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Is Type II DM A Risk Factor for Osteoporosis

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Abstract

Both Type II diabetes mellitus and osteoporosis are prevalent diseases at middle aged patients and both are associated with significant morbidity and mortality but the relationship between diabetes and osteoporosis is controversial .

Objective:
To determine that if patients with type 2 diabetes (T2DM) at increased risk of development of osteoporosis and whether T2DM was associated with a low bone mineral density (BMD).

Methods:
50 osteoporotic patients aged 50 years and older and were asked whether having T2DM for more than 10 years or not as a case group, another 50 patients non-osteoporotic patients and were asked whether having T2DM for more than 10 years or not as control group, both samples were recruited from rheumatology consultant department at Ibn Sena Teaching Hospital. All patients received a standardized questionnaire on osteoporosis risk factors and biochemical tests (include level of blood sugar) were done to all of them to exclude renal and liver disease. Diabetic patients are evaluated for presence of proteinuria and retinopathy; all patients were evaluated for bone mineral density (BMD, by using a dual energy X-ray absorptiometry).

Result:
In this study T2DM was not a risk factor for osteoporosis as p-value (0.687).There is no significant differences between both gender p- value(0.629) and no significant difference was found among smokers p-value 0.05.there is neither significant difference among two groups regarding personal history of fracture p-value (0.115) nor family history of fracture p-value(0.110).no significant differences in body mass index between two groups p-value(0.4). Although there was a significant difference for the presence of peripheral neuropathy between two groups, osteoporosis was more common among diabetic patient who have microvascular complication (proteinuria and diabetic retinopathy).

Conclusion: T2DM seem to be not a risk factor for osteoporosis unless there is microvascular complication particularly diabetic retinopathy and or nephropathy.

هل السكري النوع الثاني عامل خطورة لهشاشة العظام

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الخلاصة:

يعتبر كلا من داء السكري من النوع الثاني وهشاشة العظام من الأمراض السائدة في المرضى في منتصف العمر وكلاهما مرتبطان بأمراض ووفيات كبيرة ولكن العلاقة بين مرض السكري وهشاشة العظام مثيرة للجدل

الهدف: تحديد أن مرضى السكري من النوع الثاني معرضون لخطر متزايد للإصابة بهشاشة العظام وما إذا كان السكري النوع الثاني مرتبطً بانخفاض كثافة المعادن في العظام.

الطريقة: إجمالاً ٥٠ مريضاً مصاباً بهشاشة العظام و ٥٠ مريضاً آخرين غير مصابين بهشاشة العظام ، تم اختيار كلتا العينتين من استشارية أمراض الروماتيزم بمستشفى ابن سينا التعليمي. تلقى جميع المرضى استبيانًا موحدًا حول عوامل خطر الإصابة بهشاشة العظام وتم إجراء اختبارات كيميائية حيوية لهم جميعًا لاستبعاد أمراض الكلى والكبد. يتم تقييم مرضى السكري لوجود بيلة بروتينية واعتلال الشبكية. تم تقييم كثافة المعادن في العظام لجميع المرضى باستخدام قياس امتصاص الأشعة السينية ثنائي الطاقة

النتيجة: في هذه الدراسة لم يكن عامل خطورة لهشاشة العظام حيث بلغت القيمة الاحتمالية (٠.٦٨٧) ولا توجد فروق ذات دلالة إحصائية بين قيمة كلا الجنسين (٠.٦٢٩) ولم يوجد فرق معنوي بين المدخنين بقيمة احتمالية ٠.٠٥٤. لا يوجد فروق ذات دلالة إحصائية بين مجموعتين فيما يتعلق بالتاريخ الشخصي لكسور سابقة القيمة الاحتمالية (٠.١١٥) ولا التاريخ العائلي لكسور سابقة القيمة الاحتمالية(٠.١١٠). لا توجد فروق ذات دلالة إحصائية في مؤشر كتلة الجسم بين المجموعتين القيمة الاحتمالية (٠.٤). على الرغم من وجود فروق ذات دلالة إحصائية لوجود اعتلال الأعصاب المحيطية بين مجموعتين ، إلا أن هشاشة العظام كانت أكثر شيوعًا بين مرضى السكري الذين يعانون من بروتينية واعتلال الشبكية السكري.

الاستنتاج: السكري النوع الثاني ليس عامل خطر لهشاشة العظام ما لم يكن هناك مضاعفات الأوعية الدموية الدقيقة وخاصة اعتلال الشبكية السكري واعتلال الكلية.

Introduction

Bone is one of the hardest tissue of the human body has the ability to withstand stress. It is regarded as the main constituent of the skeletal system supporting and protecting flesh and vital organs such as those within the cranial, thoracic and vertebral cavities. In addition to this function bones acts as levers that increase the force of muscle contraction and transmit it to body movement. Bone is consist of bone matrix which is intracellular calcified material and different types of cells. Bone matrix composed of two main components an organic matrix consist of collagen and other non-collagenous proteins such as an inorganic minerals (phosphate and calcium). The cells in the bone include osteocytes which is found in the cavities (lacunas) within the matrix ,other cells like osteoblasts that synthesize the organic part of organic components of bone matrix (collagen and glycoproteins) -figure 1. Osteoclasts a large multinucleated cells, this type of cells involved in resorption and remodeling of the bone tissue (1).

In normal situation bone remodeling occur by synchronization between osteoclast activity that causes bone resorption and osteoblast activity that stimulate bone formation. This coordination preserve the bone density without any change in total bone mass. (2). Bone density gradually increases with growth of person to maximum peak is reached between 20 -45 years of age, but decreases after that in both sexes with a rapid phase of bone loss in women after menopause because of estrogen deficiency. The bone loss with advanced age is due to imbalance in remodeling cycle of the bone, because the new bone amount synthesized by osteoblasts is less than the amount of bone which is removed by osteoclasts.(3) Reduced bone minerals and matrix leads to osteoporosis which characterize by decreased bone mass due to loss of bone density and micro architectural bone resorption make the bone more susceptible for fracture. (4)

Many dietary factors influenced osteoporosis for example inadequate calcium intake which result in suboptimal bone mass thereby increasing the risk for osteoporosis. (5). *osteoporosis* characterize by increase skeletal fragility and reduced bone quantity and quality resulting in reduced bone mass and may lead to fracture.(6). Osteoporosis is usually asymptomatic disease that may cause complication and health impact includes vertebral fracture which lead to reduced height, deformity, backache and neurological morbidity which may cause inability to walk (6).

Osteoporosis is a very common metabolic bone disorder, 200 million people are affected worldwide. Nearly 28 million Americans are diagnosed with osteoporosis or may be at risk for developing it. 22 million females and 5.5 million males in the twenty seven states of the European Union (EU27) were confirmed to have osteoporosis and 3.5 million have fragility fractures, .(7). Trauma like minor fall is almost always is the leading cause of fracture in non-vertebral area. 'Fragility fracture' is a term usually refers to fracture caused by falling from standing height. Signs on clinical examination are: deformity and local tenderness. Fracture hip may be presented with inability of weight bearing and rotation of the affected side externally. Symptoms of vertebral fracture is variable ranging from severe pain and radiation of pain to the anterior chest and false suspicion of ischemia and MI, to kyphosis and loss of height with symptoms of chronic back pain sometimes discovered accidentally on radiological examination as osteopenia and deformity of shape of vertebrae. The risk factors for osteoporosis include ,advanced age, poor health, disorder of eating, low levels of testosterone in men, deficiency of estrogen in women, excessive consumption of alcohol

,sedentary life style and lack of exposure to sunlight (8,9).

Bone mineral density (BMD), can be determined by several techniques, which is often markedly reduced in osteoporotic patients with fractures. The World Health Organization (WHO) defines osteoporosis as a condition in which a BMD is less than −2.5 standard deviations (SD) below peak bone mass (i.e., a T-score measured as the units of SD below the normative mean of a 35-year old woman)... In men, osteoporosis may be diagnosed when there are signs of demineralization on conventional radiography or when there is compression fracture in vertebral bodies in spinal radiography. The conventional radiography features of osteoporosis, are not sensitive technique in diagnosing because it is estimated that more than 25% to 50% of bone mass is lost to be sufficient to appear as osteopenia in osteoporosis. Dual-Energy X-ray Absorptiometry (DEXA) is a technique for measurement of bone density emerge as important technique for measurement of bone density for diagnosis and management of osteoporosis [10).

Diabetes mellitus

(DM) is a chronic disorder characterized by the elevated fasting and or post prandial blood glucose associated with significant morbidity and mortality(11,12). There is increasing evidence that the risk of fractures is increased in older patient with type 2 diabetes mellitus (13,14).Furthermore hyperglycemia are known to interact with several proteins to generate an increasing concentration of advanced glycation end-products (AGEs) in collagen that may reduce bone strength(15). Accumulated AGEs in the body may trigger apoptosis of osteoblasts, thereby contributing to deficient bone formation (16). Another indirect effect of high glucose level in the blood is glycosuria, which causes hypercalciuria, leading to decreased levels of calcium in the body and poor bone quality, hastening bone loss(17,18). furthermore In diabetics microvascular complications may lead to reduced blood flow to bone and may contribute to bone loss and fragility (19,20).

A technique estimation of bone mineral density at hip, lumber spines, by DEXA, it act on the principle based on calcium concentration in the bone and attenuates X-rays passages via the tissue which depends on the amount of calcium and other minerals present within bone tissue , the higher content of mineral the highest bone mineral density measurement. Bone mineral density estimations are presented as T-scores, that estimate the number of standard deviations by which the value of the patient's BMD differs from BMD in a healthy young control.(21)According to DEXA technique osteoporosis is defined in men aged more than 50 years and postmenopausal women by a T-score of −2.5 or less while Osteopenia is defined when T-score between −1.0 and −2.5. If BMD is more than -1and less than +2.5 regarded as normal as shown in figure.2..

The aim of this study is:

To study if there is a relationship between osteoporosis and type II DM whether it is a risk for development of osteoporosis.

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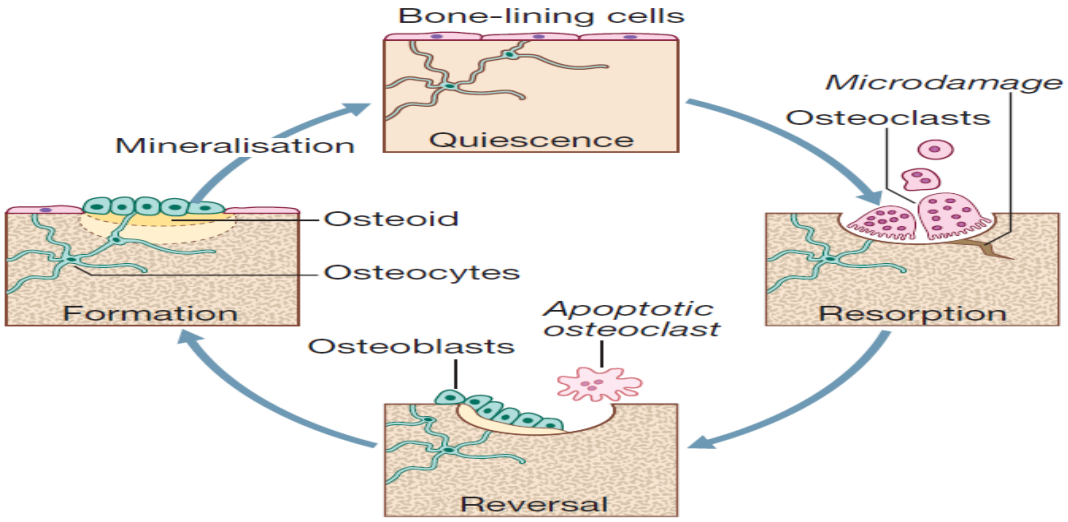
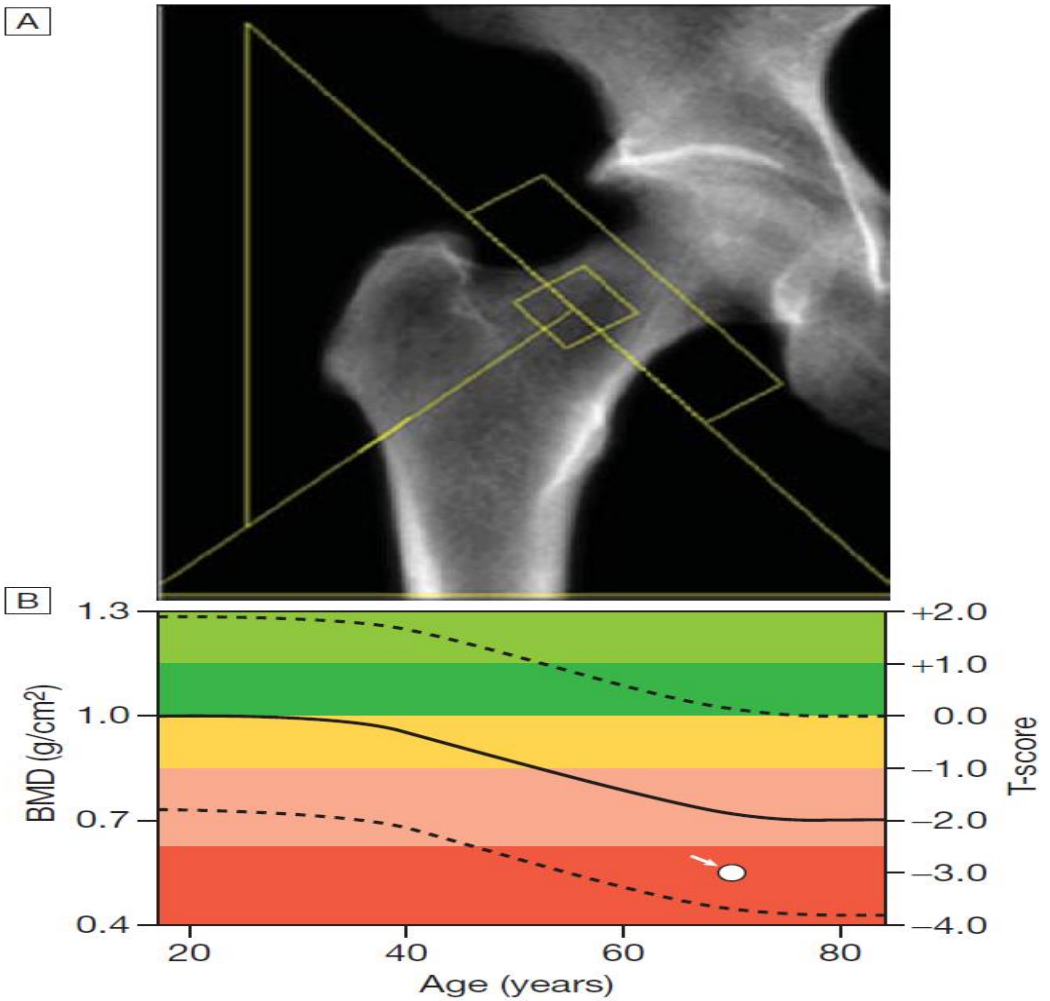


Figure (1) Basic bone histology(3).



Fig

(2)DEXA scan of hip RT axes is T-score LT axis is bone mineral density solid line indicated normal population against age. Patient T-score -3 so regarded as osteoporosis.(3).

Methods, patients & Materials

After obtaining approval from department of medicine, College Of Medicine, University Of Mosul, and the local ethics committee, of Nineveh health directorate and verbal consent from patient. A case control study has been conducted From August 2020- to April 2021.

Inclusion criteria: 100 patient are recruited and selected from rheumatology consulting clinic at Iben-Sena teaching hospital they include 50 osteoporotic patients aged 50 years and older whether having T2DM for more than 10 years or not , another 50 patients non-osteoporotic patients whether having T2DM for more than 10 years or not as control group. All had completed the answer of questionnaire about their name, age, personal history and or family history of fracture, use of calcium supplement, bisphosphonate, current smoking, presence or absence of T2DM, Furthermore, standardized questions on the history of diabetes were including diabetic specific parameters (duration of T2DM, use of oral hypoglycemic drug or insulin and the presence of symptoms of peripheral neuropathy). All these questions were done through direct interview with the patient .Biochemical tests done to the all participants in order to diagnose diabetes mellitus and to exclude renal and liver disease as they cause osteoporosis. Urine examinations for detection of overt proteinuria .Diabetic patients are evaluated by ophthalmologist to detect the presence of diabetic retinopathy. Measurement of Body mass Index (BMI) by dividing body weight of patient in kilogram by square of height in meter. Bone mineral density were carried out in the osteoporotic Unit Ibn Sena Hospital ,the measures at lumber spines and hips by using dual energy X-ray absorptiometry DEXA, Osteosys device manufactured by Korean company at 2019.

The exclusion criteria: include patient who have any disease or condition that cause osteoporosis like:

1) Endocrine disease like: hyperthyroidism, hyperparathyroidism hypogonadisim and Cushing syndrome.
2) Use of drugs like glucocorticoid ,anticonvulsant ,heparin, lithium and methotrexate.
3) GIT disorders like celiac disease, primary biliary cirrhosis.
4) Bone marrow disorders like multiple myeloma, leukemia
5) Rheumatological diseases like rheumatoid arthritis, systemic lupus erythromatosus and ankylosing spondylitis.
6) Renal insufficiency.

Statistical analysis

For quantitative data ,frequency and percentages, descriptive statistic used to express the mean and SD . Independent T-test of two means was used for quantitative variables and Chi-square test was used for catigoral variable and P value was determined and considered significant if its equal to or less than 0.05 .

Results

The mean age was(60) years, for osteoporotic cases group and was (59.4) years for non-osteoporotic group, the mean duration of diabetes (13.6) years in osteoporotic patient and (12)years in non-osteoporotic patient figure (3) and mean HbA1c 7.6%. Mean BMD scores were (-3.14) in osteoporotic case group. There are no significant differences in personal characteristics of studied samples as shown in table(1.) more over .,there are no significant differences between male and female gender on the development of osteoporosis Table (2). Regarding the BMI the results show no significant difference between osteoporotic group and control group as shown in table (3). Although there was no significant difference regarding calcium intake there was a risk for osteoporosis among

patients who didn't take calcium Table (4).

There was significant difference in mean T-score finding by DXA between osteoporotic patients and control group figure (3) but this study show that T2DM was not a risk factor for the development of osteoporosis, the P- value shows no significant differences between both samples. Even though the blood sugar was higher in the control group Table (5, 6). Furthermore T2DM with microvascular complications like diabetic retinopathy, peripheral neuropathy and proteinuria were at risk for development of osteoporosis Table (7,8).

Table (1) Personal characteristics of the study sample

Parameters	Cases "Osteoporosis" [n=50]	Control "No osteoporosis" [n=50]	P-Value
Mean age (years)	60.0 ± 6.8	59.4 ± 6.7	0.626
Mean BMI (kg/m^2)	29.6 ± 4.3	31.2 ± 5.9	0.123
Gender	No. (%)	No. (%)	---
Male	10 (20.0)	12 (24.0)	0.629
Female	40 (80.0)	38 (76.0)	
Current smokers	15 (30.0)	7 (14.0)	0.053
History of fractures	17 (34.0)	10 (20.0)	0.115
Family history of fractures	8 (16.0)	3 (6.0)	0.110

Table (2): The effect of gender on the relationship between type II DM and Osteoporosis

Gender	Cases "osteoporosis"		Control "No osteoporosis"		P-value
	No.	%	No.	%	
Female					
T2DM	17	42.5	18	47.4	0.666
No T2DM	23	57.5	20	52.6	------
Total	40	100.0	38	100.0	
Male					
T2DM	4	40.0	5	41.7	0.937
No T2DM	6	60.0	7	58.3	
Total	10	100.0	12	100.0	---

Table (3): The relationship between BMI categories and osteoporosis in the study sampled groups.

BMI categories [kg/m2]	Cases "osteoporosis"		Control "No osteoporosis"		P-value
	No.	%	No.	%	
Normal (18.5-24.99)	5	10.0	7	14.0	10.0
Over weight (25.0-29.99)	24	48.0	20	40.0	48.0
Obese (≥ 30.0)	21	42.0	23	46.0	42.0
Total	50	100.0	50	100.0	100.0

Table (4): The relationship between calcium intake and osteoporosis in the study sampled groups.

Calcium intake	Cases "Osteoporosis"		Control "No osteoporosis"		P-value
	No.	%	No.	%	
No	34	68.0	39	78.0	0.260
Yes	16	32.0	11	22.0	
Total	50	100.0	50	100.0	---

Table (5): The relationship between T2DM and osteoporosis in the study sampled groups.

Risk factor	Cases "Osteoporosis"		Control "No osteoporosis"		P-value
	No.	%	No.	%	
Type II DM	21	42.0	23	46.0	0.687
No type II DM	29	58.0	27	54.0	
Total	50	100.0	50	100.0	---

Table (6):Comparison in blood sugar profile between osteoporotic patients and control group.

Blood sugar profile	Cases "Osteoporosis" Mean ± SD	Control "No osteoporosis" Mean ± SD	P-value
FBS (mg/dl)	121.5 ± 39.8 [n = 50]	158.7 ± 90.6 [n = 50]	0.009
HbA1c (%)	8.4 ± 3.1 [n = 21]	6.7 ± 2.7 [n = 23]	0.055

* Independent T-test of two means was used.

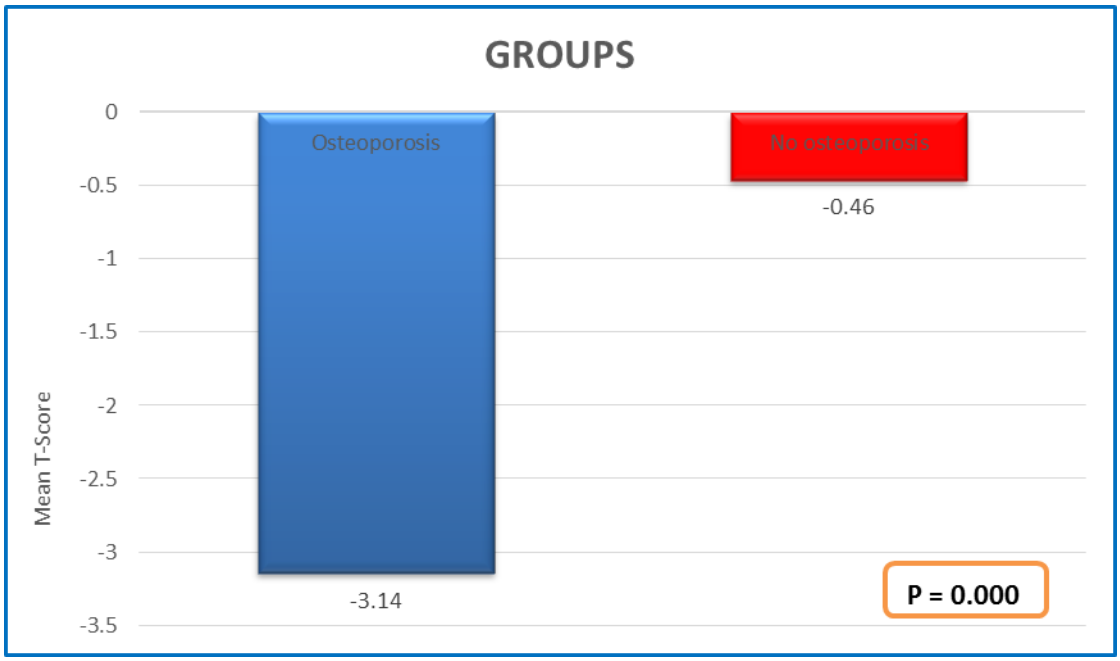


Figure (3) mean T-Score between two groups

Table (7): The relationship between proteinuria and osteoporosis in the study sampled groups.

Proteinuria	Cases "Osteoporosis"		Control "No osteoporosis"		P-value
	No.	%	No.	%	
Yes	9	18.0	3	6.0	0.05
No	41	82.0	47	94.0	
Total	50	100.0	50	100.0	---

Table (8): Comparison in T2DM complications between the two groups.

Complications	Diabetic osteoporosis [n = 21]	Diabetic non-osteoporosis [n = 23]	P-value
	No. (%)	No. (%)	
Retinopathy	11 (52.4)	5 (21.7)	0.035
Peripheral neuropathy	20 (95.2)	14 (60.9)	0.007

There is significant association between presentation with microvascular diabetic complications and development of osteoporosis.

Discussion

In this study which was case control study we tried to determine whether T2DM was risk factors or not for development of osteoporosis in our population. The result showed that there was no significant difference in the bone density with respect to the presence or absence of type II DM ,so T2DM is not a risk factor for osteoporosis, this is consistent with previous study that was done in Mexican American women which found that T2DM did not predispose to osteoporosis because their results showed increase BMD among diabetic patient (22,23).

Meema found in 1967 that T2DM was an anti-osteoporotic condition (24), as Holbrook and Barrett-Connor concluded that females with T2DM had higher BMD level than women with normal glucose tolerance(25).these results were explained by increase in body mass index in T2DM and this may be a protective factor against development of osteoporosis.

In this study there was no significant difference between male and female sex in two groups, this compatible with the study done by Bridges et al in which he assessed BMD in 90 male patient with T2DM and control group ,and he found no significant change in bone mass among diabetic patients.(26). another study was done for elderly T2DM female patients by measuring BMD by DEXA, and they found no evidence had confirmed that T2DM might alter bone metabolism or change in bone mass.(27).

Furthermore , a study carried out in Rotterdam in which they found that both men and women had increased in BMD even women at low risk of non-vertebral fracture, this explained by that women has higher androgen level whom had hyperglycemia which protect against osteoporosis .

In this study smoking does not contribute to the development of osteoporosis whether the patient was diabetic or not . This is against other studies which had showed that cigarette smoking would increase risk of development of osteoporosis in post-menopausal women because smoking decreases estrogen level and predispose

women to early menopause (28). Also, smoking may cause disturbance between bone synthesis and bone turnover(29,30) while another study was carried out in younger age group which found that smoking did not affect BMD(31).this discrepancy in the contribution of smoking for development of osteoporosis may be due to small sample size, age selection is middle age group rather than older people.

There is significant difference in mean T-Score between two groups which was an index to define osteoporosis, but there was no significant difference in blood sugar although the blood sugar was higher in the control group, which acts as a protective factor against development of osteoporosis. This is consistent with the previous study done by, Oz et al, in 2006,he found an relation between T2DM and increased BMD in 52 diabetic women and men aged from 41–64 years in comparison to 48 non-diabetic control patients. His findings concluded that diabetic patients are not at risk of bone resorption. This low bone turnover may decrease the rate of bone loss and cause increase BMD in patient with T2DM.[32].

In contrast to another study at 1997 in which the researcher was assessed BMD before and after strict glycemic control for three weeks in 78 patients who had poorly controlled T2DM and he found that good control of blood sugar decreased bone loss in a short period .[33]

In this study there is no significant difference in BMI between osteoporotic and control group. Increased BMI is protective against osteoporosis. [34]. this is against study in Asian Caucasian women relatively shorter and overweight and low BMI. [35]. Furthermore, another study was done by Seo and Torabi in US adults and they found no effect of overweight in BMD. [36].These conflicting result assumed that there is complex relationship between fat mass and bone mass depending on patient age, gender and ethnicity.[37].

In this study there is significant relation between appearance of microvascular diabetic complication like nephropathy (proteinuria) and presence of osteoporosis this consistent with the result done by Mori, whom concluded that change in the bone remodeling marker like osteocalcin in early stages of diabetic nephropathy which predispose to osteoporosis[38].

Our study show there is significant association between osteoporosis and diabetic retinopathy between two groups this consistent with the result of cross sectional study done in Korean patients which had shown that the presence of retinopathy in diabetic patient would increase the prevalence of osteoporosis because they regarded it as marker for increase fracture risk in diabetic patient because it is microvascular complication of T2DM similar to osteoporosis [39].

In this study there is significant relation between diabetic neuropathy and presence of osteoporosis this is consistent with the result done by Alec T.Beeve and J.M. Brazill in which they found that increased bone turn over in patient with diabetic neuropathy probably due to that the peripheral nervous system has directly regulate bone metabolism via local neurotransmitter and indirectly via neuroregulation of the vascular supply of skeleton.,[40],[41].

Conclusion

We have found that T2DM is not a risk factor for osteoporosis unless there is Microvascular diabetic complications particularly diabetic retinopathy and or nephropathy which are associated with increased risk of osteoporosis.

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