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ORIGINAL ARTICALE

ASSESSMENT OF BONE METABOLISM MARKERS IN DIABETIC PATIENTS: INFLUENCE OF OSTEOPOROSIS, AGE, AND GENDER

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ABSTRACT

Background: Diabetes mellitus is linked to changes in bone metabolism, which may result in osteoporosis and a heightened risk of fractures. There is still little research on the incidence and biochemical characteristics of these alterations in diabetic people in Iraq.

Objectives: The aim of this study is to assess serum bone metabolism indicators in diabetic patients, both with and without osteoporosis, and to compare these markers with those of healthy controls, while accounting for age and gender variations.

Materials and Methods: This study involved 219 individuals aged 40–80 years, including 149 diabetic patients (with and without osteoporosis) and 70 healthy controls, recruited from hospitals and clinics in Kirkuk, Iraq. Participants were grouped as follows: G1 – diabetics without osteoporosis, G2 – diabetics with osteoporosis, and G3 – healthy controls. Blood samples were collected after overnight fasting, and serum was separated for biochemical analysis. Bone metabolism markers-type I collagen, osteocalcin, and TRACP-5b—were quantified using ELISA and ECLIA techniques according to standard protocols.

Results: Results revealed statistically significant elevations ($P < 0.05$) in serum collagen type I, osteocalcin, and TRACP among diabetic patients compared to controls, indicating altered bone turnover. Additionally, these markers were significantly higher in diabetic patients with osteoporosis, especially TRACP and collagen type I, reflecting increased bone resorption. Age-related analysis showed significant increases in TRACP in older osteoporotic patients ($P < 0.0001$), while osteocalcin showed no significant age-related variation. Gender analysis revealed higher collagen type I in non-osteoporotic males ($P = 0.005$) and significantly elevated TRACP in osteoporotic females ($P < 0.0001$), suggesting gender- and age-related modulation of bone metabolism in diabetes.

Conclusion: Diabetic patients exhibit altered bone turnover, with more pronounced changes in those with osteoporosis. These alterations are modulated by age and gender, suggesting the need for targeted bone health assessment in diabetic populations.

Keywords*:* TRACP-5b and type I collagen, Diabetes and osteoporosis, Bone metabolism markers

INTRODUCTION

Diabetes mellitus (DM) is primarily defined by elevated blood glucose levels (hyperglycemia), excessive thirst (polydipsia), and increased appetite (polyphagia). Diabetes mellitus is a prevalent metabolic condition that is escalating at an alarming pace globally[1]. The WHO projects that diabetes will rank as the seventh leading cause of death by 2030[2]. There are four main types of diabetes mellitus, Type 1 Diabetes Mellitus (T1DM) results from the autoimmune destruction of pancreatic β cells, leading to the absence of insulin production[3]. This condition is often referred to as insulin-dependent diabetes mellitus (IDDM)[4]. CVD kills about 70% of type 2 diabetics, making it the major cause of mortality. Diabetes has been linked to cardiovascular disease for decades[5]. Diabetes is the predominant metabolic condition, significantly impacting global health systems. It has evolved into a significant, chronic, non-communicable disease following cardio-cerebrovascular diseases. At present, 90% of individuals with diabetes are afflicted with type 2 diabetes. Hyperglycemia is the primary characteristic of diabetes. The functionality of pancreatic

cells progressively diminishes prior to the emergence of clinical hyperglycemia. Comprehending the molecular mechanisms underlying diabetes development might furnish therapeutic therapy with essential advancements[6].

Diabetes is a chronic condition marked by hyperglycemia, stemming from either a relative or absolute lack of insulin[7], reduced sensitivity of target cells to insulin, and disturbances in glycolipid and protein metabolism[8]. Over 90% of individuals with diabetes are afflicted with type 2 diabetes[9]. Individuals with diabetes typically have four metabolic irregularities: impaired insulin action, failure in insulin secretion[10], elevated endogenous glucose production, and obesity[11].

Tartrate-Resistant Acid Phosphatase (TRACP), also known as acid phosphatase 5 (ACP5), is a glycoprotein enzyme predominantly expressed in osteoclasts and activated macrophages[12]. Elevated levels of TRACP 5a in the bloodstream are considered a biomarker for chronic inflammatory conditions such as diabetes mellitus, cancer, and autoimmune disorders. In contrast, TRACP 5b is produced by osteoclasts—specialized bone-resorbing cells—and serves as a reliable marker of bone resorption activity[13]. This isoform is particularly useful in evaluating bone metabolic diseases like osteoporosis, rheumatoid arthritis, and skeletal complications in diabetic patients. The differentiation of TRACP isoforms provides valuable insights into both inflammatory and bone-related pathologies[14].

Typically, TRAP is significantly expressed in osteoclasts, activated macrophages, neurons, and the porcine endometrium during pregnancy[15]. Some research indicates that patients with poorly controlled diabetes have elevated TRACP 5b levels, suggesting increased bone resorption. This may be due to chronic hyperglycemia-induced oxidative stress and inflammation, leading to enhanced osteoclast activity[16], Conversely, other studies have reported reduced TRACP levels in diabetic individuals, implying suppressed bone turnover. Hyperglycemia can impair osteoblast function and reduce osteoclast genesis, leading to low bone turnover. The discrepancies in TRACP levels among studies may be attributed to differences in study populations, glycemic control status, duration of diabetes, and presence of diabetic complications[17]. Collagen is among the most prevalent proteins in several living species due to its involvement in connecting biological components. It is the predominant protein in the extracellular matrix (ECM). The extracellular matrix (ECM) is a non-cellular element present in all tissues and organs, serving as a structural framework that influences cell adhesion and migration and regulates cellular growth and metabolism[18]. There are various types of collagens that can be classified based on their α-chain composition. There have been around 28 different forms of collagen discovered; however, collagen type I is the most common type of collagen. As a result of its widespread presence in virtually all connective tissues, collagen type I accounts for more than ninety percent of the total collagen found in the human body[19].

Robust data indicates that ucOC may influence metabolic processes by acting on many tissues critical for glucose and lipid metabolism. In the pancreas, ucOC can stimulate β-cell proliferation and insulin synthesis via GPRC6A[20]. The ucOC can boost the production of delta-like 1 (DLK1) in pancreatic β cells, and DLK1 prevents osteocalcin production in osteoblasts that depends on insulin signaling[21]. Consequently, a positive feedback loop exists between pancreatic islets and bone. The ucOC may indirectly enhance insulin production by promoting GLP-1 release from the gut[22]. In tissues that respond to insulin, ucOC can help increase the uptake of glucose and fatty acids, improve insulin sensitivity, make better use of nutrients, and boost mitochondrial function, while reducing the formation of glycogen in muscles and the production of fat in the liver[23].

MATERIALS AND METHODS

Study Design and Participants

There were 219 participants, 149 patients and 70 healthy controls, aged 40 to 80. Participants were divided into three groups: Group 1 (G1) included diabetic patients without osteoporosis, Group 2 (G2) had diabetics with osteoporosis, and Group 3 (G3) had healthy people. Kirkuk Teaching Hospital, Azadi Teaching Hospital, and private medical clinics in Kirkuk, Iraq, recruited between November 2024 and May 2025. Qualified experts confirmed the clinical diagnosis. Hepatic, renal, pancreatic, Alzheimer's, and stroke patients were excluded from the research to guarantee accuracy and eliminate confounding variables.

Sample Collection

Following an overnight fast, venous blood samples (6 mL) were collected aseptically from all participants via venipuncture. The samples were divided into two portions: 4 mL were transferred into plain tubes without anticoagulant and left at room temperature for 30 minutes to allow clotting. The samples were then centrifuged at 3000×g for 10 minutes, and the resulting clear serum was carefully separated and stored in sterile, dry Eppendorf tubes at −20 °C for subsequent biochemical analysis. These analyses included measurements of serum (TRACP), osteocalcin, typ1 collagen.

Biomarker Assessment Methods

Serum Collagen Type I (COL1) and Tartrate-Resistant Acid Phosphatase 5b (TRACP-5b) were measured using commercially available sandwich ELISA kits, following the manufacturers' protocols. In both assays, microplates pre-coated with specific antibodies captured the target analytes, which were then detected using HRP-conjugated secondary antibodies. After substrate addition, the color intensity was measured at 450 nm, and

concentrations were calculated using a standard curve. Osteocalcin levels were estimated using an electrochemiluminescence immunoassay (ECLIA) on the Roche Cobas e411 analyzer. The assay used biotinylated and ruthenium-labeled monoclonal antibodies in a sandwich format, and the chemiluminescent signal generated was proportional to osteocalcin concentration. All assays were performed and calibrated according to the manufacturers' instructions, and quality control samples were used to ensure accuracy and precision.

Statistical analysis

All data were analyzed by using the Minitab program according to the ANOVA test. However, the mean when compromised by the ducun multiple range test under the P. value 0.05.

RESULTS

Effect of disease on the diagnostic parameters

Table 1 demonstrates statistically significant differences ($P < 0.05$) in several bone-related biochemical markers between diabetic patients and healthy controls. Specifically, serum levels of type I collagen, osteocalcin, and tartrate-resistant acid phosphatase (TRACP) were significantly elevated in patients compared to controls. These findings suggest enhanced bone turnover or metabolic alterations associated with diabetes mellitus.

Table 1. Determination Level of typ1 collagen, Osteocalcin, Serum (TRACP) of diabetes mellitus patients and healthy controls

Group / Parameters	Patients ± St.D * (N = 149)	Control ± St.D * (N = 70)	Probability
typ1 collagen (µg/ml)	1622.9 ± 1151.85	429.5 ± 264.409	0.0001
Osteocalcin (ng/ml)	45.774 ±23.654	34.793 ± 17.084	0.0006
Serum (TRACP) (U/L)	1.552 ± 0.744	1.286 ± 0.703	0.0069

* $P < 0.05$ highly significant

Effect of disease on the diagnostic parameters

The findings presented in Table 2 reveal statistically significant differences ($P < 0.05$) in bone metabolism markers between diabetic patients with and without osteoporosis. Notably, markers of bone turnover—including type I collagen, osteocalcin, and tartrate-resistant acid phosphatase (TRACP)—were substantially higher in the osteoporotic group. The marked elevations in TRACP and type I collagen, in particular, highlight the intensified bone resorption and metabolic activity associated with osteoporosis in diabetic individuals.

Table 2. Comparison of Bone Metabolism Markers Between Diabetic Patients with and Without Osteoporosis

Group	Diabetic patients without osteoporosis (72)	Diabetic patients with osteoporosis (77)	P-value
	mean ± SD *	mean ± SD *	
typ1 collagen (µg/ml)	749.126 ± 575.7590	2607.694 ± 989.4119	0.0001
Osteocalcin (ng/ml)	42.280 ab ± 22.5309	49.511 b ± 24.5642	0.0001
Serum (TRACP) (U/L)	0.924500 a ± .2779814	2.139597 c ± .5397886	0.0001

*** P < 0.05 highly significant**

Effect of age on bone metabolism markers in diabetic patients with and without osteoporosis

Table (3) demonstrates the influence of age on bone metabolism markers among diabetic patients, both with and without osteoporosis. A statistically significant difference ($P < 0.05$) was observed in type I collagen levels across age groups, indicating that bone turnover activity may vary with age. The most prominent change was seen in serum tartrate-resistant acid phosphatase (TRACP) levels, which increased significantly in older osteoporotic patients ($P < 0.0001$), reflecting accelerated bone resorption with advancing age. Although osteocalcin levels varied between age groups, the differences were not statistically significant ($P = 0.063$).

Table 3. Effect of age on bone metabolism markers in diabetic patients with and without osteoporosis

Group / Parameters	Diabetic patients without osteoporosis (mean ± SD)			Diabetic patients with osteoporosis (mean ± SD) *			probability
Age (years)	20-40	41-60	61-80	20-40	41-60	61-80	
typ1 collagen (µg/ml)	1973.8742 ± 1245.4482	1878.803 ± 1167.004	1805.362 ± 1086.486	873.8167 ± 921.6000	1705.3348 ± 1174.2287	1097.2523 ± 878.76505	0.005
Osteocalcin (ng/ml)	50.7288 ± 25.30319	45.3222 ± 45.3222	53.7958 ± 20.09602	47.4760 ± 25.43059	47.4955 ± 23.87884	29.2536 ± 9.91078	0.063
Serum (TRACP) (U/L)	0.647885 ± 0.2554405	.990333 ± .0611945	1.209474 ± .0776004	1.616600 ± .6418021	1.993425 ± .2075913	2.761955 ± .2408381	<.0001

*** P < 0.05 highly significant**

Effect of gender on bone metabolism markers in diabetic patients with and without osteoporosis

Table (4) highlights gender-related differences in bone metabolism markers among diabetic patients with and without osteoporosis. A statistically significant difference (P = 0.005) was observed in type I collagen levels, with higher values in males from the non-osteoporotic group, suggesting sex-based variation in bone turnover. Although osteocalcin levels were higher in females in the non-osteoporotic group and slightly higher in males in the osteoporotic group, the differences were not statistically significant (P = 0.06). In contrast, serum tartrate-resistant acid phosphatase (TRACP) levels showed a highly significant difference (P < 0.0001), with notably higher concentrations in osteoporotic females, indicating increased bone resorption in this subgroup.

Table 4. Effect of gender on bone metabolism markers in diabetic patients with and without osteoporosis

Group / Parameters	Diabetic patients without osteoporosis (mean ± SD)		Diabetic patients with osteoporosis (mean ± SD) *		probability
Age (years)	Male	Female	Male	Female	
typ1 collagen (µg/ml)	2044.6340 ± 1183.57605	1705.1550 ± 1122.71788	1355.6563 ± 1164.72121	1381.2433 ± 1054.29244	0.005
Osteocalcin (ng/ml)	45.1210 ± 24.09357	54.9978 ± 24.40759	50.3909 ± 24.04047	35.5205 ± 18.94083	0.06
Serum (TRACP) (U/L)	0.739225 ± 0.2295012	1.156094 ± 0.1051657	1.739114 ± 0.4372099	2.473333 ± 0.3613518	<.0001

DISCUSSION

The current study found that patients had much higher levels of type I collagen, osteocalcin, and tartrate-resistant acid phosphatase (TRACP) compared to healthy individuals, indicating that their bone turnover activity is generally increased. Type I collagen, an essential constituent of the bone matrix and a significant indicator of bone resorption, exhibited a notable increase in the patient group. This increase shows that osteoclasts are more active, breaking down the bone matrix by releasing enzymes like cathepsin K and TRACP5b, which help break down collagen and send its pieces into the bloodstream[24].

The elevated osteocalcin levels indicate increased osteoblastic activity. Osteocalcin is produced by mature osteoblasts and functions as a specific indicator of bone formation. The elevation may indicate a compensatory response to heightened bone resorption or signify active bone remodeling[25]. TRACP, an enzyme derived from osteoclasts, was significantly elevated, further supporting the evidence of increased bone resorption. TRACP5b levels correlate directly with the number and activity of osteoclasts[26,27]. The results align with the notion of high-turnover bone disease, frequently seen in aging populations, postmenopausal women, and those with metabolic bone disorders. Age-related changes result in an imbalance between bone resorption and formation, promoting net bone loss[28], In postmenopausal women,

estrogen deficiency accelerates bone turnover by increasing the number of bone remodeling units[24].

Bone turnover is more pronounced in trabecular bone than in cortical bone, owing to its higher cellularity and metabolic activity. This may lead to elevated circulating bone turnover markers in systemic diseases like diabetes[29]. The elevated markers identified in this study indicate an increased rate of bone remodeling, likely resulting from heightened osteoclast and osteoblast activity. The findings suggest potential implications for bone fragility and fracture risk in diabetic patients, emphasizing the role of biochemical markers in evaluating skeletal health[24].

The findings of the present study, which indicate significantly elevated levels of type I collagen, osteocalcin, and TRACP in diabetic patients with osteoporosis compared to those without, are in agreement with several prior investigations.

For instance[30] reported a significant increase in bone resorption markers such as TRACP-5b and CTX in osteoporotic patients with type 2 diabetes, highlighting the role of osteoclast hyperactivity in bone loss, which supports our results regarding the elevated TRACP levels[31]. Likewise, Liu *et al*. (2021) observed that osteocalcin levels were significantly higher in diabetic individuals with poor bone density, suggesting a compensatory increase in bone turnover that aligns with our findings of increased osteocalcin in the osteoporosis subgroup[16]. In addition, the study of[32] found that type I collagen degradation products were markedly elevated in diabetic patients with osteoporosis, reinforcing the hypothesis that collagen breakdown is a critical feature of diabetic bone disease. This finding corresponds closely with the substantial increase in type I collagen levels observed in our osteoporotic group.

On the other hand, some studies present conflicting evidence. For example, the study of[33] found no significant differences in osteocalcin levels between diabetic patients with and without osteoporosis, suggesting that osteocalcin may not consistently reflect bone formation activity in all populations.

Research, including Mosekilde (2004), indicates a correlation between diabetes and the breakdown of type I collagen in bone, independent of gender, aligning with the present results[34]. Kanazawa *et al*. (2009) proposed that osteocalcin regulates glucose and bone activity and may be affected by gender, explaining the discrepancies identified in our findings between men and females[35]. Zhao *et al*. (2016) showed that diabetes patients have heightened bone resorption, with the impact being more closely associated with the level of disease management than with gender, aligning with the constant TRACP levels seen in our findings across genders[36].

DECLARATIONS

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Competing Interests

The authors have no competing interests to declare.

Ethical Approval

The study was approved by the appropriate ethics committee and conducted according to relevant guidelines and regulations.

Informed Consent

Not applicable

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