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Osteoporosis among Diabetic Male Patients in Babylon

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Abstract
Background: Diabetes mellitus and osteoporosis are chronic metabolic diseases with an elevated and growing incidence all over the world. Diabetes mellitus is a risk factor for osteoporotic fractures
Objectives
1-To evaluate the relationship between diabetes and male osteoporosis
2-To differentiate the risk of both type I and type II diabetes on bone mineral density
3-To study other risk factors of osteoporosis in the diabetic patients
Patients and Methods: This study was conducted on conveniently selected eighty diabetic male patients in Merjan teaching hospital from the diabetic consultation unit who were diagnosed by a specialist according to the ADA criteria for diagnosis of diabetes (20 with type I diabetes and the other 60 with type II diabetes) their ages ranged from 12–79 years with a mean of age (50.21± 15.94 years), BMI (28.36±5.35) , mean of duration of diabetes (9.25± 7.31) , age of onset of diabetes (40.95± 16.08) and HbA1c (10.03± 2.77.(
The control group consisted of 80 males apparently healthy age and gender matched population-based volunteers their ages ranged from 12-73 years , their mean age was (49.22± 15.28 years) , BMI (29.51± 4.77 kg/m2) was evaluated by a specialist and recruited for the study. Women and patients with concomitant diseases or treatments known to affect bone metabolism were excluded from the study. All of the patients and controls underwent a case control study for assessment of bone mineral density (BMD) at lumbar spines in the region L1–4 in the postero-anterior (PA) projection and/or hip area using Dual energy X-ray Absorptiometry
Results: The study showed a significant difference in the mean of T or Z-scores between the diabetic patients and controls (P<0.001) .The diabetic patient was at 34 times increased risk of having osteopenia (P=0.001) and 8 times increased risk of having osteoporosis (P=0.007) than the healthy person. There was a significant difference in BMD level with the type of diabetes; type I was over-represented type II DM in its negative effect on BMD (P<0.001), duration of DM 5-10 years and more (P=0.005), age of onset of diabetes (below 40 years) P=0.044 , HbA1c level (≥ 6.5%) P=0.01, with no significant effect of type of treatment used. A significant effect was found in the mean of T or Z-scores between the type I diabetic patients and controls (P<0.001), and between type II diabetic patients and the controls (P<0.001).Type I diabetic patients were 33 more times increased risk of developing osteopenia (P=0.004) and osteoporosis(P<0.001) and type II diabetic patients were at 34 times increased risk of developing osteopenia (P=0.001) and 4 times increased risk of developing osteoporosis(P=0.115) when compared with the healthy persons . There was a significant effect of physical inactivity (P=0.03), personal history of fracture (P<0.001), low BMI (P=0.006) on BMD level with no significant effect of advanced age, family history of fracture or osteoporosis, smoking, waist to hip ratio
Conclusions: The study confirms a significant effect of diabetes on BMD level .There is a significant effect of type I DM, early age of onset of diabetes, prolonged duration of diabetes, poor glycemic control on BMD level with no significant effect of type of treatment used in the treatment of diabetes on BMD level. The study also showed a significant difference between the mean of T or Z-scores of type I and type II diabetic patients as compared with the control group separately. Patients with type I and those with type II DM had an increased risk of low BMD level as compared with the healthy control group .The study showed a significant effect of physical inactivity, personal history of fracture, low BMI on BMD level in diabetic patients with no significant effect of advanced age, family history of osteoporosis or fracture, smoking or WHR on BMD
Keywords*:* Diabetes mellitus, osteoporosis, bone mineral density, Dual energy X-ray Absorptiometry

Introduction

Diabetes Mellitus is a group of pandemic debilitating metabolic diseases featuring chronic hyperglycemia which results from defective insulin secretion and/or insulin actions ,such chronic hyperglycemia typically elicits dysfunction and failure of various organs, particularly the eyes (diabetic retinopathy and cataract), kidneys (diabetic nephropathy), nerves (diabetic neuropathy), heart (diabetic cardiomyopathy) and blood vessels

(microangiopathy) (American Diabetes Association, 2009) .In addition , DM has been found to be associated with metabolic bone diseases, osteoporosis and low-impact fractures, as well as other bone-related events including falls in geriatric patients & other musculoskeletal manifestations of diabetes (Brow SA. ,Sharpless JL,2004).

Type I (insulin-dependent DM), results from insulin insufficiency which leads to hyperglycemia in the young (American Diabetes Association, 2009)

Type II (non-insulin dependent diabetes mellitus NIDDM) or adult-onset diabetes) is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency (Kumar, Vinay; Fausto,*eta*l, 2005). This is in contrast to diabetes mellitus type I, in which there is an absolute insulin deficiency due to destruction of islet cells in the pancreas (David G. Gardner, Dolores,2011). The classic symptoms of diabetes are excess thirst, frequent urination, and constant hunger. Type II diabetes makes up about 90% of cases of diabetes with the other 10% due primarily to diabetes mellitus type I and gestational diabetes (diabetes diagnosed during pregnancy that is not clearly overt diabetes (David G. Gardner, Dolores,2011)

Diabetes not only aggravates osteopenia and osteoporosis, but is also one of the "causes" of both conditions (Petit MA., Paudel ML, Taylor BC *,etal* ,2010)

DM-induced osteoporosis and DM/osteoporosis comorbidity covers alterations in bone metabolism as well as factors regulating bone growth under diabetic conditions including insulin, insulin-like growth factor-1 and angiogenesis (Kannikar Wongdee,2011).

Being a primary structural framework of the body, bone undergoes dynamic microstructural remodeling throughout life to accommodate mechanical stress and calcium demand (Sims NA., Gooi JH,2008)

Bone remodeling is a coupled process of bone resorption and formation , and requires coordination of all three types of bone cells: osteoblasts, osteoclasts and osteocytes(Teitelbaum SL,2000).Under mechanical stress, osteocytes act as mechanosensors to detect changes in the flow of bone fluid within bone canaliculi , and respond by transmitting signals to the osteoblasts via their syncytial processes(Sims NA., Gooi JH,2008).Osteoclastic bone resorption occurs in areas of structurally weak bone caused by mechanical stress or disuse (Matsuo K., Irie N.2008)

In normal bone matrix, remodeling of bone is constant; up to 10% of all bone mass may be undergoing remodeling at any point in time. The process takes place in bone multicellular units (BMUs) as first described by Frost in 1963 (Frost HM., Thomas CC,1963). Bone is resorbed by osteoclast cells (which are derived from the bone marrow), after which new bone is deposited by osteoblast cells (Raisz LG,2005).The three main mechanisms by which osteoporosis develops are an inadequate peak bone mass (the skeleton develops insufficient mass and strength during growth), excessive bone resorption, and inadequate formation of new bone during remodeling, an interplay of these three mechanisms underlies the development of fragile bone tissue (Raisz LG,2005)

The World Health Organization's (WHO) definitions of osteoporosis based on BMD measurements are summarized in (Table 1) below (World Health Organization, 2007). For each standard deviation (SD) reduction in BMD, the relative fracture risk is increased 1.5-3 times.

Table (1): WHO definition of osteoporosis

Definition	Bone Mass Density Measurement	T-Score
Normal	BMD within 1 SD of the mean bone density for young adult women.	(≤- 1)
Low bone mass (Osteopenia)	BMD 1–2.5 SD below the mean for young-adult women	)to –2.5 -1(
Osteoporosis	BMD ≥2.5 SD below the normal mean for young-adult women	(≤-2.5)
Established (Severe osteoporosis)	BMD ≥2.5 SD below the normal mean for young-adult women in a patient who has already experienced ≥1 fractures	(≤-2.5)with fragility fractures

Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue; with a consequent increase in bone fragility (Ahmed SF., Elmantaser M ,2009).It is the most common metabolic bone disease in the world and is clinically silent before manifesting in the form of fracture (Fox S,2013). Osteoporosis, a chronic progressive disease of multifactorial etiology, has been most frequently recognized in elderly white women, although it does occur in both sexes, all races, and all age groups (Nayak S., Roberts MS, Greenspan SL, 2011)

Osteoporosis in men is recognized as an increasingly important public health issue. Because of their greater peak bone mass, men usually present with hip, vertebral body, or distal wrist fractures 10 years later than women. Hip fractures in men, however, result in a 31% mortality rate at one year after fracture versus a rate of 17% in women (Janet M. , Michael J.,2003).Osteoporosis is a preventable disease that can result in devastating

physical, psychosocial, and economic consequences (Watts NB., Bilezikian JP,*etal*,2010).

It could result from advanced age (≥50 years) , female sex ,white or Asian ethnicity ,genetic factors such as a family history of osteoporosis , thin build or small stature (body weight less than 127 pounds) ,amenorrhea ,late menarche ,early menopause , postmenopausal state (Fink HA., Kuskowski MA,*etal*,2008). Physical inactivity or immobilization, use of drugs: anticonvulsants, systemic steroids, thyroid supplements, heparin, chemotherapeutic agents, insulin, alcohol and tobacco use, calcium deficiency, androgen (Yaturu S., DjeDjos S,etal,2006) or estrogen deficiency.

It can be simply diagnosed by DXA (Dual energy X-ray Absorptiometry) which is a means of measuring bone mineral density (BMD) and is currently the criterion standard for the evaluation of BMD (The International Society for Clinical Densitometry. 2007). DXA is the most widely used and most thoroughly studied bone density measurement technology and is typically used to diagnose and follow osteoporosis (International Atomic Energy Agency,2012).

OBJECTIVES of this study:

To assess the effect of diabetes mellitus on bone mineral density.1

To compare between the effect of type I and type II diabetes on bone mineral density.2

To assess risk factors of osteoporosis other than diabetes in the diabetic male patients.3

Patients & Methods:

A total of eighty male diabetic patients (60 with type II diabetes & 20 with type I diabetes) their mean of age was (50.21± 15.94 years) ranging from 12-79 years who were referred to the diabetic consultation unit at Merjan Teaching hospital at time of the study, were included in a case control study.They had been diagnosed with DM by a specialist according to the criteria of ADA, 2013.

They had been chosen in a consecutive way, a permission was taken from the patients themselves or from their care givers if they are under 18 years old, both literally and/or verbally for participation in the study after clarifying that they can withdraw from the study at any time of the study and their withdrawal will not affect their management and other services they aim to benefit from at their visit to the hospital.

Eighty apparently healthy non-diabetic, age & gender matched, population based control subjects who were assessed by a specialist, selected in a convenient manner with the same exclusion criteria of the patients, and their permission was taken to be included in this study.

The study was conducted from the beginning of February to August 2013.

Patients with one or more of the following conditions were excluded from the study as their condition may have direct or indirect effect on

DXA results:

Female sex .Recurrent stone formers .Patient with diabetic nephropathy.

Patients with history of any type of endocrine diseases such as hypo or hyperthyroidism, hyperparathyroidism disease,

Patients with Chronic digestive tract conditions that interfere with the absorption of nutrients from food, examples include celiac disease and Crohn's disease,.

Patients with Kyphosis or Scoliosis,,alcoholics.

History of taking corticosteroids ≥5 mg daily for ≥3 months.

Patients with history of cancer, Immobile patient

Secondary myositis or any inflammatory myopathy or connective tissue disease and patients on anti resorptive treatment.

Diabetic male patients who reject to participate in the study because

They were very ill or tired

We dealt with the patients in four steps as follow:

-Interview with the patient-1

-2- Anthropometric measurements

-3-Laboratory investigation

4-Bone mineral density measurement

Interview with the patient , introducing ourselves , taking the ethical consent , full history by a well-structured questionnaire was developed for the study and was filled for every participant. Regarding tobacco smoking the pack year was calculated by multiplying the number of packets of cigarettes smoked per year by the number of years of smoking according to National Cancer Institute (National Cancer Institute,2013) , and the smokers were classified as(Smoking index <20 ,20-40 , >40 classify as light smoker, medium smoker and heavy smoker respectively)

The anthropometric measurements including their weights by using balanced weight scale with shoes off and the participant wear light clothes and heights were measured by a stadiometer with shoes off to calculate their body mass index (BMI) by dividing the weight in kilograms to the square of height in meter, and the results of BMI were classified(WHO,2013) ,(BMI ≤ 18.5 : underweight, BMI18.5-24.9: normalweight,BMI 25-29.5:overweight,

BMI>30:obese)
The waist circumference was measured to the samples by a flexible non stretchable tape measure in the area lying in the midway between the lowest palpable costal margin and the outer part of iliac crest, while the hip circumference was measured as the largest diameter had been recorded at the gluteal region guided by the symphysis pubis anteriorly and greater trochanter of femur laterally, for both measurements the individual stand with feet close together, arms at the side ,wearing little clothing and the measurements taken at the end of a normal expiration. Each measurement was repeated twice; if the measurements were within 1 cm of one another, the average was calculated. If the difference between the two measurements exceeds 1 cm, the two measurements would be repeated then waist to hip ratio was calculated by dividing waist to hip circumferences(average in male 0.90-0.95,and in female 0.8-0.85)
All diabetic patients had been sent for HbA1c measurement , a patient's HbA1c value of ≤6.5% was considered good controlled and a value of >6.5% was considered badly controlled patient according to (American diabetes association,2013)
HbA1c Kit:
Test principle:
The kit contains test devices with a porous membrane filter, test tubes prefilled with reagent and a washing solution. The reagent contains agents that lyse erythrocytes and precipitate hemoglobin specifically, as well as a blue boronic acid conjucate that binds cis-diols of glycated hemoglobin. When blood is added to the reagent, the erythrocytes immediately lyse. All hemoglobin precipitates. The boronic acid conjucate binds to the cis-diol configuration of glycated hemoglobin. An aliquot of the reaction mixture is added to the test device, and all the precipitated hemoglobin, conjucate-bound and unbound , remains on top of the filter . Any excess of coloured conjucate is removed with the washing solution. The precipitate is evaluated by measuring the blue (glycated hemoglobin) and the red (total hemoglobin) color intensity, the ratio between them being proportional to the percentage of HbA1c in the sample.
Kit contents:
TD/Test Device: Plastic device containing a membrane filter.1
2-R1/Reagent : Glycinamide buffer containing dye-bound boronic acid and detergents
3-R2/Washing solution: Morpholin buffered Nacl solution and detergents
Sample material:
Capillary blood and venous blood with or without anticoagulant (EDTA , heparin and NaF) was used
A-precipitate hemoglobin:
1-A volume of 5 µl of whole blood was added to the test tube containing R1 reagent and mixed well
2-The mixture was incubated at room temperature (20-25 C)
for 2- 3minutes
B-Apply sample:
1-The mixture was remixed to obtain a homogenous suspension.
2-A volume of 25 µl of the reaction mixture was added to a TD/Test Device by holding the pipette approximately 0.5 centimeter above the test well.
3-The pipette was emptied quickly in the middle of the test well
4-The reaction mixture was allowed to soak completely into the membrane (approximately 10 seconds).
C-Apply R2/Washing Solution:
1- (25 µl) of R2/Washing Solution was applied to the TD/Test Device
2-The washing solution was allowed to soak completely into the membrane (approximately 10 seconds)
D-Read the test result:
The test result was read within 5 minutes using the NycoCard READER II.
Reference range:
The upper limit of non-diabetic reference range is approximately 6% (142)
Bone Mineral Density Measurement:4-
All the patients & control subjects were screened for BMD measurement at Rheumatology and Rehabilitation center in Merjan teaching hospital.
Their BMD of spine with or without femoral area was measured by using DXA scan and their T & Z - scores were measured.
Z-score is used instead of T-score if the person's age is below (50 years) T-score of -2.5 SD and lower with a history of low trauma fracture was considered as severely osteoporotic, a T-score of -2.5 SD and lower was considered osteoporotic, those between -1 to -2.5 SD was considered osteopenic & that > -1 was considered normal according to WHO criteria of diagnosis of osteoporosis.
Bone mineral density was measured using DXA scan a standard protocol and Densitometry (Osteosys, Korea)
Procedure of Bone Mineral Density Measurement
Weight and height were measured for each patient, height was measured with a stadiometer in centimeters, with

shoes off, using standard techniques (patient standing erect with the head in the frankfort horizontal plane) and weight (in kilograms) were measured with standard weighting scale & patient's age, sex, ethnic group, birth year had been entered in the computer of the densitometry (Moayyeri A., soltani A.etal,2005)

Bone mineral density was measured at the lumbar spine with or without hip area with Dual X-Ray Absorptiometry (DXA) Two X-ray beams with different energy levels are aimed at the patient's bones. When soft tissue absorption is subtracted out, the BMD can be determined from the absorption of each beam by bone (International Atomic Energy Agency, 2012). By a trained operator according to the manufacturer's instructions, the instrument was calibrated daily by using appropriate phantoms.

The patient was advised to wear loose, comfortable clothing, avoiding garments that have zippers, belts or buttons made of metal objects such as keys or wallets that would be in the area being scanned , should be removed ,in the Central DXA examination, which measures bone density in the hip and spine, the patient lies on a padded table. An X-ray generator is located below the patient and an imaging device, or detector, is positioned above.

To assess the spine, the patient's legs were supported on a padded box to flatten the pelvis and lower (lumbar) spine.

To assess the hip, the patient's foot was placed in a brace that rotates the hip inward, in both cases, the detector was slowly passed over the area, generating image s on a computer monitor, and the technologist walked behind a wall or into the next room to activate the X-ray machine. The DXA is usually completed within 10 to 30 minutes, depending on the equipment used and the parts of the body being examined .

Statistical Analysis:

The data were entered in the data base and analyzed using the statistical package for the social sciences software SPSS program (version 17 for windows 7) with statistical significance of $p<(0.05)$ and a confidence interval of 95%.

Results

The overall mean age of the respondents was (44.21 ± 16.68 years), majority (45.0%) of them were aged between 41-60 years. There was no significant difference between the mean age of patients (50.21± 15.94 years) and controls (49.22± 15.28 years) ($t=0.0347$, $df= 98$ $p=0.213$). Majority of patients and control were active employee (63.7%) and (93.7%), respectively.

Family history of osteoporosis: Majority (92.5%) and (98.8%) of cases and controls had no family history of osteoporosis, respectively .Majority (97.5%) and (96.3%) of cases and controls had no family history of fracture, respectively. Majority (97.5%) and (96.3%) of cases and control had no history of osteoporotic fracture , respectively, About half of the cases (57.4%) and (53.8%) of controls were non-smokers, respectively, and (41.2%) of the cases and (43.8%) of controls were overweight, respectively. Meanwhile, (40.0%) and (45.0%) of cases and controls were at high risk by their waist to hip ratio, respectively. Table (2)

Majority (75.0%) of diabetic patients were type II. The mean duration of DM was (9.25± 7.31 years), meanwhile the mean age for onset of DM was (40.95± 16.08 years). The mean HbA1c was (10.03± 2.77), and (55.0%) of diabetic patients were on oral hypoglycemic agents (OHA) as shown in table (3).

There was significant difference between the mean T score for cases (-0.33 ± 2.27) and the mean T score for control (2.29 ± 1.28) ($t= 8.967$, $df= 158$, $p< 0.001$).

There was a significant difference between cases and controls by BMD level. Cases were 34 and 8 times more than control to develop osteopenia and osteoporosis, respectively .Table (4)

There was a significant difference among BMD level by type of DM, majority (60.0%) and (80.0%) of osteoporosis and established osteoporosis were type I DM, respectively. There was a significant difference among BMD level by age of onset of DM, majority (80.0%) and (85.0%) of the normal individuals and of the osteopenic patients aged more than 40 years at time of diagnosis of DM, respectively, meanwhile majority of established

osteoporosis were type I DM. BMD level was statistically significant by HbA1c, however, almost all of the osteopenic, osteoporotic as well as those who had established osteoporosis had HbA1c more than 6.5. There were significant differences among BMD levels by duration of DM, age of onset of DM with no significant correlation with the type of treatment of DM. Table (5)

There was a significant difference between the mean of T-score for type I DM (-2.15 ± 1.98) and that for the control group (2.41 ± 1.28) ($t= 12.285$, $df= 98$, $p< 0.001$) as shown in figure (6) . There was a significant difference between type I DM patients and control group by BMD measurement. Type I DM patients were 33 times more susceptible than healthy persons to develop osteopenia and osteoporosis. Table (6)

There was a significant difference between the mean of T-score for type II DM patients (0.28 ± 2.04) and that for control (2.41 ± 1.28) ($t= 7.139$, $df= 138$, $p< 0.001$) .

There was a significant difference between the type II DM patients and the control group by BMD level. Type II diabetics were 34 times at increased risk to have osteopenia and 4 times to develop osteoporosis

than control group . Table (7).

Table(8) shows BMD level distribution among diabetic patients by some risk factors of osteoporosis other than DM with no significant differences regarding the age groups, Family History of Osteoporosis, Family History of Fracture and smoking habits and significant differences regarding History of Fracture and occupation .

Discussion

Diabetes mellitus is a pandemic and chronic metabolic disorder with a substantial morbidity and mortality. In addition, osteoporosis a global age-related health problem , insidiously deteriorates the microstructure of bone , particularly at trabecular sites , such as vertebrae , ribs and hips ,culminating in fragility fractures , pain and disability .Although osteoporosis is normally associated with advanced age , estrogen deficiency , DM especially type I also contributes to and /or aggravates bone loss in osteoporotic patients(Shaymaa A. , Syed A.,2012)

The study showed a significant difference in the mean of T-score between the diabetic patients and the control group, also this study showed that the diabetic patients are at 34 times increased risk of osteopenia and 8 times increased risk of osteoporosis than the control group

This result is supported by the study of P.V estergaard , 2007 who showed that in both genders there was an increased risk of fractures in both types of diabetes mellitus patients compared to non-diabetes mellitus healthy persons but is disagreed with the study of Shwartz et al ., 2005 who found that despite having higher baseline BMD, only diabetic white women, but not black women nor men with DM and impaired glucose metabolism, demonstrated significant bone loss.

Diabetes mellitus induces osteoporosis by increased osteoclast function, decreased osteoblast function, and impaired bone microcirculation (Hamilton EJ., Rakic V,etal,2009)

This study showed that there was a significant negative effect in heterogeneity of type of diabetes where type I had more debilitating effect on BMD level than type II DM ,type I diabetic patients had a significantly higher prevalence of osteoporosis /osteopenia and a significantly lower BMD , T-and Z- scores after adjustment for age and BMI when compared with type II DM patients which was going with the study had been done by Hamilton et al ., 2012 who showed that the rate of demineralization at the femoral neck in type I DM men is similar to that in older post-menopausal type II women , BMD did not fall at any site in type I women or type II men.

Hadjidakis et al.,2006 found that men with type I diabetes had significantly lower BMD in trabecular (L2–L4) and mixed cortical-trabecular bone (femoral neck) compared with matched healthy subjects, whereas type I female participants had significantly lower BMD values in only mixed (femoral neck) bone.

Dominguez et al ., 2004 had reported that type I diabetes is generally associated with a mild reduction in bone mineral density (BMD), type II diabetes, more prevalent in old subjects, is frequently linked to a normal or high BMD.

Lorenz et al ., 2007 reported that both genders had BMD of the proximal femur significantly lower in type I DM than in type II DM, this difference might be due to:

1-Type II diabetic patients tend to have higher BMI than type I diabetic patients making the latter more susceptible to osteoporosis.

2-Insulin is anabolic hormone (Thrailkill KM.,2005) that have both direct & indirect effects on bones, it is an osteogenic factor capable of stimulating osteoblast proliferation and differentiation (Yang J.,2010)

3-Because TIDM typically occurs in children, prior to peak bone mass attainment, while TIIDM occurs in adults who have attained their peak bone mass making type I diabetic patients more vulnerable to osteoporosis (Adami S,2009)

4-Type I DM patients were featuring low circulating insulin and IGF-1.

A significant association had been found in this recent study regarding duration of diabetes with lowered BMD, as the duration exceed five years the lower the BMD level would be expected, as supported by the study of Diane L. and Steven V.(Diane L. Chau,2002) who stated that duration of diabetes seems to play a key role given the lower BMD found among patients who have had diabetes for >5 years.

This result disagreed with the study of Hamilton et al ., 2009 who stated that there was no consistent relationship between BMD and duration of diabetes.

This study revealed a significant effect of early age of onset (<40) with low BMD as supported by the study of S.Bechtold et al ., 2007 who suggested that a defect in bone accretion occurs early in the course of type I DM ,which then ameliorates with time ,in contrast to the study of Hadjidakis et al ., 2006 who reported that there was no significant correlation between age-adjusted BMD values , and age of onset of diabetes

This study showed also a significant correlation between the level of glycemic control represented by HbA1c on BMD, T-score as supported by a study of Melton et al ., 2008who had demonstrated that glycemic control and HbA1c levels were associated with osteoporosis in diabetic patients, but in contrast to the study of Hamilton et al.,2009 who showed no significant effect of increased HbA1c level on BMD.

Uncontrolled diabetes with hyperglycemia has been suggested as a possible mechanism for

osteoporosis in both type I and type II DM. This can occur by the formation of non enzymatic glycosylation of various bone proteins, including type I collagen, leading to impaired bone quality (D. Vashishth,2001) reduced serum levels of IGF-1, microangiopathy and inflammation (Montagnani A.,2011)

There was no significant relation of type of treatment used on BMD was found in our study as supported by a study of Hadjidakis et al ., 2006 who reported that there was no significant correlation between the type of treatment and BMD values.

Tuominen et al.1999 had separately compared patients with type I and type II diabetes treated with insulin, showing that exogenous insulin is not the cause of the bone loss.

The study revealed a significant difference in the mean of T-score between type II diabetic patients and the control group. Type II DM patients were 34 times at increased risk to have osteopenia (p=0.001) and 4 times to develop osteoporosis than control group.

This result was supported by the study of Zhong et al ., 2012 who reported that the elderly patients with type II DM were prone to develop osteoporosis.

Yaturu and colleagues,2009 also found a significantly low BMD of hip in type II DM patients when compared to age-matched normal subjects.

In contrast Petit and colleagues,2010reported a higher BMD in elderly patients with type II DM when compared to age-matched non-DM volunteers.

This study showed a significant effect of physical inactivity and lowered BMI on BMD values as supported by the study of Melton et al 2008 who reported that physical activity/exercise and high BMI are both protective.

S.Tanaka et al ., 2013 concluded that overweight/obesity and underweight are both risk factors for fractures at different sites.

This might be due to the fact that low body weight ,one of the strongest predictors of osteoporosis, is more typical of patients with type I diabetes than of those with type II diabetes. The obesity commonly present in people with type II diabetes (and often for years before it develops) may have a cumulative protective effect on bone density

This study had also revealed a strong correlation between personal history of fracture and low BMD values as supported by the study of Albrand G. et al ., 2003 and Klotzbuecher C. et al ., 2000 who clarified that one of the risk factors that are consistently associated with osteoporosis is the personal history of fracture.

This result might reflect the high percentage of the established osteoporotic patients in this study.

While no significant correlation had been found in this study between low BMD and advanced age , family history of osteoporosis or fracture , smoking nor WHR on BMD measurements as supported by a study of De Laet et al ., 2005.

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Table (2) : Distribution of cases and controls according to smoking and anthropometric measurements

Characteristic	Cases (%)	Controls (%)	Mean ± SD	P value
Smoking				
Non-Smoker	46 (57.4)	43 (53.8)		
Light Smoker	8 (10.0)	22 (27.5)	16.86±25.04	**0.020***
Medium Smoker	13 (16.3)	8 (10.0)		0.400
Heavy Smoker	13 (16.3)	7 (8.8)		0.284
BMI				
<18.5 kg/m^2	19 (23.8)	19 (23.8)		0.927
18.5-24.9 kg/m^2	26 (32.5)	25 (31.2)	28.94 ± 5.09	0.885
25-29.9 kg/m^2	33 (41.2)	35 (43.8)		0.584
≥ 30 kg/m^2	2 (2.5)	1 (1.2)		
Waist/ Hip Ratio				
High Risk > 1.0	32 (40.0)	36 (45.0)		0.927
Moderate Risk 0.9-1.0	23 (28.8)	21 (26.2)	0.96± 0.18	0.88
Low Risk < 0.9	25 (31.2)	23 (28.8)		

Table(3): Distribution of diabetic patients by DM-specific factors

Clinical Characteristic	Frequency (%)	Mean ± SD	Range
DM type			
Type I DM	20 (25.0)		
Type II DM	60 (75.0)		
Duration of DM			
<5 years	25(31.25)	9.25± 7.31	1.0- 34.0
5- 10 years	29(36.25)		
>10 years	26(32.5)		
Age of Onset of DM			
< 40 years	30 (37.5)	40.95± 16.08	7.0- 78.0
≥ 40 years	50 (62.5)		
HbA_{1c}			
< 6.5	30 (37.5)	10.03± 2.77	5.50- 15.0
≥ 6.5	50 (62.5)		
Treatment of DM Patients			
On Diet	5 (6.3)		
OHA	44 (55.0)		
On Insulin	30 (37.4)		
OHA + Insulin	1 (1.3)		

Table (4): Frequency distribution of BMD level among cases and controls
*p value ≤0.05 is significant
a (0.0) control for established class made OR (0.0)

BMD level	Cases (%)	Controls (%)	Total	P value	OR (95% CI)
Normal	**45 (56.3)**	**77 (96.3)**	**122 (76.3)**		
Osteopenia	**20 (25.0)**	**1 (1.2)**	**21 (13.1)**	**0.001***	**34.22 (4.44- 263.65)**
Osteoporosis	**10 (12.5)**	**2 (2.5)**	**12 (7.5)**	**0.007***	**8.56 (1.79- 40.80)**
Established	**5 (6.2)**	**0 (0.0)[a]**	**5 (3.1)**	**0.999**	**0.0[a]**
Total	**80 (100.0)**	**80 (100.0)**	**160 (100.0)**		

Table (5): Relation of Frequency Distribution of BMD level with DM-specific factors

Variable	BMD level					P value
	Normal (%)	Osteopenia (%)	Osteoporosis (%)	Established (%)	Total	
DM						
Type I	7 (15.6)	3 (15.0)	6 (60.0)	4 (80.0)	20 (25.0)	
Type II	38 (84.4)	17 (85.0)	4 (40.0)	1 (20.0)	60 (75.0)	
Total	**45 (100.0)**	**20 (100.0)**	**10 (100.0)**	**5 (100.0)**	**80 (100.0)**	**0.001***
Duration of DM						
< 5 years	19 (42.2)	5 (25.0)	4 (40.0)	3 (60.0)	25 (31.2)	
5- 10 years	9 (20.0)	11 (55.0)	2 (20.0)	1 (20.0)	29 (36.3)	**0.005***
> 10 years	17 (37.8)	4 (20.0)	4 (40.0)	1 (20.0)	26 (32.5)	
Total	**45 (100.0)**	**20 (100.0)**	**10 (100.0)**	**5 (100.0)**	**80 (100.0)**	
Age Onset of DM						
< 40 years	14 (31.1)	5 (25.0)	6 (60.0)	4 (80.0)	29 (36.2)	**0.044***
≥ 40 years	31 (68.9)	15 (75.0)	4 (40.0)	1 (20.0)	51 (63.8)	
Total	**45 (100.0)**	**20 (100.0)**	**10 (100.0)**	**5 (100.0)**	**80 (100.0)**	
HbA_{1c}						
< 6.5	15 (33.3)	1 (5.0)	0 (0.0)	0 (0.0)	16 (20.0)	**0.010***
≥ 6.5	30 (66.7)	19 (95.0)	10 (100.0)	5 (100.0)	64 (80.0)	
Total	**45 (100.0)**	**20 (100.0)**	**10 (100.0)**	**5 (100.0)**	**80 (100.0)**	
Treatment of DM						
On diet	4 (8.9)	1 (5.0)	0 (0.0)	0 (0.0)	5 (6.3)	
On OHA	27 (60.0)	13 (65.0)	3 (30.0)	1 (20.0)	44 (55.0)	0.195
On insulin	13 (28.9)	6 (30.0)	7 (70.0)	4 (80.0)	30 (37.5)	
On insulin +OHA	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	
Total	**45 (100.0)**	**20 (100.0)**	**10 (100.0)**	**5 (100.0)**	**80 (100.0)**	

Table (6): Differences of BMD level among type I DM patients and control group

BMD level	Type I DM patients (%)	Controls (%)	Total	P value	OR (95% CI)
Normal	7 (35.0)	77 (96.3)	66 (82.5)		
Osteopenia	3 (15.0)	1 (1.2)	4 (5.9)	**0.004***	**33 (3.018- 360.787)**
Osteoporosis	6 (30.0)	2 (2.5)	6 (7.5)	**<0.001****	**33(5.579-195.204)**
Established	4 (20.0)	0 (0.0)[a]	4 (5.0)	0.999	0.0[a]
Total	**20 (100.0)**	**80 (100.0)**	**100 (100.0)**		

**p value ≤0.05 is significant
****p value ≤0.001 is highly significant
a (0.0) control for established class made OR (0.0)

Table (7): BMD level Differences of type II diabetics&controls:
**p value ≤0.05 is significant
a (0.0) control for established class made OR (0.0)

Characteristic	Type II DM patients (%)	Controls (%)	Total	P value	OR (95% CI)
BMD level					
Normal	38 (63.3)	77 (96.3)	115 (80.8)		
Osteopenia	17 (28.3)	1 (1.2)	18 (15.0)	**0.001***	**34.45 (4.42- 268.62)**
Osteoporosis	4 (6.7)	2 (2.5)	6 (3.3)	0.115	**4.053(0.71-23.12)**
Established	1 (1.7)	0 (0.0)[a]	1 (0.8)	0.999	0.0[a]
Total	**60 (100.0)**	**80 (100.0)**	**140 (100.0)**		

Table(8) BMD level distribution among diabetic patients by some risk factors of osteoporosis other than DM

Variable	BMD Classification				Total	P value
	Normal (%)	Osteopenia (%)	Osteoporosis (%)	Established (%)		
Age						
20-30	1(22.0)	0 (0.0)	3(30.0)	1(20.0)	5(6.3)	
30-40	4 (8.9)	1(5.0)	1 (10.0)	2(40.0)	8(10.0)	
40-50	2 (44.0)	1(5.0)	0 (0.0)	0 (0.0)	3(3.8)	
50-60	5 (11.1)	4(20.0)	1(10.0)	0(0.0)	10(12.5)	
60-70	16 (35.6)	9(45.0)	4(40.0)	2(40.0)	31(38.8)	**0.190**
>70	14 (31.1)	3(15.0)	1(10.0)	0(0.0)	18(22.5)	
Total	3 (6.7)	2(10.0)	0 (0.0)	0(0.0)	5 (6.3)	
	45(100.0)	**20(100.0)**	**10(100.0)**	**5(100.0)**	**80(100.0)**	
Occupation						
Clerk employee						
Active employee	21 (46.7)	4 (20.0)	1 (10.0)	3 (60.0)	29 (36.3)	
Total	24 (53.3)	16 (80.0)	9 (90.0)	2 (40.0)	51 (63.8)	**0.030***
	45 (100.0)	**20 (100.0)**	**10 (100.0)**	**5 (100.0)**	**80(100.0)**	
Family History of Osteoporosis						
Yes	4 (8.9)	1 (5.0)	1 (10.0)	0 (0.0)	6 (7.5)	
No	41 (91.1)	19 (95.0)	9 (90.0)	5 (100.0)	74 (92.5)	**1.000**
Total	**45 (100.0)**	**20 (100.0)**	**10 (100.0)**	**5 (100.0)**	**80(100.0)**	
Family History of Fracture						
Yes	1 (2.2)	1 (5.0)	0 (0.0)	0 (0.0)	2 (2.5)	
No	44 (97.8)	19 (95)	10 (100.0)	5 (100.0)	78 (97.5)	**0.687**
Total	**45 (100.0)**	**20 (100.0)**	**10 (100.0)**	**5 (100.0)**	**80(100.0)**	
History of Fracture						
Yes	7 (15.6)	3 (15)	0(0.0)	5(100.0)	15 (18.8)	
No	38 (84.4)	17 (85)	10 (100)	0 (0.0)	65 (81.2)	**<0.001***
Total	**45 (100.0)**	**20 (100.0)**	**10(100.0)**	**5 (100.0)**	**80(100.0)**	
Smoking						
Non-Smoker	26 (57.8)	12 (60.0)	6 (60.0)	2 (40.0)	46 (57.5)	
Light Smoker	2 (4.4)	4 (20.0)	0 (0.0)	2 (40.0)	8 (10.0)	
Medium Smoker	10 (22.2)	2 (10.0)	1(10.0)	0 (0.0)	13 (16.3)	**0.186**
Heavy Smoker	7 (15.6)	2 (10.0)	3 (30.0)	1 (20.0)	13 (16.3)	
Total	**45 (100.0)**	**20 (100.0)**	**10 (100.0)**	**5 (100.0)**	**80(100.0)**	
BMI						
<18.5 kg/m^2	0 (0.00)	0(0.00)	0(0.00)	2(40.0)	2 (2.5)	
18.5-24.9 kg/m^2	8 (17.8)	7 (35.0)	4 (40.0)	0 (0.0)	19 (23.8)	
25-29.9 kg/m^2	13 (28.9)	7 (35.0)	5 (50.0)	1 (20.0)	26 (32.5)	**0.006***
≥ 30 kg/m^2	24 (53.3)	6 (30.0)	1 (10.0)	2 (40.0)	33 (41.2)	
Total	**45 (100.0)**	**20 (100.0)**	**10 (100.0)**	**5 (100.0)**	**80(100.0)**	
Waist/ Hip Ratio						
High Risk > 1.0	18 (40.0)	7 (35.0)	3 (30.0)	1 (20.0)	29 (363)	
Moderate Risk 0.9-1.0	13 (28.9)	8 (40.0)	3 (30.0)	1 (20.0)	25 (31.3)	**0.836**
Low Risk < 0.9	14 (31.1)	5 (25.0)	4(40.0)	3 (60.0)	26 (32.5)	
Total	**45 (100.0)**	**20 (100.0)**	**10 (100.0)**	**5 (100.0)**	**80(100.0)**	

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