Prevalence of osteoporosis among postmenopausal females with diabetes mellitus

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ABSTRACT

Objective: To assess the prevalence of osteopenia and osteoporosis among Saudi postmenopausal women with non-insulin dependent type 2 diabetes mellitus (T2DM).

Methods: The study was carried out at King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia from February 2000 to September 2002. Bone mineral density (BMD) of the lumbar spine and femoral neck using dual x-ray absorptiometry (DXA; Lunar Wisconsin), were performed in 104 postmenopausal Saudi women with T2DM, and 101 postmenopausal non-diabetic women (control). Bone mineral density was measured in gm/cm^2 and both T-score and Z-score were measured but only T-score was used for analysis based on World Health Organization criteria. Bone profile, 25 (OH) Vitamin D, 1,25(OH)^2 Vitamin D, parathyroid hormone and urine deoxypyridinoline (DPD) were measured in most patients and controls. Body fat measurement around the biceps muscles using "Futrex" (body composition analyzer) were performed in patients and controls. Years postmenopausal, duration of diabetes mellitus, parity, exercise, sun exposure and milk consumption were also recorded.

Results: In the diabetic group, the mean spine BMD was 0.928 gm/cm^2 (T-score = -2.28 SD) and for femoral neck the mean BMD was 0.817 gm/cm^2 (T-score = -1.21 SD). In control group, the mean spine BMD was 1.036 gm/cm^2 (T-score = -1.2) and mean femoral neck BMD was 0.914 gm/cm^2 (T-score = -0.608). In the diabetic group, there was 16 (16.64%) patients with normal BMD of the spine, 42 patients (43.68%) with osteopenia (mean T-score = -1.8 SD) and 45 (46.8%) with osteoporosis (mean T-score = -3.3 SD).

Conclusion: Osteoporosis is more common among Type 2 postmenopausal females in this ethnic group. Since both groups are postmenopausal, having equal percentage of Vitamin D deficiency, multi-parity, non exposure to sun, lack of exercise and negligible milk intake, one can conclude that the low BMD can be attributed to DM in the absence of other causes of osteoporosis.

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Osteoporosis is a disease of the skeleton characterized by decreased bone mass and deterioration of bone tissue architecture leading to increased bone fragility and susceptibility to fracture. The decrease in bone mass is due to activation of osteoclasts, which enhances bone resorption. Postmenopausal osteoporosis is the most common primary type and is characterized by rapid bone loss in recently postmenopausal women. In the Kingdom of Saudi Arabia, a hospital based study showed that 24% of postmenopausal Saudis had osteoporosis (aged 50-60 years).[1] Menopause is an established risk factor for osteoporosis. Other risk factors include endocrine disorders such as diabetes mellitus (DM). Decreased bone density has been reported as a complication of insulin

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dependent DM especially those with poorly controlled disease.[2] However, controversial findings were reported on the effect of type 2 diabetes mellitus (T2DM) on bone mineral density (BMD). Some authors reported low bone density,[3] others reported normal bone density,[4] and some reports showed elevated bone density.[5] On the other hand, few studies have focused on the relation between T2DM and postmenopausal osteoporosis specifically.

Diabetes is common in postmenopausal Saudi females with a prevalence of 40%, yet the pattern of osteoporosis in this sub-population is not known.[6] Therefore, we used dual energy x-ray absorptiometry (DXA) to measure the bone density in the spine and femoral neck of postmenopausal Saudi patients with T2DM and compared that with a control group of postmenopausal non-diabetic Saudi subjects. At the same time, biochemical markers bone profile and Vitamin metabolites were measured and other risk factors were considered to determine its effect on bone density.

Methods. This is a prospective study in which we evaluated 202 postmenopausal Saudi female patients. Group I was consisted of 104 patients with T2DM with a mean age of 63-years (average 55-70 years), and Group II used as control group and consisted of 101 patients without DM with a mean age of 60-years (average 54-73 years).

According to a predefined protocol, only Saudi postmenopausal females (non-menses >1-year) aged 50-70 years and eligible for care at King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia, from February 2000 to September 2002, were included. We excluded any patient with one or more of the following criteria; premature menopause (spontaneous or induced), prior use of hormonal replacement therapy, prior use of thyroid hormone or prior treatment for hyperthyroidism, drugs which affect bone metabolism, Calcitonin or other bone modifying agents, significant organ dysfunction (renal, hepatic, cardiac or neurologic) or severe illness and presence of metabolic bone disease.

All patients had a questionnaire including height, weight, history of chronic illness or drug intake, parity history, milk intake, sun exposure, exercise, duration of menopause, duration of diabetes and modality of antidiabetic therapy. Group I were recruited from diabetic clinic and Group II were from the primary health care clinic.

Bone mineral density was measured at the lumbar spine (L2-4) and proximal femur using DXA (Lunar Wisconsin). Quality assurance, including calibration, was carried out routinely every morning. Standard positioning was used for anterior-posterior scans of the lumbar spine and proximal femur. At the same time, all patients had body fat measurement using bone composition analyzer (Futrex, 6100/XL, USA) and measurement was performed around the biceps muscle. Bone mineral density results were expressed as gm/cm^2. Z-score age matched adjusted to body weight was calculated but T-score values (number of standard deviation below young adult value) was only considered for analysis as recommended by the World Health Organization (WHO), which defines the patients with normal BMD, osteopenia or osteoporosis.[7]

Blood was drawn for measurement of calcium, phosphate, alkaline phosphatase, parathyroid hormone (PTH) and vitamin D metabolites (25 hydroxy Vit D and 1,25 dihydroxy Vit D). Intact PTH was determined by monoclonal antibody coated tube immunoradiometric assay (Gamma-BCT Intact PTH - IDS). 25(OH) was determined by radioimmunoassay (Gamma-B 25-hydroxy Vitamin D RIA - IDS) and 1,25 (OH)^2 Vit D was measured by radioimmunoassay (Gamma-B 1,25 Dihydroxy Vitamin D - IDS). The urine deoxypyridinoline (DPD) was measured also by radioimmunoassay (Gamma - BCT DPD - IDS).

Data were analyzed using SPSS version 9 program. The 2 tailed T-test was used to compare BMD in both groups with the multiple variables. Differences were considered statistically significant at $p<0.05$. Correlation was measured by Pearson's correlation coefficient.

Results. **Table 1** summarizes the results of the 2 groups. The body mass index was slightly higher in control (32.1%) than diabetic patients (31%). The same was observed for Fat (32.6% and 31.2%). The mean number of parity were similar (control 7 and diabetic 8), years postmenopausal were 9 years in diabetic group and 8 years for the control. The mean duration for diabetes was 12.3 years. Both groups showed minimal exposure to sun, milk consumption and exercise. The mean results for calcium, phosphorus, alkaline phosphatase, PTH, 25 Vit D 1,25 (OH)^2 Vit D and urine DPD were within normal. However, the mean Vit D metabolites and urine DPD were slightly higher in control group compared to diabetic. According to WHO criteria, T-score was used for analysis. The mean BMD in diabetic group was 0.928 gm/cm^2 (T-score = -2.28 SD) for lumbar spine and 0.817 (T-score = -1.21 SD) in femoral neck. In the control group, the mean BMD in lumbar spine was 1.036 (T-score = -1.2 SD) and in femoral neck was 0.914 (T-score = -0.608 SD). These results show that mean BMD was lower in diabetic group compared with control group in both regions and the difference being more evident in lumbar spine than in femoral neck. The comparison between BMD of the 2 groups are shown in **Table 2**.

No significant difference in duration of diabetes between osteoporotic and osteopenic (10 years). No significant difference in mean value of 1,25(OH)^2 Vit D, urine DPD, parity, milk consumption, years post menopause, exercise or sun exposure between the 2 groups.

There was good and significant correlation between BMD of the femoral neck and lumbar spine BMD. The later was more sensitive in detecting osteopenia and osteoporosis. Bone mineral density showed also significant correlation with age, BMI, fat% and years postmenopausal. However, no correlation was found between BMD and duration of DM or parity.

In the diabetic group, 14% of patients showed low 25(OH) Vit D and only one patient showed low calcium. In the control group, 8% patients showed low 25(OH) Vit. D, and 2 patients had low calcium. In the diabetic group, 14% showed high alkaline phosphatase and 21% showed high PTH while 7 patients showed high alkaline phosphatase, calcium and PTH. There was low but significant correlation between alkaline phosphatase, PTH and 25 (OH) Vit. D. Significant correlation was observed between PTH and urine DPD and between age and calcium and low but significant correlation between age and alkaline phosphatase. The BMD in this group, showed no correlation with calcium, phosphorous, alkaline phosphatase, 25 (OH), 1,25 (OH)^2, PTH and DPD.

In the control group, 13% patients showed low 25 (OH) Vit. D, and 2 patients had low calcium and 14% had high alkaline phosphatase. Normal calcium and alkaline phosphatase with elevated PTH was found in 16% of subjects. In the control group, the correlation between alkaline phosphatase and both PTH and 25 (OH) Vit. D was low but significant. No correlation was found between BMD and calcium, phosphorous, alkaline phosphatase, 25 (OH), 1,25 (OH)^2, PTH and DPD. Low significant correlation was found between age and calcium and alkaline phosphatase and between 25 (OH) Vitamin and both fat% and BMI.

Table 1 - Comparison between mean and range of different variables in diabetic and control group.

Variables	Diabetic		Control	
	Mean	(Range)	Mean	(Range)
Age (years)	63	(55 - 70)	60	(54 - 73)
Body mass index (kg/m^2)	31.0	(38 -112)	32.1	(23 - 53)
Height (cm)	150	(135 -176)	151.2	(133 - 169)
Weight (kg)	70.5	(38 -113)	75.2	(40 - 151)
Calcium (mmol/L)	2.5	(2.00 - 2.73)	2.4	(2.05 - 2.59)
Fat%	31.2	(20 - 48)	32.6	(20 - 46)
Phosphorous (mmol/L)	1.11	(0.7 - 2.3)	1.15	(0.7 - 1.8)
Alkaline (u/L)	109.0	(46 - 210)	98	(48 - 178)
Spine body mass index (gm/cm^2)	0.928	(0.482 - 1.321)	1.036	(0.661 - 1.400)
Spine T-score	-2.28	(-6.1 - 1.1)	-1.2	(-4.3 - 1.6)
Spine Z-score	-1.3	(-4.1 - 1.1)	-0.81	(-4.1 - 2.2)
Femur body mass index (gm/cm^2)	0.817	(0.320 - 1.241)	0.914	(0.534 - 1.183)
Femur T-score	-1.21	(-4.3 - 2.0)	-0.608	(-3.7 - 1.5)
Femur Z-score	-0.53	(-3.0 - 2.1)	-0.19	(-2.7 - 2.3)
Parathyroid hormone (pg/ml)	41.40	(10 - 190)	37.70	(8 - 145)
1,25 (OH) Vit D (ng/ml)	37.10	(4 - 90)	46.2	(11 - 93)
25 (OH) Vit D (ng/ml)	20.1	(4 - 124)	20.6	(4 - 79)
Urine DPD (nm)	58.3	(7 - 191)	73.0	(14.1 - 270)
Duration (years)	12.3	(6 - 30)	Not applicable	
Parity	8.0	(0 - 17)	7.0	(0 - 15)
Milk consumption (Lt.)	0.25	(0 - 1)	0.21	(0 - 0.6)
Menopause (years)	9	(2 - 20)	8.0	(2 - 13)
Exercise (minutes)	1.76	(1 - 2)	1.71	(1 - 2)
Sun exposure (minutes)	5.8	(0 - 50)	5.9	(0 - 25)

DPD - deoxypyridinoline

Parity was approximately equal in both groups as well as non-exposure to sun, lack of exercise and minimal intake of dairy products.

Discussion. Osteoporosis is defined as a progressive systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue with consequent increase in bone fragility and susceptibility to fracture.[7] The lower BMD in healthy Saudi females compared with North American females was observed by several authors.[8,9] These findings may contribute and aggravate the development of osteoporosis among postmenopausal Saudi females. The prevalence of osteoporosis in postmenopausal Saudi women with type 1 diabetes at the age of 50-60 years was reported to be 24%.[1] However, cessation of menses is not the only risk factor for developing osteoporosis. There are many environmental, hereditary and diseases which are involved in one way or another in osteoporosis.

Diabetes mellitus was investigated as a contributing factor to osteoporosis development. It was found that DM leads to reduced metabolic activity of osteoblasts, increased osteoclastic activity due to diabetic acidosis, secondary hyperparathyroidism related to diabetic nephropathy, reduced sexual hormones secretion, increased secretion of glycocorticoids and finally decreased blood supply to bones due to diabetic angiopathy.[10-12] Low bone formation in DM has been reported. The histologic finding has been supported by low osteocalcin level in diabetic patients.[13] Diabetic osteopenia is a controversial subject. It is generally agreed that Type 1 diabetic patients have low BMD compared to non-diabetics,[13] with few reports showing increased or normal BMD.[14] However, the subject of type 2 diabetes and bone mass is even more controversial. Increased, decreased or unchanged BMD compared to non-diabetics have been reported.[15,16] This controversy could be attributed to the old non-sensitive techniques used to measure bone density such as hand radiograph and single photon absorptiometry (SPA), which measure bone density of the appendicular bones (cortical bone) rather than trabecular bone of the lumbar spine measured by DXA or computerized tomography.

Table 2 - Comparison between the bone mineral density of diabetic and controlled patients.

Characteristics	Diabetic		Control	
Bone mineral density				
Spine-bone mineral density	0.928		1.036	
Spine-SD	-2.28		-1.2	
Femur-bone mineral density	0.817		0.914	
Femur-SD	-1.21		-0.608	
Spine				
Normal (%)	16	(16.6)	31	(31.3)
Osteopenia (%)	42	(43.7)	46	(46.5)
Osteoporosis (%)	45	(46.8)	22	(22.2)
Femur				
Normal (%)	43	(44.7)	38	(38.4)
Osteopenia (%)	43	(44.7)	49	(49.5)
Osteoporosis (%)	19	(19.8)	12	(12.1)

Osteoporosis in type 1 and type 2 diabetes in postmenopausal women was the objectives of the study of Nicodemus et al,[18] which revealed lower bone density in diabetic patients compared to non-diabetic control subjects. Our results provide evidence for an association between type 2 diabetes in postmenopausal patients and osteoporosis of lumbar spine and femoral neck. From **Table 2** it can be observed that osteoporosis in lumbar spine femoral neck was more common in the diabetic group while osteopenia in lumbar spine and femoral neck was more common in the control group. In addition, the normal BMD in lumbar spine was more common in control group but there was no significant difference in number of patients with normal femoral neck BMD of both groups.

These values are much higher (more severe) than those reported by Barto et al[19] who reported decreased bone density in lumbar spine and femoral neck. Decreased BMD in patient with Type 2 diabetes was also reported by other authors.[20-23] However, as stated before, controversial results of BMD in this group of patient were observed in the literature, some authors reported unaltered BMD[21, 22] compared with controls, or even increased BMD as reported by other authors.[23,24] The high prevalence of osteoporosis observed in diabetic patients could be attributed to association of multiple variables on top of diabetes and menopause such as Vitamin D deficiency, lack of sun exposure and lack of intake of milk and dairy products, lack of exercise and probably genetic.

The general understanding that in sunny countries such as KSA, Vit. D deficiency disorders such as rickets and osteomalacia would be more rare if non-existent. However, this is not the case in Saudi women. The factors believed to have effects on Vitamin D nutritional status of Saudis include age, sex, intake of dairy products rich in Vitamin D and the degree of exposure to sunlight.[26,27] In contradiction to reports in the literature, lower levels of 25 (OH) are achieved in summer in KSA most likely due to the tendency of Saudi people to avoid direct exposure to sunlight and not to the unavailability of ultraviolet light.[26]

In the diabetic group, 14% of the patients had low Vitamin D and only 8% in the control group had low Vitamin D level. Increase in alkaline phosphatase and PTH there were 14% and 21% in

the diabetic group and 14% and 13% in the non-diabetic group. This might indicate increased osteoblastic activity and secondary hyperparathyroidism.

In both groups who are postmenopausal, the higher prevalence of osteoporosis and osteopenia could be explained to the similar risk factors including Vitamin D deficiency, multiparity, non exposure to sun, lack of exercise and poor intake of dairy products rich in vitamin D. However, the higher prevalence of osteoporosis in diabetic group compared to non-diabetic could be attributed to the possible effect of diabetes on bone metabolism.

From this study, we conclude that osteoporosis is common among type 2 diabetic postmenopausal Saudi females. In the diabetic group, osteopenia and osteoporosis account for 85.4%. Lumbar spine measurement was more sensitive in detecting low bone density compared to femoral neck measurement in both groups. Contributing risk factors beside diabetes are low Vit. D, lack of exercise, lack of exposure to sun, multiparity and ageing.

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