



ASSESSMENT OF LONG-TERM DIABETES MEDICATION USE AND ITS EFFECTS ON OSTEOPOROSIS RISK IN DIABETIC PATIENTS

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Keywords

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Abstract

Background: Diabetes mellitus is a metabolic and systematic disorder that requires individualized therapy. The disease leads to various consequences, resulting in the destruction of tissues and organs. The aforementioned outcomes also include bone mineral disorders, caused by medications as well as diet therapy and physical activity. Objective: Assessment of osteoporosis risk in diabetic patients with long-term diabetes medication use by detection some immunological and biochemical indicators. Material and methods: The current study was conducted in Baqubah city/ Diyala province for the period: 1/10/2024 to 1/3/2025. 50 blood samples were collected from diabetic patients with osteoporosis who went to Baqubah Teaching Hospital as well as to the outpatient clinics. Also, 30 blood samples were collected from healthy people and considered as a control group. Serum levels of ACCP, CRP, CK-MP, Vitamin D3, calcium, and RF in all samples were quantified by AFIAS Machine. Present data were programmed by SPSS v. 20.0 and Graph pad prism v.6 statistical software. Results: Present outcomes showed no significant differences ($p>0.05$) between males versus females and among age groups of patients. Also, current findings showed no significant differences between positivity of RF and study groups. Levels of CRP and CK-MP were high in patients compared to controls, while levels of Vitamin D3 and calcium were lowest in patients than control. In contrast, present study showed no differences ($p>0.05$) between levels of ACCP and study groups. Based on gender, present research showed no differences between positivity RF and groups (male vs. female vs. control). The levels of CRP and CK-MP scored highest mean level in males and lowest mean in females. On other hand, present findings showed the Vitamin D3 and calcium scored lowest level in males and highest mean in control. Finally, present study showed no differences ($p>0.05$) between levels of ACCP and groups (male vs. female vs. control). Conclusions: The present study concluded the ACCP and RF indicator not play role in assessment osteoporosis in DM patients due to it isn't levels affected by diseases, while CRP, calcium, CK-MB and vitamin D3 indicators have major role in assessment due to it is levels high affected by disease. Based on gender, present findings revealed there is variation in levels of CRP, calcium, CK-MB and vitamin D3 between males versus females due to hormonal and genetic disorders.

1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common metabolic disorders and has now become one of the world's major health problems, affecting nearly all organs, and its prevalence is continuously accelerating in all over the globe, particularly in developing countries (Elahi et al., 2024). Osteoporosis is a well-known common systemic bone disorder that decreases the strength of bones, which directly increases the chances of bone fractures in humans. The balance between osteoclast resorption and osteoblast production determines the integrity of bone microarchitecture. Early diagnosis and treatment of osteoporosis can help reduce osteoporosis-related fractures, thus minimizing public health problems (Chen et al., 2024). Numerous studies from several parts of the world point out that osteoporosis-related morbidity has been accelerating significantly, which has a direct or indirect impact on the quality of public health. The global occurrence of osteoporosis was

higher in women as compared to men (Salari et al., 2021). It is now well documented that diabetes mellitus (DM) causes abnormal changes in the endocrine and metabolic activities that directly or indirectly impact calcium homeostasis and bone metabolism and ultimately result in bone loss (Nugroho et al., 2024). Type 2 diabetes mellitus is one of the risk factors for fragility fractures. The role of bone mineral density (BMD) in patients with diabetes is well reported, but the pathophysiological outcomes from different research groups are controversial (Latifjonovna, 2024). Large population-based studies of osteoporosis patients show that T2DM patients constitute 18% of the osteoporosis population. Diabetes can contribute to skeletal disorders through various factors. These mechanisms involve changes in insulin and insulin-like growth factor (IGF) levels, hypercalciuria due to glycosuria, impaired kidney function, obesity, elevated levels of advanced glycation end products (AGEs) in collagen, vascular issues, nerve damage, and inflammation (Nugroho et al., 2024). Rheumatoid arthritis is associated with an increased risk of diabetes mellitus incidence. This finding supports the notion that inflammatory indicators (such as; RF) are involved in the pathogenesis of diabetes (Tian et al., 2021).

ACCP is the most recent clinically available diagnostic laboratory associated with RA. The most common ACPA is anti-CCP antibodies. Anti-CCP has a similar sensitivity for RA as does the RF, but the specificity is 96%, which serves as a great tool when considering the diagnosis in a person with inflammatory joint symptoms (Oka et al., 2022). Like RF, anti-CCP can be associated with other rheumatic and nonrheumatic conditions. These conditions include SLE, primary Sjogren syndrome, psoriatic arthritis, and active tuberculosis. A positive anti-CCP is less commonly seen in persons with hepatitis C. Knowing that RF can be positive with hepatitis C, a result of a negative anti-CCP may lead a clinician to consider investigating for hepatitis C in the appropriate clinical scenario. As with RF, a positive anti-CCP is associated with potentially increased risk of destructive or erosive RA. A positive RF and anti-CCP may lead a provider to be more aggressive with pharmacologic treatment to prevent degenerative and debilitating joint changes (Iyengar et al., 2022).

The authors present a case of a long-standing poorly controlled diabetes with diabetic cheiroarthropathy and diabetic neuropathy, along with positive ANA in the absence of any correlated autoimmune or rheumatological diseases (Abdalla et al., 2024). C-reactive protein (CRP) was discovered by Tillett and Francis in 1930. The name CRP arose because it was first identified as a substance in the serum of patients with acute inflammation that reacted with the "c" carbohydrate antigen of the capsule of pneumococcus (Fujiwara et al., 2024). CRP has both proinflammatory and anti-inflammatory properties. It plays a role in the recognition and clearance of foreign pathogens and damaged cells by binding to phosphocholine, phospholipids, histone, chromatin, and fibronectin. It can activate the classic complement pathway (Zhou et al., 2024). Creatine kinase (CK) is found in heart muscle, skeletal muscle, and the brain. It is composed of M and B subunits that form CK-BB, CK-MB, and CK-MM. CK-MB has higher specificity for the myocardium because the concentration in myocytes is arguably much greater (ACS) (Liu et al., 2024). However, CK-MB is much less sensitive than troponin, rises more slowly given contemporary assays, has less sensitive cutoff values, and is sufficient in skeletal muscle to actually impair specificity in some cases (Zhang, 2025). The main cause of elevated CK in diabetics is skeletal muscle damage, specifically the CK-MM isoenzyme. Serum CK measurement is an important aspect of evaluating individuals with muscular weakness or myalgia, as well as patients with myopathies or muscle injuries (Tiwari et al., 2024). When calcium intake is insufficient from dietary and supplemental sources, compensatory loss of calcium from the bone follows, weakening the skeleton and increasing the risk of subsequent fracture (Lin et al., 2024). The proposition that vitamin D mitigates the onset of T2DM can be elucidated by its multifaceted mechanisms of action, a subject that has been rigorously examined within both clinical and basic research spheres (Sim et al., 2024).

2. Materials and Methods

2.1 Samples collection

The current study was conducted in Baqubah city/ Diyala province for the period; 1/10/2024 to 1/3/2025. 50 blood samples were collected from diabetic patients with osteoporosis who went to Baqubah Teaching Hospital as well as to the outpatient clinics. Also, 30 blood samples were collected from healthy people and considered as a control group. A questionnaire was created for each person and filled with personal information about each patient (gender and age).

2.2 Samples processing

Blood samples were collected and placed in gel tubes and then left for several minutes and then separated using a centrifuge (4000 cycles for 5 minutes) and then serum was obtained and then placed in an AFIAS Machine for measuring all indicators (ACCP, CRP, CK-MP, Vitamin D3, calcium, and RF).

2.3 Statistical analysis

ACCP, CRP, CK-MP, Vitamin D3, and calcium markers represented like Mean± stander deviation. The differences in levels of these markers in patients versus controls were statistically measured by student t test (comparison two groups) and F test (ANOVA) (comparison more than two groups). Demographic and RF parameters were represented as numbers and percentages, and Pearson-Chi-square test was detected to reveal significant differences in percentages. $P \leq 0.05$ was depended for differences calculation. Present data were programmed by SPSS v. 20.0 and Graph pad prism v.6 statistical softwares.

3. Result

3.1 Demographic features of patients

Present outcomes showed no significant differences ($p > 0.05$) between males versus females and among age groups of patients (see Table 1).

Table 1. Frequency and percentages of gender and age groups of patients

		Count	Percent	P value
Gender	Males	30	60.00%	$p > 0.05$
	Females	20	40.00%	
Age groups (years)	41-50	10	20%	$p > 0.05$
	51-60	11	22%	
	61-70	14	28%	
	71-80	15	30%	

3.2 Positivity of RF indicator in patients and controls

Present findings showed no significant differences ($p > 0.05$) between positivity of RF and study groups as illustrated in Table 2.

Table 2. Comparative positivity of RF indicator between patients versus control

			Groups		Total
			Patients	Control	
RF	Negative	N	49	30	79
		%	98.0%	100.0%	98.8%
	Positive	N	1	0	1
		%	2.0%	0.0%	1.3%
Total	N	50	30	80	
	%	100.0%	100.0%	100.0%	
P Value			$P > 0.05$		

3.3 Levels of immunological and biochemical indicators in patients and controls

Results of present study showed there is significant differences ($p < 0.05$) between levels of CRP, CK-MP, Vitamin D3, calcium and study groups. The levels of CRP and CK-MP were high in patients (6.71 ± 2.06 and 5.51 ± 2.45) compared to controls (1.95 ± 0.97 and 1.85 ± 0.98), while levels of Vitamin D3 and calcium were lowest in patients (10.74 ± 4.99 and 5.84 ± 1.22) than control (44.80 ± 5.08 and

9.50±1.02). Finally, present study showed no differences ($p>0.05$) between levels of ACCP and study groups (see Table 3 and Figure 1)

Table 3. Comparative mean levels of immunological and biochemical indicators between patients versus control

Groups		N	Mean	Std. Deviation	P Value
ACCP (mg/dl)	Patients	50	3.16	0.18	$P>0.05$
	Controls	30	3.14	0.23	
CRP (mg/L)	Patients	50	6.71	2.06	$P<0.05^*$
	Controls	30	1.95	0.97	
CK_MP (IU/L)	Patients	50	5.51	2.45	$P<0.05^*$
	Controls	30	1.85	0.98	
Vitamin D3 (ng/ml)	Patients	50	10.74	4.99	$P<0.05^*$
	Controls	30	44.80	5.08	
Calcium (mg/dl)	Patients	50	5.84	1.22	$P<0.05^*$
	Controls	30	9.50	1.02	

$P>0.05$ (no significant different) $P<0.05^*$ (significant different)

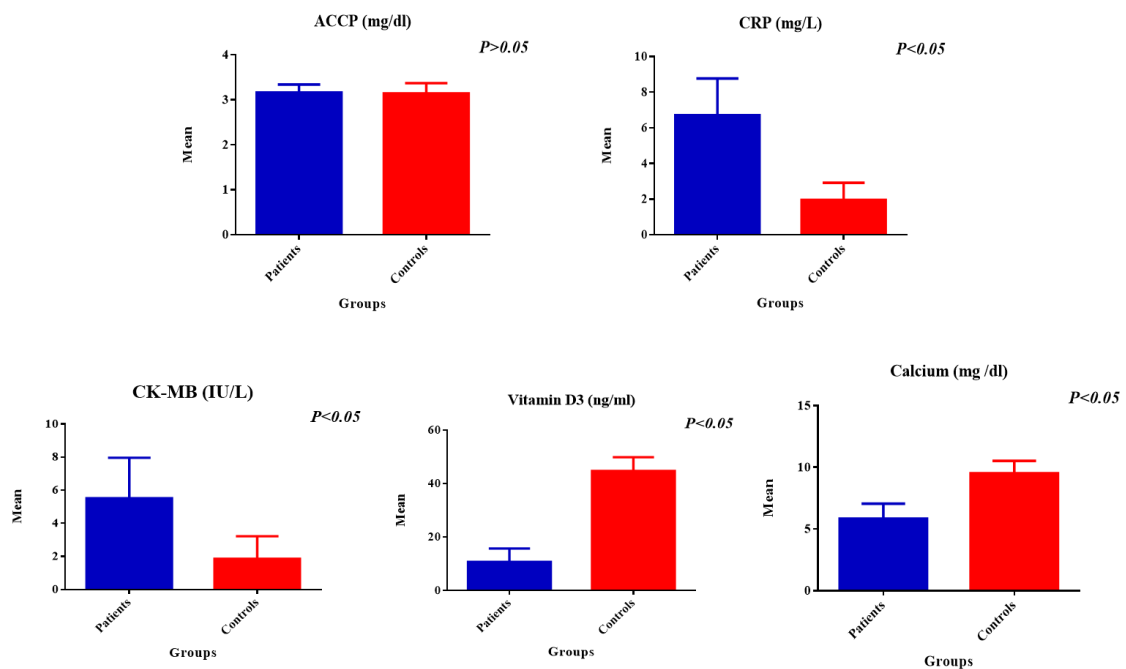


Figure 1. Comparative mean levels of immunological and biochemical indicators between patients versus control

3.4 Positivity of RF indicator among study groups

Results of present research showed no differences ($p>0.05$) between positivity RF and groups (male vs. female vs. control), as presented in Table 4.

Table 4. Comparative positivity of the RF indicator among study groups

			Groups			Total
			Males	Females	Control	
RF	Negative	N	30	19	30	79
		%	100.0%	95.0%	100.0%	98.8%
	Positive	N	0	1	0	1
		%	0.0%	5.0%	0.0%	1.3%
Total	N	30	20	30	80	
	%	100.0%	100.0%	100.0%	100.0%	
P Value			$P>0.05$			

3.5 Mean levels of immunological and biochemical indicators among study groups

Results of conducted study showed there is significant differences ($p < 0.05$) between levels of CRP, CK-MP, Vitamin D3, calcium and groups (male vs. female vs. control). The levels of CRP and CK-MP scored highest mean level in males (9.01 ± 3.03 and 8.38 ± 2.34) and lowest mean in females (3.75 ± 1.90 and 2.70 ± 1.30). On other hand, present findings showed the Vitamin D3 and calcium scored lowest level in males (7.87 ± 2.03 and 5.40 ± 1.19) and highest mean in control (44.80 ± 5.08 and 9.50 ± 1.02). Finally, present study showed no differences ($p > 0.05$) between levels of ACCP and groups (male vs. female vs. control), see Table 5.

Table 5. Comparative mean levels of immunological and biochemical indicators among study groups

		N	Mean	Std. Deviation	P Value
ACCP (mg/dl)	Males	30	3.14	0.23	$P > 0.05$
	Females	20	3.20	0.00	
	Controls	30	3.14	0.23	
CRP (mg/L)	Males	30	9.01 ^a	3.03	$P < 0.05^*$
	Females	20	3.75 ^b	1.90	
	Controls	30	1.95 ^c	0.97	
CK_MP (IU/L)	Males	30	8.38 ^a	2.34	$P < 0.05^*$
	Females	20	2.70 ^b	1.30	
	Controls	30	1.85 ^b	1.37	
Vitamin D3 (ng/ml)	Males	30	7.87 ^c	2.03	$P < 0.05^*$
	Females	20	15.06 ^b	5.03	
	Controls	30	44.80 ^a	5.08	
Calcium (mg/dl)	Males	30	5.40 ^b	1.19	$P < 0.05^*$
	Females	20	6.50 ^b	0.95	
	Controls	30	9.50 ^a	1.02	

4. Discussion

The present study aimed to assessment of long-term diabetes medication use and its effects on osteoporosis risk in diabetic patients. Present findings showed no significant differences ($p > 0.05$) between male vs. female and among age groups of patients due to randomly sample size. These findings were matched with results done (AlShomar et al., 2023).

Diabetes mellitus is a metabolic and systematic disorder that requires individualized therapy. The disease leads to various consequences, resulting in the destruction of tissues and organs. The aforementioned outcomes also include bone mineral disorders, caused by medications as well as diet therapy and physical activity. Possible deleterious effects of diabetes mellitus on bone metabolism and bone quality. Diabetes mellitus (DM) increases osteoclast function but decreases osteoblast function, thereby leading to accelerated bone loss, osteopenia and osteoporosis (Zhang et al., 2024). Some drugs may have a beneficial effect on both bone mineral density and the risk of fractures (Martiniakova et al., 2024). Nevertheless, the impact of other medications remains unknown. Focusing on pharmacotherapy in diabetes may prevent bone mineral disorders and influence both the treatment and quality of life in patients suffering from diabetes mellitus. On the other hand, anti-osteoporosis drugs, such as antiresorptive or anabolic drugs, as well as drugs with a mixed mechanism of action, may affect carbohydrate metabolism, particularly in patients with diabetes. Therefore, the treatment of diabetes as well as osteoporosis prevention are vital for this group of patients (Zawada et al., 2022).

The relationship between bone mineral density (BMD) and type 2 diabetes (T2DM) is complex and involves a complex interaction of various factors. In T2DM, the risk of fractures can be higher even with normal or increased BMD due to reduced bone turnover, changes in bone quality, and impaired structure that alters biomechanical properties and therefore leads to bone fragility, often called the "diabetic bone paradox" (Li et al., 2019). Considering the pathophysiological mechanism, it is difficult to identify patients at-risk before the pathological fracture occurs because BMD measurements using traditional DXA and FRAX may often underestimate the fracture risk in diabetic individuals (Hidayat et al., 2021). It may be worth using other available methods, such as trabecular

bone score (TBS), quantitative computed tomography (QCT), volumetric BMD (vBMD), bone turnover biomarkers concentrations, or a combination of these. Future research is needed to address this clinical issue (Wikarek et al., 2024). Present findings showed no differences between positivity of RF indicator in DM patients with osteoporosis compared to controls, because of the RF indicator is utilized for diagnosis osteoporosis that caused by rheumatoid arthritis (RA) (sensitivity 96% and specificity 95%) but not osteoporosis that caused by DM medications (Martiniakova et al., 2024). Rheumatoid factor (RF) is test checks for RF, an antibody that many people with rheumatoid arthritis can eventually have in their blood. An antibody is a special protein made by the immune system that normally helps fight invaders in the body (Steiner & Toes, 2024). Present outcomes showed no differences between levels of Anti-CCPs in DM patients with osteoporosis compared to controls, because of the Anti-CCPs indicator is utilized for diagnosis osteoporosis that caused by rheumatoid arthritis but not osteoporosis that caused by DM medications (Martiniakova et al., 2024). Anti-CCPs are antibodies also produced by the immune system. People who test positive for anti-CCP are very likely to develop rheumatoid arthritis, but not everybody with rheumatoid arthritis has this antibody (Karami et al., 2024). Authors found that RA patients with higher levels of anti-CCP antibody had lower lumbar and femoral bone mineral density (BMD). Anti-CCP levels were also associated with radiographic bone damage. Therefore, they suggest that anti-CCP may be a determinant of osteoporosis in patients with RA (Yang et al., 2025).

Present findings showed increased levels of CRP in DM patients than controls, and these findings were matched with results (Tong et al., 2023). Authors showed the serum CRP is associated with osteoporosis in elderly men, and can serve as predictors for osteoporosis due to has high sensitivity and specificity in diagnosis this diseases (area under the ROC curve = 87%) (Dong et al., 2023). Serum levels of C-reactive protein may independently predict low bone mineral density (BMD) and high fracture risk. The cause of increased CRP in DM patients with osteoporosis is related to low bone density and inflammation in beta cell in pancreas (Jiang et al., 2023). Showed increased levels of CK-MB in diabetic than controls, and these findings were matched with present investigation. The CK-MB test, or Creatine Kinase-MB test, is a blood test that measures the level of a specific enzyme called creatine kinase-myocardial band (CK-MB) in the bloodstream. CK-MB is predominantly found in the heart muscle. Previous findings indicate that individuals with type 2 diabetes exhibit markedly higher serum heart enzyme levels (CK-MB) compared to non-diabetic individuals (Alam et al., n.d.). However, creatine kinase levels can increase without muscle destruction, and in diabetes mellitus, the elevation of this enzyme level has been noted in patients with ketoacidosis (Odum & Young, 2018). Authors showed the CK-MB elevation was significantly related to adverse outcomes like acute pancreatitis (AP) patients (one complication of DM), which makes it a potentially useful laboratory parameter for predicting adverse clinical outcomes of AP (Jiang et al., 2023). In the past, clinical studies reported an increased serum CK in patients with genetic osteopetrosis (OPT) and in a patient with acquired OPT due to prolonged N-blood pressure (N-BP) therapy. A recent report evidenced an increase of serum CK in children with Osteogenesis imperfecta (OI) type I during therapy with N-BPs probably reflecting suppression of osteoclast function. The hypothesis that osteoclasts could represent an important source of CK has been confirmed in a recent in vitro study, performed on rabbit-stimulated osteoclasts incubated in medium containing various N-BPs. This study confirmed that osteoclasts are the source of CK release from the bone and that this is an osteoclast apoptosis-related event (D'Eufemia et al., 2017).

Results of present study showed decreased levels of vitamin D3 and calcium in patients compared to controls due to decrease bone mass that associated with decrease levels of vitamin D3 and calcium in those patients. These findings were compatible to results (Fu et al., 2025). Initial observational studies indicated an inverse correlation between serum vitamin D status and prevalence of diabetes, and also a possible association between poor vitamin D status and increased progression from pre-diabetes to diabetes. The worsening of glycaemic control in diabetic patients during winter was also attributed to lowering of vitamin D levels during those months. Till recently, these notions were driving clinicians to consider routine supplementation of vitamin D to patients with diabetes mellitus. Two recent independent double-blinded randomized controlled trials have shown no beneficial role of vitamin D supplementation in glycaemic outcomes including prevention of diabetes (Pittas et al., 2019). Similarly, (Wallace et al., 2019). Showed absence of any effect of vitamin D supplementation on insulin resistance, beta cell dysfunction and glycaemic control in diabetic patients. Thus, it seems vitamin D has no major-independent role in glycaemic control among patients with diabetes. Dietary supplements can contain vitamin D2 or vitamin D3. While both are good for bone health, vitamin D3 can increase a person's vitamin D levels to a greater extent and maintain higher levels longer than vitamin D2. This may mean that vitamin D3 is more effective for people with osteoporosis (De Martinis et al., 2021).

In case of insufficient calcium intake, serum free calcium level remains low, the parathyroid gland is automatically stimulated and parathyroid hormone (PTH) is released in order to get calcium released from the bones to maintain blood calcium level and prevent osteoporosis due to the Calcium deficiency potentially leads to osteoporosis (Cheng et al., 2025). Furthermore, oral calcium load could lead to increased glucose-induced insulin secretion in patients with diabetes. In addition, dietary Ca intake is related to reduced lipogenesis, less inflammation and increased lipolysis (Zawada et al., 2022). Present findings showed no differences between RF indicator and males versus females because of this indicator no specific to osteoporosis caused by DM, but it is specific to osteoporosis caused by rheumatoid arthritis. Finally, present study showed there is significant differences ($p < 0.05$) between levels of CRP, CK-MB, vitamin D3 and gender, where it is found high levels of CRP and CK-MB indicators in males than females. On other hand, it is found lowest levels of vitamin D3 in males than females. The differences between males versus females according to CRP, CK-MB, vitamin D3 are linked to hormonal factors, genes, and environmental factors.

5. Conclusion

The present study concluded the ACCP and RF indicator not play role in assessment osteoporosis in DM patients due to it isn't levels affected by diseases, while CRP, calcium, CK-MB and vitamin D3 indicators have major role in assessment due to it is levels high affected by disease. Based on gender, present findings revealed there is variation in levels of CRP, calcium, CK-MB and vitamin D3 between males versus females due to hormonal and genetic disorders.

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