Prevalence of osteoporosis and osteoporotic fractures in postmenopausal women with type 2 diabetes mellitus

Lamia Oulkadi, Bouchra Amine, Imane El binoune, Samira Rostom, Rachid Bahiri

Department of Rheumatology A, El Ayachi Hospital, Ibn Sina University Hospital, Salé, Morocco

Abstract

Type 2 diabetes mellitus (T2DM) and osteoporosis are chronic diseases with increasing prevalence. The aim of this study was to determine the prevalence of osteoporosis and osteoporotic fracture in women with T2DM and to identify predictive factors of fracture occurrence.

The prevalence of osteoporosis and fractures in postmenopausal women with T2DM was 23.1% and 16.9%, respectively. 46.2% of T2DM patients had normal bone mineral density (BMD) (P<0.01) and 58.5% of control subjects had osteopenia (P<0.01). Incidence of fracture in T2DM patients with osteopenia was significantly increased *versus* control subjects when stratified according the BMD (P=0.009). By stratifying T2DM patients according to fractures, factors that were significantly associated with occurrence included T2DM duration (P=0.038), use of insulin (P=0.017), and lower BMD (P=0.048).

Our study suggests that there was a higher prevalence of fracture in T2DM patients compared to control subjects and a significant difference in BMD was found between the groups. We also showed that insulin use, low BMD, and long duration of T2DM are factors associated with an increased risk of bone fracture.

Correspondence: Lamia Oulkadi, Department of Rheumatology A (Pr R Bahiri), El Ayachi Hospital, 11000 Sale, Morocco.
Tel.: +212.537.78.29.19/17.14 - Fax: +212.537.88.33.27.
E-mail: lamia.oulkadi@gmail.com

Key words: Type 2 diabetes mellitus; bone mineral density; osteoporosis; fracture; postmenopausal women; Morocco.

Acknowledgments: Lamia Oulkadi would like to thank all co-authors: Bouchra Amine, Imane El binoune, Ihsane Hmamouchi, Samira Rostom, Rachid Bahiri and patients who agreed to participate in this study.

Contributions: LO drafted the manuscript and reviewed the literature; BA and IE participated in article writing and reviewed critically the manuscript; SR and RB reviewed critically the manuscript. All authors read and approved the manuscript.

Conflict of interests: the authors declare no potential conflict of interests.

Availability of data and materials: available from the corresponding author on reasonable request.

Consent for publication: written informed consent for publication was obtained from the patients.

Received for publication: 3 June 2021.
Accepted for publication: 23 August 2021.

Licensee PAGEPress, Italy
Beyond Rheumatology 2021; 3:71
doi:10.4081/br.2021.71

Introduction

Type 2 diabetes mellitus (T2DM) and osteoporosis are chronic diseases with increasing prevalence, especially in the elderly population. Osteoporosis is a benign osteopathy which can remain asymptomatic until the appearance of osteoporotic fractures. The most recent epidemiological studies show that T2DM patients are at increased risk of fractures,[1-3] even if they have normal or, as is more often the case, high bone mineral density (BMD).[4] Several studies have attributed the increased risk of fracture in T2DM patients to various factors including diabetes duration, diabetic complications, inadequate glycemic control, insulin use, and increased risk of falls.[5,6] Diabetes has negative effects on bones over the long term. Diminished bone remodeling in T2DM patients tends to lead to lower bone quality. Chronic hyperglycemia causes an accumulation of advanced glycation end products (AGEs) which can reduce bone strength.[7] By interacting with the receptor for AGEs (RAGE), accumulated AGEs can inhibit the phenotypic development of the osteoblast and promote apoptosis, thus contributing to insufficient bone formation. AGEs can also increase osteoclastic resorption. Conversely, insulin use can increase the risk of fracture by inducing hypoglycemia that may cause falls.[8] Several studies have suggested that increased risk of falls in T2DM patients can also be explained by other diabetic complications, such diabetic retinopathy, neuropathy, and cardiovascular disease.[9]

The aim of this study was to determine the prevalence of osteoporosis and fractures in postmenopausal women with T2DM, and to identify factors which can predict fracture occurrence.

Materials and Methods

A total of 195 post-menopausal women were recruited between June 2018 and December 2019 for this case control study with a T2DM patient group and an age-matched control group.

All participants were asked to compete a questionnaire on the characteristics and history of their diabetes, including specific diabetic parameters (duration, therapy, and complications). Patients suffering from other diseases that would interfere with bone metabolism, such as primary hyperparathyroidism, liver or renal disease, malabsorption, inflammatory rheumatologic disorders, Paget's disease, malignancy during the previous 5 years, and any bone disease (osteomalacia or osteogenesis imperfecta) were excluded from the study. Exclusion criteria also included the use of drugs that affect bone metabolism such as bisphosphonates, raloxifene, strontium ranelate, glucocorticoids, and hormone replacement therapy. Patients with a body mass index (BMI) ≤18.5 were excluded as well.

Physical examination

A physical examination was performed on all participants which included measurements of the weight and height and BMI, which was calculated from the ratio of weight/height^2 (kg/m^2).

Biochemical analyses

Biochemical analyses of plasma samples were performed after 12 h of fasting. Fasting serum glucose was measured by the enzymatic colorimetric hexokinase method. The ARCHITECT c16000 Chemistry Analyzer (Abbott Laboratories) was used to quantify serum concentrations of glycated hemoglobin (HbA1c), triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatinine, calcium, phosphorus, alkaline phosphates, total 25-hydroxyvitamin D [25(OH)D], and parathormone.

Bone mineral density measurement

Bone mineral density (BMD) was measured using a dual-energy X-ray absorptiometry densitometer (Hologic) at the lumbar spine (LS) (L1-L4) and the femoral neck (FN). The BMD measurement was expressed by the standard deviation (SD) of the mean reference for young adults (T-score) and classified using World Health Organization (WHO) parameters.[8] Osteoporosis was defined as T-score ≤ –2.5 SD, osteopenia as T-score between –1 and –2.5 SD, and normal bone mineral density as T-score ≥ –1 SD.

Evaluation of fractures

The fracture-related questions elicited information concerning skeletal location, date of fracture occurrence (year), and trauma severity. Vertebral and non-vertebral fractures were analyzed, including, hip, tibia, humerus, and other sites. Fractures that occurred spontaneously or after a fall while standing were defined as a non-trauma fracture. Fractures caused by traumatic events were excluded from the analysis.

Lateral spine X-rays were used to define morphometric fractures of the vertebral bodies from T4 to L5. X-ray interpretation was performed by three rheumatologists, one of whom was a senior physician.

Statistical analysis

Statistical analysis was performed using SPSS software, version 13.0. Normally distributed parameters are presented as mean ± standard deviation SD. Descriptive data are presented as frequencies (number and percentage). The differences between the groups were analyzed using the Student's *t* test for continuous variables and the χ^2 test or Fisher's exact test for qualitative variables. A value of P<0.05 was considered significant.

Results

A total of 195 postmenopausal women were enrolled which included 65 T2DM patients and 130 control subjects. The mean age was 60.78±7.92 years. The mean duration of T2DM was 12.06±7.56 years. 87% of T2DM patients had inadequate glucose control (mean HbA1C: 8.46±2.08%). Degenerative complications were noted in 38.3% of cases. BMI was significantly increased in T2DM patients (P<0.01). No significant differences in 25(OH)D levels were observed between the two groups, even though it was lower in T2DM women compared to control subjects (P=0.4). 46.2% of T2DM patients had normal BMD (P<0.01) and the 58.5% of control subjects had osteopenia (P<0.01). The prevalence of fractures in T2DM patients was 16.9% compared to 4.6% in control subjects (P=0.006) (Table 1). When stratified according to BMD, fracture incidence was significantly increased in T2DM patients with osteopenia versus control subjects (P=0.009) (Table 2). When we compared the diabetics with and without fracture, the factors associated with occurrence of fractures in T2DM patients were a long duration of T2DM, the use of insulin, and lower BMD at the LS (Table 3).

Discussion and Conclusions

In our study the prevalence of osteoporosis in post-menopausal women with T2DM was 23.1% and the prevalence of fractures was 16.9%. These incidence rates are similar to what has been reported in the literature. For example, in a cross-sectional study of 112 post-menopausal women with T2DM and 171 controls, the prevalence of osteoporosis was 25% in T2DM women with 27% of them having fractures.[10] In another study, the prevalence of osteoporosis in women with T2DM was 21.9% with low trauma fractures in 5.7% of them.[11] Viégas *et al.* reported 30.4% and 23% of osteoporosis in postmenopausal T2DM women at the LS and FN, respectively, with vertebral fractures observed in 23% of them.[12]

Concerning the prevalence of fractures by location, we found 10.7% of T2DM patients with low vertebral fractures, 3.1% with forearm fractures, 1.5% with hip fractures, and 1.5% with other non-vertebral low trauma fractures compared to 3.8%, 0%, 0.8%, and 0% at the same respective locations in the control group. This result was different from that of Raška Jr. *et al.* who found 8% of low trauma vertebral fractures, 13% of forearm fractures, 0% of hip fractures, and 6% of other non-vertebral low trauma fractures in T2DM patients against 15%, 18%, 2%, and 2% at the same locations, respectively, in the control group.[10]

BMD was higher in T2DM patients at the LS and FN (P<0.01) compared to control subjects in our study. These results support what was found by Raška Jr. *et al*., namely women with T2DM had higher BMD at the LS (P<0.001), total femur (P<0.001), as well as the FN (P<0.01) *versus* the control group.[10] The higher BMD in postmenopausal women was explained in their study by the higher frequency of BMI in T2DM patients and the release of estrogen precursors from the adipose tissue which can have several effects on bones.[13]

By stratifying T2DM patients according to fractures, characteristics that were found to be associated with the occurrence of fractures included T2DM duration, use of insulin, and lower BMD. Other cross-sectional studies also showed that T2DM postmenopausal women with vertebral fractures had a longer duration

Table 1. Characteristics of the diabetic post-menopausal group compared to the age- and sex-matched control group.

	Postmenopausal T2DM Women N=65	Control nondiabetic Women N=130	P-value
Age (years)	60.78±7.92	62.72±8.00	0.11
BMI (kg/m^2)	29.92±5.68	26.02±4.95	<0.05
Serum fasting glucose (g/L)	1.67±0.66	1.10±0.11	<0.05
Serum calcium (mg/L)	91.10±2.67	91.38±2.47	0.7
Phosphorus (mg/L)	41.16±5.09	40.39±7.84	0.3
Alp (UI/L)	81.40±8.69	83.82±20.87	0.26
Serum 25(OH)D (ng/mL)	15.01±7.83	16.50±5.52	0.4
Parathormone	23.97±8.27	28.48±8.90	0.002
Serum creatinine (mg/L)	7.30±1.39	6.48±0.77	0.001
Serum total cholesterol (g/L)	1.89±0.55	1.61±0.38	0.001
Serum HDL-cholesterol (g/L)	0.46±0.09	0.57±0.25	0.05
Serum LDL-cholesterol (g/L)	1.30±0.24	1.23±0.27	0.003
Serum triglycerides (g/L)	1.44±0.64	1.18±0.21	0.006
BMD lumbar spine (g/cm^2)	0.905±0.145	0.855±0.136	0.015
BMD total femoral (g/cm^2)	0.900±0.133	0.811±0.150	0.001
Osteoporosis [n(%)]	15 (23.1%)	32 (24.6%)	0.86
Osteopenia [n(%)]	20 (30.8%)	76 (58.5%)	0.001
Normal BMD [n(%)]	30 (46.2%)	22 (16.9%)	0.001
Patients with fx [n(%)]	11 (16.9%)	6 (4.6%)	0.006
Patients with forearm fx [n(%)]	2 (3.1%)	0 (0%)	-
Patients with hip fx [n(%)]	1 (1.5%)	1 (0.8%)	-
Patients with vertebral fx [n(%)]	7 (10.8%)	5 (3.8%)	-
Patients with other low trauma fx [n(%)]	1 (1.5%)	0 (0%)	-

25(OH)D, 25-hydroxyvitamin D; Alp, alkaline phosphatase; BMD, bone mineral density; BMI, body mass index; fx, fracture; HDL, high-density lipoprotein; LDL, low-density lipoprotein; T2DM, type 2 diabetes mellitus.

Table 2. Prevalence of fractures in patients with type 2 diabetes compared to control subjects based on bone mineral density.

	Fractures		
	T2DM	Control subjects	P-value
Osteoporosis [n(%)]	4 (26.7%)	6 (18.8%)	0.7
Osteopenia [n(%)]	3 (15%)	0 (0%)	0.009
Normal BMD [n(%)]	4 (13.3%)	0 (0%)	0.11

BMD, bone mineral density; T2DM, type 2 diabetes mellitus.

Table 3. Clinical, metabolic and bone mineral density parameters in diabetic women according to the presence of fractures.

	Fractures		
	Yes	No	P-value
Age (years)	61.18±3.38	60.70±7.92	0.85
Duration of T2DM (years)	14.63±3.36	11.58±0.92	0.038
Use of insulin	10/11	27/54	0.017
Serum HbA1c (%)	8.67±1.15	7.48±1.45	
<6.5% [n(%)]	3 (37.5%)	5 (62.5%)	0.087
>6.5% [n(%)]	8 (14.8%)	46 (85.2%)	0.2
BMD lumbar spine (g/cm^2)	0.828±0.161	0.923±0.138	0.048
BMD total femur (g/cm^2)	0.875±0.123	0.905±0.135	0.49

BMD, bone mineral density; HbA1c, glycated hemoglobin; T2DM, type 2 diabetes mellitus.

of T2DM.[12,14] Jackuliak *et al.* reported that the patient group with fractures had higher HbA1c.[15] The duration of T2DM can influence the occurrence of fractures, since it has negative effects on bone pathology.[7] The relationship between the use of insulin and the risk of fractures was reported by other studies,[16,17] which however are not all in agreement.[4] Insulin can increase the risk of fractures by inducing hypoglycemia or long-term diabetic complications.[7] However, fall-related fractures increase with hypoglycemia even after adjustments for confounding factors such as the presence of microvascular complications, which are more prevalent among patients with more frequent hypoglycemic events.[18]

The occurrence of fractures was related to lower BMD values in our study and previous studies also reported this correlation.[19-21] It has been suggested that a higher risk of fractures exists in T2DM, despite higher BMD in the hip.[18] This could be explained by the fact that women with T2DM have greater bone loss, which contributes to an increased risk of fractures, even if they have higher BMD values.[22-24]

The limitation of our study was a small sample size of T2DM patients. Also, control subjects were recruited from the Rheumatology Unit, where they benefited from analysis of bone densitometric measurement. Therefore, the prevalence of osteoporosis in our control group might not reflect the prevalence of osteoporosis in the general population.

In conclusion, our study found a higher prevalence of bone fracture in T2DM patients and a significant difference in BMD between T2DM and control groups. We also showed that use of insulin, low BMD, and long duration of T2DM correlated with an increased risk of bone.

References

1. Wang J, You W, Jing Z, et al. Increased risk of vertebral fracture in patients with diabetes: a meta-analysis of cohort studies. Int Orthop 2016;40:1299-307.
2. Norris R, Parker M. Diabetes mellitus and hip fracture: a study of 5966 cases. Injury 2011;42:1313-6.
3. Rathmann W, Kostev K. Fracture risk in patients with newly diagnosed type 2 diabetes: a retrospective database analysis in primary care. J Diabet Complicat 2015;29:766-70.
4. 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.
5. Janghorbani M, Feskanich D, Willett WC, Hu F. Prospective study of diabetes and risk of hip fracture: the Nurses' Health Study. Diabetes Care 2006;29:1573-8.
6. Schwartz AV, Hillier TA, Sellmeyer DE, et al. Older women with diabetes have a higher risk of falls: a prospective study. Diabetes Care 2002;25:1749-54.
7. Oei L, Zillikens MC, Dehghan A, et al. High bone mineral density and fracture risk in type 2 diabetes as skeletal complications of inadequate glucose control: the Rotterdam Study. Diabetes Care 2013;36:1619-28.
8. Dede AD, Tournis S, Dontas I, Trovas G. Type 2 diabetes mellitus and fracture risk. Metabol Clin Exper 2014;63:1480-90.
9. Schwartz AV, Margolis KL, Sellmeyer DE, et al. Intensive glycemic control is not associated with fractures or falls in the ACCORD randomized trial. Diabetes Care 2012;35:1525-31.
10. Raška Jr. I, Rašková M, Zikán V, Škrha J. Prevalence and risk factors of osteoporosis in postmenopausal women with type 2 diabetes mellitus. Cent Eur J Public Health 2017;25:3-10.
11. Leidig-Bruckner G, Grobholz S, Bruckner T, et al. Prevalence and determinants of osteoporosis in patients with type 1 and type 2 diabetes mellitus. BMC Endocr Disord 2014;14:33.
12. Viégas M, Costa C, Lopes A, et al. Prevalence of osteoporosis and vertebral fractures in postmenopausal women with type 2 diabetes mellitus. J Diabet Complicat 2011;25:216-21.
13. Khosla S, Atkinson EJ, Riggs BL, Melton LJ 3rd. Relationship between body composition and bone mass in women. J Bone Miner Res 1996;11:857-63.
14. Kanazawa I, Yamaguchi T, Yamamoto M, et al. Serum insulin-like growth factor-I level is associated with the presence of vertebral fractures in postmenopausal women with type 2 diabetes mellitus. Osteoporos Int 2007;18:1675-81.
15. Jackuliak P, Kužma M, Killinger Z, Payer J. Good long-term glycemic compensation is associated with better trabecular bone score in postmenopausal women with type 2 diabetes. Physiol Res 2019;68:S149-56.
16. 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.
17. Melton LJ 3rd, Leibson CL, Achenbach SJ, et al. Fracture risk in type 2 diabetes: update of a population-based study. J Bone Miner Res 2008;23:1334-42.
18. Johnston SS, Conner C, Aagren M, Ruiz K, Bouchard J. Association between hypoglycaemic events and fall-related fractures in Medicare-covered patients with type 2 diabetes. Diabetes Obes Metab 2012;14:634-43.
19. Lunt M, Felsenberg D, Reeve J, et al. Bone density variation and its effects on risk of vertebral deformity in men and women studied in thirteen European Centers: The EVOS Study. J Bone Mineral Res 1997;12:1883-94.
20. Nevitt MC, Cummings SR, Stone KL, et al. Risk factors for a first-incident radiographic vertebral fracture in women ≥65 years of age: The Study of Osteoporotic Fractures. J Bone Mineral Res 2005;20:131-40.
21. The European Prospective Osteoporosis Study (EPOS) Group. Incidence of vertebral fracture in Europe: Results from the European Prospective Osteoporosis Study (EPOS). J Bone Mineral Res 2002;17:716-24.
22. Yamaguchi T, Sugimoto T. Bone metabolism and fracture risk in type 2 diabetes mellitus. Bonekey Rep 2012;1:36.
23. Schwartz AV, Garnero P, Hillier TA, et al. Pentosidine and increased fracture risk in older adults with type 2 diabetes. J Clin Endocrinol Metab 2009;94:2380-6.
24. Schwartz AV, Sellmeyer DE, Strotmeyer ES, et al. Diabetes and bone loss at the hip in older black and white adults. J Bone Mineral Res 2005;20:596-603.