Comparative Study of Bone Specific Alkaline Phosphatase, Bone Mineral Density, and Zinc in Postmenopausal Osteoporosis in Iraqi Type 2 Diabetic Women

Hussein Ali Al-Obaidi[1*]; Fadhil J. Al-Tu'ma[1]; Zena A. M. Al-Jawadi[2;] and Tamadhur S. M. Al-Hasnawy[3]

[1]Department of Chemistry and Biochemistry, College of Medicine, University of Kerbala, Kerbala/ Iraq

[2]Department of Chemistry, College of Science, University of Mosul, Mosul / Iraq

[3]M.B.Ch.B, F.I.B.M.S, Rheumatology and Medical Rehabilitation, Al-Hasan Teaching Hospital, Kerbala Health Directorates / Kerbala – Iraq

abitorab11@gmail.com

Abstract:

Background: Osteoporosis is the most common metabolic bone disorder that is common in postmenopausal women with type 2 diabetes.T2DM is linked to an increase in the fracture rate as compared to the non-diabetic population even with normal or raised bone mineral density (BMD). Hence, bone quality plays an important role in the pathogenesis of skeletal fragility due to T2DM. Zinc (Zn) an essential trace element is necessary for the normal mineralization of bone and play role in collagen metabolism, and its levels are altered in diabetes. Osteopenia describes a decrease in BMD below normal reference values, yet not low enough to meet the diagnostic criteria for osteoporosis. BMD is diagnosed via dual-energy X-ray absorptiometry bone scans. Bone alkaline phosphatase (BALP) is an ectoenzyme attached to the outer surface of the cell membrane of osteoblasts. It is partly released into circulation. BALP and liver ALP constitute about 95% of the total ALP (TALP) activity in human serum.

Aims: The aim of the present work is to compare the investigated results of BALP, Total ALP, BMD, T-scor, body mass index (BMI), age, calcium, and Zn between diabetic postmenopausal osteoporosis (diabetic PMOP) and non-diabetic postmenopausal osteopenia to see if there is any influence caused an increase in fracture risk in diabetes patients.

Materials and Methods: We performed a cross-sectional study in Kerbala medical college department of chemistry and biochemistry enrolling 80 subjects, 40 PMOP with T2DM, aged between (50-75) years, and 40 postmenopausal osteopenia without T2DM, aged between (50-76) years. All Patients had been in spontaneous menopause for at least, one year. For each subject we measured serum BALP, total ALP, Zinc, Calcium, BMI, BMD, and T-scor during Nov. 2021 to June, 2022. Diabetic patients were collected from Al-Hassan center for Endocrinology and diabetes mellitus and Osteoporosis center at Al-Hussein Medical City, Kerbala Health Directorates, Kerbala/ Iraq. The mean and standard deviation of the parameters of the two groups were computed and compared by unpaired Student's T-test. The relationship between variables was measured by Karl Pearson's correlation coefficient. A statistical significance is set at a 5% level of significance ($P < 0.05$).

Result: Age and TALP were significantly higher in diabetic PMOP compared with non-diabetic osteopenia (62.8 ± 6.8 vs. 56.4 ± 7.37 year), (227.43± 61.46 vs. 201.50 ± 41.47 U/L), P<0.05. BMI was non-significant in diabetic PMOP compared with non-diabetic osteopenia (29± 4.72 vs.30.34 ± 4.64 kg/m2) P>0.05. T-scor was significantly lower in diabetic PMOP compared with non-diabetic osteopenia (-3.04 ± 0.45 vs. -1.64 ± 0.38) P <0.05. BMD and Zinc were significantly lower in diabetic PMOP compared with non-diabetic osteopenia (0.72 ± 0.06 vs. 0.86 ± 0.04 g/cm2), (78.90 ± 7.34 vs. 83.02 ± 7.43 µg/dL) P<0.05. BALP was non-significantly higher in diabetic PMOP compared with non-diabetic osteopenia (52.33 ± 11.62 vs. 49.51 ± 7.64 ng/L) P>0.05. Calcium was non-significantly in diabetic PMOP compared with non-diabetic osteopenia (9.49 ± 0.30 vs. 9.39 ± 0.44 mg/dL) P>0.05. BMD of diabetic PMOP showed a significant strong positive correlation with T-scor and also BMD of non-diabetic osteopenia showed a significant positive correlation with T-scor. BMD of diabetic PMOP and non-diabetic osteopenia showed a non-significant negative correlation with BALP and TALP. BMD of non-diabetic osteopenia showed a significant positive correlation with Zn and in diabetic osteoporosis non-significant positive correlation with Zn.

Conclusions: Type 2 diabetic PMOP have BMD lower than the non-diabetic osteopenia. High zinc level in non-diabetic osteopenia may contribute to high BMD. Serum zinc levels may serve to be important predictors of BMD. Low BMI in diabetic PMOP is an indicator for osteoporosis and its related fracture. In diabetic PMOP, T-scor is only predict by high level of BALP and TALP and low level of zinc. Low levels of BALP, TALP and high level serum zinc are the predictors of T-score in non-diabetic osteopenia.

Keywords: Osteoporosis, PMOP, BMD, BALP, T2DM, T-score, TALP.

1. Introduction

Osteoporosis represents an increasing global health problem, with the highest incidence rates in postmenopausal women and elderly men. Osteoporosis is a systemic bone disease characterized by osteopenia and compromised bone microstructure, resulting in increased bone fragility and susceptibility to fracture [1]. The World Health Organization (WHO) defines it mainly in women as "the presence of a bone mineral density (BMD) less than or equal to - 2.5 standard deviations below the average bone mass of healthy 20-year-olds", which is carried performed using a specific radiological test, called bone mineral densitometry [2]. The risk of osteoporosis in

doi.org/10.31838/hiv22.02.128 Received: 31.01.22, Revised: 18.05.22, Accepted: 18.08.22

women is approximately 3 times higher than in men [3]. Osteoporosis and fractures severely affect the quality of life of a senior individual and generate great economic and psychological burdens for the patients and their families. The imbalance between bone formation and bone resorption is the basic mechanism for all osteoporosis [4]. Women are more susceptible to suffering from bone fractures, as a direct consequence of this disease, because faced with a calcium deficiency in the diet, together with a vitamin D deficiency, during pregnancy and lactation, the body goes to diminish the reserves of calcium in the bone, which is the cause of gradual loss of bone mass. For this reason, its appearance is later and more frequently in amenorrheic or post-menopausal women, who also have a decrease in the production of estrogens by the ovaries and other hormonal deficiencies that affect metabolism in the bone [5].

Osteoporosis and type two diabetes mellitus(T2DM) are affected by aging and often coexist in the elderly [6]. T2DM affects bone metabolism and strength by influencing osteoblast and osteoclast. The imbalance between osteoblast and osteoclast might cause osteoporosis [7]. As well, T2DM might affect bone quality and quantity, leading to a change in the structural properties of bone mass. T2DM affects bone homeostasis, so related fractures are considered a result of T2DM. Bone mineral density (BMD) is the most important single predictor for osteoporotic fractures, the dual-energy X-ray absorptiometry (DXA)-based BMD has been the benchmark technique used in osteoporosis diagnosis. (DXA)-based BMD plays a crucial role in osteoporosis/osteopenia management and fracture risk assessment [8]. Bone metabolism in diabetes is influenced by many factors, including depressed osteoblast activity and decreased numbers of osteoclasts "sweet bones" as a result of abnormal insulin secretion and/or insulin action. Insulin-like growth factors and other osteoclastogenic cytokines are also implicated [9]. In women, the abrupt decline in serum estradiol levels through menopause is closely associated with increased osteoclastic bone resorption. Low estrogen levels in postmenopausal women stimulate circulating macrophages to produce osteoclastic cytokines that activate RANK and promote osteoclast activation. Moreover, the loss of the direct pro-apoptotic effects of estrogens on osteoclasts results in the prolongation of osteoclast lifespan, leading to the acceleration of trabecular bone loss [10]. Osteopenia is a clinical term used to describe a decrease in BMD below normal reference values, yet not low enough to meet the diagnostic criteria to be considered osteoporotic. BMD is diagnosed via DXA bone scans. Osteopenia, as defined by the World Health Organization (WHO), is a T-score between -1 to -2.5, while values less than -2.5 are diagnostic for osteoporosis. Decreasing BMD values are reflective of an underlying disruption in the microarchitecture of bone and osteopenia, and osteoporosis is considered quantitative, not qualitative, disorder of bone mineralization. Alkaline phosphatase (ALP) is a ubiquitous enzyme and membrane-bound glycoprotein that catalyze the hydrolysis of phosphate monoesters, like inorganic pyrophosphate (PPi), with an optimum activity at basic pH values. Bone ALP (BALP) is a homodimer anchored to the membrane of osteoblasts and matrix vesicles (MVs). After its cleavage by a phospholipase, soluble (anchor-free) BALP is released into the circulation and can be used as a biomarker of bone formation. BALP must be anchored on the outer surface of the matrix vesicle membrane, then it will degrade PPi, an inhibitor of the hydroxyapatite formation, present in the extracellular matrix [11]. Zinc is an essential nutritional trace element that acts as an important cofactor for a number of enzymes including DNA and RNA polymerases and is necessary for organisms. In general, the human body contains 1.5–3 g of Zn, and approximately 0.1% of the amount is excreted daily, and thus needs to be supplemented through dietary intake [12]. Zn in the bone is accumulated in the osteoid layer prior to mineralization. In addition, significant associations of low serum levels of Zn with diminished BMD and the risk of osteoporosis have been reported in postmenopausal women [13, 14]. Zn affects bone metabolism via its role in many signaling pathways [15]. Calcium ion is an essential structural component of the skeleton. There is growing evidence for the importance of nutrition in maintaining of bones and joint health. Nutrition imbalance with endocrine abnormalities may be involved in osteoporosis. Extracellular calcium ion concentration is determined by the interaction of calcium absorption from the intestine, renal excretion of calcium, and bone uptake and release of calcium, each of which is regulated by parathyroid hormone and Vitamin D and calcitonin

The present work aimed to compare BALP, Total ALP, BMD, T-scor, body mass index (BMI), age, calcium, and Zn levels between diabetic postmenopausal osteoporosis (diabetic PMOP) and non-diabetic postmenopausal osteopenia to see if there is any influence caused an increase in fracture risk in diabetes patients.

2. Materials and Methods

This cross-sectional study was performed in department of chemistry and biochemistry, college of medicine, university of Kerbala during Nov. 2021 to June 2022 by enrolling totally 80 subjects, 40 PMOP with T2DM with age ranged between (50-75) years, and 40 postmenopausal osteopenia without T2DM with age ranged between (50-76) years. All Patients had been in spontaneous menopause for at least, one year. In each subject we measured serum BALP which determined by Sandwich ELISA technique, serum TALP, Zn, calcium (Ca) which were analyzed by chemistry analyzer smart 120T/H, deionized water was used as a blank solution, BMI was directly measured for each patients, BMD and T-scor by Dual energy x-ray absorptiometry scan (DEXA) at lumbar spine regions (L1–L4 vertebrae) confirmed postmenopausal osteoporosis were included. Diabetic patients were collected from Al-Hassan center for Endocrinology and diabetes mellitus and Osteoporosis center at Al-Hussein Medical City, Kerbala Health Directorates / Kerbala-Iraq.

Inclusion criteria were as follows only patients with postmenopausal osteoporosis women and age of female ≥ 50 year and T2DM patients that have duration ≥ 5 year were enrolled in the present study.

Exclusion criteria were as follows individuals with a history of medication for the treatment of PMOP or medication known to affect bone metabolism within 6 months. Patients with diseases known to affect bone metabolisms, such as severe malabsorption syndrome, chronic liver disease, inflammatory bowel disease, primary hyperparathyroidism that is not effectively controlled, hypercalcemia, Paget's bone disease, active kidney stones, osteogenesis imperfecta, and pituitary disease. Women were identified with surgical menopause, hypertensive, hormone replacement therapy and type 1 diabetic mellitus women were excluded from the study. Patients with secondary osteoporosis, such as rheumatoid arthritis, osteomalacia, multiple myeloma, and gout, patients who have been continuously treated with bisphosphonates or PTH for more than 15 days within 1 year, patients who have continuously used estrogen receptor modulators within 6 months. Patients who have continuously received calcitonin, estrogen, corticosteroids, calcitriol, and other drugs that can change bone metabolism within 3 months. Patients with severe liver and kidney diseases, peptic ulcers, immune diseases, malignant tumors, any type of thalassemia disease, and other serious underlying diseases. Patients with factors that affect the measurement results of BMD, such as the history of lumbar spine fixation surgery, ankylosing spondylitis and amputation surgery, and bone fracture were excluded. Anthropometric data were recorded by interviews during health service provision. Diagnostically confirmed cases of postmenopausal osteoporosis attending the osteoporosis unit. Permission to conduct the study was obtained from the research ethics committee on human subject's research of Kerbala medical college, Iraq. All the cases were evaluated and selected by simple random technique after fulfilling the selection criteria. The cases of osteoporosis were reported to the unit of osteoporosis. After finding the suitability as per selection criteria, they were requested to participate in the study and briefed about the nature of the study and interventions used. Informed consent was obtained. The consented patients were enrolled in the study. Further descriptive data of the participants like name, age, sex, and detailed history, were obtained by interviewing the participants and were recorded on a predesigned and pretested proforma.

BMD was determined by a diagnostic medical system Stratos Bone Densitometry equipment was designed and manufactured in France. The instrument operation and data interpretation were made according to manufacturer instructions. The interpretation was made according to BMD status, which was categorized as Osteoporotic (T-scor at or below -2.5), (osteopenic T-scor between -1 and -2.5), and normal (T-scor at above -1) postmenopausal women. Height and weight were measured at the time of DEXA measurement and body mass index (BMI) was calculated as the weight divided by the square of the height (kg/m2).

Five ml of blood sample was obtained by venipuncture from each patient during the morning (8-11 a.m.) and drawn into a gel tube, then allowed to stand at room temperature till the clot was formed. The blood tube was centrifuged, and serum was separated within 2 hours by centrifuging at 3,000 rpm for 10 min. All samples were stored in nonvacuum sterile tubes at −20 °C till further analysis. Serum TALP, Ca and Zn were measured by an automatic analyzer smart 120T/H, (GenoLAB Tech, USA). Serum BALP was measured by the enzyme linked immunosorbent assay technique, PARS BIOCHEM KIT (BIOTEK, USA).

The data were analyzed by IBM Corp, and released in 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Mean and standard deviation of the parameters of the two groups were computed and compared by unpaired Student's T-test. The relationship between variables was measured by Karl Pearson's correlation coefficient. A statistical significance is set at a 5% level of significance ($P < 0.05$).

3. Results

Bone mineral density and T-scores were evaluated in 40 types 2 diabetics' postmenopausal osteoporosis and 40 non-diabetic postmenopausal osteopenia women. Table 1 shows the Mean and Standard Deviation (SD) of Age, BMI, T-scor, BMD, BALP, TALP, Ca, and Zn.

Age and Total ALP (TALP) were significantly higher in diabetic PMOP compared with non-diabetic osteopenia. BMI was non-significant low in diabetic PMOP compared with non-diabetic osteopenia. T-scor was significantly lower in diabetic PMOP compared with non-diabetic osteopenia. BMD and Zinc were significantly lower in diabetic PMOP compared with non-diabetic osteopenia. Bone ALP (BALP) was non-significant higher in diabetic PMOP compared with non-diabetic osteopenia while TALP was a significant higher in diabetic PMOP compared with non-diabetic osteopenia. Calcium was non-significantly higher in diabetic PMOP compare with non-diabetic osteopenia. BMD of diabetic PMOP showed a significant very strong positive correlation with T-scor while BMD in non-diabetic osteopenia showed a significant strong positive correlation with T-scor. BALP and TALP of diabetic PMOP and non-diabetic osteopenia showed a non-significant negative correlation with BMD. BALP and TALP of diabetic and non-diabetic osteopenia showed a non-significant negative correlation with Zn. DM duration showed a significant very strong negative correlation with BMD.BMD of non-diabetic osteopenia showed a significant positive correlation with Zn while BMD in diabetic osteoporosis showed a non-significant positive correlation with Zn.

Table 1: The mean ± SD of the observed parameters determined in diabetic POMB and non-diabetic osteopenia.

Parameters	Reference Range	Total N = 80 Mean ± SD	Diabetic POMB N = 40 Mean ± SD	Non-Diabetic Osteopenia N = 40 Mean ± SD	P.Value
Age, Year	-----	59.6 ± 7.75	62.8 ± 6.81	56.4 ±7.37	<0.0001*
BMI, kg/m^2	-----	29.66±4.7	29.0 ± 4.72	30.34 ± 4.64	0.166
T-scor	> -1	-2.34 ± 0.82	-3.04 ± 0.45	-1.64 ± 0.38	< 0.0001*
Bone Mineral Density, g/cm^2	-----	0.79 ± 0.09	0.72 ± 0.06	0.86 ± 0.04	< 0.0001*
BALP, ng/L	7.5 - 135	50.92 ± 9.88	52.33 ± 11.62	49.51 ± 7.64	0.180
Zn, µg/dL	70 - 150	80.96 ± 7.62	78.9 ± 7.34	83.03 ± 7.43	0.028*
Ca, mg/dL	8.6 – 10.3	9.44 ± 0.38	9.49 ± 0.3	9.39 ± 0.44	0.246
TALP. U/L	98 - 279	214.45 ± 53.7	227.43 ± 61.46	201.5 ± 41.47	0.023*

***P<0.05; SD: Standard Deviation; BMI: Body mass index; BMD: Bone mineral density**

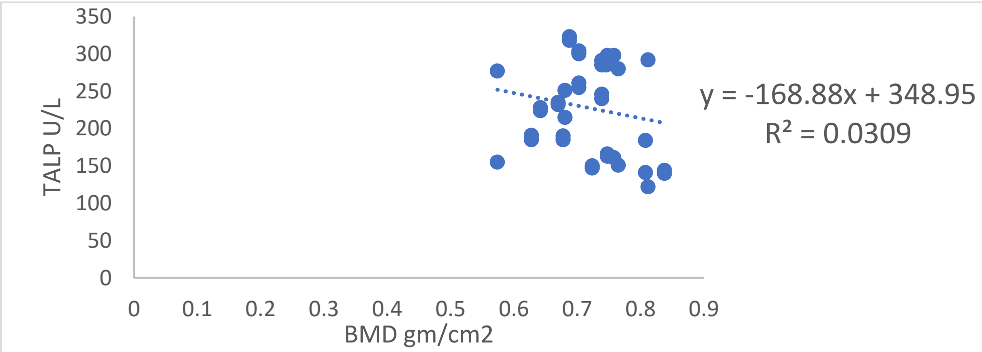

Fig 1: Correlation between BMD with TALP in diabetics POMB.

Table 2: Relationship between Age, T-scor, BMI, BMD, Serum BALP, TALP, Ca and Zinc in postmenopausal (diabetic Osteoporosis and non-diabetics Osteopenia)

Correlation between parameters	Diabetics Osteoporosis		Non-diabetics Osteopenia	
	R	Sig.	r	Sig.
Age and T-scor	0.107	0.512	-0.388*	0.013
Age and BMI	0.093	0.568	-0.616**	<0.01
T-scor and BMI	0.405**	<0.01	0.488**	<0.01
T-scor and BMD	0.969**	<0.01	0.676**	<0.01
T-scor and BALP	-0.142	0.381	-0.081	0.621
T-scor and TALP	-0.098	0.548	-0.335*	0.035
T-scor and Zn	0.157	0.335	0.208	0.199
BMI and BMD	0.375*	0.017	0.255	0.112
BMD and BALP	-0.161	0.322	-0.142	0.382
BMD and TALP	-0.176	0.278	-0.218	0.176
BMD and Zn	0.176	0.276	0.341*	0.031
BALP and Zn	-0.127	0.434	-0.045	0.783
TALP and Zn	-0.180	0.267	-0.254	0.114
Duration of DM and T-scor	-0.814**	<0.01		
Duration of DM and BMD	-0.807**	<0.01		
Ca and Zn	-0.117	0.471	0.025	0.877
BMD and Ca	-0.184	0.255	0.083	0.609

***Statistically significant at p <0.05 level (two-tailed); **Statistically significant at p < 0.01**

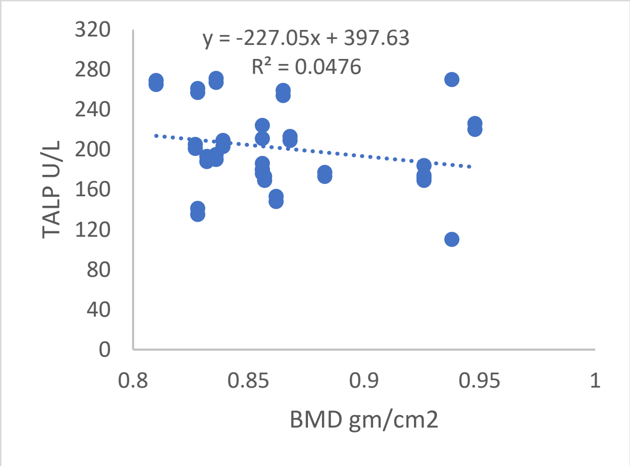

Fig. 2: Correlation between BMD with TALP in non-diabetics osteopenia

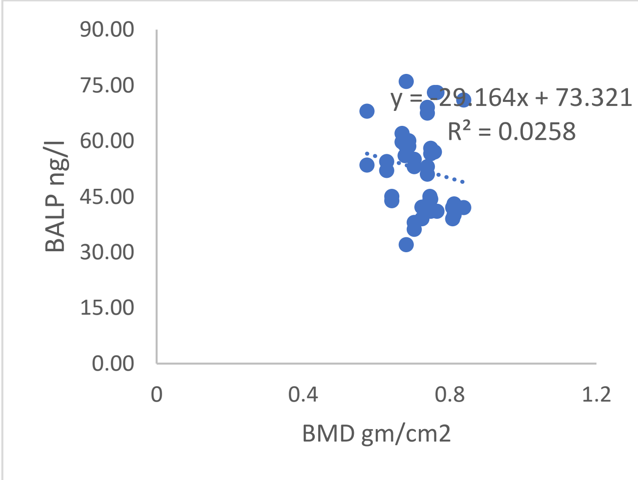

Fig. 3: Correlation of BMD with BALP in diabetics POMB

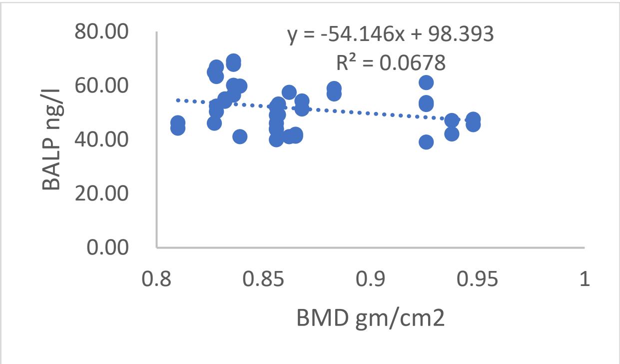

Fig. 4: Correlation of BMD with BALP in non-diabetics osteopenia

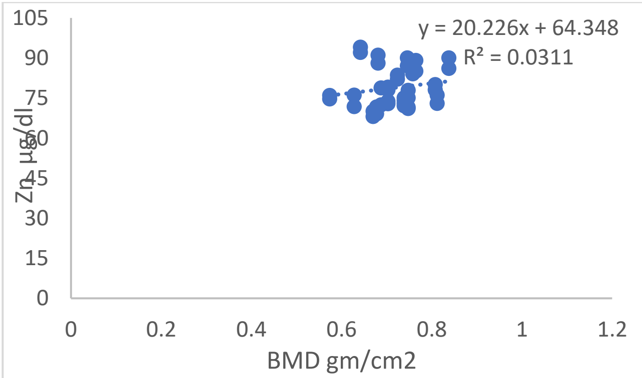

Fig. 5: Correlation of BMD with serum Zn in diabetics POMB

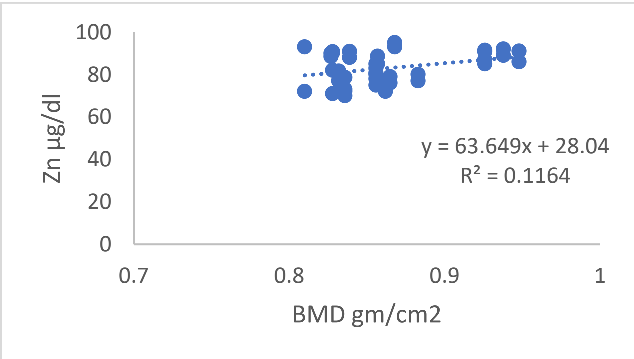

Fig. 6: Correlation of BMD with serum Zn in non-diabetics osteopenia

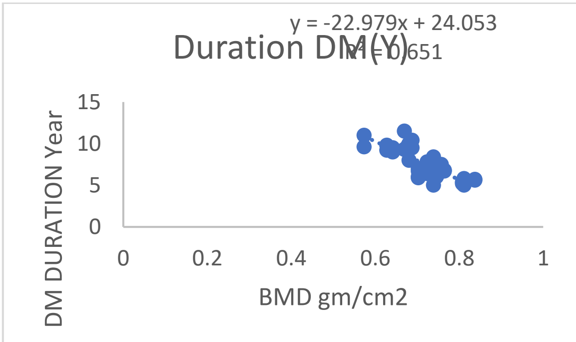

Fig. 7: Correlation of BMD with duration of diabetics POMB

4. Discussion

We showed in this study the negative effect of DM duration on the BMD, this agree with study done by Jang et al. [16]. The mean duration of diabetes among cases was 7.5 years.The data of this study showed no significantly in the level of serum Calcium between two groups but higher in diabetic postmenopausal osteoporosis compared with non-diabetic osteopenia within normal range, This is consistent with the findings of a research conducted by Wen et al. [17], Sudjaroen et al. [18]. There was negative correlation between BMD and calcium in diabetic PMOP group. Our work was in agreements with other investigators [18]. In diabetic PMOP, the bone mineral density was significantly lower as compared with non-diabetic osteopenia. A significant positive correlation was found by others between BMD and body mass index in diabetic PMOP and a non-significant result was obtained in non-diabetic osteopenia group [19]. Serum alkaline phosphatase activity levels were significantly higher in diabetic PMOP as compared with non-diabetic osteopenia groups which also in agreement with other study [20, 21].This may be due that ALP can be drain from osteoblast which is rich with its activity also it found in plasma membrane of the cell in the liver, intestine, and placenta, all of which may contribute to the total amount of alkaline phosphatase [21]. The age was significantly higher in diabetic PMOP as compared with non-diabetic osteopenia groups which also in agreement with other study [17]. BMI was non-significant higher in non-diabetic osteopenia compared with diabetic

PMOP groups [17].

Moreover, several studies demonstrated the relationship between low BMI, low bone mineral density levels, and the risk of osteoporotic fractures, and some studies found that increased BMI is associated with elevated BMD levels and a reduced risk of fractures due to osteoporosis [22, 23]. Further studies are needed to explore the relationship between BMI and BMD levels, especially among older diabetic women patients. Previous studies concluded that when BMI increases, BMD levels will also increase, which further supports our findings [24], the data of this study showed decrease BMI and BMD in diabetic osteoporosis as compared with non-diabetic osteopenia groups and this corresponds to the positive relationship between BMI and BMD and may be high mean of BMD and BMI in diabetic osteoporosis patients and this confirm positive correlation between BMD and BMI. Other studies explained that such relationship exists because heavy body weight could result in bone remodeling to compensate for the heavy mechanical load [25]. Another study suggested that an increased BMI could subsequently increase the levels of leptin, which contributes to the relationship by promoting osteoblast production and functions [26]. In this study, a negative association was observed between the duration of diabetes and BMD. These results were consistent with other findings performed by various works [27] [28]. They demonstrated that the duration of diabetes as a risk factor for decreased BMD in T2DM subjects. However these findings were against the observation of Weinstock *et al.* who found no significant relationship between BMD and the duration of diabetes [29]. Type 2 diabetes has been recognized as an independent risk for fragile fractures [30]. The high fracture risk in T2DM patients can be induced by hypoglycemia, muscle weakness, and chronic complications (such as retinopathy and neuropathy) which usually happen in a patient with a longer duration of T2DM [31]. However, hyperglycemia should always be kept in mind because it plays a vital role in the impaired bone metabolism in T2DM patients, leading to reduced bone strength [32]. Hyperglycemia and its associated hyperosmolarity also suppress the expression of genes associated with osteoblast maturation [33]. Hyperglycemia causes calcium homeostasis imbalance by inhibiting the bone formation and accelerating bone resorption. Increased osteoblast apoptosis induced by high glucose has been demonstrated [34].The loss of BMD in osteoporotic group was supported by the increased activity of ALP [35].

The study showed raised levels of BALP in osteoporotic patients as compared to osteopenic group, and these high levels may be associated with prevalent vertebral fractures and higher levels of ALP were related with reduced T-scores which showed an imbalance between osteoblastic and osteoclastic activity shifting the equilibrium towards increase osteoclastic activity and In diabetic groups BALP levels could increase the risk of osteoporosis [17, 36]s. Serum ALP is a clinical marker of bone metabolism, and its activity arises from the bone and liver. The ALP level of the diabetic osteoporosis and non-diabetic osteopenia groups was significantly different. ALP elevation has been commonly seen in patients with bones diseases and/or renal hyperfiltration [37], they have been associated with diabetic patients. In particular, renal hyperfiltration has been observed in patients with newly diagnosed type 2 diabetes [38]. However, further investigations on the causal effects of ALP level on the development of diabetes are needed [20]. Previous studies reported higher Ca and ALP (within reference ranges) in women with osteoporosis [39]. Serum Ca was controlled and maintained homeostasis between the serum and bone compartment. Increasing of serum Ca and BMD reduction in osteoporotic women were implied to have a negative correlation between serum Ca and BMD status [40]. Serum Zn was significantly lower in diabetic PMOP compared with non-diabetic osteopenia. Zn is an essential element for over 200 enzymes, collagen production, and bone mineralization [41]. Oxidative stress is implicated in postmenopausal osteoporosis by loss of balance between antioxidative and oxidative markers. Monitoring of oxidative stress-related markers is useful for the diagnosis and prognosis of osteoporosis [42]. Hence, reduction of serum Zn in osteoporosis may affect the antioxidant status, especially antioxidant enzymes. Our finding was summarized in that serum Ca and ALP in the osteoporosis group were higher than in osteopenia group, and serum Zn will reduce along with BMD during osteoporosis progress. High serum Ca in postmenopausal women is a risk for bone loss, and estrogen deficit increases bone turnover and bone resorption. Hence, the hormonal and BMD status in females are important factors, which should be addressed in osteoporosis studies [18, 43]. This study found that diabetics and non-diabetic groups showed a non-significant negative correlation between BMD and ALP. BALP is an enzyme that promotes bone mineralization by inactivating pyrophosphate and osteopontin, which are both inhibitors of bone mineralization. ALP and BALP measurements were widely recommended, to evaluate not only the bone mineral status disorder but also the rate of vascular calcification [44-46]. Low BMD levels in diabetic osteoporosis compared with non-diabetic osteopenia was in agreement with others [47, 48].The relationship between Zn and BMD was a significant positive correlation in non-diabetic while non-significant positive correlation in diabetic groups [49, 50].

Conclusions:

Type 2 diabetic PMOP has BMD lower than non-diabetic osteopenia. ALP activity level was the strongest predictor of T-score. Elevated serum ALP levels may help in determining loss of BMD in postmenopausal females.

Diabetic patients with low BMI and BMD possibly have a high risk of osteoporosis than those with high BMI and BMD. All patients with diabetes should be encouraged and educated about controlling their diabetes and maintaining normal BMI or increasing BMI for those with low BMD by having well-balanced and healthy diets to prevent the risk of fragility fractures and osteoporosis. The BMD had a strong negative correlation with the duration of diabetes; additional studies are warranted to understand the decreasing BMD among T2DM patients more thoroughly to prevent fractures and their subsequent deleterious consequences on individuals with diabetes. In diabetic group BALP, TALP levels could increase the risk of osteoporosis. There is a negative correlation between BMD and ALP in non-diabetic osteopenia. Therefore, the measurement of ALP can provide supplementary data as an early predictive marker for osteoporosis. High zinc levels in non-diabetic osteopenia may contribute to high BMD and may be a protective factor against zincuria.

5. References

1. Coll PP, Phu S, Hajjar SH, Kirk B, Duque G, Taxel P. The prevention of osteoporosis and sarcopenia in older adults. J Am Geriatr Soc. 2021;69(5):1388-98. https://doi.org/10.1111/jgs.17043
2. Elonheimo H, Lange R, Tolonen H, Kolossa-Gehring M. Environmental Substances Associated with Osteoporosis–A Scoping Review. International Journal of Environmental Research and Public Health. 2021;18(2):738. https://doi.org/10.3390/ijerph18020738
3. Noh J-W, Park H, Kim M, Kwon YD. Gender differences and socioeconomic factors related to osteoporosis: a cross-sectional analysis of nationally representative data. Journal of Women's Health. 2018;27(2):196-202. https://doi.org/10.1089/jwh.2016.6244
4. Cai X, Dong J, Lu T, Zhi L, He X. Common variants in MAEA gene contributed the susceptibility to osteoporosis in Han Chinese postmenopausal women. Journal of Orthopaedic Surgery and Research. 2021;16(1):38. https://doi.org/10.1186/s13018-020-02140-4
5. Kim K-T, Lee Y-S, Han I. The Role of Epigenomics in Osteoporosis and Osteoporotic Vertebral Fracture. International Journal of Molecular Sciences. 2020;21(24):9455. https://doi.org/10.3390/ijms21249455
6. Paschou SA, Dede AD, Anagnostis PG, Vryonidou A, Morganstein D, Goulis DG. Type 2 diabetes and osteoporosis: a guide to optimal management. The Journal of Clinical Endocrinology & Metabolism. 2017;102(10):3621-34. https://doi.org/10.1210/jc.2017-00042
7. Sassi F, Buondonno I, Luppi C, Spertino E, Stratta E, Di Stefano M, Ravazzoli M, Isaia G, Trento M, Passera P, Porta M, Isaia GC, D'Amelio P. Type 2 diabetes affects bone cells precursors and bone turnover. BMC Endocrine Disorders. 2018;18(1):55. https://doi.org/10.1186/s12902-018-0283-x
8. Ferrari SL, Abrahamsen B, Napoli N, Akesson K, Chandran M, Eastell R, El-Hajj Fuleihan G, Josse R, Kendler DL, Kraenzlin M, Suzuki A, Pierroz DD, Schwartz AV, Leslie WD, Ferrari SL, Abrahamsen B, Akesson K, Ardawi MSM, Chandran M, Cooper C, Eastell R, El-Hajj Fuleihan G, Josse R, Kendler DL, Kraenzlin M, Leslie WD, Mithal A, Napoli N, Suzuki A, Schwartz AV, on behalf of the B, Diabetes Working Group of IOF. Diagnosis and management of bone fragility in diabetes: an emerging challenge. Osteoporosis International. 2018;29(12):2585-96. https://doi.org/10.1007/s00198-018-4650-2
9. Xu Y, Wu Q. Trends in osteoporosis and mean bone density among type 2 diabetes patients in the US from 2005 to 2014. Scientific Reports. 2021;11(1):3693. https://doi.org/10.1038/s41598-021-83263-4
10. Golden NH. Bones and Birth Control in Adolescent Girls. Journal of Pediatric and Adolescent Gynecology. 2020;33(3):249-54. https://doi.org/10.1016/j.jpag.2020.01.003
11. Nizet A, Cavalier E, Stenvinkel P, Haarhaus M, Magnusson P. Bone alkaline phosphatase: An important biomarker in chronic kidney disease – mineral and bone disorder. Clinica Chimica Acta. 2020;501:198-206. https://doi.org/10.1016/j.cca.2019.11.012
12. Almsaid H, Khalfa HM. The effect of Ketogenic diet on vitamin D3 and testosterone hormone in patients with diabetes mellitus type 2. 2020. Available from: https://www.researchgate.net/publication/349442324
13. Lim KHC, Riddell LJ, Nowson CA, Booth AO, Szymlek-Gay EA. Iron and Zinc Nutrition in the Economically-Developed World: A Review. Nutrients. 2013;5(8):3184-211. https://doi.org/10.3390/nu5083184
14. Nakano M, Nakamura Y, Miyazaki A, Takahashi J. Zinc Pharmacotherapy for Elderly Osteoporotic Patients with Zinc Deficiency in a Clinical Setting. Nutrients. 2021;13(6):1814. https://doi.org/10.3390/nu13061814
15. Kenkre J, Bassett J. The bone remodelling cycle. Annals of clinical biochemistry. 2018;55(3):308-27. https://doi.org/10.1177%2F0004563218759371
16. Jang M, Kim H, Lea S, Oh S, Kim JS, Oh B. Effect of duration of diabetes on bone mineral density: a population study on East Asian males. BMC Endocrine Disorders. 2018;18(1):61. https://doi.org/10.1186/s12902-018-0290-y
17. Wen Y, Li H, Zhang X, Liu P, Ma J, Zhang L, Zhang K, Song L. Correlation of Osteoporosis in Patients With Newly Diagnosed Type 2 Diabetes: A Retrospective Study in Chinese Population. Frontiers in endocrinology. 2021;12:531904. https://doi.org/10.3389/fendo.2021.531904
18. Sudjaroen Y, Thongkao K, Thongmuang P, Pongstaporn W, Aounchat D, Suwannahong K. VDR gene polymorphism and trace elements in Thai postmenopausal women with risk of osteoporosis: Cross-sectional study. Journal of Applied Pharmaceutical Science. 2022;12(2):152-7. https://doi.org/10.7324/JAPS.2021.120215
19. Polyzos SA, Anastasilakis AD, Efstathiadou ZA, Yavropoulou MP, Makras P. Postmenopausal osteoporosis coexisting with other metabolic diseases: Treatment considerations. Maturitas. 2021;147:19-25. https://doi.org/10.1016/j.maturitas.2021.02.007
20. Chen SC-C, Tsai SP, Jhao J-Y, Jiang W-K, Tsao CK, Chang L-Y. Liver Fat, Hepatic Enzymes, Alkaline Phosphatase and the Risk of Incident Type 2 Diabetes: A Prospective Study of 132,377 Adults. Scientific Reports. 2017;7(1):4649. https://doi.org/10.1038/s41598-017-04631-7
21. Lim ZW, Chen W-L. Exploring the association of Bone Alkaline Phosphatases And Hearing Loss. Scientific Reports. 2020;10(1):4006. https://doi.org/10.1038/s41598-020-60979-3
22. Felson DT, Zhang Y, Hannan MT, Anderson JJ.

Effects of weight and body mass index on bone mineral density in men and women: the Framingham study. Journal of Bone and Mineral Research. 1993;8(5):567-73. https://doi.org/10.1002/jbmr.5650080507

23. Morony S, Capparelli C, Lee R, Shimamoto G, Boone T, Lacey DL, Dunstan CR. A chimeric form of osteoprotegerin inhibits hypercalcemia and bone resorption induced by IL-1β, TNF-α, PTH, PTHrP, and 1, 25 (OH) 2D3. Journal of Bone and Mineral Research. 1999;14(9):1478-85. https://doi.org/10.1359/jbmr.1999.14.9.1478

24. Doğan A, Nakipoğlu-Yüzer GF, Yıldızgören MT, Özgirgin N. Is age or the body mass index (BMI) more determinant of the bone mineral density (BMD) in geriatric women and men? Archives of Gerontology and Geriatrics. 2010;51(3):338-41. https://doi.org/10.1016/j.archger.2010.01.015

25. Kang D, Liu Z, Wang Y, Zhang H, Feng X, Cao W, Wang P. Relationship of body composition with bone mineral density in northern Chinese men by body mass index levels. Journal of Endocrinological Investigation. 2014;37(4):359-67. https://doi.org/10.1007/s40618-013-0037-6

26. Russell M, Mendes N, Miller KK, Rosen CJ, Lee H, Klibanski A, Misra M. Visceral fat is a negative predictor of bone density measures in obese adolescent girls. The Journal of Clinical Endocrinology & Metabolism. 2010;95(3):1247-55. https://doi.org/10.1210/jc.2009-1475

27. Wakasugi M, Wakao R, Tawata M, Gan N, Koizumi K, Onaya T. Bone mineral density measured by dual energy X-ray absorptiometry in patients with non-insulin-dependent diabetes mellitus. Bone. 1993;14(1):29-33. https://doi.org/10.1016/8756-3282(93)90252-6

28. Linda Kao WH, Kammerer CM, Schneider JL, Bauer RL, Mitchell BD. Type 2 diabetes is associated with increased bone mineral density in Mexican-American women. Archives of Medical Research. 2003;34(5):399-406. https://doi.org/10.1016/j.arcmed.2002.07.001

29. Weinstock RS, Goland RS, Shane E, Clemens TL, Lindsay R, Bilezikian JP. Bone mineral density in women with type II diabetes mellitus. Journal of Bone and Mineral Research. 1989;4(1):97-101. https://doi.org/10.1002/jbmr.5650040114

30. Neglia C, Argentiero A, Chitano G, Agnello N, Ciccarese R, Vigilanza A, Pantile V, Argentiero D, Quarta R, Rivezzi M, Di Tanna GL, Di Somma C, Migliore A, Iolascon G, Gimigliano F, Distante A, Piscitelli P. Diabetes and Obesity as Independent Risk Factors for Osteoporosis: Updated Results from the ROIS/EMEROS Registry in a Population of Five Thousand Post-Menopausal Women Living in a Region Characterized by Heavy Environmental Pressure. International Journal of Environmental Research and Public Health. 2016;13(11). https://doi.org/10.3390/ijerph13111067

31. Majumdar SR, Leslie WD, Lix LM, Morin SN, Johansson H, Oden A, McCloskey EV, Kanis JA. Longer Duration of Diabetes Strongly Impacts Fracture Risk Assessment: The Manitoba BMD Cohort. The Journal of Clinical Endocrinology & Metabolism. 2016;101(11):4489-96. https://doi.org/10.1210/jc.2016-2569

32. Napoli N, Chandran M, Pierroz DD, Abrahamsen B, Schwartz AV, Ferrari SL. Mechanisms of diabetes mellitus-induced bone fragility. Nat Rev Endocrinol. 2017;13(4):208-19. https://doi.org/10.1038/nrendo.2016.153

33. Botolin S, Faugere M-C, Malluche H, Orth M, Meyer R, McCabe LR. Increased Bone Adiposity and Peroxisomal Proliferator-Activated Receptor-γ2 Expression in Type I Diabetic Mice. Endocrinology. 2005;146(8):3622-31. https://doi.org/10.1210/en.2004-1677

34. Wu M, Ai W, Chen L, Zhao S, Liu E. Bradykinin receptors and EphB2/EphrinB2 pathway in response to high glucose-induced osteoblast dysfunction and hyperglycemia-induced bone deterioration in mice. Int J Mol Med. 2016;37(3):565-74. https://doi.org/10.3892/ijmm.2016.2457

35. Macdonald HM, New SA, Golden MH, Campbell MK, Reid DM. Nutritional associations with bone loss during the menopausal transition: evidence of a beneficial effect of calcium, alcohol, and fruit and vegetable nutrients and of a detrimental effect of fatty acids. The American Journal of Clinical Nutrition. 2004;79(1):155-65. https://doi.org/10.1093/ajcn/79.1.155

36. Biver E, Chopin F, Coiffier G, Brentano TF, Bouvard B, Garnero P, Cortet B. Bone turnover markers for osteoporotic status assessment? A systematic review of their diagnosis value at baseline in osteoporosis. Joint Bone Spine. 2012;79(1):20-5. https://doi.org/10.1016/j.jbspin.2011.05.003

37. Oh SW, Han KH, Han SY. Associations between renal hyperfiltration and serum alkaline phosphatase. PloS one. 2015;10(4):e0122921. https://doi.org/10.1371/journal.pone.0122921

38. Vora JP, Dolben J, Dean JD, Thomas D, Williams JD, Owens DR, Peters JR. Renal hemodynamics in newly presenting non-insulin dependent diabetes mellitus. Kidney International. 1992;41(4):829-35. https://doi.org/10.1038/ki.1992.127

39. Mishra S, Manju M, Toora B, Mohan S, Venkatesh B. Comparison of bone mineral density and serum minerals in pre and post-menopausal women. Int J Clin Trials. 2015;2(4):85-90. https://doi.org/s10.18203/2349-3259.ijct20151237

40. Hamdi RA. Evaluation of Serum Osteocalcin level in Iraqi Postmenopausal women with primary osteoporosis. Journal of the Faculty of Medicine Baghdad. 2013;55(2):166-9. https://doi.org/10.32007/jfacmedbagdad.552649

41. Hyun TH, Barrett-Connor E, Milne DB. Zinc intakes and plasma concentrations in men with osteoporosis: the Rancho Bernardo Study. The American Journal of Clinical Nutrition. 2004;80(3):715-21. https://doi.org/10.1093/ajcn/80.3.715

42. Zhao F, Guo L, Wang X, Zhang Y. Correlation of oxidative stress-related biomarkers with postmenopausal osteoporosis: a systematic review and meta-analysis. Archives of Osteoporosis. 2021;16(1):4. https://doi.org/10.1007/s11657-020-00854-w

43. Liu M, Yao X, Zhu Z. Associations between serum

calcium, 25(OH)D level and bone mineral density in older adults. Journal of Orthopaedic Surgery and Research. 2019;14(1):458. https://doi.org/10.1186/s13018-019-1517-y
44. Akin O, Göl K, Aktürk M, Erkaya S. Evaluation of bone turnover in postmenopausal patients with type 2 diabetes mellitus using biochemical markers and bone mineral density measurements. Gynecological Endocrinology. 2003;17(1):19-29. https://doi.org/10.1080/gye.17.1.19.29
45. Buchet R, Millán JL, Magne D. Multisystemic Functions of Alkaline Phosphatases. In: Millán JL, editor. Phosphatase Modulators. Totowa, NJ: Humana Press, 2013. p. 27-51. https://doi.org/10.1007/978-1-62703-562-0_3
46. Baralić M, Brković V, Stojanov V, Stanković S, Lalić N, Đurić P, Đukanović L, Kašiković M, Petrović M, Petrović M. Dual roles of the mineral metabolism disorders biomarkers in prevalent hemodilysis patients: in renal bone disease and in vascular calcification. Journal of Medical Biochemistry. 2019;38(2):134. https://doi.org/10.2478%2Fjomb-2018-0026
47. Forst T, Beyer J, Pfützner A, Kann P, Schehler B, Lobmann R, Schäfer H, Andreas J, Bockisch A. Peripheral osteopenia in adult patients with insulin-dependent diabetes mellitus. Diabetic Medicine. 1995;12(10):874-9. https://doi.org/10.1111/j.1464-5491.1995.tb00389.x
48. Kwon DJ, Kim JH, Chung KW, Kim JH, Lee JW, Kim SP, Lee HY. Bone mineral density of the spine using dual energy X-ray absorptiometry in patients with non-insulin-dependent diabetes mellitus. J Obstet Gynaecol Res. 1996;22(2):157-62. https://doi.org/10.1111/j.1447-0756.1996.tb00959.x
49. Siddapur PR, Patil AB, Borde VS. Comparison of bone mineral density, T-scores and serum zinc between diabetic and non diabetic postmenopausal women with osteoporosis. Journal of laboratory physicians. 2015;7(01):043-8. https://doi.org/10.4103/0974-2727.151681
50. AL-Msaid HL, AL-Sallami AS. Study the level of cytokine in unexplained and idiopathic infertile men. Journal of Pharmaceutical Sciences and Research. 2018;10(4):808-11. Available from: https://www.researchgate.net/publication/324845254