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Factors Affecting Bone Mineral Density in Type 2 Diabetic Female Patients Referred to Dual-Energy X-Ray Absorptiometry Scan (DXA-Scan)

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Abstract

Objectives: To identify factors affecting bone mineral density (BMD) in Type 2 Diabetes Mellitus (T2DM) female patients referred to DXA-Scan.

Method: We conducted a retrospective cohort study at tertiary care hospital in Ajman, United Arab Emirates (UAE), and reviewed electronic hospital records for patients referred to DXA-Scan. Based on inclusion and exclusion criteria, 569 were enrolled in the study; diabetic and control groups.

Results: Diabetic group showed significantly higher percent of liver impairment ($p \leq 0.01$), renal impairment ($p \leq 0.001$), and had significantly higher comorbid conditions such as depression ($p \leq 0.01$), hypertension ($p \leq 0.001$), dyslipidemia ($p \leq 0.001$), Ischemic Heart Disease (IHD) ($p \leq 0.001$) and osteoarthritis ($p \leq 0.01$), as well as taking significantly higher medications compared with control group.

The result from stepwise multiple linear regression analysis showed that BMD in the diabetic group can be predicted by weight, height, body mass index, age, systolic blood pressure, diastolic blood pressure, stroke, hypothyroidism, fracture, and taking thyroid hormone, oral steroids and anticonvulsant with variation based on skeletal site.

Conclusion: Many diseases and medication-related variables can predict BMD values in diabetic and control groups.

Keywords: Bone mineral density; Type 2 Diabetes Mellitus; DXA-Scan; Osteoporosis; United Arab Emirates

Introduction

Osteoporosis defines as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. The most widely validated method to measure BMD is through DXA-Scan. There is an estimation that osteoporosis and its complication will cost 28 billion in 2025 in the United States alone [1]. In the UAE, 24% of the population suffers from osteopenia, while 2.5% have osteoporosis [2].

There are few studies that investigated the association between type 2 diabetes mellitus and osteoporosis in the Arabian Gulf region. In this research, we intend to know more about clinical characteristics of diabetic female patients referred to DXA-scan in UAE population and to understand their BMD values, and factors affecting BMD [3].

Materials and Methods

A retrospective cohort study was performed in a tertiary care hospital in Ajman, UAE. All electronic records of female patients who went through DXA-Scan between 24/7/2010 and 25/12/2012 were reviewed. Exclusion criteria were:

a) Individuals with type 1 diabetes mellitus

b) Male gender

c) Patients age <25 years [4] lack of electronic record in the hospital database. Patients were divided between diabetic and control group. DXA-Scan results were extracted from Eazix software of DXA-Scan instrument (Osteocore 3 densitometer, Medilink Inc, France). The first DXA-Scan done for each patient was the one used in the analysis. Each patient was assigned index date at which time in opening electronic record in the hospital database. Individuals were followed from their index date until 27/12/2012

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 20. Mean and standard deviation (SD) were calculated for different continuous variables, while categorical variables are expressed as a percentage. Student's t-test and chi-square test were used to assess significance level.

Relative risk (RR) and its 95% Confidence Interval (CI) were obtained from cross-tabulation. The relation between BMD and different demographic, disease and medications related factors were analyzed using Pearson's correlation coefficient. BMD at lumbar spine (L1-L4) and left femur-total hip was the dependent variable, independent variables were: age, height, weight, Body Mass Index (BMI), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), menopausal status, spine fracture, hip fracture, femur fracture, Colles' fracture, covariates, comorbidity, and medications.

Significant variables were then entered in stepwise multiple linear regression analysis as independent variable and BMD as the dependent variable. All tests were two-tailed, and the level of significance was: significant at $p \leq 0.05$, highly significant at $p \leq 0.01$, and very highly significant at $p \leq 0.001$.

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Results

Study population composed of 569 patients, 141 in the diabetic group, 428 in the control group, while 66 patients were excluded based on exclusion criteria. Patient's mean follow up period was (35.66 ± 11.63) months from their index date.

Most patients were elderly, with a mean age of (63.55 ± 9.15) years in the diabetic group, and (58.88 ± 11.71) years in the control group. There was significantly higher percent ($p \leq 0.001$) of patient (≥ 60) years of age in the diabetic group. Obesity accounts for high percent in both groups. Mean BMI value in the diabetic group were (30.27 ± 6.73) and (29.78 ± 5.66) in the control group (Table 1).

It was noticeable that more than half of patients were Emarati, with significantly higher percentages in the diabetic group ($p \leq 0.001$), additionally postmenopausal female accounted for 92% from the whole sample. Mean value of systolic blood pressure in both groups categorized under the prehypertension stage. While the mean values of diastolic blood pressure were within the normal range.

Incidence of the spine, hip and femur fractures were slightly higher in the diabetic group. Diabetic patients were significantly ($p \leq 0.001$) more prone for the second request of DXA-scan compared to control group (Table 1). Moreover, the time between the first and the second request of DXA-scan in the whole sample was (10.81 ± 8.70) months.

As shown in Table 2, clinical characteristics of diabetic patients demonstrated high values exceeding normal reference range of HbA1c, random blood glucose, fasting blood glucose and glucose postprandial. In addition, biguanide was the preferred line of treatment in most patients (82%), followed by sulphonylurea (48%). Distributions of covariates, comorbidities, and medication are shown in Table 3. Diabetic group showed significantly higher percent of depression ($p \leq 0.01$), liver impairment ($p \leq 0.01$), renal impairment ($p \leq 0.001$), hypertension ($p \leq 0.001$), dyslipidemia ($p \leq 0.001$), ischemic heart disease ($p \leq 0.001$), hypothyroidism ($p \leq 0.001$), osteoarthritis ($p \leq 0.01$), cataract ($p \leq 0.01$), glaucoma ($p \leq 0.01$) and retinopathy ($p \leq 0.01$). They were taking a significantly higher amount of antacid, H2-antagonist, inhaled corticosteroids, loop diuretics, thiazide diuretics, nitrates, Proton Pump Inhibitor (PPI), Selective Serotonin Reuptake Inhibitor (SSRI), statins, thyroid hormone, and vitamin A. It was clear from Table 4 that BMD were similar in diabetic and control groups.

Results from Pearson's correlation coefficient analysis between

Variable	Diabetes (n=141)	Control (n=428)	Total (n=569)
Age (years)	63.55 ± 9.15	58.88 ± 11.71***	59.96 ± 11.45
≥ 60% (n)	63.1 (89)	43.9 (188)***	48.7 (277)
Height (cm)	158.44 ± 5.840	158.33 ± 5.514	158.36 ± 5.59
Weight (Kg)	76.19 ± 18.34	75.02 ± 16.01	75.31 ± 16.61
Obese % (n)	44.7 (63)	47 (201)	46.4 (264)
BMI (Kg/m^2)	30.27 ± 6.73	29.78 ± 5.66	29.90 ± 5.94
SBP (mmHg)	139.81 ± 19.40	136.52 ± 22.70	137.51 ± 21.79
DBP (mmHg)	75.56 ± 11.62	79.33 ± 13.07**	78.19 ± 12.75
Emarati % (n)	74.1 (103)	58.2 (244)***	62.2 (347)
Pre-menopausal % (n)	5 (7)	8.9	7.9
Post-menopausal % (n)	95 (134)	91.1	92.1
Fracture % (n)	9.9 (14)	9.3	9.5
Spine fracture % (n)	4.3	2.3	2.8
Hip fracture % (n)	0.7	0.2 (1)	0.4 (2)
Femur fracture % (n)	5 (7)	3.5	3.9
Colles fracture % (n)	0	1.2 (5)	0.9 (5)
Other fracture % (n)	1.4	2.2 (9)	2 (11)
Second request of DXA-scan % (n)	41.8	25.7 (110)***	29.7
Values are percent OR means ± SD, * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure			

Table 1: General characteristics of patients in diabetic and control groups.

Variable	Value
n	141
HbA1c	7.50 ± 2.12
Random blood glucose (mmol/L)	9.981 ± 5.09
Fasting blood glucose (mmol/L)	7.57 ± 3.02
Glucose post prandial (mmol/L)	10.96 ± 5.80
Diabetic medications	
Insulin (%)	32.6 (n=46)
Biguanide (%) ∫	82.3 (n=116)
Sulphonylurea (%) §	47.5 (n=67)
Thiazolidinidiones (%) ‡	1.4 (n=2)
Values are percent OR means ± SD; ∫ Metformin; § Gliclazide; glibenclamide, glimepiride; ‡ Pioglitazone	

Table 2: Clinical Characteristics of diabetic patients.

Variable	Diabetes (n=141)		Control (n=428)		Total (n=569)	
	n	%	n	%	n	%
Covariate						
Ankylosing spondylitis (%)	12	8.5	27	6.3	39	6.9
Cancer (%)	1	0.7	4	0.9	5	0.9
Congestive heart failure (%)	1	0.7	4	0.9	5	0.9
COPD (%)	0	0	6	1.4	6	1.1
Depression (%)	11	7.8	12	2.8**	23	4
IBS (%)	3	2.1	9	2.1	12	2.1
Liver impairment (%)	5	3.5	2	0.5**	7	1.2
Renal impairment (%)	14	9.9	13	3***	27	4.7
Rheumatoid arthritis (%)	0	0	2	0.5	2	0.4
Stroke (%)	1	0.7	3	0.7	4	0.7
Thalassemia (%)	1	0.7	2	0.5	3	0.5
Comorbidity						
Cataract (%)	12	8.5	12	2.8**	24	4.2
Dyslipidemia (%)	47	33.3	43	10***	90	15.8
Glaucoma (%)	4	2.8	2	0.5**	6	1.1
Hypertension (%)	90	63.8	80	18.7***	170	29.9
Hypothyroidism (%)	21	14.9	23	5.4***	44	7.7
Ischemic heart disease (%)	16	11.3	11	2.6***	27	4.7
Osteoarthritis (%)	29	20.6	49	11.4**	78	13.7
Retinopathy (%)	6	4.3	3	0.7**	9	1.6
DVT (%)	1	0.7	1	0.2	2	0.4
Medications affecting BMD						
Aluminum (in antacid) (%)	17	12.1	30	7*	47	8.3
Anticoagulant (%) ‡	2	1.4	7	1.6	9	1.6
Anticonvulsants (%) §	1	0.7	0	0	1	0.2
H2-antagonist (%)	50	35.5	110	25.7*	160	28.1
Inhaled corticosteroids (%)	22	15.6	38	8.9*	60	10.5
Immunosuppressants	1	0.7	4	0.9	5	0.9
Loop diuretics (%)	13	9.2	14	3.3**	27	4.7
Nitrates (%)	10	7.1	5	1.2***	15	2.6
Oral corticosteroids (%)	1	0.7	4	0.9	5	0.9
PPI (%)	87	61.7	150	35***	237	41.7
SSRI (%)	10	7.1	13	3*	23	4
Statins (%)	105	74.5	67	15.7***	172	30.2
Tamoxifen (%)	1	0.7	1	0.2	2	0.4
Thiazide diuretics (%)	57	40.4	42	9.8***	99	17.4
Thiazolidinediones (%) ∫	2	1.4	0	0	2	0.4
Thyroid hormone (%)	20	14.2	20	4.7***	40	7
Vitamin A (%)	28	19.9	54	12.6*	82	14.4

Values are percent, * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$; ‡ Chronic use of heparin OR warfarin; § Carbamazepine or phenytoin; ∫ Pioglitazone; PPI: Proton Pump Inhibitor; SSRI: Selective Serotonin Reuptake Inhibitor

Table 3: Covariate, comorbidities and medications affecting BMD in diabetic and control groups.

BMD and different diseases and medications variables were presented in (Tables 5 and 6). Results of interring significant variable from Pearson's correlation coefficient in multiple stepwise linear regression analyses were shown in (Tables 7 and 8) and prediction equations in (Tables 9 and 10).

Pearson's correlation coefficient demonstrated dialectical finding with positive and negative results. In diabetic patients, it was clear that weight correlated significantly with BMD in all studied skeletal regions. Body mass index (BMI) and hypothyroidism also showed a significant positive correlation with BMD in most of the studied skeletal regions. The interesting finding were shown in the significant negative correlation between age, systolic as well as diastolic blood pressure with BMD in some skeletal regions. Spine fracture correlated significantly with BMD in L2, L3, and L4, while hypertension and congestive heart failure correlated negatively ($p \leq 0.05$) with BMD in left femur-total hip and some other skeleton sites. Oral corticosteroids correlated negatively ($p \leq 0.001$) with BMD in L4, while anticonvulsant correlated positively ($p \leq 0.001$) with BMD in the left femur-total hip (Table 5).

In the control group, height, weight, BMI and spine fracture correlated significantly with BMD in all studied skeletal regions, with negative correlation shown with a spine fracture. Additionally, negative correlation appeared with age and BMD in most skeletal regions.

Variable	Diabetes (n=141)	Control (n=428)	Total (n=569)
BMD (g/cm^2)			
Lumbar spine (L1-L4)	0.890 ± 0.196	0.899 ± 0.198	0.896 ± 0.198
L1	0.890 ± 0.356	0.860 ± 0.230	0.868 ± 0.267
L2	0.885 ± 0.263	0.890 ± 0.241	0.889 ± 0.246
L3	0.903 ± 0.277	0.900 ± 0.234	0.901 ± 0.245
L4	0.948 ± 0.326	0.959 ± 0.313	0.956 ± 0.316
Left femur-total hip	0.881 ± 0.184	0.895 ± 0.180	0.891 ± 0.181

Table 4: BMD in diabetic and control groups.

Variable	BMD					
	LS	L1	L2	L3	L4	LF-TH
	r	r	r	r	r	r
Height (cm)	0.187*	0.232**	0.389***	0.212**		
Weight (Kg)	0.374***	0.166*	0.290***	0.317***	0.206**	0.384***
Age (years)	-0.392***		-0.252**	-0.352***	-0.203**	-0.462***
Menopausal						-0.175*
BMI (Kg/m^2)	0.344***		0.199**	0.276***	0.174*	0.382***
Spine fracture			0.242**	0.185*	0.248**	
Femur fracture	-0.232**					
Hip fracture						-0.185*
Other fracture						-0.238
Systolic blood pressure		-0.247**	-0.166*			-0.19
Diastolic blood pressure	-0.202**			-0.218**	-0.187*	
Congestive heart failure	-0.167*			-0.195*		-0.184*
Stroke	0.238**			0.182*		
Hypertension			-0.186*			-0.185*
Hypothyroidism	0.257**		0.299**	0.246**	0.161*	0.200**
Anticonvulsant §						0.339***
Oral corticosteroids					-0.359***	
Thyroid hormone	0.246**		0.215**	0.254**		0.167*

Table 5: Correlation coefficients (r) of BMD as (dependent variable) and demographic, disease and medications related factors (independent variables) in diabetic group. Only statistically significant variables are shown.

Variable	BMD					
	LS	L1	L2	L3	L4	LF-TH
	r	r	r	r	r	r
Height (cm)	0.239***	0.215***	0.203***	0.177***	0.108*	0.257***
Weight (Kg)	0.401***	0.377***	0.293***	0.340***	0.302***	0.413***
Age (years)	-0.283***	-0.188***	-0.261***	-0.217***		-0.371***
Menopausal	-0.109*		-0.116**			
BMI (Kg/m^2)	0.365***	0.349***	0.257***	0.318***	0.301***	0.378***
Spine fracture	-0.131**	-0.131**	-0.101*	-0.115**	-0.114**	-0.132**
Hip fracture	-0.093*					
Systolic blood pressure						-0.131*
Congestive heart failure	-0.101*		-0.099*	-0.119**		
Glaucoma					0.109*	
Irritable bowel syndrome	0.100*	0.105*				
Renal impairment			-0.121**			-0.178***
Stroke						-0.093*
Retinopathy						0.115**
Inhaled corticosteroids		0.125**				
Loop diuretics	-0.117**					-0.165***
*p ≤ 0.05, ** p ≤ 0.01, *** p ≤ 0.001						

Table 6: Correlation coefficients (r) of BMD as (dependent variable) and demographic, disease and medications related factors (independent variables) in control group. Only statistically significant variables are shown.

Inhaled corticosteroids correlated with BMD in L1 only ($p \leq 0.01$), while loop diuretics correlated negatively with BMD in the lumbar spine and left femur-total hip. It was noticeable that lumbar spine and left femur-total hip accounted for many significant correlations with different variables (Table 6).

Regression analysis showed that in diabetic group weight and age were the most common variables associated with BMD. Systolic

blood pressure had a role in the prediction equation of BMD at L1 and L2, while diastolic blood pressure helped in the prediction of BMD at the lumbar spine, L3 and L4. Hypothyroidism played a role in the prediction of BMD at L2 and L4, whereas stroke and presence of other fracture had an important role in the prediction of BMD at the lumbar spine, L3 and left femur-total hip. Forty-three percent of BMD value at left femur-total hip could be predicted from the equation (Tables 7 and 9).

Similar to the diabetic group, weight and age were the most common variables that predicted BMD values in the control group, followed by height. Irritable bowel syndrome helped in the prediction of BMD in the lumbar spine and L1 more than other coefficients (B=0.135, 95% CI=0.019-0.251) and (B=0.171, 95% CI=0.033-0.308) respectively. Furthermore, glaucoma and stroke predicted BMD in L4 and left femur-total hip more than other coefficients (Tables 8 and 10). All prediction equations in diabetic and control groups fitted the model significantly ($p \leq 0.001$) (Tables 9 and 10).

In diabetic patients common reasons for referral to DXA-scan are: follow up (36%), to exclude osteoporosis in the post-menopausal patient (9%) and bone pain (7%). Regarding control group follow up accounted for (27%), bone pain (10%) while following up a postmenopausal patient (6%). Approximately, 23% of physicians used DXA-scan to exclude the presence of osteoporosis in the diabetic group, and 18% in the control group.

Variable	LS		L1		L2		L3		L4		LF-TH	
	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI
Constant	1.344***	1.024-1.664	-1.069	-3.168	-5.655**	-8.395	1.589***	1.128-2.051	1.686***	1.225-2.146	1.297***	1.055-1538
Height			0.017***	0.007-0.027	0.042**	0.016-0.068						
Weight	0.003***	0.001-0.004			-0.028*	-0.051	0.003**	0.001-0.005				
Age	-0.007***	-0.006					-0.009***	-0.009	-0.007**	-0.01	-0.008***	-0.011-0.005
BMI §					0.076*	0.011-0.142					0.005*	0.000-0.009
Spine					0.330**	0.115-0.544	0.330**	0.122-0.538				
fracture												
Other fracture											-0.418***	-0.622-0.215
SBP ‡			-0.005***	-0.006	-0.003**	-0.004						
DBP ∫	-0.003**	-0.005					-0.006**	-0.007	-0.004*	-0.008		
Stroke	0.573***	0.252-0.894					0.620**	0.157-1.083				
Hypertension											-0.066**	-0.118-0.014
Hypothyrodism					0.138**	0.033-0.243			0.193**	0.062-0.324		
Anticonvulsant											0.567***	0.237-0.898
Oral corticosteroids									-1.432***	-1.1		
Thyroid hormone	0.103**	0.025-0.182					0.157**	0.044-0.271				

* $p \leq 0.05$, ** $p \leq 0.01$,*** $p \leq 0.001$; § Body Mass Index; ‡ Systolic Blood Pressure; ∫ Diastolic Blood Pressure; B: values are unstandardized regression coefficients; CI: Confidence Interval

Table 7: Multiple stepwise linear regression analysis of BMD as (dependent variable) and demographic, disease and medications related factors as (independent variable) in diabetic group.

Variable	LS		L1		L2		L3		L4		LF-TH	
	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI
Constant	-0.345	-0.993	0.603***	0.454-0.753	0.175	-1.288	0.752***	0.595-0.908	0.505***	0.369-0.641	-0.285	-1.026
Height	0.007***	0.004-0.010			0.005*	0.000-0.009					0.007***	0.004-0.010
Weight			0.005**	0.004-0.006	0.003***	0.002-0.005	0.005***	0.003-0.006	0.006***	0.004-0.008		
Age	-0.004***	-0.003	-0.002**	-0.003	-0.004***	-0.003	-0.003***	-0.004			-0.004***	-0.003
BMI §	0.011***	0.008-0.014									0.010***	0.007-0.013
Spine			-0.141*	-0.262								
fracture												
IBS ‡	0.135*	0.019-0.251	0.171**	0.033-0.308								
Renal impairment											-0.107**	-0.177
Stroke											-0.212**	-0.351
Glaucoma									0.593**	0.178-1.007		
Inhaled corticosteroids			0.115***	0.046-0.185								

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$; § Body Mass Index; ‡ Irritable Bowel Syndrome; B: values are unstandardized regression coefficients; CI: Confidence Interval

Table 8: Multiple stepwise linear regression analysis of BMD as (dependent variable) and demographic, disease and medications related factors as (independent variable) in control group.

Area	R2	Prediction equation
LS	0.371***	y=1.344+(0.003 × weight)+(-0.007 × age)+(-0.003 × DBP)+(0.573 × stroke)+(0.103 × thyroid hormone)
L1	0.366***	y=-1.069+(0.017 × height)+(-0.005 × SBP)
L2	0.338***	y=-5.655+(0.042 × height)+(-0.028 × weight)+(0.076 × BMI)+(0.330 × spine fracture)+(-0.003 × SBP)+(0.138 × hypothyroidism)
L3	0.355	y=1.589+(0.003 × weight)+(-0.009 × age)+(0.330 × spine fracture)+(-0.006 × DBP)+(0.620 × stroke)+(0.157 × thyroid hormone)
L4	0.277***	y=1.686+(-0.007 × age)+(-0.004 × DBP)+(0.193 × hypothyroidism)+(-1.432 × Oral corticosteroids)
LF-TH	0.433***	y=1.297+(-0.008 × age)+(0.005 × BMI)+(-0.418 × other fracture)+(-0.066 × hypertension)+(0.567 × anticonvulsant)
p ≤ 0.05, ** p ≤ 0.01, *** p ≤ 0.001; LS: Lumbar Spine; LF-TH: Left Femur-Total Hip; DBP: Diastolic Blood Pressure; SBP: Systolic Blood Pressure; BMI: Body Mass Index		

Table 9: Prediction equation of BMD in diabetic group.

Area	R2	Prediction equation
LS	0.234	y=-0.345+(0.007 × height)+ (-0.004 × age)+(0.011× BMI)+(0.135 × IBS)
L1	0.197***	y =0.603+(0.005 × weight)+(-0.002 × age)+(-0.141 × spine fracture)+(0.171 × IBS)+(0.115 × inhaled corticosteroids)
L2	0.139***	y=0.175+(0.005 × height)+(0.003 × weight)+(-0.004 × age)
L3	0.139***	y=0.752+(0.005 × weight)+(-0.003 × age)
L4	0.106***	y=0.505+(0.006 × weight)+(0.593 × glaucoma)
LF-TH	0.293***	y=-0.285+(0.007 × height)+(-0.004 × age)+(0.010 × BMI)+(-0.107 × renal impairment) +(-0.212 × stroke)
*p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001; LS: Lumbar Spine; LF-TH: Left Femur-Total Hip; BMI: Body Mass Index; IBS: Irritable Bowel Syndrome		

Table 10: Prediction equation of BMD in control group.

Discussion

In this retrospective cohort study, we compared the data of diabetic and control female patients referred to DXA-scan. We noticed that most diabetic patients were not well controlled, and their glycemic follow-up values exceeded normal reference ranges. This may explain the significantly higher percent of micro- and macro-vascular complication in the diabetic group. Results from a prospective observational study in England, Scotland and Northern Ireland concluded that hyperglycemia strongly associated with diabetes complication, and any reduction in HbA1c value decreases complications risks [3].

Systolic blood pressure values in both groups were in the upper limit of the normal reference range, with slightly higher values in the diabetic group. These values match with the results of the Dubai Health Authority (DHA) survey that 1 out of 6 Emirati suffers from hypertension [4]. A Study by Adler and his colleagues found that elevated blood pressure was strongly associated with diabetes complications, and any reduction in blood pressure value helped in decreasing complication risks. They also noticed that the lowest risks of complication were in patients with systolic blood pressure less than 120 mmHg [5].

We found that depression accounts for significant higher percent in the diabetic group. Similar finding were also reported by Goldney and his colleagues, and they noticed that depressed diabetic patients have a significantly lower quality of life compared to depressed non-diabetic patients [6]. The relationship between depression and diabetes varies since it can be two-way.

Data from an epidemiologic study with 13 years of follow up period concluded an increased onset of type 2 diabetes mellitus among individuals with the major depressive disorder [7]. Results from meta-analysis found that depression increases the risk of type 2 diabetes mellitus 60%, (RR 1.15, 95% CI 1.02-1.30) [8]. While results from another meta-analysis by Nouwen and his colleagues demonstrated that type 2 diabetes mellitus increases the risk of suffering from depression 24% [9]. A Study by Pan and his colleagues concluded that the diabetes-depression association is bi-directional [10].

As shown earlier, the prevalence of liver disease is significantly higher among diabetic individuals. These finding came in the same line with a study by Williamson et al. [11]. In a study by Ortiz-Lopez et al., they found that prediabetes and type 2 diabetes mellitus accounted for 85% ($p \leq 0.001$) of patients with Non-Alcoholic Fatty Liver Disease (NAFLD), and they recommended an early screening for type 2 diabetes mellitus in NAFLD patients. They demonstrated also another finding that NAFLD patients having insulin resistance in adipose tissue, liver, and muscle ($p \leq 0.01$-0.001). Additionally, they noticed only worsening of adipose tissue insulin resistance in diabetic patients, and they concluded that adipose tissue insulin resistance in diabetic patients may have a major role in NAFLD severity [12]. Moreover, Cusi stated that routine screening of fatty liver diseases among type 2 diabetic patients is not less important than the usual assessment of the presence of micro- and macro-vascular complications, and he advised using of new imaging technology rather than liver transaminases tests which may not reflect the actual liver status [13]. One of the interesting findings in our research is the significantly high prevalence of osteoarthritis among type 2 diabetes mellitus patients. This result supports an earlier hypothesis by Schett et al about the metabolic role in osteoarthritis pathophysiology. They found in their longitudinal cohort study that type 2 diabetes mellitus is an important predictor of osteoarthritis independent of age and BMI (Hazard Ratio, HR=3.8, 95% CI=2.1-6.8) [14]. Results from Louati et al meta-analysis showed an association between osteoarthritis and diabetes mellitus, and recommend for subclassification of diabetes-related osteoarthritis under metabolic osteoarthritis type [15]. Courtesies Sellam mentioned about the effect of diabetes in inducing oxidative stress and pro-inflammatory cytokines in joint tissue. They highlighted the negative effect of local insulin resistance in diabetic patients synovial membrane [16]. Significant high medications affect BMD in diabetic patients which can be explained as a consequence of the significantly higher prevalence of its corresponding diseases. When comparing BMD values between diabetic and control group, we found that both groups have approximately similar values. These result support findings from previous researches that found similar values [17,18], but contrast other studies that found higher [19,20] or lower values [21,22].

As stated earlier, BMI correlated with BMD in diabetic and control groups, and have a role in the prediction of BMD values in both groups. This came in line with a study by Bener et al., when they found that BMI is a strong positive predictor of BMD [23]. Furthermore, results from a meta-analysis by Vestergaard notified about the significant

impact of BMI in the prediction of BMD value in type 2- not type 1 diabetes mellitus [24]. Thomas et al suggested the hormonal influence of high BMI on BMD value and related it to high serum leptin level which believed to have a protective effect on skeleton [25]. Results from Ziliang et al. meta-analysis confirmed the significant effect of hypertension in decreasing BMD at different skeletal regions [26]. In a study by Jeon et al about the association between BMD and metabolic syndrome, the researchers demonstrated the role of systolic and diastolic blood pressure as a predictive variable of BMD [27]. Additionally, a prospective study by Cappuccio et al assessing the relation between blood pressure and BMD found that elevated blood pressure strongly associated with the regular bone loss [28]. Our results support the previous finding since we reported the negative predictive effect of blood pressure in BMD value in the diabetic group. Researchers commented about increase calcium loss with elevated blood pressure as a possible justification [28].

Regarding the correlation between fracture and BMD, Yamamoto et al. showed that there is no significant association between vertebral fracture and BMD at any site [29]. While Schnatz et al confirm the association between the presence of previous fractures and risk of osteoporosis [30]. In addition, results from community-based cohort study by Shin et al found that fracture history is among the important risk factor for the development of osteoporosis [31]. On the other hand, our results showed a positive relation between BMD and spine fracture in diabetic patients, which sustain even in the regression analysis and have a role in the prediction of BMD at L2 and L3.

Our results from correlation and regression analysis highlighted the relation between IBS and BMD. Research by Stobaugh et al showed a higher risk of osteoporosis and it's related fractures in patients with IBS (OR 4.28, 95% CI 4.21-4.35) and (OR 2.36, 95% CI 2.26-2.47), respectively. They advocated toward screening for osteoporosis in these patients to define osteoporosis early and protect from its related fractures [32]. Compston commented about possible rationalization of association between IBS and osteoporosis as: (1) increase serum level of cytokines such as IL-1B, IL-6, IL-8 and Tumor Necrosis Factor (TNF) which may contribute to bone loss, (2) avoidance of dairy products intake by many patients with IBS leading in reduction of total daily intake of calcium, and (3) the use of SSRI in management of IBS [33].

Regarding our finding of the positive association between BMD and anticonvulsant, it came in the line with a study by Lee et al who noticed that patients who were taking newer non-enzyme inducer anticonvulsant have significant higher T-score, and less likely to develop osteoporosis [34]. Farhat et al. also found that patients treated with enzyme-inducing anticonvulsants such as phenytoin, phenobarbital, carbamazepine, and primidone have lower BMD than a patient on non-enzyme-inducers such as valproic acid, lamotrigine, clonazepam, gabapentin, topamirate, and ethosuximide [35]. In contrast, Salimipour et al found that patients receiving anticonvulsant have significantly lower BMD compared to control, regardless of its type (enzyme inducer or non-enzyme inducer) [36].

It is well known from the literature that thyrotoxicosis is among risk factors behind the development of osteoporosis [37]. We noticed in our research that hypothyroidism correlated positively with BMD in most of the studied skeletal site in the diabetic group, and the association exist in the regression analysis also, resulting in the prediction of BMD in L2 and L4. This gives us insinuation that thyroid disorder hypo- OR hyperthyroidism affect bone renewal cycle.

As to our knowledge that the association between glaucoma and BMD has not been studied deeply in the literature until now. Our findings regarding the significant positive correlation between glaucoma and BMD and its role in the estimation of L4 BMD value open the door for further research work to understand the pathophysiology behind this correlation.

Despite the presence of corticosteroids among osteoporosis risk factors [37]. We found a positive correlation between inhaled corticosteroids and BMD with a respective role in the estimation of BMD value at L1 region.

Conclusion

Our research found that there are many diseases and medications affect BMD values positively or negatively and recommend toward screening of type 2 diabetic patient for osteoporosis on a regular basis.

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