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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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ORIGINAL ARTICLE

Retrospective Study

Risk factors for developing osteoporosis in diabetic kidney disease and its correlation with calcium-phosphorus metabolism, FGF23, and Klotho

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Abstract

BACKGROUND

The progression of diabetic kidney disease (DKD) affects the patient's kidney glomeruli and tubules, whose normal functioning is essential for maintaining normal calcium (Ca) and phosphorus (P) metabolism in the body. The risk of developing osteoporosis (OP) in patients with DKD increases with the aggravation of the disease, including a higher risk of fractures, which not only affects the quality of life of patients but also increases the risk of death.

AIM

To analyze the risk factors for the development of OP in patients with DKD and their correlation with Ca-P metabolic indices, fibroblast growth factor 23 (FGF23), and Klotho.

METHODS

One hundred and fifty-eight patients with DKD who were admitted into the Wuhu Second People's Hospital from September 2019 to May 2021 were selected and divided into an OP group (n = 103) and a normal bone mass group (n = 55) according to their X-ray bone densitometry results. Baseline data and differences in Ca-P biochemical indices, FGF23, and Klotho were compared. The correlation of Ca-P metabolic indices with FGF23 and Klotho was discussed, and the related factors affecting OP in patients with DKD were examined by multivariate logistic regression analysis.

RESULTS
The OP group had a higher proportion of females, an older age, and a longer diabetes mellitus duration than the normal group (all $P < 0.05$). Patients in the OP group exhibited significantly higher levels of intact parathyroid hormone (iPTH), blood P, Ca-P product (Ca × P), fractional excretion of phosphate (FeP), and FGF23, as well as lower estimated glomerular filtration rate, blood Ca, 24-hour urinary phosphate excretion (24-hour UPE), and Klotho levels (all $P < 0.05$). In the OP group, 25-(OH)-D_3, blood Ca, and 24-hour UPE were negatively correlated with FGF23 and positively correlated with Klotho. In contrast, iPTH, blood Ca, Ca × P, and FeP exhibited a positive correlation with FGF23 and an inverse association with Klotho (all $P < 0.05$). Moreover, 25-(OH)-D_3, iPTH, blood Ca, $FePO_4$, FGF23, Klotho, age, and female gender were key factors that affected the lumbar and left femoral neck bone mineral density.

CONCLUSION
The Ca-P metabolism metabolic indexes, FGF23, and Klotho in patients with DKD are closely related to the occurrence and development of OP.

Key Words: Diabetic kidney disease; Osteoporosis; Calcium-phosphorus metabolism; FGF23; Klotho

Core Tip: The risk of developing osteoporosis (OP) in patients with diabetic kidney disease (DKD) increases with the worsening of DKD. In addition, the risk of fractures in DKD is greatly increased, which affects the patient's quality of life and elevates the risk of death. Therefore, it is of great importance to identify the risk factors that affect the occurrence of OP in patients with DKD to guide appropriate interventions. In this study, we analyzed the risk factors of OP in patients with DKD to enable planning appropriate fracture prevention strategies.

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INTRODUCTION

Diabetic kidney disease (DKD), an important cause of chronic kidney disease (CKD), is a condition in which glomerular filtration rate (GFR) progressively declines (with or without proteinuria) because of longstanding uncontrolled diabetes mellitus (DM), and is one of the most important complications in patients with DM[1,2]. China has a large and aging population base, which has resulted in China becoming the country with the largest number of patients with diabetes. DKD has become the leading cause of end-stage renal disease (ESKD), and the number of patients with newly diagnosed ESKD in China has exceeded all other causes including glomerulonephritis[3,4]. When kidney function is impaired, the metabolic processes of the body are also affected by changes in blood sugar and kidney function, which affect various body systems[5]. CKD-related mineral bone disorders, including fibrous osteitis and osteoporosis (OP), are common complications in patients with DKD[6]. Furthermore, DM-induced chronic complications, like microvascular and macrovascular disease, reduce the quality of life and productivity of patients with diabetes and predispose them to varying degrees of psychological burden[7,8].

OP is a pathophysiological change of abnormal bone metabolism, where the function of osteoclasts exceeds that of osteoblasts, which is clinically manifested as a reduction in bone mass, erosion of bone tissue microstructure, and the development of brittle bones that fracture easily[9,10]. As OP is a disease that is characterized by abnormal calcium (Ca) and phosphorus (P) metabolism, any factor that influences the normal Ca-P metabolism may affect the patient's bone mass to a certain extent. With the advancement of research, a variety of cytokines that play an important role in the development of OP in patients with DKD have been discovered. For example, fibroblast growth factor 23 (FGF23), which is mainly secreted by osteoblasts and osteocytes, is involved in P excretion, inhibition of parathyroid hormone (PTH) secretion, and suppression of the conversion of vitamin D to the active form 1,25 dihydroxy cholecalciferol (1,25-$[OH]_2D$) [11,12]. In CKD, the signaling axis composed of FGF23 and its cofactor, human anti-aging Klotho protein (Klotho), influences Ca-P metabolism by directly reducing the expression of sodium-phosphate cotransporter proteins (NaPi) in the renal proximal tubule brush border membrane. This suppresses vitamin D synthesis, which in turn inhibits the activity of vitamin D-dependent NaPi in the brush border of the intestinal epithelial cells and affects PTH synthesis and secretion, indirectly influencing NaPi viability[13-15].

Currently, greater focus is on the management of diabetic complications in the heart, nervous system, kidneys, and other important organs, while OP is often overlooked. However, an increasing number of patients with DM-related OP complications have been identified in recent years. Evidence has revealed a higher risk of OP and fractures in patients with CKD than in the general population, adversely affecting patients' quality of life and increasing the risk of death[16].

Diabetes is associated with an increased risk of fractures, although type 2 DM is typically associated with a normal or high bone mineral density (BMD)[17]. In addition, patients with DKD are more susceptible to developing Ca-P metabolism disorders, which can lead to osteopenia and bone density reduction and may eventually result in the development of OP[18].

Given the role of FGF23/Klotho in the development of CKD, we propose that FGF23/Klotho also plays a regulatory role in the development of DKD by affecting the systemic metabolism of patients. Based on this, this study explored the correlation of Ca-P metabolic indices, FGF23, and Klotho with OP in patients with DKD, thus providing a foundation for further clarifying the regulatory role of FGF23/Klotho in DKD.

MATERIALS AND METHODS

Study population

A retrospective analysis was performed using the data from 158 patients with DKD who were admitted to the Wuhu Second People's Hospital from September 2019 to May 2021. The inclusion criteria were: (1) The diagnostic criteria for DKD were met, with random urinary albumin (Alb)/creatinine ratio ≥ 30 mg/g or urinary Alb excretion rate ≥ 30 mg/24 hours; GFR < 60 mL/min (1.73 m^2) for more than three months; meeting any of the above criteria and DKD diagnosis was confirmed by renal biopsy; (2) The patient could undergo X-ray absorptiometry (except for pregnant women, those with open wounds at the measurement site, and those who were seriously allergic to the coupling agents) for BMD measurement; and (3) The patient's clinical data was complete. The exclusion criteria were: (1) Other types of DM (type I, pregnancy type, other specific types of diabetes); (2) Heart, liver, kidney (congenital renal insufficiency or renal dysplasia), and other vital organ dysfunction; (3) Primary or secondary bone-related diseases, or thyroid, parathyroid, adrenal gland, gonad, or pituitary-associated diseases; (4) Use of drugs within the past three months that affect bone metabolism, such as glucocorticoids, immunosuppressants, Ca tablets, and vitamin D; (5) Acute and chronic nephritis, urinary tract infections, and rheumatic/immunological diseases; (6) Breastfeeding and pregnant women; (7) Difficulty in cooperating with research due to illness or other non-disease factors; (8) Patients undergoing long-term maintenance dialysis; and (9) The patient's clinical data was incomplete. According to X-ray bone densitometry results, patients were divided into an OP group (with at least one site having a T-score value ≤ -2.5; OP group) with 103 cases and a normal bone mass group (Normal group) with 55 cases. This study was reviewed and approved by the hospital's Medical Ethics Committee. A flow chart of patient selection is presented in Figure 1.

Patient data collection

General information was collected on patients' age, gender, course of DM, body mass index (BMI), and other chronic diseases (hypertension, coronary heart disease, *etc.*).

Biochemical indicators were collected from all patients. Five milliliters of venous blood were collected on an empty stomach during the early morning on the second day after admission, which was left to stand at room temperature for 10-20 minutes and then centrifuged at 4000 rpm for 10 minutes to collect the supernatant. The samples of each patient were packed into EP tubes, labeled, and frozen at −80 ℃ for later use. Fasting blood glucose (FBG), hemoglobin A1c (HbA1c), blood Ca^{2+}, blood P, serum creatinine (Scr), estimated GFR (eGFR), serum Alb, and 25-(OH)-D_3 were measured using an automatic biochemical detector (Roche C-77), and the intact PTH (iPTH) was measured using a Cobas600 immunoluminescence instrument. The 24-hour urine electrolyte levels of patients without intervention (interventions that affect urine electrolyte levels, such as ingestion of antibiotics, diuretics, or excessive use of electrolyte water) were also collected.

Other biochemical parameters were calculated according to the detected known indicators: The CKD Epidemiology Collaboration (CKD-EPI) equation was used to calculate the patient's eGFR, Female + Scr ≤ 0.7 mg/dL, EPI-GFR = 144 × $(Scr/0.7)^{-0.329}$ × 0.993^{age}; Female + Scr > 0.7 mg/dL, EPI-GFR = 144 × $(Scr/0.7)^{-1.209}$ × 0.993^{age}; Male + Scr ≤ 0.9 mg/dL, EPI-GFR = 141 × $(Scr/0.9)^{-0.411}$ × 0.993^{age}; Male + Scr > 0.9 mg/dL, EPI-GFR = 141 × $(Scr/0.9)^{-1.209}$ × 0.993^{age}. The Ca-P product was calculated as (Ca × P) = blood Ca × blood P × 12.4, and the fractional excretion of phosphate ($FePO_4$) was calculated as = (24-hour urinary P × 1000)/(1440 × blood P × eGFR) × 100%.

For FGF23 and Klotho protein level detection, the patient's serum samples were evaluated using an enzyme-linked immunosorbent assay (ELISA), and all operations were performed in strict accordance with the manufacturer's instructions. ELISA kits for Klotho and FGF23 were purchased from Shanghai Recordbio Biological Technology.

BMD measurement

All patients underwent DXA-MD dual-energy X-ray absorptiometry to determine the BMD of their orthoposterior lumbar spine L1–4 and the left femoral neck during admission. The specific operation method used was as follows: When detecting the lumbar spine BMD, the patient lay flat on the detection bed and raised the lower limbs on a cushion. The position of the laser light was adjusted to be flashed with the navel according to the patient's posture and body shape. During the left hip BMD examination, the patient's lower limbs were straightened, adducted, and internally rotated, and the legs were then immobilized with a tripod. The laser light was aimed at the left iliac spine approximately 15 cm below the patient's left iliac spine, and the left femoral neck BMD was measured. At present, the detection of BMD is mainly based on the detection of the lumbar spine and hip. Because of aging, there is severe bone loss in the lumbar spine, which can provide false positives. The bone mass in the hip decreases with age and exhibits regular changes, with fewer occurrences of factors such as bone hyperplasia and ectopic calcification. Therefore, based on the BMD T-score values of the left hip, > -1.0, ≤ -1.0, and ≤ -2.5 were considered normal bone mass, osteopenia, and OP, respectively.

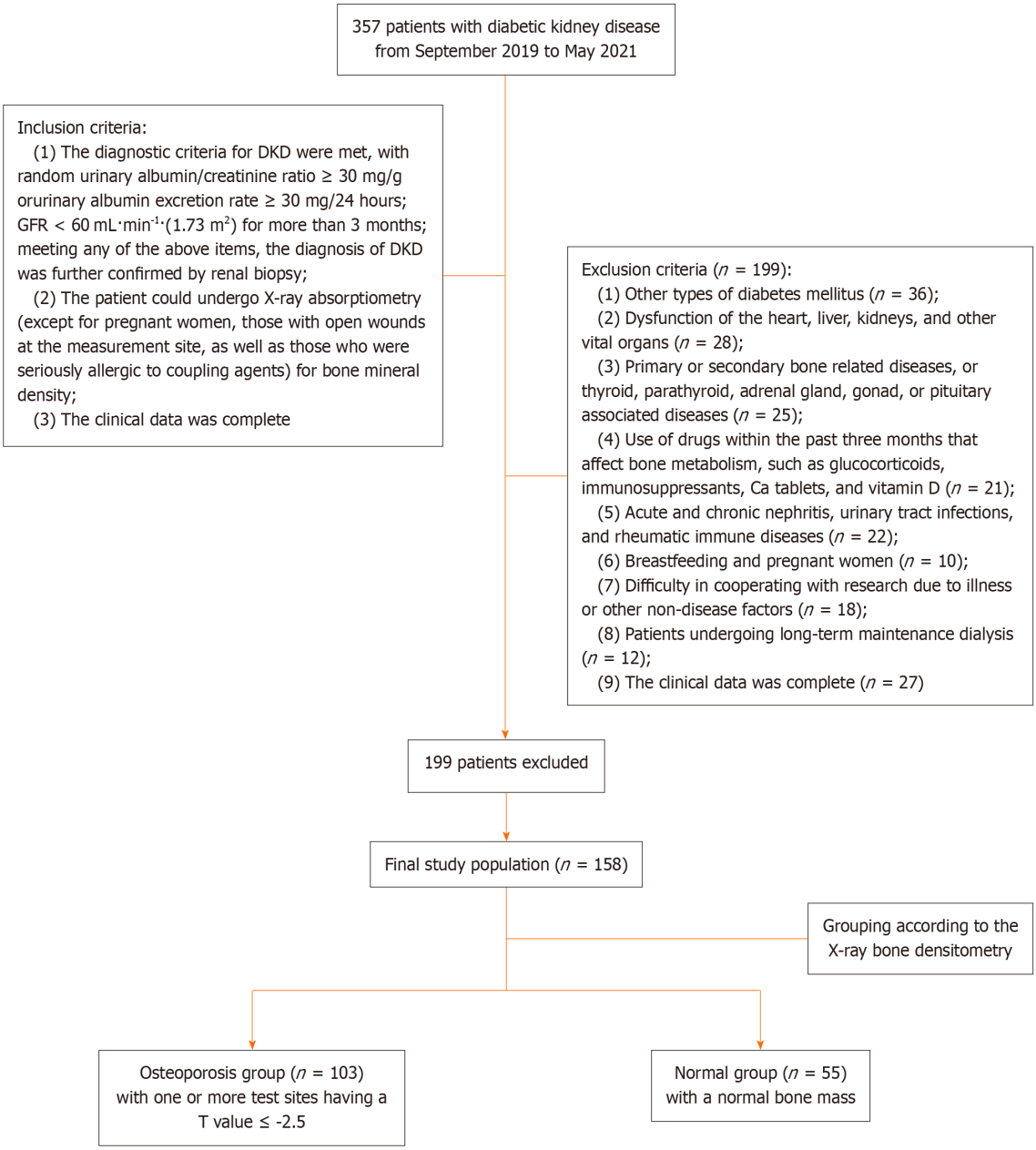

Figure 1 Diagram flow chart of the patient selection. DKD: Diabetic kidney disease.

Statistical analysis

SPSS version 25.0 was used for data analysis. All data were tested for normality and homogeneity of variance. Continuous variables were expressed as the mean ± SD, and the independent sample *t*-test was used for comparisons. Categorical variables were described in the form of percentages, and a χ^2 test was applied. The Spearman's test was used for correlation analysis, and the analysis of influencing factors employed the multivariate logistic analysis. A significance level of $P < 0.05$ was used.

RESULTS

Patient general information

According to the BMD data obtained *via* X-ray absorptiometry, the 158 patients with DKD were divided into Normal (n = 55) and OP (n = 103) groups based on the left hip T-value. The two groups exhibited no marked differences in their BMI and other comorbidities ($P > 0.05$). Female gender, older age, and longer duration of DM were the significant risk factors for OP in univariate analysis (all $P < 0.05$), as shown in Table 1.

Table 1 Comparison of patient biographical information

	Normal (*n* = 55)	OP (*n* = 103)	t/χ^2	*P* value
Gender, *n* (%)			5.313	0.021
Male	33 (60.0)	42 (40.8)		
Female	22 (40.0)	61 (59.2)		
Age (years)	51.39 ± 10.84	62.32 ± 10.34	6.224	< 0.0001
Body mass index (kg/m^2)	24.93 ± 3.72	24.87 ± 3.44	0.102	0.919
Comorbidities, *n* (%)	17 (30.9)	37 (35.9)	0.401	0.527
Disease duration (years)	7.32 ± 3.22	13.42 ± 3.84	10.042	< 0.0001

OP: Osteoporosis.

Biochemical and Ca-P metabolic indexes

The OP risk indicators included seven biochemical indicators (FBG, HbA1c, Scr, eGFR, Alb, 25-(OH)-D_3, and iPTH), five Ca-P metabolic indexes [blood Ca, blood P, Ca × P, 24-h urinary phosphate excretion (24-hour UPE)], and $FePO_4$], as well as FGF23 and Klotho. Through comparative analysis, we found no marked inter-group differences in FBG, HbA1c, Scr, and Alb ($P > 0.05$). However, in the OP group, iPTH, blood P, Ca × P, $FePO_4$, and FGF23 exhibited a significant upward trend compared to the Normal group ($P < 0.05$), while eGFR, blood Ca, 24-hour UPE, and Klotho exhibited a significant downward trend ($P < 0.05$), as shown in Table 2.

Correlation analysis between Ca-P metabolic indices with FGF23 and Klotho

The results revealed that in patients with normal bone mass, 25-(OH)-D3 and blood Ca levels were negatively correlated with FGF23 ($P < 0.05$) and positively related to Klotho ($P < 0.05$). In contrast, iPTH, blood P, Ca × P, and FeP were positively correlated with FGF23 and inversely associated with Klotho ($P < 0.05$). In the OP group, 25-(OH)-D_3, blood Ca, and 24-hour UPE were negatively correlated with FGF23 ($P < 0.05$) and positively correlated with Klotho ($P < 0.05$). In addition, iPTH, blood P, Ca × P, and $FePO_4$ were positively correlated with FGF23 and negatively associated with Klotho ($P < 0.05$), as shown in Table 3.

Analysis of risk factors for OP in DKD

Considering the influence of age and gender on the occurrence of OP, eight indices, including 25-(OH)-D_3, iPTH, blood Ca, blood P, urinary P fractional excretion, FGF23, and Klotho, as well as the patient's age, gender (male = 1, female = 2), BMI, comorbidities (no comorbidities = 1, with comorbidities = 2), and duration of DM were used as independent variables, and the patient's lumbar spine and left femoral neck BMD were used as dependent variables for multiple linear regression analysis. The results revealed that 25-(OH)-D_3, blood Ca, urinary P excretion fraction, FGF23, Klotho, age, and female gender were key factors that affected lumbar BMD and left femoral neck BMD in patients, as shown in Table 4.

DISCUSSION

Epidemiological studies have demonstrated a markedly higher incidence of OP in patients with diabetes than in the general population[19,20], possibly due to chronic hyperglycemia with increased levels of advanced glycation end products and oxidative stress in DM patients[21,22]. However, the specific mechanism of the development of OP in DKD has not been fully elucidated. In this study, we analyzed the risk factors for the development of OP in patients with DKD and found that 25-(OH)-D_3, iPTH, blood Ca, $FePO_4$, FGF23, Klotho, age, and female gender were key factors that affected the lumbar and left femoral neck BMD.

This study found that females, older subjects, and those with a longer duration of DM were at higher OP risk. Female patients experience a gradual decline in ovarian function after menopause, which leads to a decrease in estrogen levels, resulting in an imbalance in bone metabolism and a subsequent decrease in BMD[23,24]. The Third National Health and Nutrition Examination Survey (NHANES III) confirmed that 14646 American men and women had low femoral BMD. Based on the World Health Organization's criteria for the use of the T-score (SD below peak bone mass), 13%-18% of women aged 50 or above suffer from OP, and another 37%-50% suffer from osteopenia[25]. Moreover, worldwide estimates suggest that one-third of women and one-fifth of men over the age of 50 will suffer from an osteoporotic fracture as they age older[26]. Thus, OP disproportionately affects the elderly. We also found that the iPTH, blood P, Ca-P product (Ca × P), FeP, and FGF23 values in patients with OP exhibited a significant upward trend, while the eGFR, blood Ca, 24-hour UPE, and Klotho values exhibited an obvious downward trend compared to the Normal group. This is because the lower the eGFR level, the worse the renal tubular reabsorption function of patients with DKD, resulting in the loss of bone minerals, such as Ca, P, magnesium, potassium, and sodium, which further leads to hyperparathyroidism and the excessive secretion of PTH that cause increased osteoclast activity and ultimately a decline in BMD. A large

Table 2 Comparison of biochemical indicators and calcium-phosphorus metabolic indexes

	Normal (*n*= 55)	OP (*n* = 103)	*t*/χ^2	*P* value
FBG (mmol/L)	8.32 ± 2.83	8.39 ± 2.31	0.167	0.867
HbA1c (%)	7.44 ± 2.10	7.59 ± 2.09	0.429	0.668
Scr (μmol/L)	93.42 ± 20.13	94.32 ± 21.38	0.257	0.797
eGFR (mL/min × 1.73 m^2)	89.42 ± 20.31	80.74 ± 24.23	2.265	0.025
Alb (g/L)	34.29 ± 8.39	32.83 ± 7.36	1.131	0.260
25-(OH)-D_3 (ng/mL)	37.42 ± 17.32	25.33 ± 9.27	5.723	< 0.0001
iPTH (pg/mL)	39.72 ± 18.42	72.43 ± 18.48	10.610	< 0.0001
Blood Ca (mmol/L)	2.21 ± 0.19	1.98 ± 0.34	4.640	< 0.0001
Blood P (mmol/L)	1.13 ± 0.17	1.37 ± 0.34	4.912	< 0.0001
Calcium-phosphorus product ($mmol^2/L^2$)	2.64 ± 0.32	3.11 ± 0.78	4.276	< 0.0001
24-hour urinary phosphate excretion (mmol/24 hour)	20.42 ± 9.45	14.32 ± 5.97	4.961	< 0.0001
Fractional excretion of phosphate (%)	12.42 ± 1.74	40.28 ± 7.42	27.408	< 0.0001
FGF23 (ng/L)	267.32 ± 48.42	358.79 ± 53.72	10.544	< 0.0001
Klotho (ng/L)	253.79 ± 0.48	352.91 ± 0.57	1098.0	< 0.0001

OP: Osteoporosis; FBG: Fasting blood glucose; HbA1c: Hemoglobin A1c; Scr: Serum creatinine; eGFR: Estimated glomerular filtration rate; Alb: Albumin; iPTH: Intact parathyroid hormone; Ca: Calcium; P: Phosphorus.

Table 3 Correlation of calcium-phosphorus metabolic indexes with FGF23 and Klotho

	Normal (*n* = 55)				OP (*n* = 103)			
	FGF23		Klotho		FGF23		Klotho	
	r	*P* value	*r*	*P* value	*r*	*P* value	*R*	*P* value
25-(OH)-D_3	−0.201	0.029	0.195	0.031	−0.342	< 0.001	0.356	< 0.001
iPTH	0.211	0.023	−0.205	0.028	0.352	< 0.001	−0.370	< 0.001
Blood Ca	−0.198	0.031	0.220	0.020	−0.364	< 0.001	0.377	< 0.001
Blood P	0.231	0.018	−0.221	0.020	0.337	< 0.001	−0.357	< 0.001
Calcium-phosphorus product	0.199	0.030	−0.035	0.774	0.384	< 0.001	−0.366	< 0.001
24-hour urinary phosphate excretion	−0.083	0.610	0.138	0.104	−0.379	< 0.001	0.401	< 0.001
Fractional excretion of phosphate	0.242	0.016	−0.244	0.015	0.338	< 0.001	−0.378	< 0.001

OP: Osteoporosis; iPTH: Intact parathyroid hormone; Ca: Calcium; P: Phosphorus.

amount of clinical evidence has demonstrated that during the early stages of CKD development, there is no significant change in the patient's PTH. However, the expression level of FGF23 in the body exceeds 2-3 times that of pregnant women, demonstrating the predictive value of FGF23 during the early development of CKD[27,28]. Therefore, FGF23 is not only the cause of the changes in Ca-P metabolism within the body but also the result of fluctuations in blood Ca and P levels. In addition, Klotho is an important cofactor for FGF23 that is required for its activity, and the Klotho protein itself can directly reduce the expression of the related proteins in the proximal convoluted tubules. Furthermore, it inhibits the renal reabsorption of P in a form that is independent of FGF23 and regulates the body's Ca-P metabolism[29]. Membrane Klotho forms a complex with the FGF receptor. The form of receptor-ligand binding that is created between the membrane Klotho and FGF, the regulatory effect of Klotho on FGF23, and the endocrine effect of soluble Klotho all play a key role in pathophysiological processes, such as ion transport regulation, Wnt signal transduction, and anti-aging[30,31]. Finally, through multivariate logistic regression analysis, it was demonstrated that 25-(OH)-D_3, iPTH, blood Ca, $FePO_4$, FGF23, Klotho, age, and gender were the key factors that affect the BMD of patients' lumbar vertebrae and left femoral neck, and that they influenced each other.

Table 4 Logistic regression analysis of osteoporosis in diabetic kidney disease

Variable	B	Standard error	Standardization coefficient	*t*	*P* value
Lumbar bone mineral density					
Constant	0.732	0.078		13.924	< 0.001
25-(OH)-D_3	0.164	0.013	-0.372	8.942	< 0.001
iPTH	-0.329	0.030	0.201	7.995	< 0.001
blood Ca	0.228	0.017	0.101	10.424	< 0.001
Urinary phosphorus excretion fraction	-0.101	0.002	0.282	9.049	< 0.001
FGF23	-0.284	0.019	0.118	8.024	< 0.001
Klotho	0.118	0.005	-0.208	13.229	< 0.001
Age	-0.332	-0.032	-0.394	12.049	< 0.001
Gender	-0.492	0.074	-0.220	10.004	< 0.001
Bone mineral density of the left femoral neck					
Constant	0.809	0.067		15.424	< 0.001
25-(OH)-D_3	0.180	0.040	-0.394	8.492	< 0.001
iPTH	-0.364	0.038	0.233	6.824	< 0.001
Blood Ca	0.275	0.020	0.164	7.663	< 0.001
Urinary phosphorus excretion fraction	-0.128	0.008	0.840	5.312	0.003
FGF23	-0.295	0.042	0.175	4.990	0.007
Klotho	0.131	0.007	-0.232	9.402	< 0.001
Age	-0.347	-0.012	-0.384	8.448	< 0.001
Gender	-0.488	0.067	-0.214	7.940	< 0.001

iPTH: Intact parathyroid hormone; Ca: Calcium.

We also found that in the OP group, 25-(OH)-D_3, blood Ca, and 24-hour UPE had a significant inverse association with FGF23 and a significant positive correlation with Klotho; iPTH, blood P, Ca × P, and $FePO_4$ were positively correlated with FGF23 and negatively with Klotho. Other studies have found that FGF23 is an important regulator of blood P, involved in the production of serum phosphate and PTH, and plays an important role in the stabilization of body minerals[32]. In CKD caused by various factors, the decline of glomerular function results in an impediment of excretion of P, leading to the elevation of blood P, which in turn induces an increase in FGF23. Therefore, to a certain extent, with the development of CKD, the level of FGF23 in the body gradually increases, which is also a compensatory mechanism for the body to maintain the Ca-P metabolism balance[33]. Previous studies have shown that PTH promotes the production of FGF23 in a non-vitamin D-dependent manner and affects the secretory function of the parathyroid glands *via* the mitogen-activated protein kinase pathway and that a regulatory complex composed of FGF23, the FGF receptor, and the cofactor of FGF23, the human anti-aging protein (Klotho), induces early FGF1 production and inhibits the expression of PTH[34-36].

This study has some limitations. First, the sample size of the study is small, which may have an impact on the conclusion obtained. Second, although this study explored the potential link between DKD and OP, the quantification of OP in this study only demonstrated the disparity in BMD. Moreover, the degree of OP in patients is related to their age, gender, menopausal status, as well as their dietary structure and lifestyle. *i.e.*, patients in the OP group had a higher age and a longer disease course, and these additional biases may influence the conclusions in this study. Third, the study only analyzed factors that are closely related to BMD from the perspective of correlation and multiple linear regression. However, Ca-P metabolism and OP development are affected by several different factors, which may be indirect. Analyzing whether there is an effect on BMD merely at the numerical level yields somewhat inadequate results. Therefore, a study with a larger sample size and prospective and multi-factor analyses should be performed to further confirm these results.

CONCLUSION

Taken together, this work elucidates the correlation of Ca-P metabolism, Klotho, and FGF23 with OP in patients with DKD through a retrospective cohort study. Ca-P metabolic indices, FGF23, and Klotho are closely related to the occur-

rence and development of OP in patients with DKD. FGF23 expression was higher and Klotho expression was lower in patients with DKD and OP. Females and older patients with DKD are more susceptible to developing OP. Therefore, special attention should be given to female patients, and their Klotho and FGF-23 levels should be closely monitored.

FOOTNOTES

Author contributions: Yang F and Wu Y conceived and designed the experiments; Yang F and Wu Y analyzed the data; Yang F and Wu Y contributed to the data curation; Yang F and Wu Y wrote-original draft preparation; Yang F, Wu Y and Zhang W participated in the writing-review and editing. Yang F and Wu Y contributed equally to this work as co-first authors.

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