Biochemical Risk Determinants of Osteoporosis in Overweight and Obese Postmenopausal Women with Type 2 Diabetes Mellitus

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ABSTRACT

Background: Several studies suggested that skeletal system is adversely affected by diabetes and is associated with increased risk of osteoporosis and fragility fractures

Objectives: The study was a case-control study that designed to assess the level of bone turnover markers (BTMs) among patients with type 2 diabetes mellitus (T2DM) and to investigate the effect of body weight and diabetic control on the level of bone turnover

Type of the study: Cross- sectional study.

Methods: The present study included 100 postmenopausal women with type 2 diabetes mellitus. Sixty-six non-diabetic postmenopausal women were enrolled as a control. Fasting blood samples were collected to measure Alkaline phosphatase (ALP),stoeocalcin(OC), fasting blood sugar (FBS)and glycated hemoglobin (HbA1c). Urine samples were collected to measure deoxypyridinolin(DPD). The results were expressed as a ratio to urine creatinine

Results: The mean level of serum osteocalcin was significantly lower in the diabetic group than in the control group,while the level of urinary deoxypyridinolin was significantly higher in the diabetic group than in the control group . There was no significant difference in the level of Alkaline phosphatase between diabetic patients and control. An inverse association was found between osteocalcin with body mass index(BMI), glycated hemoglobin and fasting blood sugar. On the other hand appositive association was found between the level of deoxypyridinolin with body mass index

Conclusions: Altered bone metabolic markers in patients with T2DM with more significant alterations in those who hsd poor glycemic control . Decrease in formation marker osteocalcin and increased resorption markers such as (DPD) has been found.

Keywords: post menopausal, diabetes, skeletal.

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Skeletal system is adversely affected by diabetes mellitus (DM) and is accompanied by increased risk of osteoporosis and fragility fractures (1). High glucose levels enhance the differentiation, fusion of osteoclast that result in a more resorptive state, the bone matrix affected by hyperglycemia via the Advanced glycated end products (AGEs) accumulation leading to reduced bone strength(2) Obese women have been considered to be protected against osteoporosis and osteoporotic fractures. However, recently several reports have shown that obesity may not protect individual from osteoporosis and in fact it might be a risk factor for certain fractures(3,4).The bone has metabolic activity and in a continuous remodeling process with dynamic equilibrium between bone resorption by osteoclast and bone formation by osteoblast (5,6). An imbalance in these processes can result in the loss of bone tissue, Rates of bone turnover can be indirectly evaluated by the measurement of bone turnover markers concentrations that are released into the blood stream during bone remodelling (7). This study aims to estimate the level of bone markers in postmenopausal women with T2DM, also to test the effect of glycemic control indices on the rate of bone turnover and to investigate the association between body mass index and bone turnover markers.

Methods : This is a case-control study was carried out in Basrah governorate, southern Iraq. This study was conducted on 100 postmenopausal women with T2DM who attend Al-Fayha Center for Diabetes and Endocrinology at AL-Fayha general hospital. Patients received different treatment such as insulin and oral antihyperglycemic drugs (OAHD). Sixty-six non-diabetic postmenopausal women who attended 5 different primary health care centers a signed as control group. Patient with chronic liver disease, renal, impairment, thyroid disorder , Type 1 diabetes mellitus(T1DM), Patients on hormone replacement therapy ,antiresorptive therapy, calcium ,vitamin D supplements and chronic glucocorticoid therapy were excluded from this study. Fasting blood samples were obtained from each subject , about(2ml) was dispended in an EDTA tube and used for the estimation of HbA1c. The rest of blood were placed in plain tubes and was left at room temperature for 30 minutes . followed by centrifugatioin for 5 minutes . Then the collected serum stored in plastic tubes to be used for estimation of glucose, ALP and OC. Urine samples were collected from each subject , then the samples were centrifuged 5 minutes and then stored in the freezer for subsequent measurement of DPD , the results were expressed as a ratio to urine creatinine. Body weight, height and BMIwere measured for each participant in the study. The level of OC was determined

by Enzyme linked immunosorbent assay method using kit provided by My Biosource, USA. Serum ALP was determined by colorimetric method using kit provided by Analytican, Biotechnologies AG /Germany, BIOLYZER 300 Analyzer was employed to perform the assay. The level of urinary DPD was determined by ELISA method using kit provided by My Biosource, USA. The level of HbA1c was measured by ion exchange high-performance liquid chromatography using glycosylated hemoglobin HbA1c kit provided from Bio-Rad ,USA. Fasting serum glucose is measured by enzymatic method using kit provided from Randox Ltd. UK. Statistical analysis:The data were analyzed in the computer by using SPSS "Statistical Package for Social Sciences programme" version20. The results in this study are expressed as [mean ±SD]. Independent t-test was used for comparing two different groups, While one-way ANOVA analysis was used to find the significance of variables between three or more groups . Finaly pearson correlation was used to find the correlation coefficients among OC, ALP,DPD, HbA1c and FBS in diabetic patients . P less than 0.05 was significant.

Result :The mean age of post menopausal women with T2DM was (58.64 ± 5.55) years and the mean age of non-diabetic postmenopausal women was (56.8 ± 6) years. The average duration of menopause for diabetic patients was (8.29 ± 5.46 years) , while the control group had an average of (7.1 ± 5.13 years). The mean duration of T2DM was (7.45 ± 5.01). The mean value of BMI for diabetic patients was (29.83 ± 6.35 kg/m²) and (2 7.8 ± 4.7 kg/m²) for control group with significant difference (p <0.005).The mean value of FBS was significantly higher in the diabetic group (237.2 **±** 104.04mg/dl) than the control group (97.014 ± 12.1 mg/dl) and the mean level of HbA1c was significantly higher in diabetic group(9.68 ± 2.55 %) than the control(5.2 ± 1.2%). Regarding bone formation markers ,serum OC levels were significantly lower in the diabetic patients as compared to controls . Levels of ALP were not different (T2DM, 115.7 ± 27.2 U/L vs. controls, 109.2 ± 38.2U/L . the level of urinary DPD were significantly higher in the diabetic women than the control group. The mean level of serum OC was significantly higher in diabetic patients with good glycemic control (HbA1c < 7.5 %) . The level of ALP was significantly lower in diabetic group with good glycemic control than in patients with uncontrolled diabetes. However, there was a positive association between the mean value of urinary DPD and HbA1c % (p value Â o.o5). The mean value of OC revealed a negative association with respect to BMI. No significant difference in the results of ALP with respect to BMI, while urinary DPD was higher among over weight diabetic patients as compaired to those with normal and obese diabetic patients respectively. serum OC correlate negatively and significantly with DPD, HbA1c and FBS while the level of serum ALP correlate positively with HbA1c.while the level of serum ALP correlate positively with HbA1c.

Table-1.1-The baseline characteristics and biochemical parameters for both diabetes patients and control.

*P -Value	**Controls N = 66**	**Patients N =100**	**Variables**
NS	57 ± 6.1	58.56 ± 5.86	Age (years) Means ± SD
NS	7.28 ± 5.13	8.29 ± 5.46	Duration of menopause Means ± SD
--	------	7.45 ± 5.01	Duration of DM (years) Means ± SD
Â 0.05	2 7.8 ± 4.7	29.8 ± 6.35	BMI (kg/m²) Means ± SD
Â 0.05	97.014 ± 12.1	221.6 ± 110.9	S.FBS (mg/dl)
Â 0.05	5.2 ± 1.2%	9.68 ± 2.55 %	HbA1c (%)
Â 0.05	17.56 ± 15.8	7.4 ± 6.7	S. OC (ng /ml)
NS	109.2 ± 38.2	115.7 ± 27.2	S. ALP (U/l)
<0.05	7.4 ± 5.4	9.5 ± 8.5	U. DPD nmol/mmol cr

Table (1.2): The distribution of bone turnover markers among diabetic patients according to glycemic control (HbA1c %).

P Value*	HbA1c ≥ 7.5 % N=78	HbA1c < 7.5 % N=22	Parameter
<0.05	6.3 ± 5.6	11.5 ± 10.3	S. OC(ng/ml)
<0.05	118.1 ± 26.4	107.1 ± 29.1	S. ALP U/l
<0.05	10.5 ± 8.5	6.6 ± 7.8	U. DPD nmol/mmol cr

Table-1.3. the distribution of bone turn over markers among diabetic patients according to BMI.

*P Value	Obese N=49 BMI ≥ 30 (kg/m²)	Over weight N=16 BMI 25-29.9(kg/m²)	Normal weight N=35 BMI 18.5-24.9(kg/m)	Parameter
<0.05	5.4 ± 4.2	7.2 ± 4.9	10.3 ± 8.9	S. OC (ng/ml)
NS	116 ± 29.7	109.2 ± 25.9	118.2 ± 24.1	S. ALP (U/l)
<0.05	11.2 ± 9.1	11.4 ± 12.4	7.7 ± 4.7	U. DPD(nmol/mmolcr)

Table (1.4): The pearson correlation analysis among OC, ALP, DPD, HbA1c and FBS in diabetic patients group

FBS	HbA1c	DPD	ALP	OC	Analytes
-.238 *	-.236 *	-.322 **	-.073	1	OC
.085	.209*	-.096	1	-.073	ALP
.133	.135	1	-.096	-.322**	DPD
.633**	1	.135	.209*	-.236*	HbA1c
1	.633**	.133	.085	-.238*	FBS

- *Correlation is significant at 0.05- two tailed
- ** correlation is significant at 0.01- two tailed

Discussion: The results in this study revealed that the level of osteocalcin was signifacantly lower in diabetic women as compared to the control group. Similar findings results were reported by several studies(8,9). In T2DM, bone formation might decreased because of increased AGEs levels in the collagen of bone which markedly increased in diabetes. The AGEs disturbe the normal osteoblastic function , impair development of osteoblast and the attachment to the bone collagen matrix (10). In this study an inverse association was reported between the OC levels and the In this study an inverse association was reported between the OC levels and the BMI of diabetic patients, this in agreement with the findings of other studies (11, 12)While Lee et al (13).found no association between BMI and OC level. The mechanisms suggested to be responsible for the increased risk of bone fragility in mechanisms suggested to be responsible for the increased risk of bone fragility in both T2DM and obesity include metabolic, structural and dynamic abnormalities However, the relative participation of each factor separately and their combined influence on skeletal fragility remain obscure (14) An inverse association was found between the level of OC and HbA1c . A study on animal models have shown that OC is released into the blood stream and exerts biological effects on pancreatic beta cells and adipose tissue. Thus, glycemic control may protect patients with T2DM from bone loss (15) . In the present study the mean level of ALP in diabetic patients was higher but insignificant as compared to controls. Similar finding were reported by Zhou et al (16). The role of ALP in the formation of bone tissue has been vigorously debated . However, controversial mechanisms have been suggested to explain the function of ALP in bone tissue metabolism (17). The values of DPD was significantly higher in T2DM patients than in control group with positive association with HbA1c. This similar to the results obtained by other researchers(18) . Elevated urinary DPD in diabetics, especially those with poor metabolic control in whom the rate of bone

resorption is increased, exposes diabetic patients to the risk of bone loss(19) .

Conclusion: Altered bone metabolic markers in patients with T2DM with more significant alterations in the uncontrolled group. This could reflect the strong impact of glycemic control on diabetic bone turnover. Decreased bone formation marker OC were found in postmenopausal women with T2DM . Higher levels of bone resorption marker DPD have been found in diabetic patients and it associated positively with BMI supporting that obesity is not protective from OP and may impose negative effect on bone.

Recommendations:

. 1-Further studies are required that include measuring bone mineral density to clarify the relationship between BTMs and bone mineral density which may be an important for the explanation of bone fragility in postmenopausal women with T2DM

2. Larger sample size might required in order to establish the association between osteoporosis and BTMs.

3. It may be recommended to assess bone health during the management of diabetic patients especially in women after menopause with encouragement of weight reduction and better glycemic control.

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