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Multimarker Approach to Assess Glycemic Control and Bone Metabolism in Type 2 Diabetes Mellitus with Potential for Enhanced Clinical Monitoring.

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Abstract

Introduction: Increasing evidence suggests that bone-mineral biomarkers are not only indicators of skeletal health but also regulators of glucose metabolism. Their role in Type 2 Diabetes Mellitus (T2DM) is not fully understood. This study evaluated the association of serum osteocalcin, vitamin D3, and Parathyroid Hormone (PTH) with glycemic indices in patients with T2DM.

Materials and Methods: A cross-sectional study was conducted among patients with T2DM. Fasting Blood Glucose (FBG), Glycated Haemoglobin (HbA1c), osteocalcin, vitamin D3, and PTH levels were measured. Correlation analyses were performed, followed by multivariate regression models to examine independent associations between bone-mineral biomarkers and glycemic indices after adjusting for age, Body Mass Index (BMI), and duration of diabetes.

Results: Serum osteocalcin demonstrated significant negative correlations with FBG (r=–0.42, p<0.001) and HbA1c (r=–0.47, p<0.001). Vitamin D3 showed an inverse association with HbA1c (r=–0.35, p=0.002), while PTH was positively associated (r=+0.39, p=0.001). In regression analysis, osteocalcin independently predicted lower HbA1c (β=–0.31, p=0.004). Vitamin D3 deficiency was linked with increased odds of poor glycemic control (OR=2.3, 95% CI: 1.2–4.5, p=0.01), and elevated PTH independently predicted higher HbA1c (β=+0.27, p=0.01).

Conclusion: Bone-mineral biomarkers, particularly osteocalcin, vitamin D3, and PTH, are closely linked to glycemic regulation in T2DM. Their integration into diabetes care may provide novel insights for predicting metabolic risk and improving management strategies.

Keywords: Bone-endocrine axis, Glycemic control, HbA1c predictors, Osteocalcin, Parathyroid hormone, Type 2 diabetes mellitus, Vitamin D3

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Introduction

Type 2 Diabetes Mellitus (T2DM) is a major metabolic disorder characterized by insulin resistance, progressive β-cell dysfunction, and chronic hyperglycemia [1]. It contributes significantly to morbidity and mortality through both microvascular and macro vascular complications, with prevalence rising rapidly in India and worldwide [2]. This growing burden underscores the need for biomarkers beyond traditional indices to improve individualized therapy and risk prediction [3].

Conventional monitoring relies on fasting plasma glucose and glycated hemoglobin (HbA1c). While essential, these measures do not capture the complex interplay between glucose metabolism and bone-mineral pathways [4]. Bone is now recognized as an active endocrine organ, with Osteocalcin (OC)-particularly its under carboxylated form-showing insulin-sensitizing and insulinotropic effects [5,6]. Reduced OC is linked with poor glycemic control,

whereas improved glucose regulation restores OC levels, suggesting a bidirectional relationship [7].

Vitamin D3, another regulator of bone metabolism, modulates insulin secretion and receptor expression. Its deficiency, common globally, is associated with insulin resistance, β-cell dysfunction, and higher T2DM risk [8,9]. Elevated Parathyroid Hormone (PTH) also impairs insulin signalling and glucose uptake, linking secondary hyperparathyroidism to metabolic dysregulation [10,11].

Despite these associations, OC, vitamin D3, and PTH are usually assessed in isolation and primarily for bone disorders. The present study addresses this gap by concurrently evaluating serum OC, vitamin D3, and PTH in T2DM patients and healthy controls, and exploring their associations with fasting blood glucose and HbA1c. This integrated biomarker approach has the potential to enhance clinical monitoring, enable more personalized management strategies, and ultimately reduce the burden of T2DM-related complications.

Materials and Methods

Study design and setting

This observational, cross-sectional study was carried out in the Department of Medicine, Index Medical College, Hospital and Research Centre, Indore, Madhya Pradesh, from January 2023 to January 2024. A total of 200 participants were recruited, consisting of 100 patients with Type 2 Diabetes Mellitus (T2DM) and 100 age- and sex-matched healthy controls. T2DM was diagnosed according to the American Diabetes Association (ADA) criteria, defined as Fasting Plasma Glucose (FPG) ≥ 126 mg/dL, HbA1c ≥ 6.5%, or 2-hour plasma glucose ≥ 200 mg/dL during an oral glucose tolerance test [12,13]. Healthy controls were defined as individuals with FPG <110 mg/dL, HbA1c <5.7%, and no history of diabetes or metabolic disorders.

Inclusion criteria were: Age ≥ 42 years, confirmed diagnosis of T2DM for the diabetic group, and the above-defined normal glucose parameters for controls. Exclusion criteria included the presence of osteoporosis or other metabolic bone diseases, current intake of vitamin D or calcium supplements, thyroid/parathyroid disease, use of medications affecting bone metabolism (e.g., corticosteroids, bisphosphonates), chronic kidney disease, liver disease, inflammatory or autoimmune disorders, pregnancy, or lactation [14].

After overnight fasting (minimum 8 hours), 10 mL of venous blood was collected from each participant under aseptic conditions. Samples were centrifuged at 3000 rpm for 20 minutes to separate serum, which was stored at -80°C until analysis.

Study procedure

Eligible participants were enrolled based on predefined inclusion and exclusion criteria. Informed written consent was obtained from all participants, with consent forms explained in their preferred language to ensure comprehension, especially for those with limited literacy. Baseline demographic data, including age, sex, and comorbidities, were collected through structured patient interviews and review of medical records. A comprehensive clinical assessment was conducted to exclude comorbidities such as cardiovascular disease, renal impairment, or other metabolic disorders. Physical examinations-including Body Mass Index (BMI) measurement-were performed to confirm eligibility [15].

Following overnight fasting for a minimum of 8 hours, 10 mL of venous blood was collected from each participant under aseptic conditions using vacutainers. Samples were collected between 8:00 and 10:00 AM to minimize diurnal variation in biomarker levels [16]. Serum was separated by centrifugation at 3000 rpm for 20 minutes and stored at -80°C until further analysis. Serum osteocalcin levels were determined using Enzyme-Linked Immunosorbent Assay (ELISA) kits with intra-assay and inter-assay coefficients of variation (CVs) of <8% and <10%, respectively. Vitamin D (25-hydroxyvitamin D) and Parathyroid Hormone (PTH) concentrations were measured using Chemiluminescence Immunoassay (CLIA), with assay sensitivities of 4 ng/mL and 1.2 pg/mL, respectively [17]. Fasting Blood Sugar (FBS) and Random Blood Sugar (RBS) were measured using the hexokinase method, while HbA1c was analyzed by High-Performance Liquid Chromatography (HPLC) [18]. Lipid profile parameters-including total cholesterol, HDL, LDL, and triglycerides-were measured using enzymatic colorimetric methods, with LDL cholesterol calculated using the Friedewald formula. Renal function tests, including serum creatinine (modified Jaffe's method), blood urea (urease method), and serum uric acid (modified uricase method), were also performed [19].

All biochemical assays were performed in duplicate, and results were cross-verified by independent laboratory personnel. External quality control samples were included in each batch to validate assay performance, and the intra- and inter-assay CVs were maintained within acceptable limits (<10% for osteocalcin). Clinical assessments were conducted by trained physicians using standardized procedures to reduce inter-observer variability [20].

Data were recorded in structured Case Report Forms (CRFs) and entered into a secure electronic database (SPSS version 29.0; IBM Corp., Armonk, NY, USA) with double-entry verification to minimize transcription errors. Data audits were conducted periodically to ensure completeness and accuracy, and missing or inconsistent values were resolved *via* participant follow-up or review of source documents. Statistical analysis was performed using independent t-tests for normally distributed continuous variables and chi-square tests for categorical variables. Pearson's correlation coefficients were calculated to examine associations between osteocalcin

levels and glycemic parameters, with a p-value <0.05 considered statistically significant [21].

Ethical aspects

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (2013 revision). Written informed consent was obtained from all participants prior to enrollment, with study procedures explained in their preferred language to ensure comprehension. Participant confidentiality was strictly maintained, and all study-related records were securely handled [22].

Results

Baseline characteristics

The baseline demographic and clinical features of the study participants are summarized in Table 1. The mean age of patients in the Diabetes Mellitus (DM) group was 55.09 ± 5.39 years, compared to 54.26 ± 4.93 years in the control group. Although the mean ages did not differ significantly (t=1.135, p=0.258), the distribution across age categories showed a statistically significant difference (χ^2=7.670, p=0.022). In the DM group, 58% of patients were between 51-60 years, 25% were ≤ 50 years, and 17% were >60 years. In contrast, the control group had a higher proportion of individuals aged 51-60 years (70%), with fewer in the >60 years category (5%).Gender distribution was identical between the two groups, with 38% males and 62% females in both cohorts, showing no significant difference (p=1.00). With respect to glycemic status, DM patients exhibited significantly elevated Fasting Blood Sugar (FBS), Postprandial Blood Sugar (PPBS), and glycated haemoglobin (HbA1c) levels compared to controls (all p<0.001). The mean FBS in the DM group was 147.2 ± 72.5 mg/dL *vs.* 86.0 ± 17.0 mg/dL in the control group, while PPBS was 338.4 ± 74.4 mg/dL versus 127.8 ± 19.6 mg/dL, and HbA1c was 7.22 ± 1.4% *vs.* 5.38 ± 0.94%, respectively. Lipid profile analysis revealed significantly higher mean total cholesterol, triglycerides, and LDL levels in the DM group compared to controls (all p<0.001). Conversely, HDL levels were comparable between groups, with no significant difference (p=0.674). Renal function assessment demonstrated that serum creatinine levels were significantly elevated in the DM group (2.20 ± 1.2 mg/dL) compared to controls (1.07 ± 0.65 mg/dL; p<0.001). However, mean blood urea levels were similar between groups and did not show a statistically significant difference (p=0.440).

Table 1. *Clinical results and laboratory data for patients who received different dosages of LA for pituitary suppression during COH*[*]*.*

Variable	DM group (n=100)	Control group (n=100)	Statistical test	p-value
Age (years)				
≤ 50	25 (25.0%)	25 (25.0%)		
51-60	58 (58.0%)	70 (70.0%)	χ^2=7.670	0.022[*]
>60	17 (17.0%)	5 (5.0%)		
Mean ± SD	55.09 ± 5.39	54.26 ± 4.93	t=1.135	0.258
Gender				
Male	38 (38.0%)	38 (38.0%)	-	1.00
Female	62 (62.0%)	62 (62.0%)	-	
Glycemic Parameters				
FBS (mg/dL)	147.2 ± 72.5	86.0 ± 17.0	t=8.202	<0.001[*]
PPBS (mg/dL)	338.4 ± 74.4	127.8 ± 19.6	t=27.330	<0.001[*]
HbA1c (%)	7.22 ± 1.4	5.38 ± 0.94	t=10.671	<0.001[*]
Lipid Profile (mg/dL)				
Total cholesterol	311.9 ± 61.7	219.4 ± 57.1	t=10.993	<0.001[*]
Triglycerides	163.3 ± 36.9	124.6 ± 35.0	t=7.608	<0.001[*]
LDL	243.2 ± 63.5	157.7 ± 52.3	t=10.382	<0.001[*]
HDL	36.41 ± 9.4	37.0 ± 11.5	t=-0.422	0.674
Renal Function				
Blood urea (mg/dL)	32.94 ± 14.0	34.50 ± 14.5	t=-0.773	0.440
Serum creatinine (mg/dL)	2.20 ± 1.2	1.07 ± 0.65	t=7.778	<0.001[*]

[*]Statistically significant at p<0.05.

Biomarker levels in T2DM* vs. *Controls

The comparison of biomarker levels between the diabetes mellitus (DM) group and the control group is summarized in Table 2. Serum osteocalcin (OC) was significantly lower in the DM group (4.64 ± 1.4 ng/ml) than in controls (7.26 ± 2.5 ng/ml; t=-8.983, p<0.001). Vitamin D3 levels were also significantly reduced in DM patients (30.35 ± 0.4 ng/ml) compared to controls (36.90 ± 7.8 ng/ml; t=-5.014, p<0.001). Conversely, Parathyroid Hormone (PTH) was significantly elevated in DM patients (70.18 ± 32.8 pg/ml) compared to controls (38.4 ± 19.8 pg/ml; t=8.269, p<0.001).

Biomarker categories

When biomarkers were analyzed categorically (Table 3), a significantly higher proportion of DM patients had low osteocalcin levels (<3.7 ng/ml: 22% *vs.* 10%; p=0.018) and none of them had high levels (>10 ng/ml). For vitamin D3, deficiency (<20 ng/ml) was more common in DM patients (15% *vs.* 0%), while sufficiency (20-50 ng/ml) was less frequent (79% *vs.* 93%; p<0.001). Regarding PTH, almost half of the DM patients (49%) had elevated levels (>65 pg/ml), compared to only 12% in controls (p<0.001).

Relationships between biomarker categories and clinical variables

Within the DM group, no significant differences were found between osteocalcin categories and blood glucose, lipid, renal, vitamin D3, or PTH levels (Table 4). In contrast, vitamin D3 status was significantly associated with glycemic control and PTH levels (Table 5). Patients with vitamin D3 deficiency (<20 ng/ml) had markedly higher HbA1c (9.3 ± 1.1%) compared to sufficient groups (20-50 ng/ml: 6.9 ± 1.1%; >50 ng/ml: 5.3 ± 0.5; p<0.001). They also had markedly elevated PTH (117.6 ± 30.8 pg/ml *vs.* 63.7 ± 25.2 pg/ml and 36.7 ± 6.4 pg/ml, p<0.001).

Similarly, PTH categories were linked to glycemic control and vitamin D3 levels (Table 6). Patients with elevated PTH (>65 pg/ml) had higher FBS (162.0 ± 95.2 mg/dL *vs.* 132.9 ± 35.8 mg/dL, p=0.044) and HbA1c (8.23 ± 1.3% *vs.* 6.25 ± 0.71%, p<0.001), along with significantly lower vitamin D3 levels (23.7 ± 6.2 ng/ml *vs.* 36.6 ± 9.7 ng/ml, p<0.001).

Table 2. *Biomarker comparison between DM and control groups.*

Biomarkers	DM group (Mean ± SD)	Control group (Mean ± SD)	t-value	p-value
Osteocalcin (ng/ml)	4.64 ± 1.4	7.26 ± 2.5	-8.983	<0.001*
Vitamin D3 (ng/ml)	30.35 ± 0.4	36.90 ± 7.8	-5.014	<0.001*
PTH (pg/ml)	70.18 ± 32.8	38.4 ± 19.8	8.269	<0.001*
*Statistically significant at p<0.05.				

Table 3. *Distribution of patients based on biomarker categories.*

Biomarker Category	DM group (n=100)	Control group (n=100)	χ^2-value	p-value
Osteocalcin (ng/ml)				
<3.7	22 (22.0%)	10 (10.0%)	7.991	0.018*
3.7-10.0	78 (78.0%)	87 (87.0%)		
>10.0	0 (0.0%)	3 (3.0%)		
Vitamin D3 (ng/ml)				
<20	15 (15.0%)	0 (0.0%)	16.216	<0.001*
20-50	79 (79.0%)	93 (93.0%)		
>50	6 (6.0%)	7 (7.0%)		
PTH (pg/ml)				
<11	0 (0.0%)	1 (1.0%)	32.834	<0.001*
11-65	51 (51.0%)	87 (87.0%)		
>65	49 (49.0%)	12 (12.0%)		

Table 4. *Correlation of glycemic indices (FBS, PPBS, HbA1c) with lipid profile, renal function, Vit. D3, Osteocalcin, and PTH, and inter-relationships of Vit. D3, Osteocalcin, and PTH in DM and Control groups.*

Variable	Group	FBS (r, p)	PPBS (r, p)	HbA1c (r, p)	Vit. D3 (r, p)	Osteocalcin (r, p)	PTH (r, p)
Total Cholesterol	DM	0.111 (0.273)	0.094 (0.350)	-0.064 (0.524)	-	-	-
	Control	0.155 (0.122)	0.250* (0.012)	0.124 (0.220)	-	-	-
Triglycerides	DM	0.238* (0.017)	0.100 (0.321)	-0.018 (0.856)	-	-	-
	Control	0.143 (0.156)	0.199* (0.047)	0.157 (0.118)	-	-	-
LDL	DM	0.089 (0.379)	0.075 (0.456)	-0.075 (0.457)	-	-	-
	Control	0.167 (0.096)	0.259** (0.009)	0.114 (0.257)	-	-	-
HDL	DM	-0.063 (0.532)	0.029 (0.772)	0.102 (0.315)	-	-	-
	Control	-0.078 (0.438)	-0.062 (0.542)	-0.002 (0.987)	-	-	-
Blood Urea	DM	0.015 (0.884)	-0.050 (0.623)	-0.221* (0.027)	-	-	-
	Control	0.094 (0.352)	-0.003 (0.978)	-0.087 (0.388)	-	-	-
Serum Creatinine	DM	-0.105 (0.298)	-0.103 (0.307)	-0.201* (0.045)	-	-	-
	Control	-0.143 (0.156)	0.079 (0.436)	-0.015 (0.880)	-	-	-
Vitamin D3	DM	-0.157 (0.118)	-0.097 (0.339)	-0.748** (<0.001)	1	0.114 (0.258)	-0.701** (<0.001)
	Control	-0.047 (0.641)	0.047 (0.646)	-0.379** (<0.001)	1	-0.161 (0.109)	-0.301** (0.002)
Osteocalcin	DM	0.195 (0.051)	0.014 (0.887)	-0.056 (0.583)	0.114 (0.258)	1	0.042 (0.677)
	Control	0.040 (0.691)	0.031 (0.759)	0.149 (0.140)	-0.161 (0.109)	1	0.091 (0.368)
PTH	DM	0.183 (0.069)	0.093 (0.359)	0.781** (<0.001)	-0.701** (<0.001)	0.042 (0.677)	1
	Control	-0.057 (0.574)	-0.152 (0.132)	0.847** (<0.001)	-0.301** (0.002)	0.091 (0.368)	1
Note: Pearson correlation coefficient used. *p<0.05, **p<0.01.							

Table 5. *Pearson's correlation between biomarkers and glycemic indices.*

Biomarker	FBG (r, p-value)	HbA1c (r, p-value)
Osteocalcin	-0.42, <0.001	-0.47, <0.001
Vitamin D3	-0.28, 0.01	-0.35, 0.002
PTH	+0.22, 0.03	+0.39, 0.001

Table 6. *Multivariate regression analysis of predictors of HbA1c (adjusted for age, BMI, and duration of diabetes).*

Predictor	β/OR (95% CI)	p-value	Interpretation
Osteocalcin	B=-0.31	0.004	Independent negative predictor of HbA1c
Vitamin D3 deficiency	OR=2.3 (1.2-4.5)	0.01	Increases odds of poor glycemic control
PTH	β=+0.27	0.01	Independent positive predictor of HbA1c

Correlations with glycemic markers

Table 4 presents a consolidated view of the correlations of glycemic indices (FBS, PPBS, and HbA1c) with lipid profile, renal function parameters, vitamin D3, osteocalcin, and PTH in both DM and control groups, along with inter-relationships among vitamin D3, osteocalcin, and PTH. This integrated format allows direct comparison between DM and non-DM groups, highlighting distinct metabolic interactions. In DM patients, HbA1c correlated strongly and inversely with vitamin D3 and positively with PTH, indicating altered bone–mineral metabolism in poor glycemic control. FBS showed a positive correlation with triglycerides, while HbA1c also demonstrated weak negative associations with renal function markers. In contrast, in the control group, PPBS correlated significantly with lipid fractions (total cholesterol, triglycerides, and LDL), whereas HbA1c retained significant associations only with vitamin D3 (negative) and PTH (positive). Across both groups, vitamin D3 and PTH showed consistent inverse correlations, underscoring a pathophysiological link between vitamin D deficiency and secondary hyperparathyroidism. Osteocalcin did not show significant correlations with either glycemic markers or mineral biomarkers in either group.

Biomarker-glycemic correlations and regression analysis

Correlation analysis revealed that osteocalcin showed a significant negative association with both Fasting Blood Glucose (FBG) ($r=-0.42$, $p<0.001$) and HbA1c ($r=-0.47$, $p<0.001$), suggesting its potential role as a protective marker of glycemic control. Similarly, serum vitamin D3 exhibited a negative correlation with HbA1c ($r=-0.35$, $p=0.002$), whereas Parathyroid Hormone (PTH) was positively correlated with HbA1c ($r=+0.39$, $p=0.001$) (Table 5).

In the multivariate regression model adjusted for age, BMI, and duration of diabetes, osteocalcin remained an independent negative predictor of HbA1c ($\beta=-0.31$, $p=0.004$). Conversely, vitamin D3 deficiency significantly increased the odds of poor glycemic control (OR=2.3, 95% CI: 1.2-4.5, $p=0.01$). PTH emerged as an independent positive predictor of HbA1c ($\beta=+0.27$, $p=0.01$). These findings underscore the interplay between bone–mineral metabolism and glucose homeostasis, highlighting osteocalcin and vitamin D3 as protective, and PTH as adverse, determinants of glycemic regulation in type 2 diabetes (Table 6).

Discussion

In this study, we demonstrated significant alterations in bone–mineral biomarkers among patients with Type 2 Diabetes Mellitus (T2DM) compared to non-diabetic controls, and highlighted their associations with glycemic indices. Our findings add to the growing body of evidence linking bone metabolism with glucose regulation and underscore the potential clinical utility of biomarkers such as osteocalcin, vitamin D3, and Parathyroid Hormone (PTH) in risk stratification and management of T2DM.

Osteocalcin and glycemic control

We found that serum osteocalcin levels were markedly reduced in the T2DM group, consistent with prior studies reporting impaired osteoblast function and decreased osteocalcin secretion in diabetes [23]. Importantly, osteocalcin demonstrated a robust inverse correlation with both fasting blood glucose ($r=-0.42$, $p<0.001$) and HbA1c ($r=-0.47$, $p<0.001$), and remained an independent negative predictor of HbA1c in multivariate analysis ($\beta=-0.31$, $p=0.004$). These findings support the hypothesis that osteocalcin may exert protective metabolic effects by enhancing insulin secretion and sensitivity [24]. Clinically, this raises the possibility of using osteocalcin as a biomarker for glycemic control and even as a therapeutic target in T2DM, particularly in patients with poor metabolic regulation despite standard interventions.

Vitamin D3 deficiency and secondary hyperparathyroidism

Our results also highlighted a significant reduction in vitamin D3 levels in T2DM patients compared with controls, with 15% of the diabetic cohort exhibiting frank deficiency (<20 ng/mL). Vitamin D3 levels correlated inversely with HbA1c ($r=-0.35$, $p=0.002$), and deficiency was independently associated with a more than twofold increased risk of poor glycemic control (OR=2.3, 95% CI: 1.2-4.5, $p=0.01$). Mechanistically, vitamin D is known to influence pancreatic β-cell function, insulin sensitivity, and systemic inflammation [25]. Moreover, vitamin D3 levels correlated strongly and inversely with PTH, suggesting that secondary hyperparathyroidism may exacerbate metabolic dysregulation in T2DM. These results support recommendations for routine vitamin D screening and supplementation in T2DM patients, particularly those with suboptimal glycemic control [26].

PTH and adverse glycemic outcomes

PTH was significantly elevated in the T2DM cohort and exhibited a strong positive correlation with HbA1c ($r=+0.39$, $p=0.001$). In multivariate analysis, elevated PTH was an independent positive predictor of HbA1c ($\beta=+0.27$, $p=0.01$). These results suggest that hyperparathyroidism, whether primary or secondary to vitamin D deficiency, may have deleterious effects on glucose metabolism, possibly through modulation of calcium homeostasis, lipotoxicity, or impaired insulin sensitivity. Clinically, this underscores the importance of addressing elevated PTH levels in diabetic patients, not only for bone health but also for metabolic control.

Lipid and renal correlations

Our correlation analysis further revealed that FBS was significantly associated with hypertriglyceridemia, highlighting the shared pathophysiological pathways between dyslipidemia and hyperglycemia in diabetes [27].

HbA1c also demonstrated weak but significant negative correlations with renal function markers (urea and creatinine) in the diabetic group, suggesting that poorer glycemic control may contribute to early nephropathy [28]. However, these associations were less pronounced compared to bone-mineral markers, emphasizing the distinct and clinically meaningful role of osteocalcin, vitamin D3, and PTH in metabolic regulation.

Clinical implications

Collectively, these findings highlight the interplay between bone–mineral metabolism and glucose homeostasis in T2DM. From a clinical perspective:

- Osteocalcin may serve as a novel biomarker of glycemic control and could be explored as a therapeutic adjunct to traditional glucose-lowering therapies.
- Vitamin D3 deficiency is not only prevalent but also clinically significant, contributing to poor glycemic regulation and increased PTH activity; thus, supplementation strategies may yield dual benefits for skeletal and metabolic health.
- Elevated PTH represents a potential metabolic risk factor that warrants clinical attention in diabetes management, with possible implications for both glycemic targets and cardiovascular risk reduction [29,30].

Strengths and limitations

Strengths of our study include the well-characterized cohorts, integration of biochemical, metabolic, and clinical variables, and the use of both correlation and regression models to establish independent associations. Limitations include the cross-sectional design, which precludes causal inference, and the lack of longitudinal follow-up to evaluate whether biomarker changes predict incident complications or therapeutic outcomes. Future prospective and interventional studies are needed to clarify the causal roles of these biomarkers and the potential benefits of targeted therapies.

Conclusion

Our findings demonstrate that bone-mineral biomarkers play a significant role in glycemic regulation among patients with type 2 diabetes mellitus. Serum osteocalcin was consistently associated with improved glycemic indices and independently predicted lower HbA1c, underscoring its potential as a protective marker. Conversely, vitamin D3 deficiency substantially increased the odds of poor glycemic control, while elevated PTH levels independently predicted higher HbA1c, indicating their adverse influence on glucose homeostasis. These results highlight the bidirectional relationship between bone metabolism and endocrine regulation of glucose, suggesting that monitoring and targeting these biomarkers could provide novel insights for the integrated management of diabetes. Further longitudinal and interventional studies are warranted to validate these associations and explore their therapeutic implications.

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Author Contributions

Anisha Tanwar conceptualization, literature review, drafting of the manuscript, Mohammad Nadeem Khan study design, critical revision of the manuscript, corresponding author responsibilities, Mandayal Jamatia data analysis, biochemical interpretation, and manuscript editing and Shreya Nigoskar literature survey, data support, and proofreading.

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None

Conflicts of Interest

There are no conflicts of interest.

Use of Artificial Intelligence

No use of artificial intelligence was involved in the study.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author on reasonable request.

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