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# Relationship between bone turnover markers and renal disease in elderly patients with type 2 diabetes: a cross-sectional study

Shuwu Wei<sup>1,2</sup>, Xinyu Pan<sup>1</sup> and Junping Wei<sup>1\*</sup>

## Abstract

**Objective** The prevalence of type 2 diabetes mellitus (T2DM) and bone metabolism disorders increase with age. Diabetic kidney disease (DKD) is one of the most serious microvascular complications of T2DM, and bone metabolism disorders are closely linked to the occurrence of DKD. The relationship between bone turnover markers (BTMs) and the kidney disease in elderly patients with T2DM remains unclear. Therefore, this study aims to investigate the association between common BTMs and DKD in a large sample of elderly patients. The goal is to provide a basis for early identification of high-risk individuals for DKD among elderly T2DM patients from a bone metabolism perspective.

**Methods** In this cross-sectional study, BTMs were collected from a cohort of 2,051 hospitalized Chinese patients. The relationships between 25-hydroxyvitamin D (25-OH-D),  $\beta$ -CrossLaps ( $\beta$ -CTX), osteocalcin (OSTEOC), intact parathyroid hormone (iPTH), and total type I collagen N-terminal propeptide (TP1NP), and DKD, as well as urinary albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) were analyzed using regression analysis and restrictive cubic spline (RCS) curves.

**Results** Higher 25-OH-D levels were independently linked to a lower incidence of DKD and decreased UACR. The RCS curves showed a linear association of 25-OH-D and DKD, approaching the L-shape.  $\beta$ -CTX was independently and positively correlated with UACR. There is an independent positive correlation between OSTEOC and UACR and a negative correlation with eGFR. iPTH is independently and positively correlated with DKD incidence and UACR, and negatively correlated with eGFR. Additionally, the RCS curves showed a non-linear association of OSTEOC and iPTH and DKD, approaching the J-shape, and the point of inflection is 10.875 ng/L and 34.15 pg/mL respectively. There is an independent positive correlation between TP1NP and UACR incidence, and a negative correlation with eGFR. Risk estimates significantly increase with higher TP1NP levels in the RCS model.

**Conclusion** BTMs are closely associated with kidney disease in elderly patients with T2DM. These discoveries potentially assist clinicians in establishing more preventive measures and targeted treatment strategies for elderly patients with T2DM.

**Keywords** Diabetic kidney disease, Bone turnover markers, 25-hydroxyvitamin D,  $\beta$ -CrossLaps, Osteocalcin, Intact parathyroid hormone, Total type I collagen N-terminal propeptide, Type 2 diabetes mellitus, Elderly

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## Introduction

As the population ages, the proportion of elderly individuals (aged  $\geq 60$ ) in China was approximately 17.3% in 2017. By 2050, this percentage is projected to exceed 30%, with more than 20% of the elderly population expected to suffer from diabetes, of which over 95% will be type 2 diabetes mellitus (T2DM) [1]. Chronic hyperglycemia has been observed to reduce osteoblast numbers, impair bone formation, slow bone mineralization, and enhance osteoclast activity, resulting in an imbalance in bone metabolism, particularly in elderly patients [2, 3]. Diabetic kidney disease (DKD) is a prevalent microvascular complication of diabetes mellitus [4]. The presence of DKD significantly complicates the management of diabetes in elderly patients and poses a serious threat to their health and mortality worldwide. Research indicates that bone metabolism disorders may be a risk factor for the development of kidney complications in T2DM [5]. Identifying potential bone metabolism markers related to incident DKD is essential for screening elderly populations with diabetes mellitus who are at high risk for DKD. It also aids in researching the mechanisms of DKD onset and benefits early intervention and correction of risk factors.

Osteoblasts form new bone, while osteoclasts resorb old bone to maintain bone structure integrity. The metabolites produced during this process are known as bone turnover markers (BTMs). Commonly assessed BTMs include 25-hydroxyvitamin D (25-OH-D),  $\beta$ -CrossLaps ( $\beta$ -CTX), osteocalcin (OSTEOC), intact parathyroid hormone (iPTH), and total type I collagen N-terminal propeptide (TP1NP). Previous studies have suggested that these bone metabolic indicators may be involved in the crosstalk between bone, islet, and adipose tissues [6–9] and may be associated with early renal damage in DKD [10, 11]. However, these findings remain controversial and inconclusive. Only four studies have reported the association between BTMs and the risk of DKD or eGFR and UACR [12–15]. Two studies showed that OSTEOC, TP1NP, and  $\beta$ -CTX levels negatively correlated with eGFR in diabetes patients (one did not differentiate between type 1 and type 2 disease) [13, 14]. Another study found that UACR was positively associated with OSTEOC, TP1NP,  $\beta$ -CTX and 25-OH-D in T2DM patients [15]. In contrast, one study indicated that serum concentrations of BTMs were not associated with the risks of DKD [12]. Notably, most of these studies are limited by small sample sizes and did not clarify the non-linear relationship between BTMs and DKD. Additionally, there are no studies investigating the relationship between BTMs and DKD in the elderly T2DM population currently.

The relationship between BTMs and the occurrence of kidney disease in elderly patients with T2DM remains

unclear. Therefore, this study aims to investigate the association between these five common BTMs and kidney disease in a large sample of elderly patients with T2DM. The goal is to provide a basis for early identification of high-risk individuals for DKD among elderly T2DM patients from a bone metabolism perspective. This approach is beneficial for correcting bone metabolism disorders and, concurrently, slowing the progression of DKD, ultimately contributing to an improved quality of life for elderly individuals with diabetes.

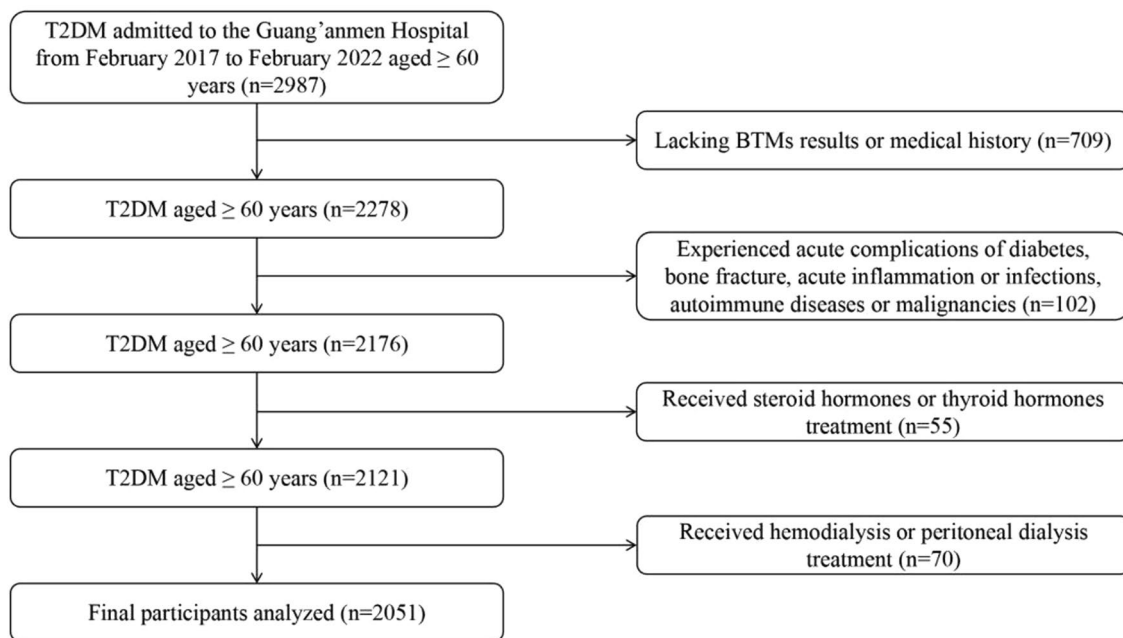
## Materials and methods

### Study design and participants

A total of 2,987 individuals aged  $\geq 60$  years with T2DM admitted to the Guang'anmen Hospital from February 2017 to February 2022 were enrolled in this study. The flow chart of the study is shown in Fig. 1. T2DM was diagnosed according to the criteria established by the American Diabetes Association [16]. The exclusion criteria were as follows: (1) lacking BTMs results or medical history, (2) experiencing acute complications of diabetes, bone fractures, acute inflammation or infections, autoimmune diseases, or malignancies, (3) receiving steroid or thyroid hormone treatment, and (4) receiving hemodialysis or peritoneal dialysis treatment. Ultimately, 2,051 participants were included in the analysis. This retrospective study obtained approval from the Medical Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences (2023-187-KY), and strictly adhered to the principles outlined in the Declaration of Helsinki.

### Measurements

Information on sex, age, height, weight, duration of diabetes, systolic blood pressure (SBP), diastolic blood pressure (DBP), and medication use was extracted from electronic medical records using standardized questionnaires by the same trained personnel. The medications included anti-osteoporosis drugs (calcium, vitamin D, bisphosphonate, or other drugs), anti-diabetic agents (pioglitazone, SGLT-2 inhibitors, and GLP-1 analogues), and ACEI/ARB. Body mass index (BMI) was calculated as body weight (kg) divided by the square of height ( $m^2$ ). Levels of 25-OH-D,  $\beta$ -CTX, OSTEOC, iPTH, and TP1NP were assayed using electrochemiluminescence assays. Fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), albumin (ALB), serum calcium, serum phosphorus, serum uric acid, serum creatinine, and hemoglobin were measured using an automated analyzer with standard methods. Urine albumin-to-creatinine ratio (UACR) was



**Fig. 1** Flow chart of the study

calculated from urine albumin and urine creatinine levels. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation designed for individuals of Asian origin. DKD was defined as persistent proteinuria and/or progressive renal insufficiency. In patients without other chronic kidney diseases, those with  $\text{UACR} \geq 30 \text{ mg/g}$  and/or  $\text{eGFR} < 60 \text{ mL/min per } 1.73 \text{ m}^2$  twice after three tests in 3~6 months were considered to have developed DKD, in accordance with the criteria set by the American Diabetes Association [17].

### Statistical analysis

The current analysis was conducted using IBM SPSS Statistics (v 26), R (v 4.4.1), and Zstats (v1.0). Statistical significance was established at a two-sided  $P$ -value  $< 0.05$ . Continuous variables were presented as means  $\pm$  standard deviation (SD) or medians  $\pm$  interquartile range (IQR), while categorical variables were expressed as percentages (%). For the comparison of continuous variables, the nonparametric rank-sum test or Student's  $t$ -test was used, and the Chi-square test was applied for categorical variables. BTMs levels were categorized into quartiles. Regression analysis was performed to identify associations between BTMs and DKD, UACR, and eGFR. The first quartile of BTMs was used as a reference in logistic regression. The associations were evaluated by a crude model 0 with no adjustments, a multivariable model 1 adjusted for age, sex, BMI, and duration of diabetes, and a multivariable model 2 adjusted for age, sex, BMI, duration of diabetes, SBP, DBP, FPG, HbA1c, TC, TG, HDL,

LDL, ALT, AST, ALP, Hemoglobin, Serum calcium, Serum phosphorus, Serum uric acid and medications. and age and family history of diabetes. Data were summarized as odds ratios or beta coefficients with 95% confidence intervals (CIs). The association of BTMs with the incidence of DKD was further evaluated on a continuous scale with restrictive cubic spline (RCS) curves.

### Results

The general and sociodemographic characteristics of the study participants are shown in Table 1. The final analysis included 2,051 diabetic participants. Among them, 1,267 participants (61.7%) were diagnosed without DKD (Non-DKD), while 784 participants (38.2%) were diagnosed with DKD. Compared to Non-DKD participants, those with DKD exhibited significantly higher values for age, the number of men, BMI, duration of diabetes, iPTH, FPG, HbA1c, TG, ALP, serum creatinine, serum uric acid, UACR, HbA1c, number of anti-diabetic agents and the number of ACEI/ARB (all  $P < 0.05$ ). No differences were observed in DBP,  $\beta$ -CTX, TP1NP, TC, LDL, AST, serum phosphorus, or number of anti-osteoporosis drugs between the two groups. However, SBP, 25-OH-D, OSTEOC, HDL, ALT, ALB, hemoglobin, serum calcium, and eGFR were significantly lower in DKD patients compared to those without DKD (all  $P < 0.05$ ).

We developed several models to evaluate the independent effects of BTMs on DKD, UACR, and eGFR. As presented in Table 2, elevated 25-OH-D levels were associated with a decreased likelihood of DKD, and reduced UACR without any adjustments. After controlling for

**Table 1** General characteristics of the participants by DKD

Characteristics	Non-DKD	DKD	P value
Age, years	66 ± 6	67 ± 8	<0.001
Men, %	532(42%)	377(48.1%)	0.007
BMI, kg/m <sup>2</sup>	25.31 ± 4.10	26.70 ± 5.41	<0.001
Duration of diabetes, years	16 ± 12	18 ± 15	<0.001
SBP, mmHg	138 ± 19	137 ± 20	0.001
DBP, mmHg	78 ± 15	78 ± 15	0.924
25-OH-D, nmol/L	17.31 ± 10.46	15.40 ± 9.54	<0.001
β-CTX, ng/mL	0.35 ± 0.24	0.336 ± 0.25	0.077
OSTEOC, ng/L	11.26 ± 5.45	10.48 ± 5.40	0.017
iPTH, pg/ml	34.00 ± 17.20	34.30 ± 22.75	0.013
TP1NP, µg/L	39.25 ± 21.26	38.64 ± 24.65	0.808
FPG, mmol/L	11.12 ± 6.99	11.125 ± 7.49	<0.001
HbA1c, %	8.00 ± 2.20	8.50 ± 2.90	<0.001
TC, mmol/L	4.33 ± 1.55	4.53 ± 1.81	0.330
TG, mmol/L	1.39 ± 0.94	1.54 ± 0.87	<0.001
HDL, mmol/L	1.16 ± 0.34	1.12 ± 0.30	<0.001
LDL, mmol/L	2.69 ± 1.16	2.93 ± 1.32	0.183
ALT, U/L	18.10 ± 11.40	17.75 ± 11.32	0.002
AST, U/L	19.30 ± 8.13	18.85 ± 7.80	0.344
ALP, U/L	80.0 ± 33.00	83.50 ± 34.75	0.030
ALB, g/L	43.20 ± 3.72	41.15 ± 4.50	<0.001
Hemoglobin, g/L	138 ± 19	131 ± 21	<0.001
Serum calcium, mmol/L	2.395 ± 0.12	2.38 ± 0.14	<0.001
Serum phosphorus, mmol/L	1.15 ± 0.21	1.18 ± 0.26	0.636
Serum creatinine, umol/L	62 ± 21	77.95 ± 40.75	<0.001
Serum uric acid, umol/L	310 ± 114.5	341.5 ± 131.75	<0.001
UACR, mg/g	9.16 ± 8.74	94.84 ± 303.53	<0.001
eGFR, mL/min per 1.73 m <sup>2</sup>	95.64 ± 17.80	80.73 ± 38.38	<0.001
Medications			
ACEI/ARB, %	1061(84.2%)	718(91.6%)	<0.001
Anti-osteoporosis drugs, %	820(64.7%)	487(62.1%)	0.234
Anti-diabetic agents, %	350(27.6%)	321(40.9%)	<0.001
Diabetic retinopathy	177(14.0%)	520(66.3%)	<0.001

The data are presented as means ± SD for continuous variables with a normal distribution, medians ± IQR for continuous variables with a skewed distribution, and as numerical proportions for categorical variables. For the comparison of continuous variables, the nonparametric rank-sum test or Student's t-test was used, and the Chi-square test was applied for categorical variables

DKD Diabetic kidney disease, BMI Body mass index, SBP Systolic blood pressure, DBP Diastolic blood pressure, 25-OH-D 25-hydroxyvitamin D, β-CTX β-CrossLaps, OSTEOC Osteocalcin, iPTH Intact parathyroid hormone, TP1NP Total type I collagen N-terminal propeptide, FPG Fasting plasma glucose, HbA1c Hemoglobin A1C, TC Total Cholesterol, TG Triglyceride, HDL High-density lipoprotein, LDL Low-density lipoprotein, ALT Alanine aminotransferase, AST Aspartate aminotransferase, ALP Alkaline phosphatase, ALB Albumin, UACR Urine albumin to creatinine ratio, eGFR Estimated glomerular infiltration rate

various confounding variables in model 1 and model 2, the associations between 25-OH-D and the prevalence of DKD, as well as UACR, remained statistically significant. In these three models, β-CTX was positively associated with UACR, elevated OSTEOC levels were associated with increased UACR and reduced eGFR, and iPTH was positively associated with the likelihood of DKD in models 1 and 2, positively associated with UACR in all three models, and negatively associated with eGFR in all three

**Table 2** The associations between BTMs and DKD, UACR, and eGFR

	β-CTX		OSTEOC		iPTH		TP1NP	
	OR or β(95%CI)	P value	OR or β(95%CI)	P value	OR or β(95%CI)	P value	OR or β(95%CI)	P value
DKD <sup>0</sup>	0.951(0.929, 0.973)	<0.001	0.711(0.319, 1.587)	0.405	1.007(0.980, 1.036)	0.601	1.014(1.005, 1.024)	0.003
DKD <sup>1</sup>	0.953(0.930, 0.976)	<0.001	1.343(0.571, 3.160)	0.499	1.024(0.994, 1.056)	0.118	1.012(1.002, 1.021)	0.016
DKD <sup>2</sup>	0.969(0.944, 0.995)	0.02	1.048(0.357, 3.071)	0.932	1.003(0.963, 1.045)	0.880	1.012(0.999, 1.025)	0.064
UACR <sup>0</sup>	-8.312(-11.268, -5.356)	<0.001	134.853(18.521, 251.185)	0.023	11.378(7.310, 15.447)	<0.001	2.485(1.142, 3.828)	<0.001
UACR <sup>1</sup>	-8.445(-11.457, -5.434)	<0.001	170.464(49.078, 291.851)	0.006	12.654(8.455, 16.853)	<0.001	2.394(1.040, 3.748)	0.001
UACR <sup>2</sup>	-6.294(-9.206, -3.382)	<0.001	128.944(9.116, 248.772)	0.035	9.145(4.801, 13.488)	<0.001	1.972(0.588, 3.356)	0.005
eGFR <sup>0</sup>	0.096(-0.102, 0.293)	0.342	-5.260(-12.894, 2.374)	0.177	-0.532(-0.801, -0.262)	<0.001	-0.308(-0.394, -0.223)	<0.001
eGFR <sup>1</sup>	-0.033(-0.220, 0.155)	0.734	-9.709(-17.104, -2.315)	0.010	-0.639(-0.897, -0.381)	<0.001	-0.270(-0.350, -0.189)	<0.001
eGFR <sup>2</sup>	-0.133(-0.309, 0.043)	0.138	-6.720(-13.878, 0.438)	0.066	-0.421(-0.682, -0.161)	0.002	-0.230(-0.311, -0.149)	<0.001

Binary logistic regression analysis was performed to identify the relationships between the prevalence of DKD and BTMs levels, and the findings were summarized as odds ratios and regression coefficients, both with 95% CIs. Linear regression analysis was utilized to examine the associations between UACR and eGFR with BTMs levels, and the results were summarized as beta and regression coefficients, again accompanied by 95% CIs

<sup>0</sup> The model was not adjusted

<sup>1</sup> The model was adjusted for age, sex, BMI, and duration of diabetes

<sup>2</sup> The model was adjusted for model 1 and SBP, DBP, FPG, HbA1c, TC, TG, HDL, LDL, ALT, AST, ALP, Hemoglobin, Serum calcium, Serum phosphorus, Serum uric acid and medications, and the medications included anti-osteoporosis drugs (calcium, vitamin D, bisphosphonate, or other drugs), anti-diabetic agents (pioglitazone, SGLT-2 inhibitors, and GLP-1 analogues), and ACEI/ARB

DKD Diabetic kidney disease, UACR Urine albumin to creatinine ratio, eGFR Estimated glomerular infiltration rate, 25-OH-D 25-hydroxyvitamin D, β-CTX β-CrossLaps, OSTEOC Osteocalcin, iPTH Intact parathyroid hormone, TP1NP Total type I collagen N-terminal propeptide

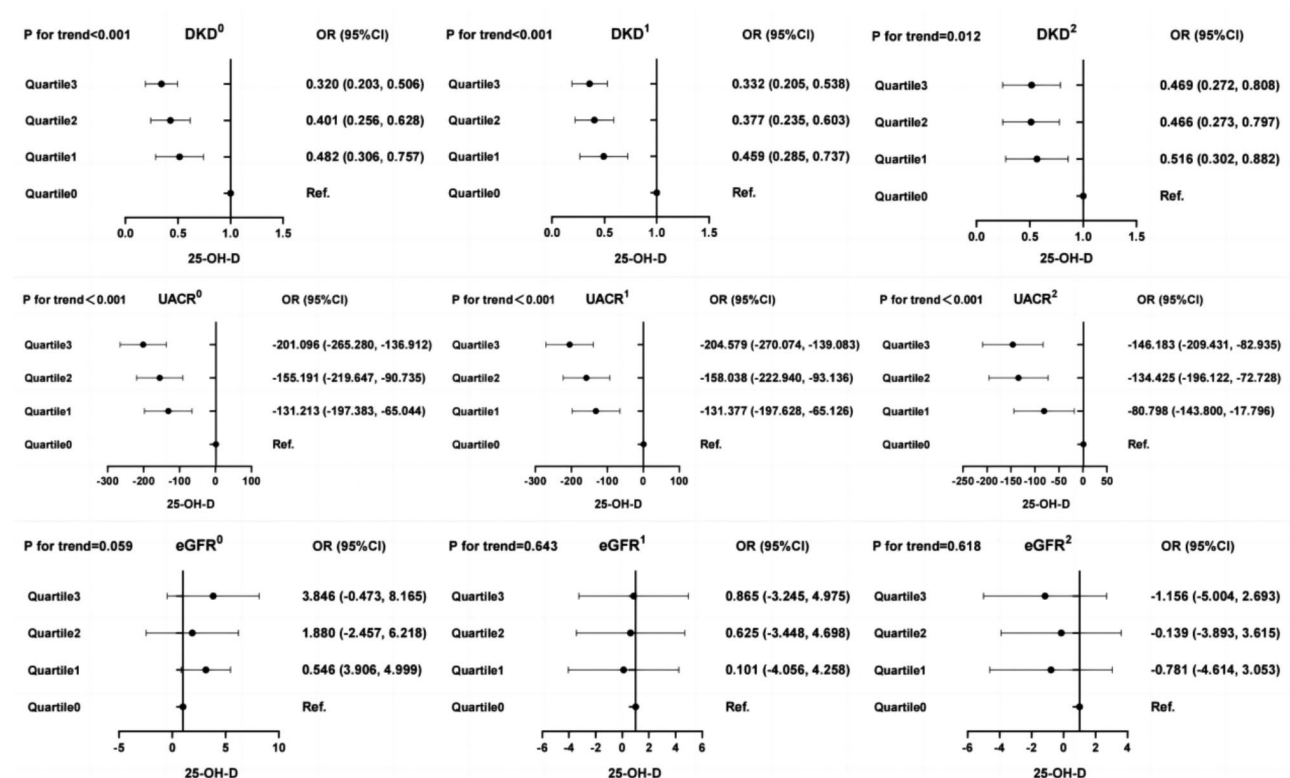
models. TP1NP was positively associated with UACR in all three models and negatively associated with eGFR in models 1 and 2. Multifactor analysis revealed that 25-OH-D is an independent protective factor for DKD, potentially contributing to a decreased UACR, while iPTH is an independent risk factor for DKD, potentially contributing to increased UACR and decreased eGFR. In addition,  $\beta$ -CTX, OSTEOC, iPTH, and TP1NP were independently associated with elevated UACR. OSTEOC and TP1NP were identified as independent risk factors for eGFR.

We evaluated the associations between 25-OH-D quartile levels and DKD, UACR, and eGFR, as shown in Fig. 2. Elevated 25-OH-D quartile levels were significantly associated with a decreased prevalence of DKD and reduced UACR after adjusting for potential confounders. However, no significant associations were observed between 25-OH-D quartile levels and eGFR. Compared to participants in the first quartile of 25-OH-D levels, those in the highest quartile exhibited a significant 68% decrease in the odds of having DKD in model 0. These associations remained significant in both model 1 and model 2. Notably, in modes 1 and 2, the prevalence of DKD among participants in the highest 25-OH-D quartile showed a

66.8% decrease and a 53.1% decrease, respectively, compared to those in the first quartile. Furthermore, our findings revealed that, in these models, as 25-OH-D quartile levels gradually increased, UACR showed a decreasing trend. Compared with the lowest quartile, individuals in the highest quartile exhibited the lowest  $\beta$  for UACR in model 2.

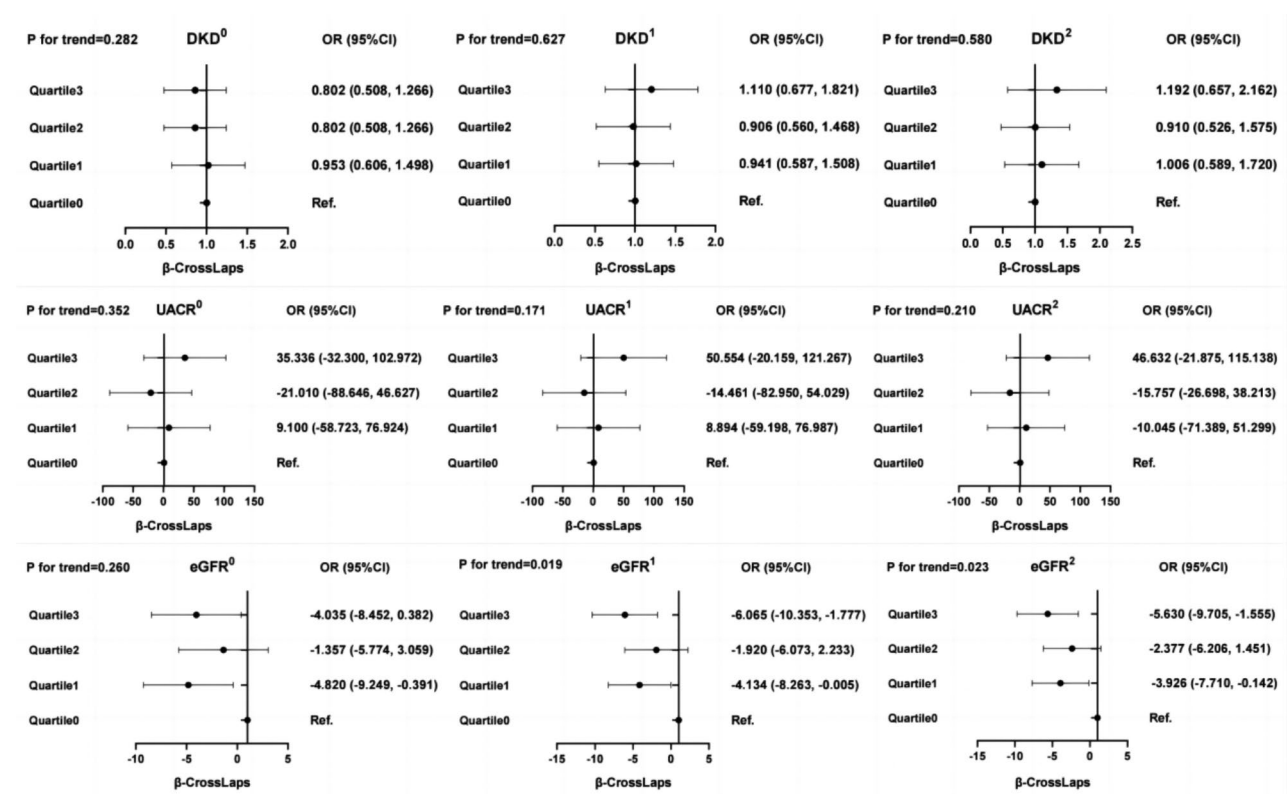
We evaluated the associations between  $\beta$ -CTX quartile levels and DKD, UACR, and eGFR, as shown in Fig. 3. No significant associations were observed between  $\beta$ -CTX quartile levels and the prevalence of DKD or UACR. However, elevated  $\beta$ -CTX quartile levels were found to be significantly associated with decreased eGFR. In these models, as  $\beta$ -CTX quartile levels increased, eGFR showed a decreasing trend after controlling for various confounding variables such as age, sex, BMI, duration of diabetes, SBP, DBP, FPG, HbA1c, TC, TG, HDL, LDL, ALT, AST, ALP, hemoglobin, serum calcium, serum phosphorus, serum uric acid and medications. Compared with the lowest quartile, individuals in the highest quartile exhibited the lowest  $\beta$  for eGFR in both model 2 and model 3.

We evaluated the associations between OSTEOC quartile levels and DKD, UACR, and eGFR, as shown in



**Fig. 2** The associations between 25-OH-D quartile levels and DKD, UACR, and eGFR. 0 The model was not adjusted. 1 The model was adjusted for age, sex, BMI, and duration of diabetes. 2 The model was adjusted for model 1 and SBP, DBP, FPG, HbA1c, TC, TG, HDL, LDL, ALT, AST, ALP, Hemoglobin, Serum calcium, Serum phosphorus, Serum uric acid and medications, and the medications included anti-osteoporosis drugs (calcium, vitamin D, bisphosphonate, or other drugs), anti-diabetic agents (pioglitazone, SGLT-2 inhibitors, and GLP-1 analogues), and ACEI/ARB. DKD Diabetic kidney disease, UACR Urine albumin to creatinine ratio, eGFR Estimated glomerular infiltration rate





**Fig. 3** The associations between  $\beta$ -CTX quartile levels and DKD, UACR, and eGFR. 0 The model was not adjusted. 1 The model was adjusted for age, sex, BMI, and duration of diabetes. 2 The model was adjusted for model 1 and SBP, DBP, FPG, HbA1c, TC, TG, HDL, LDL, ALT, AST, ALP, Hemoglobin, Serum calcium, Serum phosphorus, Serum uric acid and medications, and the medications included anti-osteoporosis drugs (calcium, vitamin D, bisphosphonate, or other drugs), anti-diabetic agents (pioglitazone, SGLT-2 inhibitors, and GLP-1 analogues), and ACEI/ARB. DKD Diabetic kidney disease, UACR Urine albumin to creatinine ratio, eGFR Estimated glomerular infiltration rate

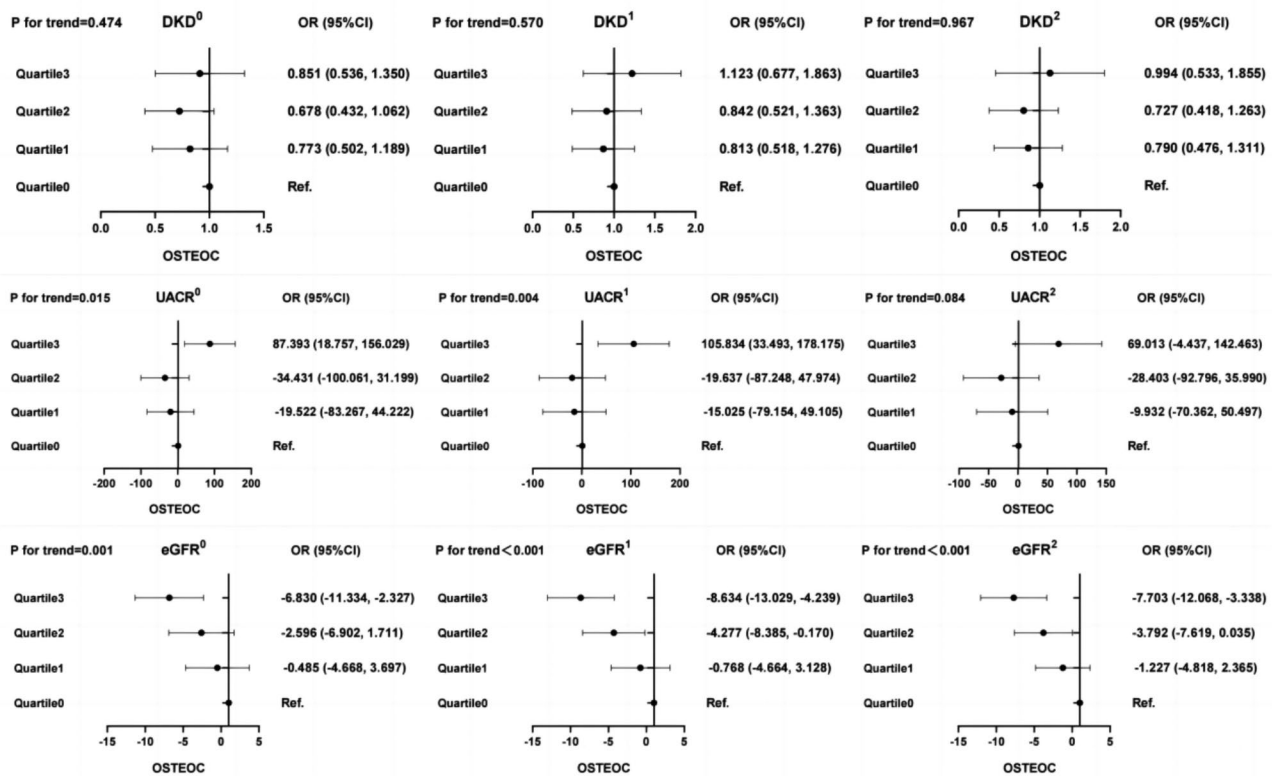
**Fig. 4.** No significant associations were observed between OSTEOC quartile levels and the prevalence of DKD. However, elevated OSTEOC quartile levels were found to be significantly associated with increased UACR in models 0 and 1, and decreased eGFR in all three models. In these models, as OSTEOC quartile levels increased, UACR showed an increasing trend, while eGFR showed a decreasing trend. Compared to the lowest quartile, individuals in the highest quartile exhibited the highest  $\beta$  for UACR and lowest  $\beta$  for eGFR in all three models.

We evaluated the associations between iPTH quartile levels and DKD, UACR, and eGFR, as shown in Fig. 5. Compared to participants in the first quartile of iPTH levels, those in the highest quartile exhibited a significant 81.5% increase in the odds of having DKD in model 0. However, after adjusting for various variables, the association between iPTH and the prevalence of DKD was not significant. Furthermore, elevated iPTH quartile levels were found to be significantly associated with a reduced eGFR after adjusting for potential confounders in all three models. Our findings revealed that, as iPTH quartile levels increased, eGFR showed a decreasing trend in all models. Compared to the lowest quartile, individuals

in the highest quartile exhibited the lowest  $\beta$  for eGFR in all three models.

We evaluated the associations between TP1NP quartile levels and DKD, UACR, and eGFR, as shown in Fig. 6. No significant associations were observed between TP1NP quartile levels and the prevalence of DKD. However, elevated TP1NP quartile levels were found to be significantly associated with increased UACR and decreased eGFR in all three models. In these models, as TP1NP quartile levels increased, UACR showed an increasing trend, while eGFR showed a decreasing trend. Compared to the lowest quartile, individuals in the highest quartile exhibited the highest  $\beta$  for UACR and the lowest  $\beta$  for eGFR in all models.

Figure 7 shows that the associations between 25-OH-D and TP1NP levels and the prevalence of DKD were linear in the adjusted RCS model. The risk estimates significantly decreased with increasing 25-OH-D levels, and the association approached the L-shape, while they significantly increased with rising TP1NP levels.  $\beta$ -CTX did not exhibit any independent effects on DKD in the multivariable model. Moreover, the RCS curves showed a non-linear association of OSTEOC and iPTH and DKD, approaching the J-shape, and the point of inflection



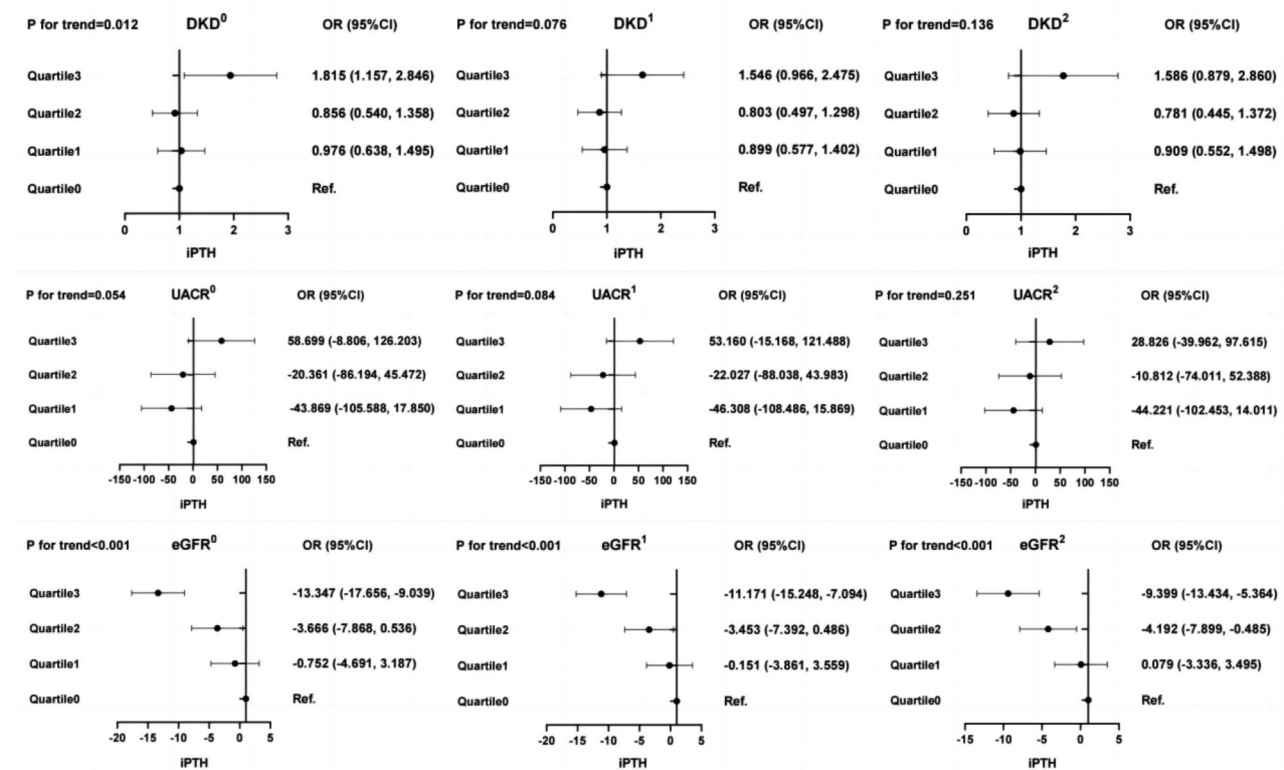
**Fig. 4** The associations between OSTEOC quartile levels and DKD, UACR, and eGFR. 0 The model was not adjusted. 1 The model was adjusted for age, sex, BMI, and duration of diabetes. 2 The model was adjusted for model 1 and SBP, DBP, FPG, HbA1c, TC, TG, HDL, LDL, ALT, AST, ALP, Hemoglobin, Serum calcium, Serum phosphorus, Serum uric acid and medications, and the medications included anti-osteoporosis drugs (calcium, vitamin D, bisphosphonate, or other drugs), anti-diabetic agents (pioglitazone, SGLT-2 inhibitors, and GLP-1 analogues), and ACEI/ARB. DKD Diabetic kidney disease, UACR Urine albumin to creatinine ratio, eGFR Estimated glomerular infiltration rate

is 10.875 ng/L and 34.15 pg/mL respectively. The risk estimates markedly increased when OSTEOC levels exceeded 10.875 ng/L and iPTH levels surpassed 34.15 pg/mL.

**Discussion**

We observed that 25-OH-D levels were significantly lower in patients with DKD compared to those without DKD. Elevated 25-OH-D levels were independently associated with a reduced incidence of DKD and a decrease in UACR. As 25-OH-D levels increased across quartiles, there was a trend of decreasing DKD incidence and UACR. After adjusting for confounding factors, the highest quartile of 25-OH-D demonstrated a significant 53.1% reduction in the prevalence of DKD compared to the first quartile. In the adjusted RCS model, the relationship between 25-OH-D levels and DKD prevalence was linear, approaching the L-shape, with risk estimates markedly decreasing as 25-OH-D levels increased. This suggests that higher levels of 25-OH-D may act as a protective factor against kidney complications in elderly patients with T2DM. These findings are consistent with previous findings [18–37], although some studies have reported inconsistent conclusions [38–45]. The discrepancies in

these findings may be attributed to differences in the populations studied, methodologies used, and the confounding factors controlled for. By dividing patients into pathological subgroups, it was found that up to 91.5% of patients with DKD were affected by vitamin D deficiency and insufficiency [18]. Vitamin D, a fat-soluble vitamin essential for human health, is catalyzed by the liver into 25-OH-D, which is further converted in the kidneys into biologically active 1,25-dihydroxyvitamin D3. This active form binds to receptors in target tissues, participating in the regulation of calcium and phosphorus metabolism [46–50]. Nakai et al. [52] demonstrated that 25-OH-D partially antagonizes nuclear factor κB activation induced by advanced glycation end products in mouse podocytes [53]. Additionally, the vitamin D analog masalone has been shown to reduce oxidative stress through the Nrf2-Keap1 pathway, thereby delaying the progression of diabetic nephropathy in rats. Vitamin D acts as a potent inhibitor of the renin-angiotensin aldosterone system [54], potentially mitigating glomerulosclerosis and fibrosis [55], regulating apoptosis and autophagy, ameliorating podocyte injury, and maintaining the structure of the glomerular filtration barrier [55, 56]. Lower levels of 25-OH-D are particularly detrimental in the context



**Fig. 5** The associations between iPTH quartile levels and DKD, UACR, and eGFR. 0 The model was not adjusted. 1 The model was adjusted for age, sex, BMI, and duration of diabetes. 2 The model was adjusted for model 1 and SBP, DBP, FPG, HbA1c, TC, TG, HDL, LDL, ALT, AST, ALP, Hemoglobin, Serum calcium, Serum phosphorus, Serum uric acid and medications, and the medications included anti-osteoporosis drugs (calcium, vitamin D, bisphosphonate, or other drugs), anti-diabetic agents (pioglitazone, SGLT-2 inhibitors, and GLP-1 analogues), and ACEI/ARB. DKD Diabetic kidney disease, UACR Urine albumin to creatinine ratio, eGFR Estimated glomerular filtration rate

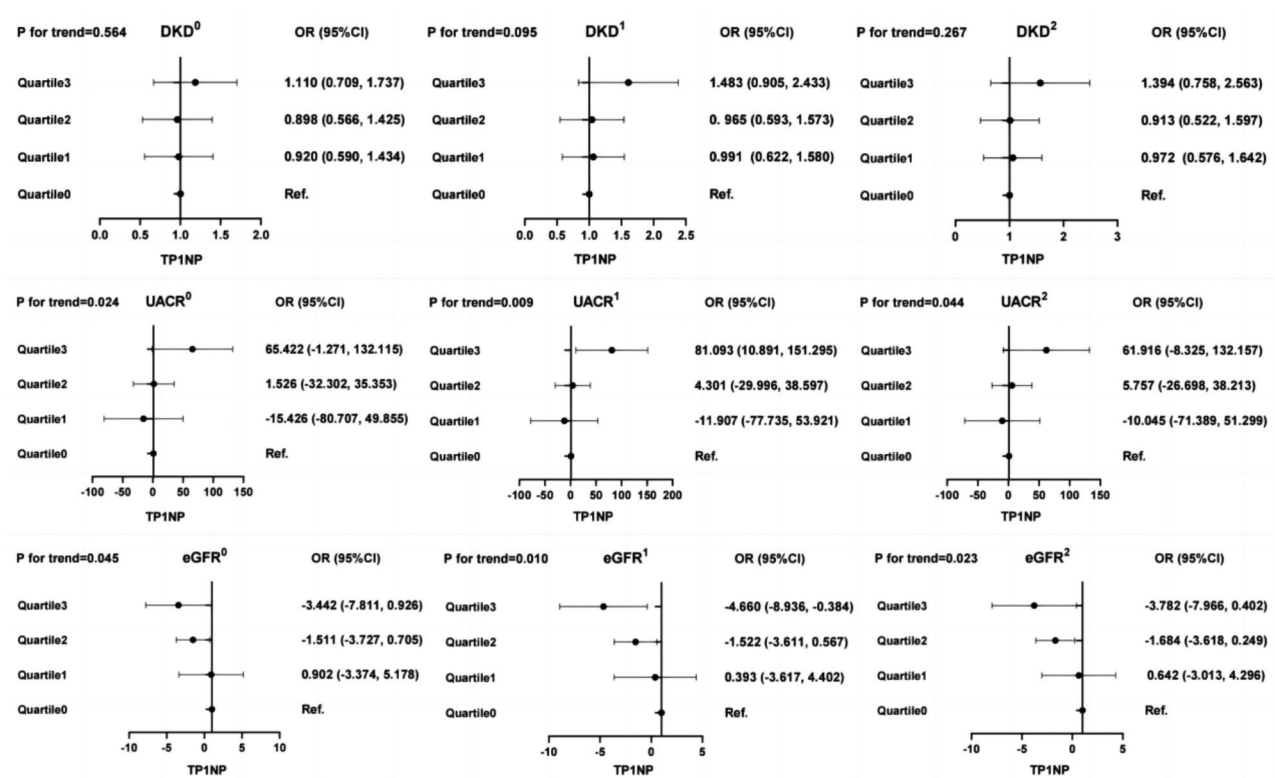
of renin-angiotensin-aldosterone system activation and hyperfiltration in diabetic mice [57]. Moreover, vitamin D may reduce the expression of transforming growth factor- $\beta$  and inflammation, maintain vascular homeostasis, improve glucose and lipid metabolism, and enhance antioxidant defense and immune function [57–59]. Animal studies have suggested that vitamin D insufficiency may contribute to the pathogenesis of albuminuria [19]. 25-OH-D can decrease proteinuria by suppressing the renin-angiotensin system and TGF- $\beta$  in mesangial and juxtaglomerular cells, consistent with the findings of this study.

The findings of this study demonstrate that  $\beta$ -CTX is independently and positively correlated with UACR. As quartiles of  $\beta$ -CTX levels increase, there is a trend towards decreasing eGFR. However,  $\beta$ -CTX did not exhibit any independent effects on DKD in the multivariable model using RCS.  $\beta$ -CTX serves as a degradation product of type I collagen, reflecting the biological activity of osteoclasts and indicating the extent of bone resorption [61]. Previous research has highlighted a negative correlation between  $\beta$ -CTX and eGFR in diabetic patients [13, 14], and a positive correlation with UACR [15], which is consistent with the current findings.

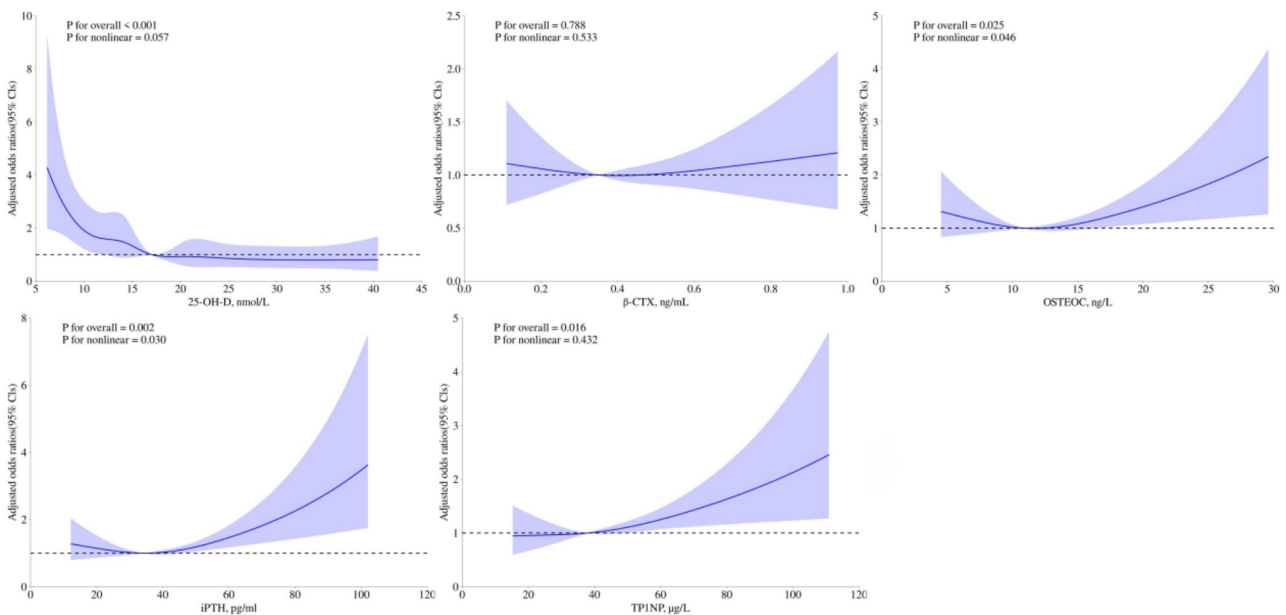
Nonetheless, the specific mechanism by which  $\beta$ -CTX influences the progression from T2DM to DKD remains unclear and warrants further investigation.

Furthermore, our research reveals an independent positive correlation between OSTEOC and UACR, while it is independently negatively correlated with eGFR. As quartile levels of OSTEOC increase, there is a trend towards increasing UACR and decreasing eGFR. Moreover, the associations between OSTEOC and DKD were non-linear, approaching the J-shape, with risk estimates markedly increasing when OSTEOC levels exceeded 10.875 ng/L. OSTEOC, a specific protein secreted by osteoblasts and composed of 49 amino acids, plays crucial roles in various physiological processes including bone metabolism, energy metabolism, reproduction, and cognition [62]. It reflects the activity status of osteoblasts. OSTEOC has also been implicated in stimulating islet beta cells to release insulin and prompting adipocytes to release adiponectin, thereby enhancing insulin sensitivity [63]. Studies investigating the relationship between OSTEOC and glucose-lipid metabolism have yielded conflicting results, and the underlying mechanisms remain unclear [7, 63–67]. Zhao et al. found a significant positive correlation between UACR and OSTEOC in a cross-sectional





**Fig. 6** The associations between TP1NP quartile levels and DKD, UACR, and eGFR. 0 The model was not adjusted. 1 The model was adjusted for age, sex, BMI, and duration of diabetes. 2 The model was adjusted for model 1 and SBP, DBP, FPG, HbA1c, TC, TG, HDL, LDL, ALT, AST, ALP, Hemoglobin, Serum calcium, Serum phosphorus, Serum uric acid and medications, and the medications included anti-osteoporosis drugs (calcium, vitamin D, bisphosphonate, or other drugs), anti-diabetic agents (pioglitazone, SGLT-2 inhibitors, and GLP-1 analogues), and ACEI/ARB. DKD Diabetic kidney disease, UACR Urine albumin to creatinine ratio, eGFR Estimated glomerular infiltration rate



**Fig. 7** Adjusted RCS for BTMs and the prevalence of DKD. Adjusted for age, sex, BMI, and duration of diabetes. DKD Diabetic kidney disease, UACR Urine albumin to creatinine ratio, eGFR Estimated glomerular infiltration rate, 25-OH-D 25-hydroxyvitamin D,  $\beta$ -CTX  $\beta$ -CrossLaps, OSTEOC Osteocalcin, iPTH Intact parathyroid hormone, TP1NP Total type I collagen N-terminal propeptide

study involving 297 T2DM patients [12], consistent with our findings. However, caution is warranted regarding the potential for reverse causality. A prospective cohort study demonstrated that even after adjusting for baseline eGFR and UACR, serum OSTEOC maintains an independent and robust negative correlation with DKD events [69]. In cross-sectional studies, reduced renal function may lead to decreased OSTEOC excretion and consequently higher circulating OSTEOC levels, potentially distorting the exposure-disease relationship.

The findings of this study indicate that iPTH levels are significantly higher in DKD patients compared to those without DKD. iPTH is independently and positively correlated with the incidence of DKD and UACR, while being independently negatively correlated with eGFR. As quartile levels of iPTH increase, there is a downward trend in eGFR. iPTH, a peptide hormone, exerts biological effects by regulating calcium and phosphorus metabolism through actions on target tissues such as bones and kidneys, and it is ultimately cleared by the kidneys. PTH strengthens osteolysis, enhances renal tubular reabsorption of calcium, mobilizes calcium into the bloodstream, and increases blood calcium levels. Previous research has suggested that elevated iPTH levels can act as a uremic toxin, influencing mitochondrial function and contributing to cell death and organ damage [69–71]. Our observations reveal a non-linear association between iPTH and DKD, approaching the J-shape, with risk estimates significantly increasing when iPTH levels exceed 34.15 pg/mL. This reflects the dual nature of iPTH, where within a physiological range it exerts beneficial effects, while beyond this range it may have detrimental effects, consistent with previous findings.

Furthermore, our study reveals an independent positive correlation between TP1NP and the incidence of UACR, while being independently negatively correlated with eGFR. As quartile levels of TP1NP increase, there is a trend of increasing UACR and decreasing eGFR. Additionally, the risk estimates markedly increase with rising TP1NP levels. TP1NP is an extension peptide of type I procollagen [72, 73], synthesized and released into circulation by osteoblasts [74, 75]. It serves as a sensitive marker of bone formation [76]. Previous research supports our findings, indicating a negative correlation between TP1NP levels and eGFR in diabetes patients, and a positive association between TP1NP and UACR in T2DM patients. We propose two potential explanations for this association. First, TP1NP may accumulate in the body as eGFR declines, leading to elevated circulating levels [77]. Second, given that bone remodeling is metabolically demanding, disturbances in energy metabolism and microcirculation in T2DM patients may contribute to observed decreases in bone formation markers [78].

The findings suggest BTMs homeostasis may be related to the etiology and pathogenesis of DKD in elder patients with T2DM. These results highlight the potential utility of BTMs as biomarkers for kidney disease, aiding in the identification of individuals at increased risk for T2DM-related renal complications. This has significant clinical implications for managing bone metabolism disorders and kidney complications in elderly patients with diabetes. Therefore, in clinical practice, attention should be given to the dynamic monitoring of BTMs in elderly T2DM patients. Additionally, maintaining optimal BTM levels from an early age may be associated with a reduced future risk of DKD development.

Our study possesses several strengths. Firstly, we conducted a large-scale population study involving hospitalized elderly T2DM patients, ensuring a substantial sample size and comprehensive data collection, which allowed us to assess common confounders. This is the first study to report the association between BTMs and the prevalence of DKD in an elderly cohort. Secondly, we emphasized the nonlinearity in the study, better illustrating the dose-response relationship. Thirdly, we examined BTMs as both continuous and categorical variables to reduce data analysis contingency and enhance the robustness of our results. Nevertheless, this study has certain limitations. Firstly, selection bias could not be avoided in this single-center, hospital-based study. Secondly, detecting BTMs at a single time point only provides a snapshot and does not allow for an understanding of the dynamic changes in BTMs and their association with DKD. Thirdly, all participants were of Han Chinese ethnicity, which may limit the generalizability of the results to other ethnic groups, as bone metabolism and osteoporosis vary among different races. Fourthly, potential confounding factors affecting BTMs levels, such as sun exposure, outdoor exercise, nutritional status, dietary habits, and seasonal variations, were not included in this analysis.

## Conclusions

BTMs are closely associated with kidney disease in elderly patients with T2DM. These discoveries potentially assist clinicians in establishing more preventive measures and targeted treatment strategies for elderly patients with T2DM.

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## Author contributions

Shuwu Wei conceived the study, participated in its design and coordination, analyzed the data and drafted the manuscript. Xinyu Pan recruited patients and collected data. Junping Wei participated in its design and coordination, and was responsible for project administration, and visualization. All authors read and approved the final manuscript.

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## Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

## Declarations

### Ethical approval and consent to participate

The ethics committee has waived the requirement of informed consent for this study. The full name of the Institutional Review Board that waived the informed consent procedure is "Ethical Committee in Guan'anmen Hospital, China Academy of Chinese Medical Sciences" (registration code:2023-187-KY). We confirm that methods were performed in accordance with declaration of Helsinki's guidelines and regulations.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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