Are Diabetes Mellitus and Diabetic Nephropathy Good Predictors of Osteoporosis

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ABSTRACT

Background: Osteoporosis is a metabolic bone disorder with a tendency for fracture and diabetes mellitus (DM) has a close relation to osteoporosis.

Objective: Is to study the role of diabetes mellitus (DM) and diabetic nephropathy in the acceleration and production of osteoporosis.

Patient and Methods: This study included 88 cases which were divided into 2 groups; 44 patients with DM and 44 patients as a control group with no sex predilection. Both groups were exposed to full history taking, bone mineral density (BMD) measurement, fasting blood sugar, urinary albumin, postprandial blood sugar, HA1C, creatinine, urea, HOMA- IR.

Result: There is a strong and positive correlation between DM, diabetic nephropathy, and incidence of osteoporosis as BMD was -0.59 (-5.0:1.0) and -0.08 (-3.0:1) for cases and control respectively and 36.4% of diabetic cases had osteoporosis and only 11.4% of control had osteoporosis.

Conclusions: Osteoporosis (OP) is a more complication in patients with DM. Increased risk of OP present in older age group, and female sex. Diabetic patients on long-term insulin therapy are at high risk of OP. due to high bone turnover and low bone formation.

Keywords: DM, Diabetic nephropathy, Osteoporosis.

INTRODUCTION

Osteoporosis is a progressive bone disorder characterized by decreased bone mass, bone mineral density, and destruction of the microarchitecture of the bone, which can progress and increased the risk of fracture. Osteoporosis is defined by the world health of organization (WHO) by the limitation of the active lives of half of the osteoporotic patients older than 50 years and most patients over 70 years. There are several methods to diagnose osteoporosis; measuring bone mineral density (BMD) is the best and most accurate method[(1)].

The bone density of the lumbar spine and femur length of postmenopausal women is the best to measure by dual x-ray absorptiometry (DXA) and interpreted as follows: if lowest T score higher than -1.0; it is normal, osteopenia between -1.0 and -2.5 and osteoporosis if less than -2.5 [(2)].

DM is a metabolic disorder characterized by increased fasting blood sugar ≥ 126 mg/dl. The number of diabetic patients expected to be approximately 300 million in 2025. Type II DM represents more than 90% of that expected range. DM is often associated with comorbid conditions. The most important top chronic complication are peripheral vascular, cardiac, renal, and neurological complications. The endocrinal and metabolic changes that DM produces can alter calcium (Ca^{++}) homeostasis, skeletal metabolic function, and bone cell mass [(3)].

Most of the cross-sectional studies have shown that increased bone fracture and osteoporosis are associated with DM owing to reduced bone formation and increased bone resorption. So we decided to study the relationship between osteoporosis and DM with associated diabetic nephropathy and to evaluate other risk factors on the development of osteoporosis.

PATIENTS AND METHODS

This study was carried out at internal medicine and outpatient clinic of Endocrinology and Diabetes Units of Zagazig University Hospital in the period between August 2017 and August 2020.

Ethical approval:

This study was done after the consent from all participants in the study and **approval of the search Ethics Committee of Zagazig University.**

The study included 88 patients 44 as a control group and 44 as a diseased group with mean age of 62.0 ± 5.02 for cases and mean age of 51.06 ± 3.83 for the control group with no sex predilection.

- All enrolled persons in the study were submitted for the following.
- Clinical assessment including history taking with special attention to the drugs associated with osteoporosis; such as drugs that interfere with bone metabolism as anti-thyroid drugs, steroids, anticonvulsants, benzodiazepines, and vitamin D or Ca^{++} supplementation.
- All participants (cases and control) were free from any illness that may interfere with bone metabolic changes as chronic chest diseases, rheumatoid arthritis, thyroid disorders, liver disease cardiac or renal disease, SLE, chronic pancreatitis, or history of gastric surgery.

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- Recruited patients were subjected to clinical history, detailed examination biochemistry evaluation, age gender, sex, weight, and body mass index (BMI kg/m^2). BMD was measured using DEXA (Hologic explorer DEXA system, USA) and T-score was calculated.

Biochemical measurements:

All included participants were subjected to the withdrawal of 10 ml of fasting venous blood under complete aseptic conditions for the routine lab. Investigations as CBC, liver functions, PT, PTT, INR serum Ca^{++}, phosphorus, ALP, complete lipid profile, blood urea, and creatinine by routine enzymatic methods and glycosylated Hb (HbA1C%) by (Cobasintegra 800 Analyzer), HOMA IR was calculated using the following equation [(4)].

HOMA- IR = FPI x FBG / 22.5[(4)]

Where; P: plasma, F: fasting, I: insulin, G: glucose

Also, 24 hours urine was collected, and albumin measurements were calculated as <30 mg → inormal, from 30- 300 mg microalbuminuria > 300 mg →overt or gross albuminuria. Serum vitamin D (250H) was measured using electrochemiluminescence immune assay using CobasAutoanalyzer (Roche diagnostics UK).

Statistical analysis

Data collected throughout history, basic clinical examination, laboratory investigations, and outcome measures were coded, entered, and analyzed using Microsoft Excel software.

Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. According to the type of data; qualitative were represented as number and percentage and quantitative data were represented as mean ± SD. Difference and association of qualitative variable were tested by Chi-square test (X^2).

Mann-Whitney U Test: Non-parametric test used to compare two non-parametric quantitative variables.Differences in quantitative variables between groups were calculated by independent t-test. Correlation was calculated by Pearson's correlation coefficient and independent predictors by logistic regression. P-value was set at <0.05 for significant results and <0.001 for a highly significant result.

RESULTS

There was no significant difference between case and control as regard age and sex (Table 1).

Table (1): Age and sex distribution between cases and control

			Case (N=44)	Control (N=44)	t/X^2	P
Age			**52.0±5.02**	**51.06±3.83**	**1.1136**	**0.2686**
Sex	**Male**	**N**	**24**	**18**	**1.64**	**0.20**
		%	**54.5%**	**40.9%**		
	Female	**N**	**20**	**26**		
		%	**45.5%**	**59.1%**		
Total		**N**	**44**	**44**		
		%	**100.0%**	**100.0%**		

BMD was not significantly different between cases and control. As regard osteoporosis, cases were significantly associated with osteoporosis (Table 2).

Table (2): BMD and osteoporosis between cases and control

			Case (N=44)	Control (N=44)	MW/ X^2	P
BMD: Mean±SD			**-1.40±1.25**	**-0.14±0.73**	**4.196**	**<0.01**
Osteoporosis	**-VE**	**N**	**28**	**39**	**7.56**	**0.006**
		%	**63.6%**	**88.6%**		
	+VE	**N**	**16**	**5**		
		%	**36.4%**	**11.4%**		
Total		**N**	**44**	**44**		
		%	**100.0%**	**100.0%**		

Older age, longer duration of DM, higher FBG, PP2H, HA1C, HOMA_R, Cr, urea and albuminuria were significantly associated with osteoporosis, and also female sex were significantly associated with osteoporosis, and also nephropathy was a significant predictor for osteoporosis (Table 3).

Table (3): Univariate analysis for predictors of osteoporosis

			No (N=28)	Osteoporosis (N=16)	t/MW / X^2	P
Age (years)			**49.92±4.43**	**55.62±3.86**	**4.285**	**<0.01**
Duration of DM			**7.5±2.54**	**18.75±3.95**	**11.48**	**<0.01**
FBG			**131.78±7.69**	**171.5±23.1**	**8.378**	**<0.01**
PP2H			**217.89±5.49**	**301.0±8.75**	**3.934**	**<0.01**
HA1C (mg/dL)			**7.73±0.62**	**9.15±1.1**	**5.457**	**<0.01**
HOMA_R (mg/kg/min)			**2.31±0.34**	**2.91±0.59**	**4.218**	**<0.01**
Cr			**1.52±0.05**	**2.82±0.85**	**4.735**	**<0.01**
Urea (mg/dL)			**43.85±7.63**	**78.31±5.92**	**4.422**	**<0.01**
Albuminuria (mcg/mg)			**25.89±8.02**	**181.0±5.69**	**5.597**	**<0.01**
Sex	**Male**	**N**	**19**	**5**		
		%	**67.9%**	**31.2%**		
	Female	**N**	**9**	**11**	**5.5**	**0.019**
		%	**32.1%**	**68.8%**		
Nephropathy	**-VE**	**N**	**22**	**5**		
		%	**78.6%**	**31.2%**		
	+VE	**N**	**6**	**11**	**9.61**	**0.002**
		%	**21.4%**	**68.8%**		
Total		**N**	**28**	**16**		
		%	**100.0%**	**100.0%**		

BMD was sig negatively correlated with all parameters (Table 4).

Table (4): Correlation between BMD and other parameters

		BMD
Age (years)	**r**	**-0.611**
	P	**<0.001**
Duration of DM	**r**	**-0.851**
	P	**<0.001**
FBG	**r**	**-0.829**
	P	**<0.001**
PP2H	**r**	**-0.585**
	P	**<0.001**
HA1C (mg/dL)	**r**	**-0.577**
	P	**<0.001**
HOMA_R (mg/kg/min)	**r**	**-0.483**
	P	**0.001**
Cr	**r**	**-0.645**
	P	**0.000**
Urea (mg/dL)	**r**	**-0.609**
	P	**0.000**
Albuminuria (mcg/mg)	**r**	**-0.735**
	P	**0.000**

Female, longer duration of DM, insulin resistance, and nephropathy were significant independent predictors for osteoporosis (Table 5).

Table (5): Multivariate logistic regression for independent predictors of osteoporosis

	Wald	OR (CI 95%)	P
Age (years)	**1.258**	**13.3 (0.95-28.56)**	**0.058**
Sex female	**3.258**	**5.5 (1.58-16.95)**	**0.019**
Duration DM	**4.521**	**33.3 (2.58-158.6)**	**<0.01**
HA1C (mg/dL)	**2.265**	**18.25 (0.98-51.23)**	**0.085**
HOMA_R (mg/kg/min)	**4.856**	**13.09 (2.69-23.58)**	**<0.01**
Cr	**2.321**	**15.3 (0.87-26.9)**	**0.341**
Urea (mg/dL)	**1.258**	**13.97 (0.82-31.69)**	**0.254**
Nephropathy	**6.251**	**9.61 (2.32-31.85)**	**0.002**

DISCUSSION

Although a lot of studies have reported the association between DM and high risk of pathological bone fractures; the true relationship between DM and OP is still controversial [4], with the development of economic lifestyle, changes in lifestyle behavior, and increased population life expectancy increased the incidence of DM especially type II (T_2DM), which gradually increased year after year. The preventable complications of DM on the brain, heart, kidney, and others are well recognized but the effect of DM on BMD is still not clear. BMD in patients with DM was reported to be decreased [5], unchanged [6] or increased [7]**.** There are conflicting researches about the relation between DM and OP [8]. Most of the studies carried out to reveal the relation between DM and OP shows that normal or increased bone mass at the appendicular and axial skeletal sites occurred [9].

Rotterdam's study [10] evaluated the association between DM and BMD in elderly people and concluded that fracture risk increases by about 3% than the young population. In our study, the relationship between DM and OP was studied to investigate the role of DM and BMD changes.

Our results as regard sex, had shown a significant difference between male and female with female predominance in osteoporotic changes, which is in close association with the study done by **Schwartz *et al.* [11]** and this can be explained by decreased estrogen production in postmenopausal women.

Also our study shows significant differences between cases and aging progress, which is in accordance with a study done by **Hanley *et al.* [12]** with the most probable factor were increased bone turnover, osteopenia prolonged toxic effect of hyperglycemia. From our study there was significant correlation between bone mineral density (BMD) and prolonged hyperglycemia, post prandial blood sugar and elevated glycosylated hemoglobin (HAIC), which is in agreement with studies done by **Boonen *et al.* [13]** and **Eastell *et al.* [14],** which postulated that prolonged toxic effect of glycosylated hemoglobin on bone forming cells (Osteoblasts) together with hyperinsulinemia and their precipitations in the collagen tissue of the bone with reduced serum level of insulin like growth factor, hypercalciuria, inflammation, microangiopathy and renal failure with advancement of DM, prolongation of duration and prolonged toxic effect of glycosylated hemoglobin; renal micro vascular changes begin to appear.

From the result of our study there was strong and positive significant effect of DM and renal changes in the form of albuminuric nephropathy, creatinine and urea changes and development of OP, which is in a close association with studies done by **Selby *et al.* [15] and Gregorio *et al.* [16]; w**here the kidney was the most important organ in calcium and phosphorus homeostasis and not only the target organ for parathyroid hormone but also for (1.25 dihydroxy vitamin D) production. So bone disease as renal osteodystrophy is present in about 75- 100% of patients with chronic renal failure **Kosaku *et al.* [17]**.

In our study, micro or macroalbuminuria was associated with osteoporosis in comparison to normoalbuminuria, which is in close association with a study done by **Meyer *et al.* [18],** which stated that the injurious effect of micro or macroalbuminuria on renal endothelium modify glomerular basement membrane function and permeability together with the atherosclerotic effect of DM on the renal arterial system. Our study only showed negative significance between BMD and all measured parameters of the study as age, sex, DM, duration of DM HAIC level, creatinine, and renal Albuminuria.

CONCLUSIONS

- Osteoporosis is a more complication in patients with DM.
- Increased risk of OP present in older age group, and female sex.
- HbA1C is related to BMD and positively correlated with osteoporosis due to loss of bone mass.
- Prolonged complications of DM especially micro or macroalbuminuria and decline in kidney function are associated with OP.
- Diabetic patients on long-term insulin therapy are at high risk of OP due to high bone turnover and low bone formation.

RECOMMENDATIONS

- More studies are recommended to evaluate the level of estrogen in OP or the effect of medications.
- We recruited patients with creatinine less than 2 but evaluation of gross renal failure is recommended.
- This is a cross-sectional study but a prospective one is recommended.

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