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Fibroblast growth factor 23 predicts incident diabetic kidney disease: A 4.6-year prospective study

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Abstract

Aims: Fibroblast growth factor (FGF) 23 is a bone-derived phosphaturic hormone that participates in the regulation of mineral metabolism and the development of chronic kidney disease. This study aimed to investigate the association between FGF23 and diabetic kidney disease (DKD) in a community-based prospective cohort.

Materials and Methods: Of 7230 individuals who completed a 4.6-year follow-up survey, 1614 individuals with diabetes at baseline were included in this study. Baseline serum FGF23 levels were measured by enzyme-linked immunosorbent assay. Multiple and ordinal logistic regression analyses were used to examine the predictive performance of baseline FGF23 for incident DKD.

Results: Baseline serum FGF23 levels exhibited an earlier elevation in the course of DKD and a gradual increase with the progressive stages of DKD ($p < 0.05$), while no statistical changes were observed in serum calcium and phosphorus levels. Over a 4.6-year follow-up, 198 individuals with diabetes developed incident DKD. Baseline FGF23 was significantly associated with the incidence of DKD (odds ratio 1.290 [95% CI 1.063, 1.565]) after adjusting for conventional DKD risk factors, especially in individuals with lower body mass index (<24 kg/m^2), worse glycaemic control (HbA1c ≥7%), and shorter duration of diabetes (<5 years). Moreover, FGF23 models exhibited great performances in DKD risk prediction and yielded increments compared to traditional DKD risk factors ($p < 0.05$).

Dan Liu and Shujie Yu contributed equally to this study.

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Conclusions: Serum FGF23 level increased at early stages of DKD, and it was an independent predictor of incident DKD, suggesting its potential for early identification of individuals at risk.

KEYWORDS
cohort study, diabetic kidney disease, FGF23, mineral metabolism disorder

1 | INTRODUCTION

Chronic kidney disease (CKD) causes substantial global morbidity and increases cardiovascular and all-cause mortality.[1] Mineral metabolism disorder is a ubiquitous complication of CKD that is characterized by abnormal serum calcium, phosphorus, and vitamin D levels, develops early in the course of the disease, and is associated with an increased risk of cardiovascular diseases and mortality.[2–6] Fibroblast growth factor (FGF) 23 is a bone-derived phosphaturic hormone that regulates mineral homeostasis by activating FGF receptors and the co-receptor α-Klotho.[7–9] Evidence from basic and clinical research demonstrated the role of FGF23 and α-Klotho in CKD, and FGF23 levels increased persistently as the estimated glomerular filtration rate (eGFR) declined.[10–13]

Individuals with diabetes have an earlier onset and more severe disordered mineral metabolism and a higher risk of fracture.[14,15] Previous studies have demonstrated a chronic inflammatory state in type 2 diabetes,[16,17] and basic studies revealed that inflammation is a major trigger of FGF23 production.[18] Clinical studies reported that elevated serum FGF23 levels were related to disordered bone metabolism, CKD progression, and vascular diseases in individuals with diabetes.[19,20] Diabetic kidney disease (DKD) is a major microvascular complication of diabetes, characterized by complex pathophysiology, such as endothelial dysfunction, insulin resistance, and chronic inflammation.[21–23] Microalbuminuria, an early and detectable clinical manifestation of DKD,[24] is associated with a higher risk of progression to end-stage renal disease (ESRD).[25] However, measuring urine albumin-to-creatinine ratio (ACR) poses significant challenges in primary care and low-resource settings,[26] due to the limited awareness of DKD and the inconvenience of ACR measurement. Given the crucial role of FGF23 in CKD and mineral metabolism regulation, further research is needed to explore changes in serum FGF23 and mineral metabolism at early stages of DKD, as well as the predictive ability of FGF23 for DKD outcomes.

To address these knowledge gaps, we investigated the association between FGF23 and DKD and further evaluated the clinical usability of FGF23 for predicting incident DKD in a large-scale, community-based prospective cohort.

2 | METHODS

2.1 | Study population

The Shanghai Nicheng cohort was a community-based, longitudinal, prospective cohort study, aiming to evaluate the prevalence, incidence, and related factors of cardiometabolic diseases in Chinese adults. The study design has been described previously.[27] A total of 17 212 individuals aged 45–70 years were enrolled and completed the baseline survey between April 2013 and August 2014. From May to September 2018, individuals aged 55 to 70 years at baseline were invited to participate in the follow-up study ($n = 10\,075$), and 7230 individuals completed the follow-up survey. Individuals with diabetes at baseline ($n = 1898$) were included in this study. Furthermore, individuals with the following conditions were excluded from this study analysis: (1) diagnosed with kidney disease attributed to other primary causes except for diabetes; (2) missing eGFR, ACR, or FGF23 data at baseline and follow-up; (3) eGFR <15 mL/min/1.73 m^2 at baseline; (4) using antibiotics in the last 2 weeks; (5) diseases that may affect bone metabolism at baseline, including malignancy, thyroid diseases, parathyroid diseases, and osteoporosis; and (6) drugs that affect FGF23 levels: anticoagulants, glucocorticoids, thyroid hormones, vitamin D and related substances, etc. Finally, a total of 1614 individuals with diabetes were included in our final analysis, which comprised 199 individuals with DKD and 1415 individuals without DKD at baseline (Figure S1).

The study was approved by the Ethics Committee of Shanghai Sixth People's Hospital, following the principles of the Declaration of Helsinki. All participants provided written informed consent before data collection.

2.2 | Clinical measurements

Information on demographics and lifestyle factors were collected by structured questionnaires at baseline and follow-up, including body weight, height, waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking status, and medical history. Body mass index (BMI) was calculated by taking weight in kilograms, divided by height in meters squared. Furthermore, after overnight fasting, blood and urine samples were collected in the morning. Participants without a prior diagnosis of diabetes underwent an oral glucose tolerance test, while those with a history of diabetes underwent a standardized bread meal test. Blood samples were uniformly collected and processed at the survey day and then stored at −80°C until further measurement. Fasting plasma glucose (FPG) and 2-h plasma glucose (2hPG) were measured by glucose oxidase method. Haemoglobin A1c (HbA1c) was tested by high-performance liquid chromatography. Fasting insulin (FINS) was quantified using electrochemiluminescence immunoassay. Triglyceride (TG) and total cholesterol (TC) were measured by the enzymatic colorimetric method. High-density lipoprotein

cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were assessed by direct method. Serum creatinine was measured by sarcosine oxidase-phenol-aminophenazone peroxidase method. Serum urea and retinol-binding protein 4 concentrations were determined with a Hitachi 7600 automated analyser. Homeostasis model assessment-estimated insulin resistance (HOMA-IR) and β-cell function (HOMA-β) were calculated as follows: HOMA-IR = FINS (mU/L) × FPG (mmol/L)/22.5, HOMA-β = 20 × FINS (mU/L)/(FPG [mmol/L]-3.5).[28] eGFR was calculated based on the CKD Epidemiology Collaboration (CKD-EPI) Equation.[29] Urine samples were used to measure urine creatinine and albumin via rate nephelometry assay. Urine ACR level was calculated by dividing urine microalbumin by urine creatinine.

2.3 | Serum FGF23 measurement

Serum intact FGF23 concentrations were measured using the same batch of enzyme-linked immunosorbent assay kits (CY-4000, Kainos Laboratories Inc., Tokyo, Japan, RRID:AB_2782966). The lower limit of FGF23 detection was 3 pg/mL. The intra- and inter-assay variations were 4.19% and 7.43%, respectively.

2.4 | Outcome definition

Based on the 2024 American Diabetes Association (ADA) guidelines, diabetes was defined as HbA1c ≥6.5%, FPG ≥7.0 mmol/L, and/or 2hPG ≥11.1 mmol/L during oral glucose tolerance test in individuals without hyperglycemia symptoms.[30] Patients with a prior diagnosis of diabetes were also included in our study. DKD was clinically diagnosed with the presence of albuminuria (ACR ≥30 mg/g) and/or a reduced eGFR (eGFR <60 mL/min/1.73 m^2) in individuals with diabetes, in the absence of symptoms of other primary causes of kidney damage.

In this study, we stratified individuals with DKD into three stages according to the corresponding risk based on the 2022 ADA/Kidney Disease: Improving Global Outcomes Consensus Statements[31]: (1) moderately increased risk group: eGFR 45–59 mL/min/1.73 m^2 with ACR <30 mg/g or eGFR ≥60 mL/min/1.73 m^2 with ACR 30–299 mg/g; (2) high risk group: eGFR 30–44 mL/min/1.73 m^2 with ACR <30 mg/g or eGFR 45–59 mL/min/1.73 m^2 with ACR 30–299 mg/g or eGFR ≥60 mL/min/1.73 m^2 with ACR ≥300 mg/g; and (3) very high risk group: eGFR ≤30 mL/min/1.73 m^2 or eGFR 30–44 mL/min/1.73 m^2 with ACR 30–299 mg/g or eGFR 45–59 mL/min/1.73 m^2 with ACR ≥300 mg/g.

2.5 | Statistical analysis

The Kolmogorov–Smirnov tests were used to evaluate the distribution of continuous variables. Normal and non-normal distribution variables were reported as mean ± standard deviations (SD) and median (interquartile range), respectively. Categorical variables were presented as frequencies (percentages). Non-normal distribution variables were logarithmically transformed before further analysis. The differences between the two groups were compared using χ^2 test for categorical variables, and the Student's *t*-test for continuous variables. Pearson correlation coefficient and partial correlation coefficient were calculated to assess the relationship between serum FGF23 and baseline clinical variables. Univariable logistic regression analysis was conducted to investigate the relationship between baseline clinical variables and incident DKD. Multiple logistic regression models were established to estimate the odds ratio (95% CI) of FGF23 for incident DKD. Baseline indicators significantly associated with incident DKD in univariable logistic regression or biologically relevant to kidney function were included in the DKD risk prediction models. We also developed an ordinal logistic regression model to extend logistic regression for the classification of an ordinal response, specifically incident DKD stages. This model was performed to investigate the association between baseline FGF23 and the progression from non-DKD to moderately increased risk DKD, as well as from non-DKD to high-risk and very high risk DKD.

Furthermore, we used the area under the receiver operating characteristic curve (AUC), net reclassification improvement (NRI), and integrated discrimination improvement (IDI) to evaluate the performances of different risk prediction models for incident DKD. NRI assesses any upward or downward reclassification, and a positive NRI value indicates an improvement in classification performance. IDI considers the change in the estimation prediction probabilities, and higher positive IDI values indicate better overall improvement of the prediction model. We also conducted subgroup analyses to further evaluate the predictive performance of FGF23 for incident DKD. All the above statistical analyses were performed using IBM SPSS Statistics software version 29.0 and R Studio version 4.0.4. Data visualization was conducted using GraphPad Prism version 10.0. A two-sided *p* value <0.05 was considered statistically significant.

3 | RESULTS

3.1 | FGF23 is higher at early stages of DKD

Baseline demographic and clinical characteristics of individuals with and without DKD at baseline are summarized in Table S1. There were no significant differences in age and sex between individuals with and without DKD at baseline. However, compared to individuals without DKD, patients with DKD had a higher BMI, waist circumference, SBP, HbA1c, FPG, 2hPG, FINS, HOMA-IR, HOMA-β, hs-CRP, TG, serum urea, and retinol-binding protein 4, but lower serum calcium levels (all $p < 0.05$). Notably, patients with DKD at baseline demonstrated elevated serum FGF23 levels ($p < 0.001$, Table S1). Figure 1 illustrates elevated FGF23 levels at the early stages of DKD and a progressive increase in serum FGF23 levels corresponding to the severity of DKD stages (*p* for trend <0.001), while no statistically significant differences were observed in serum calcium and phosphorus levels.

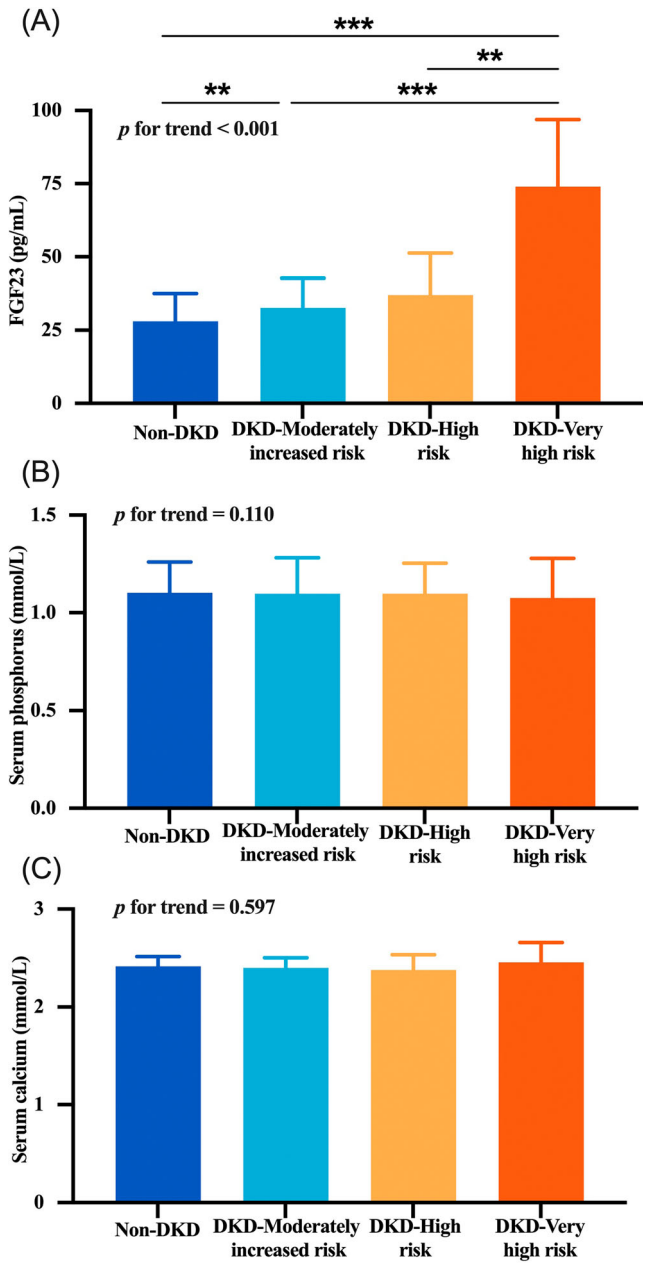

FIGURE 1 Baseline mineral metabolism parameters levels in different diabetic kidney disease (DKD) stages. Baseline serum FGF23 (A), calcium (B), and phosphorus (C) levels in different DKD stages according to the 2022 American Diabetes Association/Kidney Disease: Improving Global Outcomes Consensus Statements. Number of total subjects = 1614. One-way ANOVA was used for comparisons among groups, with multiple comparisons corrected using Bonferroni's test. ***$p < 0.001$;**$p < 0.01$; *$p < 0.05$. DKD, diabetic kidney disease; FGF23, fibroblast growth factor 23.

Furthermore, Figure S2 shows a significant increase in serum FGF23 levels among patients with albuminuria only, reduced eGFR only, and a combination of both, compared to individuals without DKD. The above results suggested an earlier detectable change in serum FGF23 levels in the course of DKD.

As shown in Table S2, serum FGF23 levels were positively associated with BMI, waist circumference, HbA1c, 2hPG, duration of diabetes, FINS, HOMA-IR, HOMA-β, hs-CRP, TG, serum calcium, serum phosphorus, serum urea, retinol-binding protein 4, and ACR, while negatively associated with HDL-C and eGFR, after adjusting for age and sex (all $p < 0.05$).

3.2 | FGF23 independently predicted incident DKD

After a median 4.6-year follow-up, among 1415 participants without DKD at baseline, 198 participants developed incident DKD. Individuals who were older and had higher BMI, SBP, TG, worse glycaemic control, and lower HDL-C were more susceptible to develop DKD (Table 1). Baseline FGF23 levels were significantly elevated in individuals with incident DKD compared to those without incident DKD ($p < 0.001$). Specifically, baseline FGF23 levels also increased among individuals who progressed from non-DKD to any stages of incident DKD (all $p < 0.001$, Figure S3).

We investigated the relationship between baseline clinical variables and incident DKD using univariable logistic regression analysis (Table S3). Baseline age, sex, smoking status, diabetes duration, BMI, SBP, FPG, 2hPG, HbA1c, HOMA-IR, hs-CRP, TG, HDL-C, eGFR, ACR, and FGF23 were significantly associated with the development of incident DKD (all $p < 0.05$). Multiple logistic regression analysis was used to further evaluate the predictive ability of FGF23 for incident DKD (Table 2). The results showed that after adjusting for multiple conventional DKD risk factors, baseline FGF23 was an independent predictor of incident DKD (odds ratio [OR] 1.290 [95% CI 1.063, 1.565]). Furthermore, we used ordinal logistic regression to assess the association of baseline FGF23 and the transition from non-DKD to different stages of DKD: from non-DKD to moderately increased risk DKD, as well as from non-DKD to high-risk and very high risk DKD (Table S4). Regardless of the stage at which DKD developed, baseline FGF23 consistently served as a reliable predictor of incident DKD (OR 1.300 [95% CI 1.073, 1.576]).

Sensitivity analyses based on Model C in Table 2, replacing BMI with waist circumference (Model C1) or HbA1c with FPG and 2hPG (Model C2), were conducted to further evaluate the predictive ability of FGF23 for incident DKD. As presented in Table S5, the positive association of FGF23 with incident DKD remained significant. In addition, when FGF23 was included as a categorical variable, the highest tertile of FGF23 (≥34.63 pg/mL) remained positively associated with an increased risk of developing DKD compared to the reference group, with OR values ranging from 1.281 to 1.723 ($p < 0.05$, Table S6).

3.3 | FGF23 assisted in establishing DKD risk prediction models

To demonstrate the clinical usability of FGF23 for predicting DKD, we assessed the predictive performance of traditional risk factors for incident DKD, both with and without FGF23, using AUC, NRI, and IDI analyses (Table 3). The results showed that the addition of FGF23 to

TABLE 1 Baseline characteristics of subjects with and without incident DKD.

	Without incident DKD ($n = 1217$)	With incident DKD ($n = 198$)	p-Value
Age (years)	62.06 ± 3.92	63.24 ± 4.01	<0.001
Female: male, *n*	724: 493	140: 58	0.003
Current smoking status, *n* (%)	230 (18.90)	25 (12.63)	0.033
BMI (kg/m^2)	25.85 ± 3.37	26.45 ± 3.14	0.021
Waist circumference (cm)	87.21 ± 9.18	88.49 ± 8.77	0.071
SBP (mmHg)	137.25 ± 15.50	142.59 ± 16.18	<0.001
DBP (mmHg)	84.22 ± 7.65	84.29 ± 7.28	0.917
FPG (mmol/L)	7.64 ± 1.87	8.27 ± 2.20	<0.001
2hPG (mmol/L)	14.30 ± 4.50	16.20 ± 4.30	<0.001
HbA1c (%)	6.66 ± 1.15	7.04 ± 1.29	<0.001
FINS (μU/mL)[a]	8.26 (5.71, 11.92)	9.81 (6.29, 15.20)	<0.001
HOMA-IR[a]	2.64 (1.85, 4.11)	3.40 (2.23, 5.29)	<0.001
HOMA-β (μU/mL)[a]	43.88 (27.82, 67.53)	48.56 (29.53, 77.75)	0.165
Duration of diabetes (years)[a,b]	4.87 (2.41, 9.16)	5.89 (2.54, 9.92)	0.260
Diabetes duration ≥5 years, *n* (%)	224 (18.41)	68 (34.34)	<0.001
hs-CRP (mg/L)[a]	1.14 (0.62, 2.38)	1.37 (0.76, 2.86)	0.009
TC (mmol/L)	5.35 ± 0.99	5.30 ± 1.08	0.472
TG (mmol/L)[a]	1.54 (1.09, 2.31)	1.79 (1.26, 2.58)	<0.001
HDL-C (mmol/L)	1.30 ± 0.33	1.24 ± 0.33	0.011
LDL-C (mmol/L)	3.26 ± 0.84	3.15 ± 0.86	0.082
Serum calcium (mmol/L)	2.41 ± 0.10	2.42 ± 0.09	0.490
Serum phosphorus (mmol/L)	1.10 ± 0.16	1.12 ± 0.15	0.076
Serum urea (mmol/L)	5.36 ± 1.31	5.47 ± 1.36	0.289
Retinol-binding protein 4 (mg/L)	54.74 ± 16.03	55.63 ± 16.16	0.469
eGFR (mL/min/1.73 m^2)[a]	97.02 (92.08, 101.31)	93.81 (80.29, 99.50)	<0.001
ACR (mg/g)[a]	6.97 (4.91, 10.57)	12.03 (6.79, 18.72)	<0.001
FGF23 (pg/mL)[a]	26.97 (19.97, 36.85)	33.91 (23.76, 42.43)	<0.001

Note: Data were presented as 'mean ± SD', 'median (interquartile range)' for continuous variables, or 'frequencies (percentages)' for categorical variables. Abbreviations: 2hPG, 2-h plasma glucose; ACR, albumin-to-creatinine ratio; BMI, body mass index; DBP, diastolic blood pressure; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; FINS, fasting insulin; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-estimated insulin resistance; HOMA-β, homeostatic model assessment of beta-cell function; hs-CRP, hypersensitive C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

[a]Log_e-transformed before analysis. Differences between the two groups were assessed using χ^2 test for categorical variables and Student's *t*-test for continuous variables.

[b]The duration of diabetes was calculated for the 572 subjects with a prior diagnosis of diabetes.

the traditional risk factors significantly improved the predictive performance for incident DKD in Models A, B, and C, with increments in NRI and IDI (all $p < 0.05$). The findings suggest that FGF23 may have the potential to assist in early DKD risk warning in clinical practice.

We then examined the association between baseline FGF23 and incident DKD across various subgroups to further demonstrate the generalizability of FGF23 in predicting incident DKD. As shown in Figure 2, baseline FGF23 independently predicted incident DKD in individuals with lower BMI, worse glycaemic control (HbA1c ≥7%), and shorter duration of diabetes (<5 years) (all $p < 0.05$). In addition, significant associations were observed between FGF23 and incident DKD in individuals with baseline diabetic retinopathy (OR 2.769 [95% CI 1.245, 6.160], Table S7). Adding FGF23 to traditional DKD risk factors resulted in a marked improvement in predicting incident DKD, particularly among those with diabetic retinopathy (Table S7).

4 | DISCUSSION

To our knowledge, this is currently the largest community-based prospective cohort study to investigate the association between FGF23 and DKD. This study demonstrated that serum FGF23 levels elevated at early stages of DKD, increased markedly and persistently with the progressive stages of DKD and independently predicted incident

TABLE 2 Baseline clinical variables predictive of incident DKD over 4.6 years.

	Model A	Model B	Model C
Age	1.277 (1.091, 1.495)	1.317 (1.120, 1.549)	1.045 (0.872, 1.251)
Sex	1.487 (0.977, 2.261)	1.493 (0.949, 2.349)	2.052 (1.181, 3.563)
Current smoking status	1.001 (0.570, 1.760)	0.998 (0.555,1.791)	1.246 (0.654, 2.374)
Diabetes duration ≥5 years	2.094 (1.489, 2.946)	1.583 (1.064, 2.354)	1.521 (0.997, 2.321)
BMI	1.119 (0.952, 1.315)	1.058 (0.878, 1.274)	0.999 (0.822, 1.214)
SBP	1.364 (1.173, 1.586)	1.343 (1.150, 1.569)	1.347 (1.135, 1.598)
HbA1c		1.190 (0.959, 1.478)	1.345 (1.066, 1.697)
HOMA-IR[a]		1.135 (0.851, 1.515)	1.082 (0.803, 1.459)
HOMA-β[a]		0.965 (0.735, 1.267)	0.989 (0.748, 1.306)
hs-CRP[a]		1.047 (0.876, 1.252)	0.963 (0.792, 1.169)
TG[a]		1.157 (0.952, 1.406)	1.181 (0.952, 1.465)
HDL-C		0.937 (0.755, 1.162)	0.954 (0.757, 1.203)
Serum calcium			0.878 (0.725, 1.064)
Serum phosphorus			0.881 (0.711, 1.093)
eGFR[a]			0.420 (0.338, 0.521)
ACR[a]			2.980 (2.217, 4.006)
FGF23[a]	1.458 (1.226, 1.734)	1.422 (1.190, 1.700)	1.290 (1.063, 1.565)

Note: Data are presented as OR (95% CI). ORs were estimated as per SD increase. Multiple logistic regression analysis was used to evaluate the association between baseline clinical variables and incident DKD. Model A was adjusted for age, sex, current smoking status, diabetes duration, BMI, SBP. Model B was adjusted for age, sex, current smoking status, diabetes duration, BMI, SBP, HbA1c, HOMA-IR, HOMA-β, hs-CRP, TG, HDL-C. Model C was adjusted for age, sex, current smoking status, diabetes duration, BMI, SBP, HbA1c, HOMA-IR, HOMA-β, hs-CRP, TG, HDL-C, serum calcium, serum phosphorus, eGFR, ACR.

Abbreviations: ACR, albumin-to-creatinine ratio; BMI, body mass index; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-estimated insulin resistance; HOMA-β, homeostatic model assessment of beta-cell function; hs-CRP, hypersensitive C-reactive protein; SBP, systolic blood pressure; TG, triglyceride.

[a]Log_e-transformed before analysis.

TABLE 3 Predictive performance of FGF23 for incident DKD.

		AUC (95% CI)	*p*-Value	NRI (95% CI)	*p*-Value	IDI (95% CI)	*p*-Value
Model A	–	0.670 (0.628, 0.711)	Ref.	–	–	–	–
	+FGF23	0.693 (0.653, 0.732)	0.428	32.02 (17.19, 46.85)	<0.001	1.43 (0.70, 2.17)	<0.001
Model B	–	0.695 (0.655, 0.736)	Ref.	–	–	–	–
	+FGF23	0.712 (0.673, 0.751)	0.558	34.29 (19.24, 49.33)	< 0.001	1.22 (0.50, 1.94)	0.001
Model C	–	0.803 (0.770, 0.836)	Ref.	–	–	–	–
	+FGF23	0.806 (0.772, 0.839)	0.901	22.16 (6.84, 37.48)	0.005	0.76 (0.23, 1.30)	0.005

Note: Model A was adjusted for age, sex, current smoking status, diabetes duration, BMI, SBP. Model B was adjusted for age, sex, current smoking status, diabetes duration, BMI, SBP, HbA1c, HOMA-IR, HOMA-β, hs-CRP, TG, HDL-C. Model C was adjusted for age, sex, current smoking status, diabetes duration, BMI, SBP, HbA1c, HOMA-IR, HOMA-β, hs-CRP, TG, HDL-C, serum calcium, serum phosphorus, eGFR, ACR.

Abbreviations: ACR, albumin-to-creatinine ratio; AUC, area under the receiver operating characteristic curve; BMI, body mass index; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-estimated insulin resistance; HOMA-β, homeostatic model assessment of beta-cell function; hs-CRP, hypersensitive C-reactive protein; IDI, integrated discrimination improvement; NRI, net reclassification improvement; SBP, systolic blood pressure; TG, triglyceride.

DKD over 4.6 years. Additionally, our findings suggested that FGF23 models provided a potential clinical tool to identify individuals at risk of DKD.

Previous studies have reported that serum FGF23 levels increase early in the course of CKD and continue to rapidly accelerate as kidney function further declines.[10] In this study, we found a significant

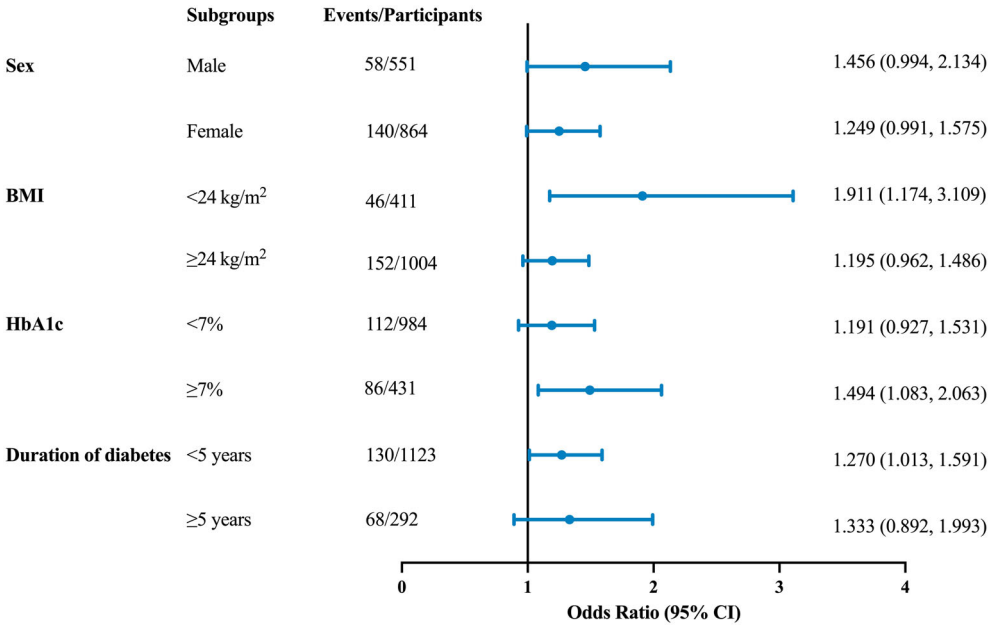

FIGURE 2 Effect of baseline FGF23 on incident diabetic kidney disease (DKD) in various subgroups. Odds ratios (95% CI) were obtained from multiple logistic regression analysis, referring to 1 SD change in $\log_e$-transformed serum FGF23 levels. The model was adjusted for age, sex, current smoking status, diabetes duration, BMI, SBP, HbA1c, HOMA-IR, HOMA-β, hs-CRP, TG, HDL-C, serum calcium, serum phosphorus, eGFR, and ACR. ACR, albumin-to-creatinine ratio; BMI, body mass index; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-estimated insulin resistance; HOMA-β, homeostatic model assessment of beta-cell function; hs-CRP, hypersensitive C-reactive protein; SBP, systolic blood pressure; TG, triglyceride.

elevation in serum FGF23 at early stages of DKD and a progressive increase in FGF23 levels corresponding to the severity of DKD stages, but not in serum calcium and phosphorus concentrations. Albuminuria, an early detectable clinical manifestation of DKD,[24] is considered as a reflection of early damage to the glomerular vascular endothelium.[32] Our results showed that baseline FGF23 levels increased among patients with albuminuria only. The above findings indicated an earlier detectable change in serum FGF23 in the course of DKD. Endothelial dysfunction plays a crucial role in the development of diabetic microvascular complications.[33,34] Mechanism studies also reported that FGF23 impaired endothelium-dependent vasorelaxation by increasing asymmetric dimethylarginine and superoxide levels and reducing nitric oxide bioavailability.[35,36] In our study, the addition of FGF23 to traditional risk factors led to a greater improvement in predicting incident DKD in patients with diabetic retinopathy, suggesting that endothelial dysfunction may contribute to the observed relationship between FGF23 and DKD.

Evidence from basic research demonstrated that inflammation could stimulate the production of FGF23.[18] In CKD animal models, elevated FGF23 levels play a significant role in inflammation regulation by interference with chemokine signalling and integrin activation directly.[37] Additionally, *Fgf-23*$^{-/-}$ mice were hypoglycaemic and had profoundly increased peripheral insulin sensitivity and improved subcutaneous glucose tolerance.[38] A clinical study reported that insulin resistance was associated with FGF23 in stages 3–5 CKD patients with diabetes.[39] Results from this study also demonstrated that FGF23 is positively correlated with HOMA-IR and hs-CRP. Chronic inflammation and insulin resistance may be the potential pathways through which FGF23 contributes to DKD development. Of note, some studies reported a benefit with FGF23 lowering. The anti-FGF23 antibody was reported to improve serum phosphorus levels and reduce the severity of rickets in patients with X-linked hypophosphatemia,[40] which is characterized by FGF23 excess. Moreover, in a secondary analysis of a randomized clinical trial of calcimimetic cinacalcet in patients with dialysis, treatment-induced reductions in serum FGF23 were associated with lower rates of major cardiovascular events and cardiovascular death.[41] Further basic studies, clinical research, and randomized clinical trials are needed to prove the causality and underlying mechanism between FGF23 and DKD.

Approximately 20% to 40% of individuals with type 2 diabetes presenting microalbuminuria are going to progress to macroalbuminuria in the absence of specific intervention,[42,43] and the risk of ESRD in patients with macroalbuminuria is 9.3 times higher compared with that in individuals with normoalbuminuria.[25] Annually measuring eGFR and ACR is recommended for regular screening among individuals with diabetes.[44] However, it poses significant challenges in clinical workflows, especially in primary care and low-resource settings. Some studies reported that only under 40% of individuals with diabetes received annual eGFR and ACR testing according to clinical practice guideline recommendations.[45] In this study, we assessed the clinical usability of FGF23 for incident DKD. Our results demonstrated that FGF23 performed well in DKD risk prediction, with an

improvement when added to established DKD risk factors. Additionally, subgroup analysis revealed that elevated FGF23 levels were significantly related to a higher risk of incident DKD especially in individuals with lower BMI, worse glucose control, and shorter duration of diabetes. Currently, the best approach to attenuating the adverse effects of DKD and its complications is prevention, including early detection and effective therapies. Our data support the clinical utility of FGF23 in the identification of individuals at risk of DKD who may require early detection and management.

This study provides insight into changes in FGF23 during the course of DKD and its potential utility for early risk warning and clinical decision-making in DKD, based on a large-scale community-based cohort. Several limitations should also be considered. First, this study was conducted in middle-aged and older adults in China. Investigations in diverse multiethnic populations are needed to validate the generalizability and robustness of our findings. Second, DKD was diagnosed based on the presence of albuminuria and/or a reduced eGFR in individuals with diabetes, lacking of renal biopsy information. Third, a single urine sample was collected from each participant, while the potential confounding factors (such as urinary tract infection and high-intensity exercise) that may influence the variability of albuminuria tests were controlled in this study.[27,46,47] Fourth, given the relatively short follow-up time, the association between FGF23 and incident DKD needs further investigation.

5 | CONCLUSION

Our study reveals an early and gradual increase in serum FGF23 levels during the course of DKD, which is significantly associated with incident DKD, suggesting that FGF23 could serve as a reliable independent biomarker for DKD risk prediction. Moreover, our findings demonstrate the clinical usability of FGF23 for the early identification of individuals at risk of DKD. Further clinical research and basic studies are needed to validate the causality, mechanism, and clinical value of FGF23 in DKD.

AUTHOR CONTRIBUTIONS

D.L. and S.Y. contributed to literature search, data analysis, and interpretation and wrote the manuscript. Y.Z., Q.L., X.H., L.W., S.Z., and Q.F. contributed to data collection and reviewed and edited the manuscript. P.K., L.W., R.H., D.C., and A.C. contributed to discussion and reviewed the manuscript. W.J. and H.L. contributed to the study design, data interpretation, and critical review of the manuscript and the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Restrictions apply to the availability of data generated or analysed during this study to preserve patient confidentiality or because they were used under licence. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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