The Relationship Between Type 2 Diabetes Mellitus And Bone Density In Postmenopausal Women

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T his study was carried out to determine the importance of type 2 Diabetes mellitus as a risk factor for osteoporosis in postmenopausal women.

Materials and Methods: This study was conducted in 2004 on 40 diabetic and 40 healthy postmenopausal women attending the endocrine clinics in Zanjan. These two groups were matched in terms of age, length of their menopausal period and body mass index. Serum calcium, phosphorus, alkaline phosphatase and estradiol were measured in all cases and bone densities at three sites (Femoral neck, lumbar spine and forearm) were evaluated with dual X-ray absorptiometry (DXA). All data were analyzed using t-test, analysis of variance, chi-square and multiple regression tests.

Results: The frequency of osteoporosis and osteopenia in diabetic women were not significantly different from non-diabetics. The mean bone density in the femoral neck was higher in the diabetic group (0.806±0.13 gr/cm2 vs 0.726 ± 0.15 gr/cm2), (p: 0.002). In the diabetic group there was a negative correlation between bone density and length of menopause in the femoral neck (r:-0.49, p:0.004), lumbar spine (r:-0.58, p: 0.005) and mid radius (r:-0.37, p: 0.03). The relationship between BMI and bone density was significant in the femoral neck (r: 0.55, p: 0.01) in diabetic women. In diabetic women, the higher the HbA1c the lower the bone density in lumbar spine.

Conclusion: Although the level of HbA1c as a marker of blood glucose control has a relationship with lumbar spine density in diabetics, diabetes type 2 is not a risk factor for osteoporosis. Hence measures should be taken individually similar to non diabetic patients, for screening, diagnosis and management of osteoporosis in diabetes type 2.

Introduction

Osteoporosis has long been considered as the main cause of hip and spine fractures with a high morbidity and mortality rate in the elderly. Annual costs of osteoporosis complications, care is nearly 14 billion dollars in the United States[1] and nearly 40% of all white postmenopausal women eventually sustain osteoporotic fractures.[2] The mortality rate of hip fractures are about 20%,[2] so early diagnosis of osteoporosis and its predisposing factors can be considered as a priority in health systems.

Among a large number of disorders leading to osteoporosis, diabetes mellitus regarding to its prevalence, is of importance. While the relationship between type 1 diabetes mellitus and osteoporosis is well documented in literature,[2,3] data on the presence of this com-

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plication in type 2 diabetes mellitus have not been well established.[4] In one study in Saudi Arabia the frequency of osteoporosis in diabetic postmenopausal women was higher than normal group.[5] In another study in Japan, no difference was found between diabetic and normal people in terms of their bone density in the lumbar spine and femoral neck.[6]

Some studies, for instance in Turkey, have detected even higher bone density in lumbar spine and femoral neck in diabetics than in normal people.[7]

Taking into consideration these discrepancies, this study was designed and conducted in Zanjan to determine if postmenopausal women with type 2 diabetes mellitus are more prone to osteoporosis than are normal women and also whether metabolic control has any effect on their bone density.

Materials and Methods

40 postmenopausal patients with type 2 diabetes, randomly selected from patients attending the diabetes clinic of Vali asr Hospital between March 2003 and March 2004, were included in this study (Table 1). Type 2-diabetes was diagnosed on the basis of classic symptoms and laboratory findings. The inclusion criteria for this study were duration of diabetes of over 2 years and no history of ketosis or diabetic retinopathy, nephropathy or peripheral neuropathy. Non-diabetic healthy control subjects were 40 postmenopausal women (Table 1) selected from patients attending the clinic for medical checkup during the same period; their Fasting Plasma Glucose (FPG) was below 100mg/dL and neither they not their first degree relatives had any history of diabetes mellitus. Diabetic patients and controls were physically active persons, and both groups were matched in terms of age, body mass index, and length of menopause; amenorrhea for at least one year and an elevated FSH level was considered as menopause.

All people with other additional risk factors for osteoporosis such as using corticoster-

oids, smoking, chronic disorders, and those with a history of bone fractures in their first degree relatives and bedridden patients were excluded as were individuals that had been treated with calcium or vitamin D or statins or diuretics.

In the diabetic group no one was using insulin to control their diabetes, and all patients were under treatment with sulfonylurea without any changes in their sulfonylurea dosage for the past 6 months.

A questionnaire covering data on age, length of menopause, weight, height, Body Mass Index (BMI) and waist to hip ratio was completed by an internist for each subject. 5cc of blood was collected from each of the subjects to evaluate serum levels of fasting plasma glucose, calcium, phosphorus, alkaline phosphatase and Estradiol. Bone density in three regions of the body including femoral neck, lumbar spine and mid radius was measured with Dual X-ray absorptimetry (DXA) (osteocore, France, CV<0.5%) in a single centre and with the same instrument for all the subjects. HbA1c was also measured in diabetic patients with the Ion exchange method (DS5) in a single laboratory centre. The last two values of HbA1c of the patients were extracted from their medical files and their mean was calculated.

Based on WHO criteria all subjects with T-scores below-2.5 were diagnosed as osteoporotic patients, and T- scores between -1 and -2.5 were classified as having osteopenia.

All diabetic cases with a mean HbA1C of less than 7% were considered as the "good" control group, 7-8% as an "acceptable" and those with HbA1c ≥ 8% as the "poor" control group.

We analyzed the correlation between bone density and variables mentioned above calculating correlation coefficient and odds ratio and using analysis of variance and multiple regression tests. t-test, X2 test and Fisher exact test were also used to compare different variables.

P-values less than 0.05 were considered statistically significant. Data are expressed as mean±SD.

Results

The mean age length of menopause, body mass index (BMI) and estradiol levels of diabetic patients did not differ from the control group (Table 1). Mean bone density of femoral neck in diabetics was significantly higher than that of control group (p:0.002). The mean bone density of lumbar spine and mid radius were not different in the two groups (Table 1, Table 2).

Twelve (30%) diabetic patients and 16 (40%) normal subjects had osteopenia in the femoral neck; 2 of the controls had osteoporosis in femoral neck whereas none of the subjects in the (p:0.19). Odds ratio for abnormal femoral neck bone density in normal people was 1.9 (C.I:0.7-4.7, P: 0.1).

The frequency of osteopenia and osteoporosis in lumbar spine did not differ between the diabetic and control groups (osteopenia: 45% in diabetics vs. 50% in control group,

osteoporosis: 27.5% in diabetic vs. 35% in normal subjects) (p:0.25). Odds ratio for abnormal lumbar spine bone density in normal people was 2.5 (C.I:0.8- 8, p:0.1).

The frequency of osteopenia and osteoporosis in the forearm of both groups did were not differ. Odds ratio for abnormal bone density in this region of normal people was 0.7(C.I:0.2- 1.8, P: 0.4).

There was a significant direct correlation between the bone density of lumbar spine and femoral neck (r:0.64, p:0.00) in the both groups, and a weak but significant correlation was detected between forearm bone density and lumbar spine as well (r:0.39, p:0.01).

In the diabetic group, the higher the BMI, the higher was the bone density in both the lumbar spine (r:0.55, p:0.01) and in the femoral neck (r:0.51, p:0.01). The correlation between BMI and bone density was significant only in the lumbar spine(r:0.49, p:0.001) in the control group. There was no correlation between waist to hip ratio and

Table 1. Variables (Mean ± SD) assessed in examined subjects

Variable	Control subjects (N=40)	Diabetic Women (N=40)	P Value
Age (years)	56.7± 9.0	58.6±7.0	0.3
BMI (kg/m2)	26.5± 4.5	28.1 ± 4.1	0.1
Length of menopause (years)	9.3 ± 8.4	9.4 ±6.8	0.6
Calcium (mg/dL)	9.1 ± 0.7	9.1 ±0.3	0.9
Phosphate (mg/dL)	3.4 ± 0.6	3.5±0.6	0.9
Alkaline phosphatase (Iu/L)	188 ± 37	175±63	0.6
FPG (mg/dL)	90 ± 8	161±32	0.001
Estradial (pg/mL)	88.2± 6.6	87.5±10.3	0.2

Table 2. Bone mineral density (gr/cm^2) (Mean ± SD) at the femoral neck, lumbar spine and distal radius in type 2 postmenopausal women and controls

Site of evaluation	Diabetic women (N=40)	Contral subjects (N=40)	P Value
Femoral neck	0.806 ± 0.13	0.726 ± 0.15	0.013
Lumbar spine	0.820 ± 0.16	0.770 ± 0.14	NS
Distal radius	0382 ± 0.06	0.396 ± 0.12	NS

Table 3. Bone density in diabetic postmenopausal women based on their HbA1c

HbA1c (%)	Mean ± SD of bone density(gr/cm2)		
	Forearm	lumbar spine	Hip
<7	0.380±0.07	0.871± 0.21	0.774 ± 0.14
7-8	0.319±0.06	0.868 ± 0.135	0.859 ± 0.102
>8	0.358±0.057	*0.710±0.115	0.744±0.13

*p < 0.01

bone density in the lumbar spine or in the femoral neck (r:0.03, p:0.8 in diabetics and r:0.02,p:0.8 in controls).

In the diabetic group, the longer the menopausal period, the lower the bone density in the femoral neck (r:-0.49, p:0.004), lumbar spine (r:-0.58, p:0.005) and mid radius (r:-0.37, p:0.03). This correlation also was significant in the control group in the femoral neck (r:-0.57, p:0.001) and lumbar spine(r:-0.49, p: 0.002)

There was a negative correlation between the mean of HbA1C, as an index of metabolic control of diabetics, and bone density in the lumbar spine (r:-0.38, p:0.02) but not in the femoral neck (r:-0.3, p:0.059) (table 2). Regression analysis illustrated that 14.5 % of density changes in the lumbar spine are due to HbA1c. We did not find any correlation between age and mid radius (r:-0.03, p:0.8), lumbar spine (r:-0.3,p:0.055) or femoral neck density (r:-0.29, p:0.06) in diabetic subjects; in normal subjects, however, the older age the lower the density in the lumbar spine (r:-0.4, p:0.01) and femoral neck (r:0.52, p:0.001).

Discussion

This study revealed that after adjusting for age, sex, length of menopause and BMI, diabetes type 2 cannot be considered as a risk factor for osteoporosis, although in diabetic patients, metabolic control of diabetes can be related to bone density.

Type 1 diabetes has been known as a risk factor for osteoporosis.[1] In one study fracture rate was higher in these patients[2] and their relative risk of fracture was 12 times higher than non diabetics.[3] In some studies, presence of osteopenia has been seen at the beginning of diagnosis of type 1 DM[8] although no relationship was found between bone density and the length of the disease or metabolic control of the disease,[9-11] there was some relationship between bone density and using OCP and BMI.[9]

There is a lack of data on osteoporosis in type 2 diabetes mellitus. In most studies, bone density in the femoral neck and lumbar spine have been reported as unchanged or to be increased[7,12,13,14] and the reported fracture rate in diabetics was equal or lower than that of non diabetics.[13] In one study conducted on 57 postmenopausal diabetic women in Turkey bone turnover markers were lower and femoral neck density was higher in diabetics.[7] Over-weight and consequently higher levels of estradiol in this group of patients may be the cause of their increased bone mass.[12]

Lower bone mass in diabetes type 2 in comparison with nondiabetic persons was reported in a few studies.[16] In one study, BMC and serum estradiol were lower in diabetic patients, whereas higher PTH and cortisol levels with lower calcitonin was reported.[13,16,17]

In another study, the fracture rate in diabetic women was 1.7 times higher than nondiabetic women and was related to the length of the disease and use of insulin.[3] In diabetics, bone density was inversely related to the age and length of menopause.[15]

In our study, the BMI and serum estradiol levels did not differ between groups and hence cannot be the cause of higher bone mass in the femoral neck of diabetics. Higher insulin levels in diabetic patients can be a probable cause of this difference. Higher bone density in diabetic patients without considering BMI, has been shown in some previous studies too.[18] Our data also did not demonstrate any relationship between type of obesity (W/H ratio) and bone density in either group. Also lower lumbar spine bone density was detected in diabetics with higher HbA1C and poorer control of diabetes. Some studies found no relationship between metabolic control of DM type 2 and bone density.[14,18] But recently, one study in the USA illustrated a significant relationship between bone density and the mean of HbA1c in diabetic patients.[20] Such a significant relationship was also reported from Japan in 2005;[6] they found this relationship only for femoral neck bone density and HbA1c. We did not measure urinary calcium excretion, but hypercalciuria following hyperglucosuria in poorly-controlled diabetic subjects can be considered a cause for bone loss in this group of diabetic subjects.

The relationship between micro vascular complications of diabetes and their reduced bone density has been shown in some studies[1] and Glycosylation of proteins, AGE (Advanced Glycation End Products) formation and genetic factors predisposing diabetics to micro vascular complications can be considered as mechanisms for progressive bone loss in poorly-controlled diabetic patients.

Recently the role of Amylin in osteoporosis has been considered. This polypeptide hormone originates from beta cells and is related to the calcitonin gene-related peptide family and has a 44% homology with the calcitonin gene-related peptide and 20% homology with calcitonin.[21] One study illustrated a lower level of amylin in the plasma of osteoporotic patients.[21] Plasma levels of amylin in diabetic patients may be lower than in normal people and this can be a mechanism for higher bone mass in diabetic patients.

In conclusion, we found that diabetes type 2 cannot be considered an additional risk factor for osteoporosis; decision making for diagnosis and treatment of osteoporosis in these patients should be individualized and based on the existence of other risk factors of osteoporosis. Good glucose control for prevention of bone loss in diabetic patients is recommended.

Acknowledgement

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