores de densidad mineral ósea (DMO) de la columna lumbar (DMO-L) se midieron por DXA.

Resultados. Se observó un mayor número de mujeres con DM2 en el grupo de FV (61% frente a 31.5%). Las mujeres sin DM2 con FV eran significativamente mayores y con una DMO-L más baja que las mujeres sin DM2 sin FV. Observamos una correlación negativa entre la edad y la DMO-L (r= -0.463) en mujeres sin DM2 y FV, pero no en DM2 con FV. La DM2 fue un factor de riesgo para FV prevalente con un OR 3.540 (IC95% 1.750-7.160).

Conclusión. Nuestro estudio demostró una mayor prevalencia de DM2 en el grupo de FV. Las mujeres con DM2 y FV eran más jóvenes y tenían mayor DMO-L que las mujeres sin DM2, la DMO-L no correlacionó con la edad y las FV no se distribuyeron de acuerdo a la DMO-L y edad.

Palabras clave: *diabetes mellitus, osteoporosis, fracturas vertebrales.*

Introduction

Vertebral fractures (VF) are associated with back pain, disability, impaired quality of life, morbidity and mortality.[1]

Diabetes is a chronic disease associated with substantial comorbidities. It is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The widely recognized complications of this disease include neuropathy, nephropathy, and retinopathy, all of which can result in substantial morbidity, leading to recurrent admissions to hospital and increasing healthcare costs.[2] The skeletal system seems to be an additional target of diabetes-mediated damage. It is accepted that type 1 and type 2 diabetes are associated with an increased risk of bone fractures.[3,4]

T1 and T2DM are both associated with increased fracture risk. However, where as T1DM is associated with reductions in bone mineral density (BMD), patients living with T2DM have higher BMD.[5] Moreover some antidiabetic medications affect bone metabolism, and there is an association between diabetic complications, hypoglycemia, and risk for falls and subsequent fractures.[6]

Metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 receptor agonists should be preferred for the treatment of T2DM in patients with osteoporosis.[7] On the other hand, thiazolidinediones (TZDs), peroxisome proliferator–activated receptor γ agonists (PPARγ) have been shown in randomized studies[8-10] and meta-analyses[11,12] to reduce bone density and increased fracture risk in women. The effects of rosiglitazone and pioglitazone are similar, and fracture risk has

no clear association with duration of TZD exposure. The effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors on bone metabolism include increased bone turnover, disrupted bone microarchitecture, and reduced bone mineral density.

The objective of our study was to evaluate the factors involved in the prevalence of vertebral fractures in adult women with and without T2DM.

Materials and methods

Subjects

A cross-sectional design was used and the relationship between morphometric vertebral fractures (VF) and T2DM in adult women were analyzed in a case-control design over a previous cohort of patients in which vitamin D levels were evaluated during the period of time from January to December, 2016. The cases were adult women with morphometric VF and the controls were adult women without VF. The cases and controls were not paired.

The patients were recruited in the ambulatory clinics of the two study centers: Hospital Español (Rosario, Argentina) and Centro de Reumatología (Rosario, Argentina). Inclusion criteria were women older than 18 years with and without T2DM. Exclusion criteria were neoplastic, granulomatous, or collagen disease, chronic liver disease and chronic renal failure, diseases that affect the intestinal absorption of vitamin D and others diseases or conditions affecting bone metabolism. Treatment with antiepileptics, glucocorticoids, lithium, bone antiresorptive agents, estrogen vitamin D, and bone anabolic agents was an exclusion criterion.

Patients were interviewed by a medical doctor for diabetes related complications, medication use, and lifestyle factors. Height and weight were measured and body mass index (BMI) was calculated. Diabetes duration at the year of examination was recorded. Microvascular (diabetic nephropathy, neuropathy, and retinopathy) and macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) were ascertained by self-reporting.

This study was approved by the ethical review board of Hospital Español and in compliance with the Helsinki declaration. All subjects agreed to participate in the study and provided written informed consent.

Biochemical measurements

The following laboratory data were analyzed: glycemia (mg/dl), HbA_{1c} (%), serum creatinine (mg/dl), serum calcium (mg/dl), serum phosphate (mg/dl), alkaline phosphatase (IU/l) and total 25-hydroxyvitamin D [25(OH)D, ng/ml].

BMD measurements

BMD values of the lumbar spine (L-BMD) were measured by DXA. BMD was automatically calculated from the bone area (cm^2) and BMC (g) and expressed as an absolute value (g/cm^2).

Ascertainment of fractures

Conventional thoracic and spinal radiographs in lateral and antero-posterior projections were obtained. We defined VF as grades 1–3 according to the classification by Genant et al.[13] A VF was diagnosed if a reduction of 20% or more was observed by two investigators.

Statistical analysis

The software R version 3.6.3 was used to perform the statistical analysis. The categorical variables were expressed as number and percentage (%) and the continuous variables as mean±SD or median (percentile 25-75) for each index. Unpaired t-test or Mann Whitney tests were used to compare parameters between subjects with and without VF. Comparisons of categorical variables were performed using the de χ^2 test. Correlations analyses were performed to evaluate the interdependence of the L-BMD with other continuous variables. A

logistic regression was performed to calculate the likelihood ratios (OR) on the dependent variable. The differences were considered significant if p <0.05.

Results

Background data are shown in Table 1. There were more women with T2DM in the VF group (61% vs 40.7%, p=0.01).

Table 1. Background data of VF and control patients.

	VF (42)	No VF (162)	*p*
Age (years)	65 (59-72)	62 (52.25-70)	ns
T2D (%)	26 (61)	51 (31.5)	<0.00001
BMI (kg/m²)	31.42±6.35	29.08±7.17	ns
Hypertension (%)	18 (42.9)	73 (45.1)	ns
Dyslipidemia (%)	18 (42.9)	63 (38.9)	ns
Macrovascular disease (%)	1 (2.4)	7 (4.3)	ns
Microvascular disease (%)	7 (16.7)	11 (6.8)	0.06
Glucose (mg/dl)	114.5 (86.25-135)	97 (85-115.5)	ns
Creatinine (mg/dl)	0.81±0.28	0.80±0.18	ns
Calcium (mg/dl)	9.53±0.71	9.39±0.53	ns
Phosphate (mg/dl)	3.71±0.57	3.56±0.55	ns
Alkaline phosphatase (IU/l)	135.90±81.30	122.90±69.44	ns
25(OH)D (ng/ml)	18.4 (14.7-24.45)	21 (16.6-27.8)	0.08
L-BMD (g/cm²)	1.063±0.250	1.068±0.201	ns

Non-T2DM women with VF were significantly older and with lower L-BMD than non-T2DM without VF. As can be seen in Figure 1, Non-T2DM women with VF (A) were distributed, preferably, at an older age while the T2DM women group (B) happened at an earlier age.

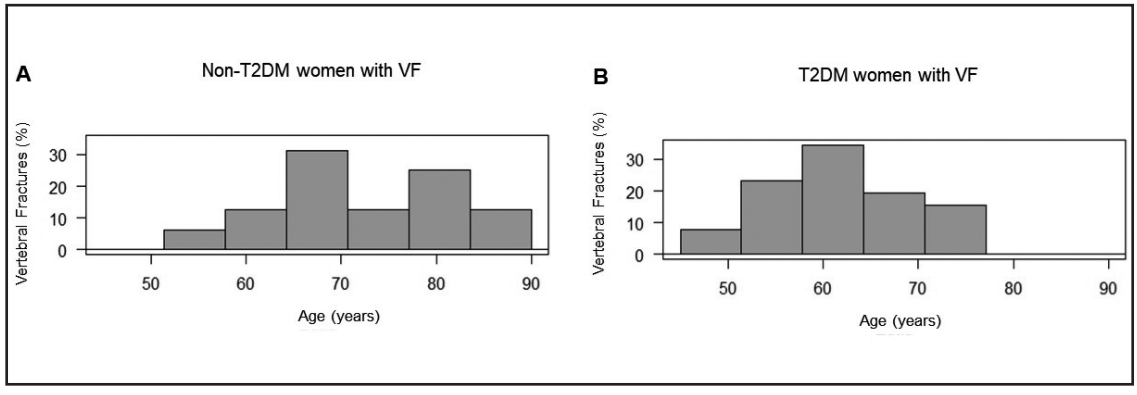

Figure 1. Histogram. Distribution of VF according to age and DM2 condition.

There were no differences in age between women with T2DM with or without VF while non-T2DM women with VF were older. No differences were found in BMI, 25(OH)D and HbA_{1c} between the groups according to the presence of VF. When comparing the T2DM women with VF versus non-DM2 with VF, the former were significantly younger [61 years (56-67) vs 71 years (69-80), p= 0.0008] (Table 2). Likewise, there were no differences in the duration of diabetes in the subgroup of women with T2DM regarding the presence of VF [T2DM with VF 6 years (2.5-12.5) *versus* T2DM without VF 7.5 years (3-15); p=0.44].

Tabla 2. Comparison of various parameters between women with and without T2DM.

	Without T2DM			**T2DM**		
	Vertebral fractures			*Vertebral fractures*		
	(+)	(-)	*p*	(+)	(-)	*p*
Age (years)	71 (65.75-80)	63 (50.5-71)	0.002	61 (56.25-67.0)	60 (54-67.5)	ns
BMI (kg/m²)	29.21±5.52	26.47±5.51	ns	32.61±6.54	34.61±7.18	ns
25(OH)D (ng/ml)	20.15 (14.68-23.55)	22 (17.05-29)	ns	16.55 (14.8-25.12)	19.20 (15.5-24.68)	ns
HbA_{1c} (%)	-	-		7.33±1.37	7.59±1.43	ns

There was no difference in L-BMD between women with T2DM with or without VF. Non-T2DM without VF had a higher L-BMD than non-T2DM women with VF (non-T2DM without VF 1.037±0.201 g/cm² *versus* with VF 0.823±0.064 g/cm²; p=0.04). T2DM women with VF also had a higher L-BMD than non-T2DM women with VF (T2DM with VF 1.153 ± 0.234 g/cm² versus non-T2DM with VF 0.823±0.064 g/cm²; p=0.044). (Fig. 2). When correlating age (years) with L-BMD women with VF, we observed a negative correlation (r= -0.463, p= 0.001) in non-T2DM but not in T2DM women. As expected, fractures occurred at a higher age and lower density (Figure 3A, pink ellipsoids) in women without diabetes. However, they did not show a homogeneous distribution in women with diabetes (Fig. 3B, pink ellipsoids).

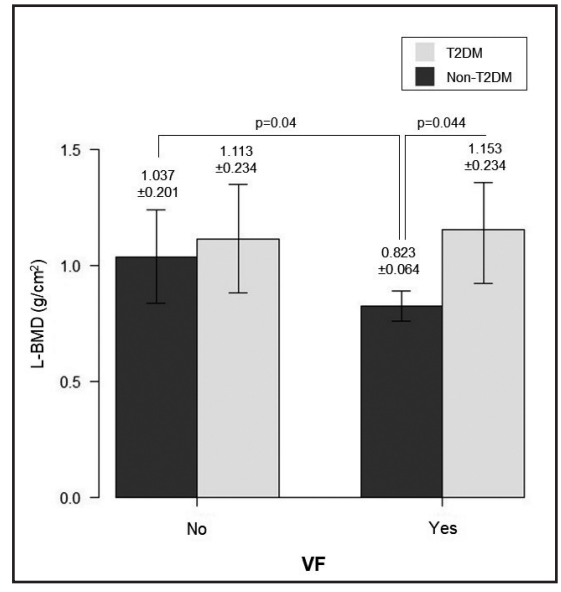

Figure 2. L-BMD of adult women according to the presence of T2DM and VF.

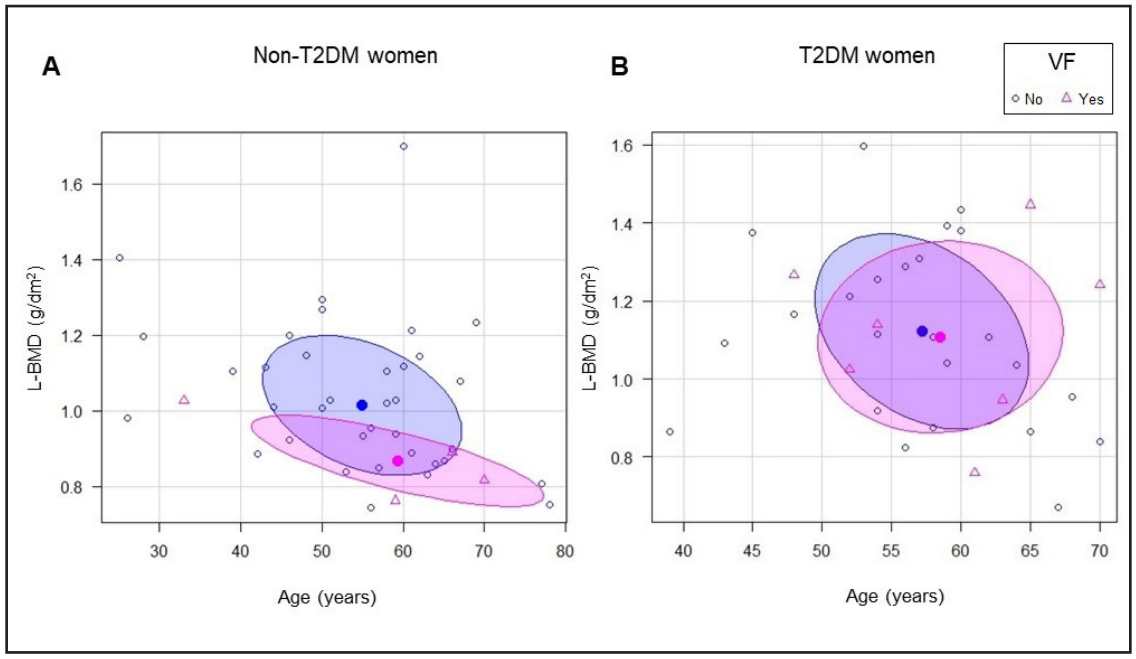

Figure 3. Analysis of correlation of age (years) with L-BMD in women in regards to the presence of VF.

Due to the low frequency of microvascular (diabetic nephropathy, neuropathy, and retinopathy) and macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke), these were evaluated together. We did not found a higher frequency of macrovascular and microvascular complications in women with T2DM with respect to the presence of VF.

Logistic analysis was performed with the presence of VF as a dependent variable and the presence of T2DM as an independent variable. The results showed that the presence of T2DM was a risk factor for prevalent VF with OR of 3.540 (IC95% 1.750-7.160); p=0.0004).

Discussion

Reports of the association between T2DM and VF have been contradictory, with some studies reporting a significant increase or a trend towards an increased vertebral fracture risk in T2DM,[14] whereas others reported no effect.[15-17] Our study showed a higher prevalence of T2DM in the VF group than non-VF group (61% vs 31.5%, p<0.0001).

As expected, non-T2DM women with VF were older and with lower L-BMD than those whithout VF. Furthermore, when comparing the T2DM women with VF versus non-T2DM with VF, the former were significantly younger and had higher L-BMD. Contrary to non-T2DM women, L-BMD did not correlate with age (data not shown) and VF were not distributed homogeneously according to L-BDM and age in T2DM women. This contrasts with previous reports where it was shown that patients with T2DM and VF were older than those without T2DM.[18] Consistent with our findings, Vestergaard et al. provide evidence for normal or even high BMD at both the hip and the spine in T2DM,[19] although there is paradoxically increased fracture risk, and we confirmed this observation. This contrasts with an expected RR 0.7 (30% lower risk) based on the degree of BMD elevation in

T2DM. This highlights the difficulty in relying on BMD alone to assess fracture risk in these patients.[20]

Previous studies examining the association between vitamin D deficiency and osteoporotic fractures have reported conflicting results. Men, but not women, with a serum 25(OH)D concentration of less than 20 ng/mL exhibited an increased risk of vertebral fractures (OR 7.87; 95% CI 1.69-36.71).[21] However, other reports found that vitamin D insufficiency is a risk factor for vertebral fragility fractures in both men and women.[22] We did not find differences in vitamin D levels between women with and without VF (with VF 18.4 ng/dl [14.7-24.45] *versus* without VF 21 ng/ml [16.6-27.8], p=0.08). Neither found differences between in T2DM women with VF *versus* without VF (data not shown). Thus, the relationship between vitamin D status and risk of VF in diabetic patients is uncertain and requires more studies.

Holmberg et al show that diabetes was the risk factor with the largest impact on VF fractures, increasing the risk more than three times (RR 3.56, 1.75–7.23; p=0.001).[14] However, a meta-analysis of observational studies revealed that T2DM was associated with higher risk for hip fractures (OR 1.296, 95 % CI (1.069-1.571), but not vertebral fractures (OR = 1.134, 95 % CI (0.936-1.374).[23] We show that T2DM significantly increases the risk of VF with an OR of 3.540 (IC95% 1.750-7.160); p=0.0004).

A recent meta-analysis across 15 studies showed individuals with T2DM had lower risk of prevalent (OR 0.84 [95% CI 0.74-0.95]) but increased risk of incident VF (OR 1.35 [95% CI 1.27-1.44]).[24] The heterogeneity introduced by the studies is important since the population, the ethnicity, the presence or absence of any skeletal disorders, the type of medical center, and the severity of the T2DM are different in the different studies.

Although BMD is the gold standard for diagnosing osteoporosis, it may be less important in the prediction of fracture risk, at least in T2DM patients.[25] BMD is increased, but bone quality is reduced in patients with T2DM compared to individuals without T2DM. In the present study, we confirmed the previous results that BMD does not discriminate the T2DM patients with increased risk of VF.[18] Trabecular microarchitecture of vertebrae is an important component of bone quality. Trabecular bone score (TBS), a recently developed parameter, may indirectly capture some aspects of 3-dimensional bone characteristics. Moreover, TBS might provide useful information in secondary osteoporosis such as in T2DM. Choi et al demonstrated that TBS has a better performance to detect VF compared to BMD in postmenopausal Korean women with T2DM.[26] Other studies also showed that TBS had the highest association with VF among all tests based on ROC analysis.[27]

Nevertheless, our study had some limitations. First, the study design was cross-sectional and the sample size was not large enough to draw definite conclusions. Second, we did not include patients with chronic kidney insufficiency in advanced stages. Therefore, the patients enrolled in this study might have had relatively less severe level of T2DM. Third, subjects received several diabetic treatments that affect bone mass and fracture risk. However, we did not analyze the effect of this factor in our findings.

In conclusion, we found that T2DM women in our population had an increased risk for VF independent of L-BMD, age, glycemic control, and vitamin D levels. This suggests that individuals with T2DM might also be good candidates for systematic VF screening beyond DXA BMD.

Conflicto de intereses: los autores declaran no tener conflicto de intereses.

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1. Johansson L, Sundh D, Nilsson M, Mellström D, Lorentzon M. Vertebral fractures and their association with health-related quality of life, back pain and physical function in older women. *Osteoporos Int.* 2018; 29(1):89-99.
2. IDF. Diabetes Atlas. 9º edición. 2019.
3. Ramírez Stieben LA, Brance ML. Mechanisms involved in the bone fragility in diabetes mellitus. *Actual Osteol.* 2018; 14(3):206:219.
4. Janghorbani M, Van Dam RM, Willett WC, Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. *Am J Epidemiol*. 2007; 166:495–505.
5. Murray CE, Coleman CM. Impact of diabetes mellitus on bone health. *Int J Mol Sci*. 2019; 20(19):4873.
6. Sellmeyer DE, Civitelli R, Hofbauer LC, et al. Skeletal Metabolism, Fracture Risk, and Fracture Outcomes in Type 1 and Type 2 Diabetes. *Diabetes*. 2016; 65(7):1757-1766.
7. Paschou SA, Dede AD, Anagnostis PG, et al. Type 2 diabetes and osteoporosis: a guide to optimal management. *J Clin Endocrinol Metab*. 2017; 102(10):3621-3634.
8. Bilezikian JP, Josse RG, Eastell R, et al. Rosiglitazone decreases bone mineral density and increases bone turnover in postmenopausal women with type 2 diabetes mellitus. *J Clin Endocrinol Metab*. 2013; 98(4):1519-1528.
9. Bone HG, Lindsay R, McClung MR, et al. Effects of pioglitazone on bone in postmenopausal women with impaired fasting glucose or impaired glucose tolerance: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab*. 2013; 98(12):4691-4701.
10. Xiao WH, Wang YR, Hou WF, et al. The effects of pioglitazone on biochemical markers of bone turnover in the patients with type 2 diabetes. *Int J Endocrinol*. 2013; 2013:290734.
11. Zhu ZN, Jiang YF, Ding T. Risk of fracture with thiazolidinediones: an updated meta-analysis of randomized clinical trials. *Bone*. 2014; 68:115-123.
12. Viscoli CM, Inzucchi SE, Young LH, et al. Pioglitazone and risk for bone fracture: safety data from a randomized clinical trial. *J Clin Endocrinol Metab*. 2017; 102(3):914-922.
13. Genant HK, Wu CY, van Kuijk C, et al. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res*. 1993;8(9):1137-1148.
14. Holmberg AH, Johnell O, Nilsson PM, et al. Risk factors for fragility fracture in middle age. A prospective population-based study of 33,000 men and women. *Osteoporos Int. 2006; 17: 1065–77.*
15. Schwartz AV, Sellmeyer DE, Ensrud KE, et al. Older women with diabetes have an increased risk of fracture: a prospective study. *J Clin Endocrinol Metab*. 2001; 86(1):32-38.
16. Hanley DA, Brown JP, Tenenhouse A, et al. Associations among disease conditions, bone mineral density, and prevalent vertebral deformities in men and women 50 years of age and older: cross-sectional results from the Canadian Multicentre Osteoporosis Study. *J Bone Miner Res*. 2003; 18:784–90.
17. Ensrud KE, Thompson DE, Cauley JA, et al. Prevalent vertebral deformities predict mortality and hospitalization in older women with low bone mass. Fracture Intervention Trial Research Group. *J Am Geriatr Soc*. 2000; 48(3):241-249.
18. Yamamoto M, Yamaguchi T, Yamauchi M et al. Diabetic patients have an increased risk of vertebral fractures independent of BMD or diabetic complications*. J Bone Miner Res*. 2009; 24(4):702-9.
19. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes–a meta-analysis. *Osteoporos Int. 2007; 18:427–44.*
20. Yamamoto M, Yamaguchi T, Yamauchi M, et al. Bone mineral density is not sensitive enough to assess the risk of vertebral fractures in type 2 diabetic women. *Calcif Tissue Int.* 2007; 80:353–358.
21. Kim YJ, Park SO, Kim TH, et al. The association of serum 25-hydroxyvitamin D and vertebral fractures in patients with type 2 diabetes. *Endocr J*. 2013; 60(2):179-84.

22. Maier GS, Seeger JB, Horas K, et al. The prevalence of vitamin D deficiency in patients with vertebral fragility fractures. *Bone Joint J*. 2015; 97-B(1):89-93
23. Dytfeld J, Michalak M. Type 2 diabetes and risk of low-energy fractures in postmenopausal women: meta-analysis of observational studies. *Aging Clin Exp Res. 2017; 29(2):301-309.*
24. Koromani F, Oei L, Shevroja E, et al. Vertebral fractures in individuals with type 2 diabetes: more than skeletal complications alone. *Diabet Care*. 2020; 43(1):137-144.
25. Schwartz AV, Vittinghoff E, Bauer DC, et al. Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. *JAMA*. 2011; 305:2184–2192.
26. Choi YJ, Ock SY, Chung YS. Trabecular Bone Score (TBS) and TBS-Adjusted fracture risk assessment tool are potential supplementary tools for the discrimination of morphometric vertebral fractures in postmenopausal women with type 2 diabetes. *J Clin Densitom*. 2016; 19(4):507-514.
27. Lin YC, Wu J, Kuo SF, et al. Vertebral fractures in type 2 diabetes patients: utility of trabecular bone score and relationship with serum bone turnover biomarkers. *J Clin Densitom*. 2020; 23(1):37-43.