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Assessment of Bone Mass Density in Type 2 Diabetic Patients in Zagazig University Hospitals.

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Abstract

Background:*Diabetes is associated with increased risk of fracture, although type 2 diabetes is often characterized by normal or high bone mineral density (BMD). Thus, diabetes may be associated with a reduction of bone strength that is not reflected in the measurement of BMD. The study aimed to measure and asses the bone mass density in type 2 diabetic patients using DEXA scan densitometer.****Methods:****This case control study were carried out on atotal number of ninty 90 participiants attending outpatient clinics of endocrinology units of internal medicine department at Zagazig University Hospitals. Participants were divided into two main groups: Group I: 30 healthy individual without diabetes mellitus "control group". Group2: 60 type 2 diabetic patients "case group". All subjects included in this study were subjected to the following: Full history taking and clinical examination including assessment of BMI.Special investigations: measurments of BMD using DEXA scan ;T score (the number of standard deviations above or below the mean for a healthy 30-yrs-old adult of the same sex and ethinicity as the patient).Measured areal density in G/CM^2..****Results:****there was statistically significant difference between non-diabetic and diabetic groups regarding BMI. We reported a non statistically significant difference regarding age , sex. We noticed a statistically significant decreasment of BMD parameters for diabetics compared to non diabetic subjects. When we compared various patient groups we noticed about 38.3 % of diabetic patients had abnormal BMD. Factors correlated with abnormal BMD were either non-modifiable as duration of diabetes and menopause or non-modifiable as hyperglycemioa, hypocalcemia and hypophosphatemia. **Conclusion:** T2DM negatively affect the bone strength through affection of BMD.*

Key words: bone mass density- type 2 diabetic patients- DEXA scan densitometer- Evaluation-

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I. Introduction:

With population growth and aging, economic *d*evelopment, and the increasing prevalence of obesity and physical inactivity; it is estimated that the total number of people with Diabetes mellitus will be more than double 171 million in 2000 to 366 million in 2030 [(1)].

Fifty years since it was demonstrated, that diabetes is associated with loss of bone mass. It has been more than 50 years and since that time, the relationship between osteopenia and type 1 diabetes has become well established, while the effects of type 2 diabetes on bone metabolism have challenged. [(2)]

Diabetes is associated with increased risk of fracture, although type 2 diabetes is often characterized by normal or high bone mineral density (BMD). Thus, diabetes may be associated with a reduction of bone strength that is not reflected in the measurement of BMD. [(3)]

The important determinants of bone strength are bone mineral density, structural properties, and tissue material quality. Bone is composed of a 2-phase composite material. Hence, the mineral composition contributes to stiffness. In contrast, collagen fibers provide the intrinsic material properties such as tensile strength, ductility and toughness. Material property of bone is regulated by not only tissue turnover rate, but also the cellular activity and the levels of oxidative stress and glycation. [(4)]

Collagen enzymatic and nonenzymatic cross-linking affect primary mineralization process and bone mechanical properties. Impaired enzymatic cross-linking and/or an excessive formation of nonenzymatic cross-links, pentosidine (Pen), which is a surrogate marker of advanced glycation end products (AGEs), may be a major cause of bone fragility in aging, osteoporosis, and diabetes mellitus. [(5)]

Interpretation of fracture data as a surrogate measure for bone metabolism is particularly difficult in patients with long-standing diabetes, because visual and neurologic complications can predispose patients to accidents resulting in an increased fracture risk not necessarily dependent on bone density alone. Other factors that make studies difficult to interpret include the presence of diabetic renal disease, autonomic and other neuropathic changes that could contribute to a loss of bone mineral, and a low level of physical activity related to diabetic complications. Also, women with diabetes are much less likely to be on estrogen replacement therapy. [(6)]

The relationship between bone mineral density (BMD) and type 2 diabetes mellitus (T2DM) has been controversial. In some studies, patients with T2DM showed no significant difference either in BMD or prevalence of osteoporosis from non-diabetic patients, while others have demonstrated either higher BMD in patients with T2DM compared to nondiabetics.[(7)]

Due to the different pathogenesis of type 1 and type 2 diabetes mellitus (T2DM), it is not surprising that there is no uniform entity of diabetic bone disease as such. While decreased bone mineral density (BMD) has consistently been observed in type 1 diabetes mellitus patients, studies on BMD investigated in T2DM showed contradictory results with higher, lower or similar values in comparison with healthy control subjects. [(8)]The study aimed to measure and asses the bone mass density in type 2 diabetic patients either males or females, also studying other factors that may affect BMD like menopause and gender using DEXA scan densitometer.

II. Patients and Methods

This study was **carried out** at Internal Medicine and radiology departments, Faculty of Medicine, Zagazig University in the period between june 2018 and December 2019.

It **included a total number of 90 individual** classified according to presence or absence of diabetes into

◙**Group 1**: it included 30 healthy individual they were further subdivided according to sex into:

●**Group 1 a** : male control group composed of ten (10) males with average age of 51.8±3.25 SD.

●**Group 1 b** : female control composed of twenty (20) diabetic patient further subdivided according to menstrual cycle into

1) Ten premenopausal female control group with average age of 44.25±4.52 SD .
2) Ten postmenopausal female control group with average of 54.98±5.3 SD .

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◙**Group 2:** it included sixty (60) diabetic patient diagnosed according to ADA 2018 guidelines for diagnosis of diabetes [(9)], they were further subdivided according to sex into:

◙**Group 2 a** : male diabetic group composed of 20 males with average age of 56.4±6.25 .

◙**Group 2 b** : female diabetics composed of 40 diabetic patient further subdivided according to menstrual cycle into

1) Twenty premenopausal female diabetic group with average age of 44.2±4.52 SD.
2) Twenty postmenopausal female diabetic group with average age of 56.25±5.21 SD.

They were recruited from outpatient clinics of endocrinology units of internal medicine department, their age ranged from 40 to 75 years with mean standard deviation value of (50±10 yr), the disease duration ranged from 5 - 20 years.

The study had the **approval** of the Institutional Review Board (IRB) at Zagazig University.

Sample size: Assuming that prevelance of osteopenia in type two diabetic patients is 60 %, in controls is 20 %. Confidence level 95 %, power 80 %. So total sample size is 90 divided to 6 subgroups calculated by open Epi.

Concent: Informed written consent was taken after explaining the study purpose, method and benefits to the patients.

- **Inclusion criteria:**
- Type two diabetic patients for more than two years.
- No history of pathological fractures.
- Age more than 40 years.
- Serum calcium and phosphorus within normal.

- **Exclusion criteria :**

- Newly diagnosed diabetes,
- History of pathological fracture.
- These with age less than 40 years.
- Past history of parathyroid problems and malignancies.
- Serum calcium and phosphorus below normal.
- End stage renal disease and anemic patients.
- Liver cell failure.
- Patient on hormonal replacement therapy and drugs affecting bone metabolism like corticosteroids.
- Disease affecting bone metabolism (Cushing, inflammatory bowel disease, malabsorption syndrome, primary hyper parathyroidism).
- Obesity and metabolic syndrome.

All participiants will be subjected to:

- Full history taking including:

- Personal history (name, gender and age).
- Presnt history including onset, course, duration and ttt of type 2DM.
- Past history of systemic diseases especially those affecting bone (egRenal,rheumatological,malignancies, osteoporosis and pathological fractures etc).
- Drug history with bone metabolism affecting drugslike corticosteroids, vitamin D supplements, biphospnonates, diuretics ,anticoagulants,antiepileptic ,hormonal, chemotherapies, etc)
- General examination body built, BP, Temp, diabetic complications as foot etc.
- Calculation of body mass index (BMI)(Kg/m^2).
- Routine laboratory investigations
- FBS,RBS,PPBS and HBA1C.
- Complete blood count.
- Liver function tests.
- Kidney function tests.
- S Calcium & S Phosphorus.
- Special investigations:

Measurments of BMD OF Both Right Proximal Femur and lumbar spine using DEXA scan densimeter;

- T score (the number of standard deviations above or below the mean for a healthy 30-yrs-old adult of the same sex and ethinicity as the patient).
- Measured areal density in G/CM^2.

Assessment of anthropometric data:

Anthropometric measurements including weight, height and waist measurements were obtained using standardized techniques. a) Height was measured with a tape to the nearest centimeter. Subjects were requested to stand upright without shoes with their back against the wall, heels together, and eyes directed forward.

b) Weight was measured with a traditional spring balance that was kept on a firm horizontal surface. The subjects were asked to stand erect in a relaxed position with both feet together on a flat surface; one layer of clothing was accepted. Subjects were asked to wear light clothing, and weight was recorded to the nearest 0.5 Kg.

c) Body mass index (BMI) was calculated by using the formula: weight (Kg / height (m^2)

1-Complete blood picture: By automated blood counter**.**

Technique **;** Skin was rubbed with antiseptic and 1 cm of blood was taken by alancet to puncture the skin and make it bleed.blood was collected in attest tube containing 20 mcg EDETA and analyzed as soon as possible using Sysmexxf 500 cell counter for red blood cell count ,hemoglobin level,hematocrite value ,white blood cell count and platelet count. Results of CBC were interpreted using Hematological scoring system.

2-Glycated Hemoglobin A1c (HbA1c) estimation:

Principle: measurement of glycated hemoglobin by using high performance liquid chromatography (HPLC) done according to method of Glycated hemoglobin analysis was performed using Bio-Rad D-10 HbA1c Testing System with anormal reference range (less than or equal 5.7%). The HbA1C determination is based on the turbid metric inhibition immunoassay (T1N1A) for hemolyzed whole blood

Test principle: this method uses TTAB (tetra decyltrimethyl ammonium bromide) as the detergent in the hemolyzing reagent to eliminate interferences from leucoctes (TTAB doesn't lyses leukocytes). All hemoglobin variants which are glycated at the ß-chain N-terminus and which have antibody recognizable regions identical to that of HbA1C are measured by the assay.

3- Serum creatinine and urea bycolorometric method

The normal S creat range is 0.6 -1.1 g/dl in women and 0.7-1.3 mg/dl in men

4-Serum albumin by colorimetric method by using spectrophotometer with anormal range between 32-45 g/L

5-S calcium and phosphorus estimated by colorimetric technique of diffuse gradients in thin films were systematically evaluatedwith anormal ranges of S ca 8.5-10.2mg/dl and phosphorus

DEXA scan measurments:DEXA scan (dual-energy X-ray absorpio-metry); body mass density measurements

done on the lumbar spine (L1 – L4) and right proximal femur.

The body mass density data are presented in areal bone density g/cm^2 and standard deviation scores (Z and T scores).

Two x-ray energies are used to estimate the area of mineralized tissue, and the mineral content is divided by the area, which partially corrects for body size and the results was estimated using the T and Z score ;

T score:

- more than -1 >> normal
- Between – 1 and – 2.5 were considered to indicate osteopenia.
- Equal or below – 2.5 were considered to indicate osteoporosis.

◙ DEXA technique exam preparatian:

- The examination requires little to no special preparation.
- All Child bearing women are asked about if they are pregnant or any possibility that she will get pregnant sooner "missed period" and if they are excluded.
- All patients are asked to remove any jewelry or any metalic subjects that may interfere with the x ray images.
- They are asked to wear loose and comfortable clothes.

We used the central DEXA device in radiology center in ZagazigUniversity and measured bone density in the hip and spine.

The patient lies on the DEXA machine table on his back:

When we examine the spine, the patients legs are supported on a padded box to flatten the pelvis and lumbar spine, to assess the hip the patients foot is placed on brace that rotate the hip inward.

In both cases, the detector is slowly passed over the area,generating images on acomputer screen.

The patient is asked to keep from breathing for a few seconds while the x-ray picture is taken to reduce the possibility of a blurred image.

The DEXA bone density test is usually completed within 10 to 30 minutes, depending on the equipment used and parts of the body being examined.

The computer will analyze the images.

Methods :

◙Statistical methodology :

◙ Statistical analysis

Results were collected, tabulated, statistically analyzed by SPSS (statistical package for social science) version 18 on IBM personal computer**.**

Two types of statistics were done

1- Descriptive: e.g. percentage (%), mean and standard deviation SD.

SD = $\sqrt{\frac{\sum\left(x-\bar{x}\right)^2}{n-1}}$

a) **Standard deviation** $\sum\left(x-\bar{x}\right)^2$ is the sum of the square of the differences of each observation from the mean .

b) Mean $\bar{x}$ **=** $\sum x$ **/ n**

$\sum x$ is the sum of the values .

nis the number of subjects.

2- Analytical: -

a)ANOVA (F test): A one-way analysis of variance (ANOVA) is a single test used to collectively indicate the presence of any significant difference between several groups for a normally distributed quantitative variable.

b)Chi-Squared (χ2): It is used to compare between two groups or more regarding one qualitative variable in 2x2 contingency table or r c complex table.

$$x^2 = \sum \frac{(O-E)^2}{E}$$

Where O : The observed value .

E : The expected value .

P value :

- Significant difference if P <0.05
- Non-significant difference if P > 0.05.
- Highly significant difference if P < 0.001

III. Results:

– **Table (1)** shows that there was statistically high significant difference between the two groups regarding BMI , However there was no significant difference between the two groups regarding age and sex .

– **Table (2)** shows that the mean values of T Score (of both RT proximal femur and lumbar spine) of diabetic patients were significantly lower than that of the control group with statistically high significant difference between the two groups(p value <0.03)., Also mean values of areal BMD G/CM2(of both neck femur and lumbar spine) of diabetic patient group were significantly lower than those of the control group (P value<0.04) .

– **Table (3)** shows the bone density status distribution among the studied groups, the control group which included 30 individuals ; 25 individual (83.35%) of them were normal , four (13.3%) were osteopenic and only one individual was osteoporotic (3.3%) . While diabetic group which included 60 patients ; 37 patient (61.6%) of them were normal ,13 (21.6%) were osteopenic and 10 (16.7%) were osteoporotic and so the percentage of abnormal bone density was higher among the case group but didn't achieve statistically significant difference between the two groups.

– **Table (4)** showsthat among all subjects; log of both BMD parameters T score & G/CM^2 of both RT proximal femur and lumbar spine were highly significantly negatively correlated with log all glycemic control parameters (FBS PPBS RBS and HbA1C), Also negativly significantly correlated with Duration of DM (Y). But positively significantly correlated with serum calcium and phosphorus. And not significantly correlated with (Age, BMI, CBC, S Creat, Urea and albumin)

Table (1) shows comparison between the two main groups all Non-diabetic control group and all diabetic case group according to demographic and clinical data.

		All Non-diabetic Control group	All Diabetic case group	Test of significance f	P-value
		No. = 30	No. = 60		
Age (year)	**Mean ± SD**	53.52 ± 9.88	55.28 ± 10.25	1.582	NS
	Range	41 – 68	42 – 70		
Sex	**Female**	20 (66.6%)	40 (66.6 %)	3.395	NS
	Male	10 (33.3%)	20 (33.3 %)		
BMI (KG/M2)	**Mean ± SD**	26.60 ± 2.081	27.92 ± 3.378	2.067	0.042*
	Range	21.5 – 28.5	23.1 – 32		

χ2=C vhi-square test. **T**=independent Student t-test.

No=number. **SD**=standard deviation. **DM**: diabetes mellitus. **BMI**=body mass index.

Table (2) comparison of mean values±SD of BMD parameters using DEXA scan between all control group and all diabetic case group.

DEXA results		All Non-diabetic control group	All Diabetic case group	Test of significance f	P-value
		No. = 30	No. = 60		
T score of RT proximal femur	Mean ± SD	-0.827 ± 0.282	- 1.376 ± 0.428	2.931	<0.03
T score of Lumbar spine		-0.813 ± 0.312	-1.393 ± 0.394	2.563	<0.02
BMD G/cm2 of RT proximal femur	Mean ± SD	0.924 ± 0.28	0.75 ± 0.24	4.87	<0.04
BMD G/CM2 of lumbar spine		0.853 ± 0.35	0.69 ± 0.32	4.98	<0.04

Table (3) Results of DEXA scan among the whole Control and whole Diabetics .

DEXA results		All Non-diabetic Control group	All Diabetic case group	X^2	Pvalue
		No. = 30	No. = 60		
NORMAL	NO	25	37	5.11	NS
	Percentage	83.3%	61.7%		
OSTEOPENIC	NO	4	13		
	Percentage	13.3%	21.6%		
OSTEOPOROTIC	NO	1	10		

	percentage	3.3%	16.7%		

Table (4): Shows correlation between log BMD and other measured laboratory parameters in all subjects .

Parameter of all (90) subject		DEXA **T score of RT proximal femur**	**DEXA T score of AP vertebral spine**	**BMD G/CM^2 of RT proximal femur**	**BMD of AP vertebral spine L 1-4**
Age	**R**	0.044	0.038	0.051	0.047
	Pvalue	NS	NS	NS	NS
Duration of dm	**R**	0.256	0.249	0.228	0.235
	P	<0.05*	<0.05*	<0.05*	<0.05*
BMI (KG/M2)	**R**	0.045	0.052	0.043	0.049
	P	NS	NS	NS	NS
FBS	**R**	0.489	0.478	0.635	0.629
	P	<0.005*	<0.005*	<0.005*	<0.005
RBS	**R**	0.666	0.670	0.688	0.664
	P	<0.005*	<0.005*	<0.005*	<0.005*
PPBS	**R**	0.567	0.583	0.585	0.597
	P	<0.005*	<0.005*	0.005*	<0.005*
HBA1C	**R**	0.495	0.50	0.489	0.479
	P	<0.005*	<0.005*	<0.005*	<0.005*
HGB	**R**	0.042	0.045	0.063	0.057
	P	NS	NS	NS	NS
PLT	**R**	0.057	0.064	0.048	0.056

	P	NS	NS	NS	NS
WBC	**R**	0.496	0.510	0.531	0.489
	P	NS	NS	NS	NS
ALBUMIN	**R**	0.087	0.081	0.07	0.078
	P	NS	NS	NS	NS
CREATININE	**R**	0.254	0.252	0.263	0.245
	P	NS	NS	NS	NS
UREA	**R**	0.124	0.127	0.130	0.126
	P	NS	NS	NS	NS
CALCIUM	**R**	0.667	0.658	0.678	0.683
	P	<0.005*	<0.005*	<0.005	<0.005*
PHOSPHORUS	**R**	0.653	0.663	0.668	0.672
	P	<0.005*	<0.005*	<0.005	<0.005*

Table (5) Illustrate the prevalence & distribution of normal and abnormal BMD among all cases in our study.

Diabetic group n = 60 (100%)					
Normal BMD n=37 (61.6%)			Abnormal BMD n=23 (38.4%)		
Males	Premenopausal	Postmenopausal	Males	Premenopausal	Postmenopausal
17 (28.3%)	13 (21.6 %)	7 (11.6 %)	3 (5%)	7 (11.6 %)	13 (21.6%)
NON-Diabetic group n = 30 (100%)					
Normal BMD n=25 (83.6%)			Abnormal BMD n=5 (16.7%)		

Males	Premenopausal	Postmenopausal	Males	Premenopausal	Postmenopausal
10 (33.3%)	8 (26.6 %)	7 (23.3 %)	0 (0 %)	2 (6.6 %)	3 (10.0%)

IV. Discussion

In the present study we compared the BMD parameters (T Score and Areal BMD G/CM^2 values) of both right neck femur ''HIP'' and lumbar vertebral spine, between whole type 2 diabetic patients and whole non-diabetic control subject ,that showed a high statistically significant decreasment of both mean values ±SD of BMD parameters of "neck femur and spine" among diabetic case group and non statistically significant increase in the number of osteopenic and osteoporotic cases among them.

Our results were in aggrement with **Yaturuet al.** [(10)]study of Diabetes and skeletal health that showed decreasment of mean values of BMD parameters of hip in men with type 2 DM, also incidence of osteoporosis was significantly higher among diabetic subjects compared with age and body mass index matched non diabetic subjects. But in contrast to our study the BMD of AP spine was significantly higher in diabetic subjects compared with non diabetic mostly due to fifference in the mean values of BMI as it showed similar density when subjects were matched for BMI.

Similar to our study results, according to **Wangand Pei,**[(11)] study of Correlation of BMD with disease duration and body mass index in elderly men with type 2 diabetes mellitus, it showed also decreasment of mean values of BMD parameters among type 2 diabetic patients, showed also negative correlation of BMD parameters with disease " type 2 DM" duration.

Also **Saneshige**[(12)] study of Spinal bone mineral density in the female diabetic patients showed decreasment of BMD among diabetic females.

These results of decreasing BMD parameter among type 2 diabetic patients may be proven and explained by the following theories ;

Higher glucose levels in the blood interact with several proteins to generate a higher concentration of advanced glycation end-products (AGEs) , these AGEs in collagen may interact with bone to reduce bone strength, resulting in osteoporosis in patients with diabetes, Accumulated AGEs in the bone may stimulate apoptosis of osteoblasts, thereby contributing to the defective bone formation [(13)].

Also, one of the indirect effect of hyperglycemia on BMD is glycosuria, which cause hypercalciuria, leading to decreased levels of calcium in the body and poor bone quality, thus hastening bone loss [(14)], our study also showed statistically significant decrease in serum calcium among diabetic cases,and this may support this theory.

Low levels of Vitamin D and altered Vitamin D metabolism in patients with diabetic osteopenia was docunented by weintroub study at 1980 [(15) & (16)] .

Microvascular complications of diabetes lead to reduced blood flow to bone and may contribute to bone loss and fragility. [(17) & (18)] .

Increased oxidative stress in diabetic patients have detrimental effect on osteoblast and may contribute to diabetic osteopenia**.**[19]

Deficiency in anabolic activation of insulin in patients with long term diabetes may also contribute to diabetic osteopenia[20]**.**

Suppression of osteoblastic bone formation proven by histo- pathologic examination study of type 2 DM patients had shown that the osteoblast surface, cortical thickness, osteoid thickness, osteoid volume, and bone volume have been found to be lower in diabetic patients than normal subjects [21] , this was attributed to the decreasment of quantitative osteoid, osteoblasts, and finally the bone cycle speed . [22]

The bone cycle speed in type 2 DM is much slower than that in healthy patients.[23]

Chronic hyperglycaemia decreases estradiol synthesis by causing ovarian damage, Estradiol has a direct stimulatory effect on osteoblasts, and this may contribute to osteoporosis. [24]

Anti-hyperglycaemic medications like TZDs " Glitazones" , SGLT2 inhibitors have adverse effect on BMD and increase fracture risk for unclear causes [25] [26] [27]. one of them may be due to increasing of bone marrow fat content observed with pioglitazone users, TZDs activate PPAR receptors which has a negative effect on bone remodeling ,SGLT2 inhibitors increase bone turnover ,disrupt bone architecture, decrease BMD due to disturbed calcium and phosphate hemostasis through increasing urinary calcium loss ,another mechanism also is weight loss and so low BMI and low BMD [28; 29]**.**

BMD is positively associated with physical activity through increasing mechanical loading. patient with metabolic syndrome like type 2 diabetics have lower physical activity and so that have lower BMD**.** [8]

Interestingly, some other studies had shown different results to our study as increasing in BMD parameters among type 2 diabetic patients, like **Barrett-Connor** [30] study of Sex differences in osteoporosis in older adults with type 2 DM showed an increase in BMD among diabetics.

On the countrary to our results and according to **Sumesh et al.**[31]study of association between BMD and T2DM , it shows a significantly higher increase in the BMD among diabetic patients than non diabetics of both sex in different sites and showed a positive correlation of young age, male sex, higher body mass index and higher HbA1c with higher BMD in diabetic patients.

Also **Hertfordshire** Cohort Study showed that Type 2 diabetic patients have increased axial bone density in men and women . [32]

And also **sahin et al.,** [33]study of Lumbar and femoral BMD in type 2 Turkish diabetic patients showed higher BMD in patient with type 2 DM with non insulin treatment when compared with normal subjects and osteoporosis can not be considered as a complication of type 2 DM

Those who reported results against our finding were attributing their results to different reasons that may explain their opinion of increasing BMD in type 2 diabetic patients,

Higher body fat percentage in type 2 DM and factors like adipocy-tokines and increased estrogen levels have been proposed as possible reasons for increasing BMD**.** [34] ,However with time chronic hyperglycaemia decreases estradiol synthesis by causing ovarian damage as previously shown.

Overweight and hyperinsulinemia have been postulated as two important features of T2DM which are positively correlated with BMD. there are several complex pathways by which obesity may influence the relation between diabetes and BMD, adipose tissue releases a wide variety of adipokines that have been implicated either directly or indirectly in the regulation of bone remodeling [(35)],Plasma leptin concentrations have been shown to be higher in diabetic men than in healthy controls [(36)] ,and last on leptin induces bone growth by stimulating osteoblast proliferation and differentiation. [(37)]

However this hypothesis may not be so accurate as it is possible that the apparent inverse relationship between changes in BMD and body weight is related, at least in part, to technical limitations of DEXA technology, as the degree of DEXA artifact is related to the extraosseous soft tissue composition so that BMD will appear to decrease more slowly in subjects with more soft tissue fat and vice versa [(38)].

Also these increase of BMD in type 2 diabetic patients may be a result of limitation of the DEXA technique quality itself and not an true decrease, like as that the patients who presented higher bone density in the lumbar spine may be to have aortic calcification - this is common among diabetics- that may give false results and so they should be submitted to radiographic evaluation of this region in order to exclude the occurrence of these calcification**.** Hyper- insulinemia, Insulin levels could mediate in part a positive association between T2DM and elevated BMD through increasing osteoblastic activity. Individuals with T2DM usually have an excess of insulin (Physiologically, insulin has an anabolic effect on bone [(39)] due to its structural homology to IGF-1 by interacting with the IGF-1 receptor which is present on osteoblasts. The IGF-1 signaling pathway is crucial for bone acquisition. [(40)]**,** however with progression of diabetes insulin deficiency also occurred due to toxic effect of hyperglycemia on the pancreas.

Medication more time used in type 2 diabetic patients as metformin through its action on AMPK pathway has a direct osteogenic effects on bone and shift progenirator cells into osteoblasts [(41)], thiazide through increasing serum calcium and statins through increasing 25 OH_2vit D level [(42)] may be associated with higher BMD at different skeletal sites. [(43)]

Our study does not confirm the results of previous studies that reported BMD values in type 2 diabetic similar to control subjects like **Sosa et al.** [(44)] study that showed normal Bone mineral metabolism in non-insulin-dependent diabetes mellitus, **Atanu Kumar Thakur** [(45)] study of Estimation of bone mineral density among type 2 diabetes mellitus patients in western Odisha**,** and **Athulyaet al.**[(46)] Evaluation study of bone mineral density among type 2 diabetes mellitus patients in South Karnataka that showed no significant difference in BMD between control and diabetics however the incidence of osteoporosis was higher among the diabetics .

However, all the mentioned studies were agreed on the increased fracture risk among diabetic patients [(47)]and so assessment of BMD alone in diabetic patient doesn't necessary reflect exactly the bone status and more advanced investigations are needed.

The percentage of abnormal mineral density was 38.4 % in diabetics while was 16.7 % in non-diabetics with the highest percentage were among the postmenopausal category of both groups 21.6% in the diabetic and 10% in the non-diabetics.

Women lose about 50% of their trabecular bone and 30% of their cortical bone during the course of their lifetime, about half of which is lost during the first 10yr after the menopause, approximately 40% of post-menopausal women will eventually experience fractures. **(48; 49)**

That is also in aggrement with the SWAN study "The Study of Women's Health Across the Nation" is a seven-center, longitudinal cohort study of the menopause transition in a community-based sample of women from multiple ethnic groups. BMD of the lumbar spine and proximal femur has been measured annually in women at five SWAN sites and had shown that BMD changes little during the pre- or early perimenopause but then begins to decline substantially during the late perimenopause.

BMD continues to decline rapidly during the early postmenopausal years.The annual rates of loss during these intervals were approximately 1.8–2.3% in the spine and 1.0–1.4% in the hip**(50).** If bone loss were to continue at these rates for 5 yr, the average woman's BMD would decline 7–10% in the spine and 5–7% in the hip, amounts that are associated with approximately 50–100% higher fracture rates **(51).**

V. Conclusion:

T2DM negatively affect the bone strength through affection of BMD.

References:

1. **Wild S, Gojka R, Anders G.**Global prevalence of diabetes;estimate for the year 2000 and projection for 2030.Diabetes care .2004 oct ;27(10);2568-9.
2. **NicodekmusKc and Folsom AR.** Type 1 and type 2 diabetes and incidence of hip fracture in postmenopausal women.Diabetes care 2001, 24;1192-1197.
3. **Vestergaard P.** Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes: A meta-analysis. OsteoporosInt 2007; 18: 427-44.
4. **Burr David** Bone quality. J musculoskeletal neuronal interact 2004 4(2);184-186.
5. **Satio M and Marumo K.** Collagen cross-links as adeterminant of bone quality ,apossible explanation for bone fragility in aging ,osteoporosis Osteoporosint .2010 Feb ;21(2) 195-214.
6. **IversRQ,CummingRG,Mitccell P** Diabetes and risk of fracture The Blue Mountain Eye Study.Diabetes care 2001 Jul;24(7);1198-203.
7. **Al-zaabiKhaled, Hanan E et al.** Bone mass density in diabetic women is there a detrimental effect.middle east journal of Age and Ageing 2008;volume 3,issue 2.
8. **Yaturu S, Humphrey S, Landry C, Jain SK.** Decreased bone mineral density in men with metabolic syndrome alone and with type 2 diabetes. Med SciMonit 2009; 15(1): CR5-9.
9. **American Diabetes Association.** Standards of Medical Care in Diabetes 2018; 41(Suppl. 1).
10. **Yaturu S, Bryant B, Jain SK.** Thiazolidinedione treatment decreases bone mineral density in type 2 diabetic men. Diabetes Care. 2007 Jun;30(6):1574-6.
11. **Wang XR, Pei Y.** Correlation of bone mineral density with disease duration and body mass in elderly men with type 2 diabetes mellitus J Clin Rehab Tissue Eng Res. 2008;15:2891–2894.

12. **Saneshige S:** [Spinal bone mineral density in the female diabetic patients]. Nippon Ronen IgakkaiZasshi, 1992, 29: 864–873.
13. **Yamagishi S, Nakamura K, Inoue H.** Possible participation of advanced glycation end products in the pathogenesis of osteoporosis in diabetic patients. Med Hypotheses. 2005;65:1013.
14. **Ishida H, Lau J, Hu FB, Dawson-Hughes B.** The role of Vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. J ClinEndocrinolMetab. 2007;92:2017–29.
15. **Wientroub S, Eisenberg D, Tardiman R, Weissman SL, Salama R.** Is diabetic osteoporosis due to microangiopathy? Lancet. 1980;2:983**.**
16. **Vogt MT, Cauley JA, Kuller LH, Nevitt MC.** Bone mineral density and blood flow to the lower extremities: The study of osteoporotic fractures. J Bone Miner Res. 1997;12:283–9.
17. **Kao WH, Kammerer CM, Schneider JL, Bauer RL, Mitchell BD.** Type 2 diabetes is associated with increased bone mineral density in Mexican-American women. Arch Med Res. 2003;34:399–406.
18. **Bonjour JP, Chevalley T, Rizzoli R, Ferrari S.** Gene-environment interactions in the skeletal response to nutrition and exercise during growth. Med Sport Sci. 2007;51:64–80.
19. **Hamada Y, Fuji HA, Fukazawa M.** Role of oxidative stress in diabetic bone disorder. Bone. 2009;45:S35–S38.
20. **Kocián J, Brunová J:** Diabetic osteopathy. VnitrLek, 1990, 36: 460–466
21. **Takizawa M, Kameyama K, Maruyama M, et al** [Bone loss in type 2 diabetes mellitus -diabetic osteopenia]. Nihon Rinsho, 2003, 61: 287–291.
22. **Leite Duarte ME, da Silva RD.**Histomorphometric analysis of the bone tissue in patients with non-insulin-dependent diabetes (DMNID). Rev HospClinFac Med Sao Paulo 1996; 51: 7–11.
23. **Akin O, Gol K, Akturk M et al. (2003):** Evaluation of bone turnover in postmenopausal patients with type 2 diabetes mellitus using biochemical markers and bone mineral density measurements. GynecolEndocrinol., 17(1):19-29.
24. **Luan X, Jin Z, Ouyang J.** Changes in sexual hormones and bone metabolism disorder in postmenopausal NIDDM patients]. J Tongji Med Univ 1996; 16: 217–233.
25. **Meier C, Kraenzlin ME, Bodmer M, Jick SS, Meier CR.** Use of thiazolidinediones and fracture risk. Arch Inter Med. 2008;168:820–825.
26. **Kahn SE, Zinman B, Lachin JM.** Rosiglitazone-associated fractures in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT) Diabetes Care. 2008;5:845–851.
27. **Zinman B, Haffner SM, Herman WH.** Effect of rosiglitazone, metformin, and glyburide on bone biomarkers in patients with type 2 diabetes. J ClinEndocrinolMetab. 2010;95:134–142.
28. **Zibellini j.,Seimon R et al.** Does diet-induced weight loss lead to bone loss in overweight or obese adult J.BoneMiner. Res 30 2168-2178.10.
29. **Ye Y, Zhao C, Liang J, Yang Y, Yu M, Qu X**. Effect of Sodium-Glucose Co-transporter 2 Inhibitors on Bone Metabolism and Fracture Risk. Front Pharmacol. 2019 Jan 8;9:1517.
30. **Barrett-Connor E, Holbrook TL**. Sex differences in osteoporosis in older adults with non-insulin-dependent diabetes mellitus. JAMA. 1992;268:3333–7.
31. **SumeshRaj ,Baiju S J,** Rajesh Vijayan and G.V. Rajan Trivandrum, . India .Britsh journal of research 2018.

32. **Dennison EM, Syddall HE, AihieSayer A, Craighead S, Phillips DI, Cooper C.** Type 2 diabetes mellitus is associated with increased axial bone density in men and women from the Hertfordshire Cohort Study: evidence for an indirect effect of insulin resistance? Diabetologia. 2004;47:1963–1968.
33. **Sahin G, Bağis S, Cimen OB, et al.:** Lumbar and femoral bone mineral density in type 2 Turkish diabetic patients. Acta Med (Hradec Kralove), 2001, 44: 141–143.
34. **Mastrandrea L. D., J. Wende, R. P. Donahue, K. M. Hovey, A. Clark, and T. Quattrin,** "Young women with type 1 diabetes have lower bone mineral density that persists over time," Diabetes Care, vol. 31, no. 9, pp. 1729–1735, 2008.
35. **Reid IR.** Relationships between fat and bone. Osteoporos Int. 2008; 19(5):595– 606.
36. **Kanabrocki EL, Hermida RC, Wright M, et al.** Circadian variation of serum leptin in healthy and diabetic men. Chronobiol Int. 2001; 18(2):273–283.
37. **Hamrick MW, Della-Fera MA, Choi YH, Pennington C, Hartzell D, Baile CA.** Leptin treatment induces loss of bone marrow adipocytes and increases bone formation in leptin-deficientmice. JBone Miner Res. 2005 ; 20(6) :994– 1001.
38. **Bolotin HH, Sievänen H, Grashuis JLJ** Bone Miner Res. Patient-specific DXA bone mineral density inaccuracies: quantitative effects of nonuniformextraosseous fat distributions.2003 Jun; 18(6):1020-7.
39. **Pun KK, Lau P, Ho PW.** The characterization, regulation, and function of insulin receptors on osteoblast-like clonal osteosarcoma cell line. J Bone Miner Res. 1989; 4 (2692404): 853–862.
40. **Kawai M, Rosen CJ.** Insulin-like growth factor-I and bone: lessons from mice and men. PediatrNephrol. 2009; 24 (7): 1277–1285.
41. **Molinuevo M.S., L. Schurman, A.D. McCarthy, A.M. Cortizo, M.J. Tolosa, M.V. Gangoiti, V. Arnol, C.** Sedlinsky Effect of metformin on bone marrow progenitor cell differentiation: in vivo and in vitro studies J J. Bone. Miner. Res., 25 (2) (2010), pp. 211-221.
42. **Hatzigeorgiou C, Jackson JL.**Hydroxymethylglutaryl-coenzyme Areductase inhibitors and osteoporosis: a meta-analysis. Osteoporos Int. 2005 Aug;16(8):990-8.
43. **Wasnich RD, Benfante RJ, Yano K, Heilbrun L, Vogel JM.** Thiazide effect onbone mineral density, and fracture risk **:**Med. 1983; 309 (6): 344–347. Geelong Osteoporosis Study.
44. **Sosa M, Dominguez M, Navarro MC, Segarra MC, Hernández D, de Pablos P** Bone mineral metabolism is normal in non-insulin-dependent diabetes mellitus**.** J Diabetes Complications. 1996;10:201–5
45. **Atanu Kumar Thakur, SatarupaDash** International Journal of Research in Medical Sciences Thakur AK. Int J Res Med Sci. 2018 Feb;6(2):459-464
46. **Athulya G. Asokan, JayakumarJaganathan, Rajeev Philip, RinoRoopakSoman,Shibu Thomas Sebastian,andFawazPullishery**; Evaluation of bone mineral density among type 2 diabetes mellitus patients in South KarnatakaJ Nat SciBiol Med. 2017 Jan-Jun; 8(1): 94–98.
47. **Vestergaard P, Rejnmark L, Mosekilde L.** Relative fracture risk in patients with diabetes mellittus, and the impact of insulin and oral antidiabetic medication on relative fracture risk. Diabetologia. 2005;48:1292-9.
48. **Riggs BL, Melton III LJ** 1992 The prevention and treatment of osteoporosis. Engl J Med 327:620–627.

49. **Finkelstein JS 2004 Osteoporosis. In: Goldman L, Ausiello D, eds.** Cecil textbook of medicine. 22nd ed. Philadelphia: Saunders; 1547–1555.
50. **Finkelstein JS, Brockwell SE, Mehta V, et al.** Bone mineral density changes during the menopause transition in a multiethnic cohort of women. *J ClinEndocrinolMetab*. 2008;93(3):861-868.
51. **Marshall D, Johnell O, Wedel H** 1996 Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 312:1254–1259.