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ORIGINAL ARTICLE

Fibroblast Growth Factor 21 and 23 as Biomarkers for Early Stage Diabetic Nephropathy in Type 2 Diabetic Patients

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ABSTRACT

Background: Albumin in the urine is an indicator of diabetic nephropathy (DN), a serious kidney condition brought on by destruction to the kidney's glomerular blood capillaries. In diabetic kidney disease (DKD), it was previously thought that albuminuria happens before kidney function declines. However, new epidemiological investigations showed that a subset of cases had kidney failure without albuminuria. It has been proposed that additional glomerular and/or tubular damage biomarkers can predict early renal failure and structural abnormalities, even prior to the onset of microalbuminuria.This study aimed to evaluate the role of fibroblast growth factor21 (FGF21) and fibroblast growth factor23 (FGF23) in early diagnosis of diabetic nephropathy in type 2 diabetes mellitus (T2DM) patients.

Methods: This case control investigation recruited 66 subjects allocated into three groups: 22 apparently healthy subjects as control group, 22 T2DM cases with normoalbuminuria and 22 T2DM cases with microalbuminuria. Serum FGF21 and FGF23 were assayed by ELISA.

Results: Serum FGF21 and FGF23 were substantially increased in patients with microalbuminuria compared to normoalbuminuric patients and control group. There was a significant positive correlation between FGF21 and FGF23 and between each of them with HbA1c, blood urea nitrogen (BUN), urine albumin creatinine ratio (UACR), and creatinine. A significant negative correlation was detected between both FGF21 and FGF23 and estimated glomerular filtration rate (eGFR). The sensitivities of FGF21 and FGF23 in predicting DN were 72.73% and 86.3% respectively. The specificities were 86.3% and 72.73% respectively. When combining both markers, the sensitivity was 86.3%.

Conclusion: FGF21 and FGF23 were significantly elevated in T2DM patients and in T2DM patients with microalbuminuria compared to those with normoalbuminuria. They can be considered promising markers for diagnosis of early stage of DN in T2DM patients.

Keywords: Diabetic nephropathy;Microalbuminuria; FGF21; FGF23.

INTRODUCTION

Diabetes mellitus (DM) is one of the most common chronic conditions globally. Egypt ranks in the top ten countries with DM incidence (15.6%), and statistics show that an additional 4.5 million cases are still undiagnosed [1].

DM cases have a triple higher chance of acquiring cardiovascular disorders. This risk is caused by both macrovascular and microvascular complications. Actually, over the last two decades, the number of deaths worldwide due to cardiovascular events in DM cases risen by 37.9% [2]. Diabetic nephropathy affects about a third of all DM cases; also, kidney damage is a leading source of morbidity and mortality in DM cases. DM is the most prevalent cause of end-stage renal disease (ESRD), which requires kidney replacement treatment [3]. Early detection and treatments with DN may halt disease development [4].

Microalbuminuria is frequently considered a sensitive preliminary sign of diabetic kidney disease (DKD) and is expected to occur before the more harmful occurrences that are monitored in the advanced stages of DN [5]. It was previously thought that albuminuria happens before kidney function declines. However, new epidemiological investigations showed that a subset of cases had kidney failure without albuminuria [6].

Fibroblast growth factor 21 is an element of the endocrine FGFs subfamily that serves several metabolic processes. Despite the conventional members of the FGFs family, FGF21 does not have mitogenic properties but is a key regulator of energy balance, lipid and glucose metabolism, and insulin sensitivity. FGF21 mediates the metabolic adaptations to starvation or fasting, particularly ketogenesis and fatty acid oxidation [7]. Serum FGF-21 is produced primarily by the hepatocytes and to a lesser extent, by adipocytes in humans [8]. Serum FGF21 values associated with nephropathy development, albuminuria and the probability of development to ESRD in T2DM cases [9].

FGF23 also, like FGF21, belongs to the endocrine FGFs subfamily. It is a secretory molecule that is primarily generated by osteoblasts. It was initially demonstrated to operate as a major mediator of the metabolism of vitamin D and phosphate [4]. Initial research discovered that uncontrolled FGF23 has a significant role in the development of mineral and bone diseases [10]. FGF23 associated with inflammation and endothelial dysfunction causing renal impairment [11].The current study designed to assess the role of FGF21 and FGF23 in early diagnosis of DN in T2DM cases.

METHODS

This case-control study was done in clinical pathology department, Zagazig University Hospitals during the period from January 2023 to September 2023. The study was approved by the Institutional Review Board (IRB). (IRB#: 10257/27-12-2022). Written informed consents were obtained from all participants in the study before sample collection.

Patients were recruited from diabetic outpatient clinics. 66 participants were included in the study allocated into three groups: 22 apparently healthy subjects as control group. Control group were age and sex matched with T2DM groups. T2DM cases were divided regarding their UACR into two groups: 22 T2DM cases with normoalbuminuria and 22 T2DM cases with microalbuminuria. Microalbuminuria is expressed in terms of UACR as 30 - 300 mg albumin/g of creatinine when a spot urine sample is collected [12]. Cases with alcohol consumption, smoking, obesity (BMI ≥30 kg/m2), indications of kidney dysfunction, having macroalbuminuria (UACR ≥300 mg/g creatinine), current infections of the urinary tract, active viral and/or bacterial infection, any sign of fatty liver disease, and the usage medications that influence serum FGF21 and FGF23 values and cases with DM macrovascular complications were excluded.

All cases were subjected to full history taking, clinical examination, BMI measurement, routine laboratory investigations including: HbA1c, UACR, serum creatinine, BUN, uric acid, eGFR, ALT, AST and alkaline

phosphatase, and specific laboratory investigations: Serum FGF21 and FGF23.

Venous blood samples (7ml) were aseptically withdrawn from all subjects and divided as follows: 5ml of blood sample delivered into sterile tube containing clot activator, allowed to clot and centrifuged at room temperature. The serum was allocated into two aliquots ,one for routine laboratory examinations; Serum creatinine, BUN, ALT, AST, alkaline phosphatase and uric acid were measured on Cobas 8000, c702 module (Roche, Germany) and the other aliquot was stored at -80°C for assay of FGF21 and FGF23 using sandwich ELISA kits (DL Sci&Tech Development Co., Ltd/ China). The other two ml of blood samples were delivered into sterile EDTA tube for assay of HbA1c. Random urine samples were collected to measure UACR. Urine albumin, urine creatinine and HbA1c were measured on Cobas 6000, c501 module (Roche, Germany).

Urine albumin /creatinine ratio was assessed by dividing urine albumin (mg/dl) by creatinine (mg/dl) then convert it to mg/g [13]. The estimated glomerular filtration rate (eGFR) was evaluated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [14].

For FGF21 kit: The lower detection limit is < 0.65 pg/mL, intra-assay CV is <10% and inter-assay CV is <12%. For FGF23 kit: The lower detection limit is <5.6 pg/mL, intra-assay CV is <10% and inter-assay CV is <12%.

Statistical Analysis:

Data analyzed by SPSS software (Statistical Package for the Social Sciences, version 24, SSPS Inc, Chicago, IL, USA). Continuous variables were checked for normality by employing Shapiro-Wilk. Frequency tables with percentages were utilized for categorical variables and descriptive statistics were employed for numerical variables. Independent Student t test and ANOVA were utilized to compare two or more quantitative variables respectively, while Chi-square test was employed to analyze categorical variables. Pearson correlation was utilized to study relationship between quantitative variables. A receiver operating characteristics (ROC) curve was plotted to evaluate diagnostic performance of studied markers. A cut off values were chosen that yield the best sensitivity with considerable specificity. $P<0.05$ is considered statistically significant.

RESULTS

Participant characteristics

Characteristics of studied groups are presented in table 1. The study was conducted on 66 individuals included: 22 apparently healthy subjects as controls, they matched well with patients as regard age and sex and they were 11 males (50%) and 11 females (50%), 22 diabetic patients with normoalbuminuria, they were 8 males (36.4%) and 14 females (63.6%) and 22 diabetic patients with microalbuminuria, they were 10 males (45.5%) and 12 females (54.5%). Duration of diabetes was substantially elevated in patients with microalbuminuria than those with normoalbuminuria.

Laboratory investigations:

HbA1c was raised in microalbuminuric group compared to normoalbuminuric diabetic cases. Diabetic groups had notably elevated serum creatinine and decreased eGFR than control group. Diabetic cases with microalbuminuria had increased serum creatinine and lower eGFR compared to those with normoalbuminuria. Uric acid and BUN concentrations were remarkably elevated in microalbuminuric group than other groups. Alkaline phosphatase was remarkably increased in T2DM cases compared to control group while no significant variance was detected between normoalbuminuric and microalbuminuric diabetic groups regarding alkaline phosphatase. FGF21 and FGF23 were significantly increased in diabetic groups compared to control group, moreover

in microalbuminuric diabetic cases compared to normoalbuminuric cases (table 2).

Correlation of FGF21 and FGF23 with other parameters:

There was a significant positive correlation between FGF21 and FGF23 and between each of them and other laboratory markers: HbA1c, UACR, creatinine and BUN. Moreover, negative correlation was revealed between both FGF21 and FGF23 and eGFR (Table 3).

Diagnostic potential of serum FGF21 and FGF23:

Roc curve analysis was employed to evaluate the diagnostic potential of FGF21 and FGF23. It showed that the area under curve (AUC) was 0.795 for FGF21 in diagnosis of microalbuminuria at cut off value 4.24 pg/ml, 16 out of 22 microalbuminuric patients were correctly diagnosed and 3 out of 22 normoalbuminuric patients were misdiagnosed. AUC was 0.897 for FGF23 in diagnosis of microalbuminuria at cut off value 5.92 pg/ml, 19 out of 22 microalbuminuric patients were correctly diagnosed and 6 out of 22 normoalbuminuric patients were misdiagnosed. The optimum sensitivity and specificity for FGF21 were 72.73% and 86.36% respectively, whereas for FGF23 were 86.36% and 72.73% respectively. Moreover, on combining FGF21 and FGF23 as diagnostic markers for microalbuminuria, sensitivity was 86.36% (table 4, figure 1).

Table (1): Characteristics of studied groups

Variable		Control (n=22)	T2D with normoalbuminuria (n=22)	T2D with microalbuminuria (n=22)	Test of significance	*P* value
Age(years)		49.68±6.69	54.09±11.85	52.95±8.76	1.31	0.275
BMI(kg/m^2)		25.27±2.68	26.64±3.33	25.4±2.36	1.57	0.21
Duration of DM(y)		…..	6.61±3.86	8.7±1.93	2.27	0.03*
Sex♦	**Male**	(11) 50%	(8) 36.4%	(10) 45.5%	0.86	0.65
	Female	(11) 50%	(14) 63.6%	(12) 54.5%		

BMI: body mass index, T2D: Type 2 diabetes, DM: Diabetes mellitus
n: Number of subjects. Data are presented as mean ± SD or number (%)♦, *p value significant.

Table (2): Biochemical characters in studied groups

Variable	Control (n=22)	T2D with Normoalbuminuria (n=22)	T2D with Microalbuminuria (n=22)	ANOVA	*P* value	LSD
HbA1c(%)	5.49±0.4	7.71±1.35	8.9±1.65	41.77	<0.001*	**(A)** P=0.003*
						(B) P<0.001*
						(C) P=0.001*
Creatinine(mg/dl)	0.78±0.14	0.89±0.08	0.99±0.09	22.65	<o.oo1*	**(A)** P=0.01*
						(B) P<0.001*
						(C) P<0.001*

BUN(mg/dl)	7.54±1.5	7.45±1.49	13.31±3.52	43.42	<0.001*	**(A)** P<0.001* **(B)** P<0.001* **(C)** P=0.91
Uric acid(mg/dl)	4.1±0.71	4.19±0.86	4.82±1	4.49	0.015*	**(A)** P=0.019* **(B)** P=0.008* **(C)** P=0.72
eGFR (ml/min/1.73 m^2)	91.59±4.36	78.18±6.79	68.09±4.81	104.21	<0.001*	**(A)** P<0.001* **(B)** P<0.001* **(C)** P<0.001*
ALT(U/l)	19.54±7.03	17.88±7.31	15.41±6.82	1.58	0.21	……..
AST(U/l)	22±5.87	22.54±12.04	22.86±21.83	0.019	0.98	……..
Alkaline phosphatase (U/l)	72.72±20.49	96.04±38.16	104±43.49	4.63	0.013*	**(A)** P=0.4 **(B)** P=.005* **(C)** P=.033*
FGF21(pg/ ml)	1.05±1.03	3.44 ±0.92	7.69 ±5.53	23.01	<.001*	**(A)** <.001* **(B)** <.001* **(C)** =.019*
FGF23(pg/ ml)	3.86 ±1.35	5.44± 1.26	8.82± 3.52	26.89	<.001*	**(A)** <.001* **(B)** <.001* **(C)** =.026*

T2D: Type 2 diabetes, LSD: least significant difference, ANOVA: Analysis of Variance, HbA1c: hemoglobin A1C, BUN: Blood Urea Nitrogen, eGFR: Estimated Glomerular Filtration Rate, ALT: Alanine transaminase, AST: Aspartate aminotransferase, FGF: Fibroblast Growth Factor

*p value significant. Data are presented as mean ± SD, n: Number of subjects.

(A) comparison of significance between T2DM patients with normoalbuminureia and T2DM patients with microalbuminuria

(B) comparison of significance between T2DM patients with microalbuminureia and control group

(C) comparison of significance between T2DM patients with normoalbuminureia and control group

Table (3): Validity of FGF21,FGF23 for differentiation between normoalbuminuric and microalbuminuric diabetic patients:

	AUC	Cutoff point	Sensitivity	specificity	Positive predictiv e value	Negative predictive value
FGF21	0.795	4.24 (pg/ml)	72.72%	86.36%	84.2%	76%
FGF23	0.897	5.92 (pg/ml)	86.36%	72.72%	76%	84%
FGF21and FGF23	0.924	…..	86.36%	68.18%	73.07%	83.33 %

AUC: Area under the curve, FGF: Fibroblast Growth Factor

Table (4): Correlation between FGF21 and FGF23 and different parameters among diabetic groups:

	FGF21		FGF23	
Parameter	**R**	**P**	**R**	**P**
Age	-0.061	0.694	-0.04	0.797
Duration	0.249	0.103	0.28	0.066
BMI	-0.142	0.358	-0.195	0.205
HbA1c	0.81	<0.001*	0.891	<0.001*
UACR	0.877	<0.001*	0.588	<0.001*
Uric acid	0.139	0.368	0.217	0.157
Creatinine	0.824	<0.001*	0.917	<0.001*
BUN	0.727	<0.001*	0.786	<0.001*
eGFR	-0.639	<0.001*	-0.299	<0.001*
ALT	0.048	0.757	0.142	0.359
AST	-0.109	0.483	-0.097	0.527
Alkaline phosphatase	0.171	0.268	0.077	0.619
FGF23	0.93	<0.001*		

FGF: Fibroblast Growth Factor, BMI: body mass index, HbA1c: hemoglobin A1C, BUN: Blood Urea Nitrogen,eGFR: Estimated Glomerular Filtration Rate, ALT: Alanine transaminase, AST: Aspartate aminotransferase

*P value significant .R: Pearson correlation coefficient .

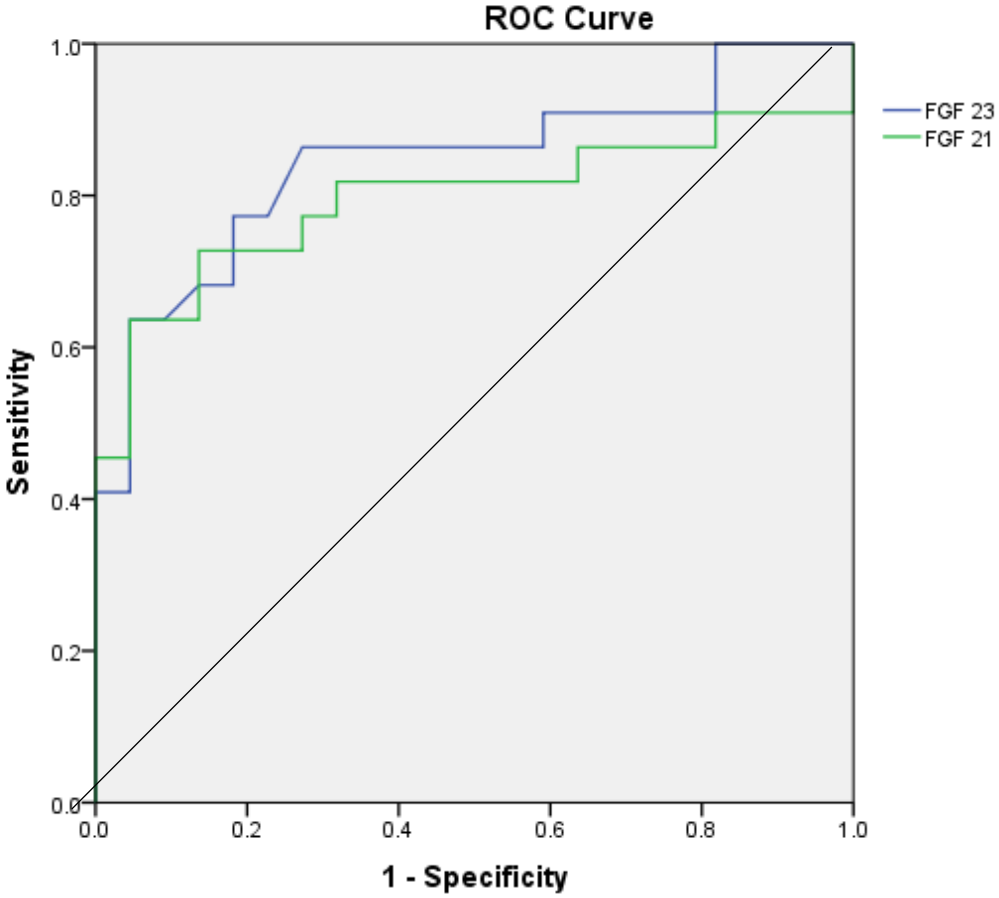

Figure (1): ROC curve of FGF21 and FGF23 in discriminating between normoalbuminuric and microalbuminuric T2DM cases.

DISCUSSION

DN is the leading cause of CKD and the most prevalent and deadly consequence of DM [4]. Despite urine albumin excretion still being an important indicator for observing disease development, severe structural abnormalities in the glomerular basal lamina may already have developed by the time microalbuminuria becomes clinically apparent [4]. So seeking for novel markers for early DN diagnosis is crucial.

Our results showed increased DM duration and poor glycemic control in microalbuminuric T2DM cases compared to normoalbuminuric cases as established previously [15,16]. Persistent hyperglycemia causes a collection of advanced glycation end products that cause progression from normoalbuminuria to microalbuminuria [17]. Poor management of glucose may had a crucial role in DN progression [18]. HbA1c has a unique affinity for oxygen, generating tissue anoxia and contributing to the development of microvascular complications [19].

Uric acid was notably elevated in microalbuminuric patients compared to normoalbuminuric and control group. Similar results were reported by Esteghamati et al. [15]. Elevated uric acid value was correlated with microalbuminuria in Korean, Taiwanese, and Chinese T2DM cases [20,21]. Increased uric acid can lead to vascular smooth muscle hypertrophy, impaired endothelial function, afferent arteriolar wall thickening, glomerular hypertrophy, and impede endothelial nitric oxide generation, resulting in a chronic inflammatory state [22].

The current study reported that FGF21 was substantially higher in both diabetic groups compared to control group. Similar findings were revealed by Esteghamati et al. [15] and Farag et al. [23]. El-Saeed and El-Mohasseb [24] also observed a remarkable elevation in FGF21 concentrations in T2DM cases with normoalbuminuria compared with control group. Increased FGF21 in T2DM patients had direct impacts in improving skeletal muscle glucose absorption and regulating glucose homeostasis [25].

We found that patients with microalbuminuria demonstrated higher FGF21 levels compared to normoalbuminuric patients. ROC-AUC of FGF21 was 0.795. At cut off value 4.24 pg/ml, sensitivity was 72.73% and specificity was 86.36% in discriminating microalbuminuric patients. Our results confirm previous results of Esteghamati et al. [15] who reported significant increase in FGF21 in microalbuminuric patients compared to normoalbuminuric. Serum FGF21was showed to predict microalbuminuria in T2DM cases with a sensitivity 88.6% and a specificity 86.4% which supported FGF21 diagnostic potential for early-stage DKD.

FGF21 has been identified as a new biomarker of advanced nephropathy. In T2DM cases, serum FGF21 values are related with nephropathy development, albuminuria and a possibility of development to ESRD [9], as the kidneys remove FGF21, and its levels rise as CKD worsens [26].

In the present study, both T2DM groups had significant elevation in FGF23 levels compared to the control group. This result came in agreement with El-Saeed and El-Mohasseb [24] who observed remarkable elevation in FGF23 values in T2DM cases with normoalbuminurea compared to control group. A cohort study which included cases with stage 2-4 CKD with and without diabetes revealed that DM was linked to higher FGF23 concentrations, and FGF23 increase was more common earlier in the course of CKD among patients with DM than those without DM [27]. Inci et al. [3] showed that FGF23 values were substantially elevated in T2DM cases than in the healthy controls.

Our study revealed a significant variance between normoalbuminuric and microalbuminuric diabetic patients, with the microalbuminuric group exhibiting the highest FGF23 level. ROC-AUC of FGF23 was 0.844. At cut off value 5.92 pg/ml, sensitivity was 86.36%.and specificity was 72.73% in discriminating microalbuminuric patients. FGF23 was considered previously as predictive marker for detection of diabetic nephropathy [28]. A case control study, enrolled T2DM cases with normoalbuminuria, microalbuminuria and macroalbuminuria, reported elevation in the level of FGF23 in diabetic cases with microalbuminuria

compared to normoalbuminuric patients. Macroalbuminuric group revealed significant higher levels of FGF23 compared to microalbuminuric group [28]. FGF23 increase was considered as an important risk factor of DN progression, as FGF23 elevation in the peripheral blood of DN cases was associated with an increase of inflammatory and fibrosis mediators as monocyte chemoattractant protein-1 and plasminogen activator inhibitor-1 [29]. FGF23 promotes inflammation by interrupting phosphate metabolism. Inhibiting FGF-23 relieves DN by boosting peripheral insulin sensitivity and improving subcutaneous glucose tolerance [30].

In contrast with our results, Farías-Basulto et al. [31] a cross-sectional investigation in Mexican cases with T2DM showed that FGF23 values were higher in diabetic cases with normoalbuminuria compared to those with microalbuminuria. However, this elevation did not attain statistical significance when compared to diabetic microalbuminuric group (P=0.6). FGF23 high levels were negatively correlated with early nephropathy. They justified their discrepancy by many factors; inflammation caused by hyperglycemia, high phosphate levels that trigger over production of FGF23, obesity, visceral fat accumulation, high levels of vitamin D and lack of healthy subjects. The difference between our study and Farías-Basulto et al. [31] may be due to different sample size, different population ,different duration of T2DM and administering drugs that influence mineral metabolism.

On combining FGF21 and FGF23 as diagnostic markers for microalbuminuria, sensitivity was 86.36% similar to that of FGF23 alone. This result indicates that measuring the two markers does not add value in predicting diabetic nephropathy in T2DM patients. Although several FGFs, including FGF1, FGF19, and FGF21, can effectively and safely lower hyperglycemia and have the ability to be developed into new medications for DM therapy, FGF23 is strongly associated with DM and its complications [32]. FGF23 promotes renal endothelial damage, a substantial risk factor for renal conditions, and a known regulator of local angiotensin II in the kidney by promoting phosphate metabolism and blocking the formation of nitric oxide (NO) [33].

We found that both FGF21 and FGF23 had statistically significant positive correlation with HbA1c, UACR, serum creatinine, BUN and statistically significant negative correlation with eGFR. They also represented statistically significant positive correlation with each other. Similarly, El-Saeed and El-Mohasseb [24] reported that FGF21 and FGF23 have a substantial positive correlation with creatinine, HbA1c, and UACR. A negative correlation was identified between both of FGF21 and FGF23 and eGFR.

The results of this study extend previous evidence suggesting that elevated FGF21 could serve as a reliable marker for renal function decline in diabetic patients [15,23,34]. FGF21 was also previously showed to be significantly positively associated with HbA1c [15,23] and UACR [23]. In addition, Azzall et al. [28] showed a positive relationship of FGF23 with creatinine and urea because Increased FGF-23 levels were independently related to quicker development of CKD in T2DM patients. Isakova et al. [35] reported that FGF23 is high in CKD cases and increased as eGFR fall. A substantial positive association between FGF23 values and UACR was also reported [3].

The present investigation has some limitations. The sample size of the included subjects was relatively small and from a single center which may limit the possibility that the study's results can be generalized.

CONCLUSION

FGF21 and FGF23 were significantly increased in T2DM patients and in diabetic patients with microalbuminuria compared to those with normoalbuminuria. They can be considered promising markers for diagnosis of early stage of DN in T2DM patients. Further studies with large sample size are recommended to confirm these results.

No potential conflict of interest was reported by the authors.

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