*Original Contribution/Clinical Investigation*

# Bone Mass Density In Diabetic Women: Is There A Detrimental Effect?

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## ABSTRACT

**Objective:** The aim of this study was to assess bone mass density (BMD) values in diabetic female patients and to determine the prevalence of osteoporosis among them.

**Methods:** A convenience sample of 210 Kuwaiti females with type 2 diabetes mellitus, aged 40-79 years were selected after excluding those with current of previous histories of any condition that can alter the BMD values. An age matched group of 655 non-diabetic healthy Kuwaiti women were selected after confirming the same exclusion criteria and they represented the control group. Bone mass measurements were performed by dual-energy X-ray absorptiometry (DXA) machine at the lumber spine (L2-L4) and femur (neck and total hip). Body size measurements and lifestyle issues were asked about.

**Results:** There were no significant differences of the BMD values or the prevalence of osteoporosis between the diabetic and the non-diabetic women. On multivariate analysis, weight showed a dominant significant constructive effect in both groups. In the non diabetic group each kg of body weight had a change of 0.6%, 0.5% and 0.7% of the spine femur neck and total hip BMD respectively. In the diabetic group, each kg of body weight showed a significant change by 0.2% and 0.3% in the femur region (neck and total hip respectively) only.

**Conclusion:** Women with type 2 DM showed no significant difference either in BMD values or osteoporosis prevalence from non-diabetic women. The aggravating factors of BMD were more apparent among the diabetic women than the non-diabetic group and vise versa.

**Key words:** Bone Mineral Density, Diabetes Mellitus, Osteoporosis.

## Introduction

Osteoporosis is a bone disorder that is characterized by low bone mass, increased bone fragility and consequently increased fracture risk. It usually remains asymptomatic and does not become clinically evident until there is a fracture. The World Health Organization (WHO) defines osteoporosis in terms of bone density measurements of postmenopausal white females compared to young adult mean[2]. Although white women are most often affected, women of all races and all ethnic groups are susceptible to osteoporosis and fractures. As the population growth and aging increases all over the world, osteoporosis is becoming an important public health problem with its great significant economic and social impact. Therefore it is important to identify population at increased risk of developing osteoporosis[2].

## Material and Methods

### Materials:

The study was carried out at the department of nuclear medicine in Amiri Hospital, Kuwait. We recruited 210 Kuwaiti females known to have type 2 DM referred from different primary care centers to the nuclear medicine department from March 2002 till October 2005.

We excluded females with one or more of the following conditions that may modify the BMD picture such as chronic diseases of the liver, kidney, heart, malabsorption syndrome, cancer or history of chemotherapy or radiation therapy; endocrine problems such as prolonged secondary amenorrhea, hyperthyroidism, hyperparathyroidism; connective tissue diseases like rheumatoid arthritis; history of oopherectomy or hysterectomy before menopause; females taking drugs known to alter bone metabolism were also excluded for example steroids, bisphosphonates, hormone replacement therapy, estrogen receptor modulators, anticonvulsants, thyroxin, calcium and vitamin D.

Non-diabetic age-matched Kuwaiti females who pursued the above mentioned exclusion criteria were invited within the same period of the study to volunteer as a control group. The total number of the eligible control sample was 655 healthy Kuwaiti females.

### Methods:

All diabetic and non-diabetic females were asked to complete an anonymous structured questionnaire during their visits after obtaining their verbal consent. This questionnaire was designed to include some personal and reproductive data like age, age of menarche, age of menopause, parity and duration of lactation. Complete medical and drug history, life style habits such as smoking, daily consumption of caffeine, daily dairy intake and practicing physical exercise were also asked about. Diabetic women were inquired about the duration of diabetes, and modality of anti-diabetic treatment.

BMD was measured at the lumbar spine (L2-L4) and the dual proximal femur (neck and total femur) using dual-energy X-ray absorptiometry (DXA) machine which is a GE Lunar-Prodigy densitometer (GE Medical Systems, Madison, WI, USA) provided with enCoreTM 2004 software (version 8.10.027). Daily quality assurance measurement was done using spine phantom to ensure the precision of the machine. The in vivo precision of error measurements, expressed as coefficient of variation, were 1.5% for the lumber spine, 2% for the femur neck and 1.8% for the total femur. This was assessed by duplicate measurements on 30 patients' representative of our clinic patient's population with repositioning the patients after each scan.

Standard positioning was used for anterior–posterior scan of the lumbar and the dual proximal femur. The BMD was expressed as g/cm2 and standard deviations (SD) from the young adult normal mean (T-score) and from the age-matched mean adjusted to body weight (Z-score). These values were compared to the Middle East Reference Population supplied by the manufacturer. Using the World Health Organization (WHO) criteria for defining osteoporosis when the T-score values is at or less than -2.5 SD, osteopenia when the T-score values between –1 SD and –2.5 SD and normal when T-score is at or above –1 SD(2,36).

### Data analysis

The collected data were analyzed using the Statistical Package for Social Sciences (SPSS) version 13. Mean and standard deviation (SD) were calculated for different continuous variables. Student-t test, chi square test, Univariate analysis of variance and Z test to compare between two proportions were used to examine the statistical differences between diabetics and non-diabetics. Univariate and multiple linear regression analysis were used to determine the predictors for the change in BMD separately in diabetics and non-diabetics. The level of significance was $p<0.05$ and Confidence Interval (CI) was 95%.

## Results

The study involved 210 diabetic women and 655 non diabetic women in the age range of 40-79 years with a significantly different mean age of about 59 and 55 years respectively as shown in table 1. Obesity was significantly higher among the diabetic group. The mean BMI of both groups were 33 and 30 respectively, where 30.5% of diabetics and 37.9% of non diabetics were overweight (BMI= 25-29.9) and 65.7% and 48.9% respectively were obese (BMI $\geq$ 30). The daily consumption of caffeine and dairy products were significantly less likely to be consumed among diabetic women than non diabetic women.

On the other hand, the later group practiced exercise significantly more than the former group. Regarding parity and lactation, the table illustrated that diabetic women had significantly more pregnancies than non diabetic women (about 6 and 4 pregnancies respectively) but with a significant shorter duration of lactation (7 and 9 months respectively). In the diabetic women, the mean duration of the DM was 11.99 ± 8.6 years with a range of 0.1-40 years. Oral hypoglycemic medications were the line of treatment of most of them (65.2%) while insulin injection was experienced by 16.2%. The rest of the diabetic sample (18.6%) was following both lines of treatment. The majority of diabetic and non-diabetic women reached menopause (86.4% and 82.7% respectively).

The mean spine and femoral region (neck and total hip) BMD in different decades were illustrated in table 2. There was no significant difference between the two groups regarding BMD values in different areas and age groups.

Although the prevalence of spine, femoral neck, and total hip osteoporosis was higher among the diabetic women than the non diabetic group but this difference was not statistically significant as shown in table 3.

The influence of age, height, weight and lifestyle factors on BMD was investigated by univariate and multiple regression analysis separately among diabetics and non diabetic women. The results of multiple regression significant influencing factors were illustrated in table 4. Age was a dominant significant injurious factor in all regions (spine, femur neck and total hip)

in both groups. There was an annual decrease ranged from 0.7% - 0.9% of BMD in diabetic women and 0.6% & 0.8% in non diabetic females.

Weight showed a dominant significant constructive effect in the non diabetic group as each kg of body weight had a change of 0.6% of the spine BMD, 0.5% of neck BMD and 0.7% of total hip BMD. In the diabetic group, each kg of body weight showed a significant change by 0.2% and 0.3% in the femur region (neck and total hip respectively) only.

Height showed a significant influence only in the femur neck BMD of the diabetic group where each cm of body height has 0.3% change of femur neck BMD. On the level of univariate analysis, height showed significant influence in spine BMD and total hip BMD in diabetic women (β 0.004, p=0.05, CI: 0.000 – 0.008 and β 0.004, p=0.04, CI: 0.000 – 0.008 respectively). In the non diabetic group it confirmed also significant effect in spine BMD (β 0.005, p<0.0001, CI: 0.003 – 0.007), femur neck BMD (β 0.005, p<0.0001, CI: 0.003 – 0.006) and total hip BMD (β 0.003, p=0.002, CI: 0.001 – 0.005) but its effect was masked when other variables entered the equation of the multivariate analysis.

Table 4 also pointed out the detrimental effect of parity on spine BMD of both groups. Each pregnancy decreased the spine BMD by 1% among diabetics and 1.5% in the other group. On the other hand, lactation drew attention to its negative effect on spine BMD among diabetics only where each month of lactation decreased spine BMD by 0.4%. On the level of univariate analysis, the harmful effect of parity and lactation were obvious in the diabetic women on the femur neck BMD (β -0.01, p=0.002, CI: -0.002 to -0.004 and β -0.005, p=0.001, CI: -0.008 to -0.002 respectively). Also they showed the same pattern in the total hip BMD (β -0.01, p=0.006, CI: -0.017 to -0.003 and β -0.006, p=0.001, CI: -0.009 to -0.002 respectively). In the non diabetic group, lactation showed no effect on BMD in all regions on the level of univariate or multivariate analysis. Parity illustrated its injurious outcome on the neck BMD in the univariate analysis only (β -0.007, p=0.013, CI: -0.012 to -0.001) but its effect disappeared in the multivariate analysis.

The duration of illness with diabetes mellitus called attention to its border line significant negative effect barely on the spine BMD just on the level of univariate analysis (β -0.002, p=0.05, CI: -0.005 to 0.000).

In the non diabetic women, the influence of daily consumption of dairy products demonstrated its positive effect on the femur region BMD (neck: β 0.054 p=0.01, CI: 0.013 - 0.096 and total hip: β 0.049, p=0.035, CI: 0.003 - 0.094) in the univariate analysis. Practicing exercise also showed a significant constructive effect on the neck BMD merely in the univariate analysis (β 0.037, p=0.032, CI: 0.003 - 0.071). But their supremacy was masked by the influence of other more prevailing factors when entered the multivariate analysis model. These factors showed no significant effect in the diabetic women in both levels of univariate or multivariate analysis.

Smoking and caffeine consumption showed no significant effect on BMD in any area in both groups of women either in univariate or multivariate analysis.

**Table 1.** General characteristics of the diabetic and non-diabetic females included in the study.

| Variables | Diabetic women n=210 | Non-diabetic women n=655 | p |
|---|---|---|---|
| Age | | | |
| Mean (SD) | 58.7 (8.6) | 54.8 (7.8) | <0.0001[a] |
| BMI | 33.3 (6.7) | 29.7 (4.2) | <0.0001[a] |
| Smoking (yes %) | 3.3 | 1.5 | NS[b] |
| Using caffeine (yes %): | 75.5 | 66.9 | <0.05[b] |
| Mean (SD) cups/day | 1.6 (1.6) | 2.1 (1.4) | <0.01[a] |
| Dairy products (yes %): | 82.9 | 84.2 | NS[b] |
| Mean (SD) cups/day | 1.3 (0.9) | 1.6 (0.9) | <0.0001[a] |
| Exercise (yes %): | 16.7 | 28.4 | <0.01[b] |
| < one hour/wk | 80.0 | 27.6 | <0.0001[b] |
| ≥ one hour/wk | 20.0 | 72.4 | |
| Parity | | | |
| Mean (SD) | 5.7 (3.0) | 4.3 (2.8) | <0.0001[a] |
| Lactation (yes %): | 76.2 | 68.3 | <0.05[b] |
| Mean months (SD) | 6.7 (6.7) | 8.8 (10.4) | <0.05[a] |

a Student-t test
b Chi square test
NS: not significant (p>0.05)

## Discussion

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing person to an increased risk of fracture[1]. The clinical relevance of osteoporosis related to type 2 DM is less acknowledged. Until now no consensus has been reached on osteoporosis risk in people with type 2 DM due to inconsistent findings among researchers. They have reported lower, equal and greater bone mass in type 2 diabetics relative to non-diabetics subjects[7, 9-33].

The present study showed that BMD values of women with type 2 DM were not significantly dissimilar to the control healthy women in all measured regions (spine, femur neck, and total hip). In addition the prevalence of osteoporosis among women with type 2 DM was not significantly different from

**Table 2.** Mean (SD) of BMD in different body areas in diabetic (n=210) and non diabetic women (n=655) according to age.

| Variables | 40-49 | 50-59 | 60-69 | 70-79 | Total |
|---|---|---|---|---|---|
| Spine | | | | | |
| Diabetics | 1.248 (0.16) | 1.118 (0.15) | 1.027 (0.18) | 0.977 (0.15) | 1.087 (0.18) |
| Non diabetics | 1.165 (0.16) | 1.105 (0.16) | 0.973 (0.16) | 0.941 (0.15) | 1.086 (0.18) |
| Neck | | | | | |
| Diabetics | 0.980 (0.12) | 0.933 (0.14) | 0.847 (0.12) | 0.726 (0.13) | 0.885 (0.15) |
| Non diabetics | 0.958 (0.12) | 0.931 (0.13) | 0.811 (0.11) | 0.721 (0.10) | 0.902 (0.14) |
| Total femur | | | | | |
| Diabetics | 1.047 (0.12) | 1.043 (0.15) | 0.932 (0.13) | 0.797 (0.14) | 0.976 (0.16) |
| Non diabetics | 1.015 (0.13) | 1.005 (0.14) | 0.893 (0.12) | 0.812 (0.13) | 0.974 (0.15) |

No significant difference was found between diabetic and non diabetic women regarding BMD in different body areas in all age groups by univariate analysis of variance.

**Table 3.** Prevalence of osteoporosis in different body areas in diabetics and non diabetics

| Variables | Diabetics n=210 n(%) | Non diabetics n=655 n(%) | p |
|---|---|---|---|
| Spine | 18 (8.6) | 44 (6.7) | NS |
| Neck | 10 (4.8) | 17 (2.6) | NS |
| Total femur | 5 (2.4) | 8 (1.2) | NS |

NS: not significant (p>0.05) by using Z test to compare between two proportions.

**Table 4.** Multiple regression analysis of significant factors associated with BMD in different body areas in diabetics and non diabetics

| Variables | Diabetics (n=210) | | Non diabetics (n=655) | |
|---|---|---|---|---|
| | β | CI | β | CI |
| Spine | | | | |
| Age | -0.007 | -0.010 to -0.004[a] | -0.006 | -0.010 to -0.003[b] |
| Weight | | | 0.006 | 0.003-0.009[a] |
| Parity | -0.010 | -0.018 to -.002[c] | -0.015 | -0.028 to -0.003[c] |
| Lactation | -0.004 | -0.007 to 0.000[c] | | |
| Neck | | | | |
| Age | -0.008 | -0.011 to -0.006[a] | -0.008 | -0.011 to -0.005 [a] |
| Weight | 0.002 | 0.001-0.003[b] | 0.005 | 0.002-0.007[a] |
| Height | 0.003 | 0.000-0.006[c] | | |
| Total femur | | | | |
| Age | -0.009 | -0.011 to -0.006[a] | -0.008 | -0.011 to -0.004[a] |
| Weight | 0.003 | 0.002-0.004[a] | 0.007 | 0.004--.009[a] |

a p<0.0001, b p<0.01, c p<0.05

- Predictors of diabetics were age, height, weight, smoking, consuming caffeine, consuming dairy products, practicing exercise, parity, lactation, duration of disease, type of treatment.
- Predictors of non diabetics were age, height, weight, smoking, consuming caffeine, consuming dairy products, practicing exercise, parity and lactation.

the healthy control group. No significant differences were found between the two groups even when further adjustments were made for other possible confounders. Our results confirm the findings of previous studies that reported similar BMD in type 2 DM to healthy subjects[7, 24-26]. Touminen J et al. examined the BMD of only proximal femur with DXA machine of 68 type 2 diabetic females on insulin treatment and found out that the BMD levels of the diabetic women did not differ significantly from the control group[7]. Also Sosa M et al. reached for the same findings in 46 type 2 diabetic females where the lumber spine BMD values were measured by DXA and QCT techniques[26]. Wakasugi M et al found same results on 78 diabetic patients (40 females and 37 males) by measuring the lumbar spine by DXA machine[25]. Weinstock RS et al showed also similar findings on 28 type 2 diabetic females by using dual photon absorptiometry[24].

On the other hand, this study' findings contradicted earlier

observations of higher and lower BMD in type 2 DM patients reported by other investigators[9-23, 27-33]. These discrepancies may be explained by methodological differences or by using the old non- sensitive techniques used to measure bone density such dual photon absorptiometry. For example Isaia G et al used dual photon absorptiometry of the lumber spine and found that the bone mineral content (BMC) was lower in 40 type 2 diabetic women on dietary and or oral treatment than the age-matched non-diabetic women[27]. Also Gregorio F et al, reported reduced BMC in 60 well-controlled and 50 poorly controlled type 2 diabetic patients on oral hypoglycemic drugs as compared to 50 healthy controls[27]. Furthermore Guven M et al observed that the BMD values of the lumber spine and the femur region were also lower in 100 type 2 diabetic patients (57 females and 43 males) than the control group by using DXA machine[30]. Al- Maatouq et al assessed the BMD of lumber spine and femur neck using DXA machine of 104 postmenopausal type 2 diabetic women and found lower BMD values of the diabetic women as compared to the controlled group[31].

Several researchers however had reported higher bone mass in type 2 diabetic patients relative to non-diabetic control subjects[9-23]. For example Kao WH et al found that type 2 diabetic Mexican-American women in 600 subjects from 34 families have higher BMD at the hip and spine compared to their non-diabetic counterparts[17]. Schwartz AV et al also reported high BMD values in 657 women with type 2 DM; 101 of them were on insulin treatment. Hanley DA et al found higher BMD at the lumber, femur neck and trochanter regions in 347 females and 182 males with type 2DM[13]. Dennison EM et al reported high BMD at the spine and proximal femur in newly diagnosed diabetic subjects consisting of 444 females and 465 males[14]. van Daele PL et al also demonstrated increased BMD at the lumber spine and proximal femur in 243 men and 335 women with non- insulin- dependant DM[11]. Sahin G et al found significantly higher levels of BMD at the lumber and femoral regions in the diabetic postmenopausal females compared to the control group[19]. Rakie V et al reported high BMD at the forearm, total hip and femoral neck regions in 194 patients with type 2 DM women vs. control subjects[23]. Kwon DJ et al found that the BMD at the lumber vertebrae was slightly higher in 185 diabetic females as compared to control group[29]. Gredhem P et al reported high BMD values at the lumber and femur neck in 74 women with type 2 DM[16].

Another output of this study was that obesity was significantly higher among diabetic females. Type 2 DM is generally associated with obesity, which is considered one of the risk factor for the development of this disease[37]. Increased body weight has been associated with an increased bone mass in both normal and diabetic individuals and may account for the relative protection seen in patients with type 2 DM[38]. A higher body weight may influence BMD through a variety of mechanisms, including higher mechanical loading on weight-bearing bones, estrogen synthesis in adipose tissue, higher levels of sex hormones and their precursors, and lower bone turnover[39]. In several studies a significant relationship was found between BMD and BMI in type 2 diabetic population[30, 18].

On the other hand, although obesity was prevalent more among diabetic women than non-diabetics, but its protective effect was apparent and noticeable among the non-diabetics than diabetics (it was almost 3 times in non-diabetics) as indicated by the multivariate analysis.

Another point was the diabetes status, as the univariate analysis illustrated negative effect of the duration of diabetes on BMD but this was masked in the multivariate analysis. This is in congruence of the study results of Wakasugi M et al who reported that BMD in 78 diabetic subjects was inversely correlated with age and duration of the diabetes[25]. These might be explained by presence of suggested detrimental role of type 2 DM as a known catabolic status on several body parts that be capable of including bone metabolism. The existence of other confounders (e.g. obesity) might disguise the real picture of BMD.

Our findings showed that age, parity, lactation and duration of the disease had significant negative effect on spine BMD in type 2 diabetic patients. This is in concordance with Kwon et al who showed also that age, duration of diabetes and duration of menopause among the risk factors for decreased BMD in 185 females with type 2 DM[29]. In addition Guven M et al also found that age, duration of diabetes and sex were additional risk factors for developing of bone loss in 100 diabetic subjects[30]. However, Weinstock RS et al did not find any significant relation between duration of diabetes and BMD in 28 diabetic females[24].

## Conclusion

Women with type 2 DM showed no significant difference either in BMD values or osteoporosis prevalence from non-diabetic women. The aggravating factors of BMD were more apparent among the diabetic women than the non-diabetic group and vise versa. Further studies are recommended on larger scale to unravel the ambiguous results of different studies regarding the actual consequence of type 2 DM on bone metabolism and BMD values.

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