BENHA MEDICAL JOURNAL bmj
**Print ISSN** 1110-208X.
**Online ISSN** 2357-0016

Original article

# Serum FGF23 as an Early Biomarker of Renal Impairment in Children with Type 1 Diabetes

Eman A. Mohammed [a], Amira O. Abdel Ghaffar [b], Mohamed K. Salamh [a],Effat H. Assar [a] Naema H. Zeriban [c]

[a] Pediatric Department, Faculty of Medicine Benha University, Egypt.

[b] Clinical and Chemical Pathology Department, Faculty of Medicine Benha University, Egypt.

[c] Pediatric Endocrinology Unit, Damanhur Teaching Hospita, Egypt.

**Corresponding to:** Mohamed K. Salamh, Pediatric Department, Faculty of Medicine Benha University, Egypt.

**Email:**

mohsalamh1993@gmail.com

**Received:**
**Accepted:**

## Abstract

**Background:** Diabetic nephropathy (DN), a leading complication of type 1 diabetes mellitus (T1DM) in children, remains a major contributor to end-stage renal disease. Emerging evidence suggests that tubular injury, rather than glomerular damage alone, may initiate renal dysfunction. Fibroblast Growth Factor 23 (FGF23), a regulator of phosphate metabolism, has been implicated in early kidney injury. **This study aimed to** assess FGF23 as a potential early biomarker of renal impairment in children with T1DM. **Methods:** This cross-sectional study included 50 children with T1DM (duration >5 years). Clinical assessments and laboratory investigations including HbA1C, eGFR, albumin/creatinine ratio (ACR), and serum FGF23 levels were conducted. Early renal impairment was defined as ACR ≥30 mg/g. **Results**: Early renal impairment was identified in 44% of patients. Children with renal impairment had significantly higher FGF23 levels (76 ± 10 vs. 51 ± 11 pg/mL, P < 0.001), higher HbA1C (10.4 ± 2 vs. 9 ± 1.5%, P = 0.009), and lower eGFR (78.9 ± 11.7 vs. 94.1 ± 21.6 mL/min/1.73m², P = 0.003). FGF23 positively correlated with phosphorus, creatinine, and ACR, and inversely with eGFR. ROC analysis showed excellent diagnostic accuracy for FGF23 (AUC = 0.955; cutoff >67 pg/mL; sensitivity: 86.4%, specificity: 96.4%). Multivariate analysis revealed FGF23 (OR = 1.414, P = 0.02) and HbA1C (OR = 5.529, P = 0.046) as independent predictors of early renal impairment. **Conclusion:** Elevated serum FGF23 is significantly associated with early renal impairment in T1DM children and may serve as a promising early biomarker to guide timely intervention.

**Keywords:** FGF23, Type 1 Diabetes Mellitus, Diabetic Nephropathy, Renal Impairment.

## Introduction

Type 1 diabetes mellitus (T1DM) represents one of the most encountered chronic conditions during childhood and adolescence. Despite advances in management, its long-term complications, particularly diabetic nephropathy (DN), also known as DKD remain a significant burden and a major clinical concern [(1)].

DKD is a leading cause of ESRD and substantially contributes to cardiovascular morbidity and mortality in cases with T1DM.Traditionally, DKD is thought to progress from persistent albuminuria to declining GFR, However recent studies have shown that some individuals with T1DM experience an early decline in GFR without preceding albuminuria, indicating an atypical disease course [(2)].

This atypical progression has raised interest in alternative mechanisms of kidney injury beyond glomerular dysfunction. Tubular damage is increasingly recognized as a possible primary event in DKD, potentially initiating glomerulosclerosis [(3)]. However, exact triggers of early tubular injury in T1DM remain unclear, and no reliable biomarker currently exists to detect such early-stage subclinical kidney damage in this population. Thus, identifying novel early markers of renal impairment is crucial for timely diagnosis and intervention to prevent irreversible kidney damage [(4)].

Among emerging candidates, FGF23 has drawn attention for its role in phosphate metabolism and renal aging. FGF23, primarily secreted by osteocytes and osteoblasts, regulates serum phosphate by acting on kidney through FGFR1c and α-Klotho co-receptor complex. It reduces phosphate reabsorption in proximal tubules and suppresses vitamin D activation, thereby decreasing intestinal phosphate absorption and serum phosphate levels [(5)]. Elevated FGF23 levels have been implicated in CKD progression, partly by promoting tubular dysfunction and renal senescence [(6)].

Therefore, this study aims to evaluate FGF23 role as a potential early marker in the assessment of DN in T1DM children.

## Patients and methods

This cross-sectional study was conducted on fifty children diagnosed with T1DM at Pediatrics Department, Faculty of Medicine, Benha University, in collaboration with Outpatient Endocrinology Clinic at Damanhour Teaching Hospital from February 2024 to September 2024.

The study was approved by the Institutional Ethical Committee, Faculty of Medicine, Benha University (Approval code: MS 27-1-2024). Informed written consent was obtained from the parents or guardians of all

participating children, ensuring their voluntary involvement in the study.

**Inclusion criteria** comprised diabetic children under the age of 18 years with a disease duration exceeding five years. Children were excluded if they had renal diseases unrelated to DN.

Early renal impairment was defined as an ACR ≥30 mg/g, consistent with pediatric guidelines that recognize this threshold as an early marker of nephropathy in children and adolescents with T1DM [(7)].

**All participants were subjected to the following assessments:**

**Clinical evaluation**

A comprehensive history was obtained, including personal, present, past, perinatal, developmental, vaccination, and family history. Diabetes-specific data including disease duration, total daily insulin dose, type of insulin used, treatment compliance, and dietary adherence were also documented. This was followed by a thorough clinical examination, including regional assessments, BMI calculation, and measurements of DBP and SBP.

**Laboratory Investigations and Blood Sampling**

Participants underwent routine laboratory testing including serum urea, serum creatinine, urine analysis, HbA1c, albumin/creatinine ratio (ACR), and eGFR. Additionally, FGF23 levels were measured using a sandwich ELISA kit (Catalog No. DL-FGF23-Hu, DEVELOP, China), according to manufacturer's instructions.

For blood sampling, 6 ml of venous blood were collected under aseptic conditions. Two milliliters of blood were collected into a K2-EDTA tube for HbA1c analysis, whereas the remaining 4 mL were transferred into a plain vacutainer, left to clot, and subsequently centrifuged at 1500 rpm for 15 minutes. The obtained serum was subsequently divided :one part for immediate assessment of kidney function and eGFR, and the other stored at -70°C for later analysis of FGF23.

**Sample size calculation.**

The sample size was calculated using Epi-info software version 7.2.5.0 based on a previous study by Alleyn et al., who reported renal impairment in 9.3% of children with type I diabetes mellitus. The total sample size needed to detect such a prevalence will be fifty children. The confidence level and margin of error were adjusted at 95% and 8%, respectively.

**Statistical analysis**

Statistical analysis and data management were conducted using IBM SPSS Statistics, version 27 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was examined for normality utilizing Shapiro–Wilk test, supplemented by graphical assessment methods. Quantitative data were

expressed as mean ± SD for variables following a normal distribution, and as median with range for those not normally distributed. Categorical variables were summarized using absolute frequencies and corresponding percentages. Comparisons between groups for continuous variables were conducted using independent t-test for parametric data and Mann–Whitney U test for non-parametric data. Categorical variables were analyzed using Chi-square test or Fisher's exact test, as appropriate. Correlations between serum FGF23 and different parameters were done using Pearson and Spearman's correlations. ROC analysis was done for serum FGF23 to predict early renal impairment. ROC curve analysis was conducted to determine AUC with corresponding 95% confidence intervals, along with optimal cutoff value and associated diagnostic metrics. To assess predictors of early renal dysfunction, univariate logistic regression was initially applied, followed by a stepwise multivariate logistic regression model. For each variable, ORs and their 95% CIs were estimated. All statistical tests were performed as two-tailed, with a significance threshold set at $p < 0.05$.

## Results

### General and clinical characteristics

General and clinical characteristics laboratory investigations were reported in **Tables 1 and 2**, respectively.

The children were then categorized according to their renal function status based on urinary Alb/ Creat ratio into two groups: those with early renal impairment (n = 22, Alb/Creat ratio ≥ 30 mg/g) and those without renal impairment (n = 28, Alb/Creat ratio < 30 mg/g).

### General and clinical characteristics according to the early renal impairment status

Cases with early renal impairment were significantly older than those without renal impairment (15.2 ± 1.5 vs. 12.8 ± 2.5 years, P < 0.001). No substantial variations were detected between groups regarding sex distribution, weight, or weight centile. However, cases with early renal impairment had a significantly lower height centile relative to those without renal impairment (9 (0.5 - 38) vs. 24.5 (0.4 - 87), P = 0.006). BMI did not differ markedly between the two groups (21.3 ± 3.1 vs. 20.4 ± 3.9 kg/m², P = 0.557). SBP measurements showed no significant differences between groups. However, DBP centile was markedly higher in the early renal impairment group (82 ± 9 vs. 72 ± 16, P = 0.007). **Table 3**

Compliance with dietary recommendations was markedly poorer in cases with early renal impairment (77.3% vs. 39.3%, P = 0.007). However, there was no substantial variation in insulin dose per kilogram of body weight (1.15 ± 0.29 vs. 1.01 ± 0.25 IU/kg, P = 0.583). Additionally, diabetes duration

was longer among cases with early renal impairment relative to those without (9.8 ± 2.6 vs. 7.5 ± 1.9 years); however, this variation was not significant (P = 0.191). **Table 3**

**Laboratory investigations according to the early renal impairment status**

Regarding laboratory investigations, cases with early renal impairment had higher serum phosphorus levels than those without renal impairment (4.9 ± 0.5 vs. 3.7 ± 0.7 mg/dL, P < 0.001. The mean HbA1C was markedly higher in cases with early renal impairment (10.4 ± 2 % vs. 9 ± 1.5 %, P = 0.009). Additionally, cases with early renal impairment had a significantly lower eGFR relative to those without (78.9 ± 11.7 vs. 94.1 ± 21.6 mL/min/1.73m², P = 0.003). Notably, the mean FGF23 level was significantly elevated in the early renal impairment group (76 ± 10 vs. 51 ± 11 Pg/mL, P < 0.001). Conversely, no substantial variations were observed between studied groups in terms of urea and creatinine levels (P = 0.091 and 0.161, respectively). **Table 4, Figures 1**

**Correlation between serum FGF23 (Pg/mL) and different parameters**

Serum FGF23 levels exhibited a notable positive correlation with diabetes duration (r = 0.658, P = 0.001), serum creatinine (r = 0.574, P = 0.005), serum phosphorus (r = 0.97, P < 0.001), and albumin/create ratio (r = 0.766, P < 0.001). Additionally, FGF23 showed a substantial negative correlation with eGFR (r = -0.538, P = 0.01). **Figure 2A-E**

No substantial correlations were observed between FGF23 levels and age (P = 0.614), weight (P = 0.857), height (P = 0.580), weight centile (P = 0.994), height centile (P = 0.392), BMI (P = 0.617), insulin dose per kg (P = 0.390), SBP (P = 0.502), DBP (P = 0.158), SBP centile (P = 0.942), DBP centile (P = 0.274), urea (P = 0.085), HbA1C (P = 0.295), and albumin-to-creatinine ratio (P = 0.068).

**ROC analysis of serum FGF23 to predict early renal impairment.**

ROC curve analysis was performed for serum FGF23 to predict early renal impairment. It revealed a substantial AUC of 0.955, with a 95% CI ranging from 0.901 to 1.00, indicating an excellent ability to predict early renal impairment. The best cutoff value was >67 Pg/mL, at which sensitivity, specificity, PPV, and NPV were 86.36%, 96.43%, 94%, and 90%, respectively. **Figure 3**

**Logistic regression analyses to predict early renal impairment.**

All variables which showing notable associations with early renal impairment and are applicable for regression analysis were included in univariate and stepwise multivariate logistic regression analyses.

In the stepwise multivariate analysis, HbA1C and FGF23 remained significant independent predictors of early renal

impairment. Specifically, for each 1% increase in HbA1C, the risk of early renal impairment increased by 452.9% (OR = 5.529, 95% CI: 1.035–29.547, P = 0.046). Likewise, for each 1 pg/mL increase in FGF23, the risk of early renal impairment increased by 41.4% (OR = 1.414, 95% CI: 1.056–1.894, P = 0.02). **Table 5**

Additionally, DBP centile showed a borderline association with early renal impairment. For each 1-unit increase in DBP centile, the risk of early renal impairment increased by 18%, though this association did not reach statistical significance (OR = 1.18, 95% CI: 0.991–1.405, P = 0.063). **Table 5**

**Table 1:** General and clinical characteristics of the studied children (n = 50)

| **Demographic & general characteristics** | | |
|---|---|---|
| **Age (years)** | Mean ±SD | 13.8 ±2.4 |
| **Sex** | | |
| Males | n (%) | 26 (52) |
| Females | n (%) | 24 (48) |
| **Weight (kg)** | Mean ±SD | 49 ±13 |
| **Weight centile (%)** | Median (range) | 50 (3 - 96) |
| **Height (cm)** | Mean ±SD | 151 ±11 |
| **Height centile (%)** | Median (range) | 15.5 (0.4 - 87) |
| **BMI (kg/m$^2$)** | Mean ±SD | 20.8 ±3.6 |
| **SBP (mmHg)** | Mean ±SD | 114 ±6 |
| **DBP (mmHg)** | Mean ±SD | 72 ±6 |
| **SBP centile (%)** | Mean ±SD | 72 ±14 |
| **DBP centile (%)** | Mean ±SD | 76 ±14 |
| **Diabetes duration (years)** | Mean ±SD | 8.5 ±2.5 |
| **Insulin dose (unit/kg)** | Mean ±SD | 1.07 ±0.27 |
| **Good compliance to treatment** | n (%) | 50 (100) |
| **Compliance to diet** | | |
| **Good** | n (%) | 22 (44) |
| **Poor** | n (%) | 28 (56) |

BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, IU: International Units, HbA1C: Glycated Hemoglobin, SD: Standard Deviation, n: Number.

**Table 2:** Laboratory investigations of the studied children (n = 50)

| **Lab investigations** | | |
|---|---|---|
| **Urea (mg/dL)** | Mean ±SD | 27 ±5 |
| **Creatinine (mg/dL)** | Mean ±SD | 0.74 ±0.14 |
| **Serum phosphorus(mg/dL)** | Mean ±SD | 4.3 ±0.9 |
| **Alb/Creat ratio** | Median (range) | 27.3 (1.4 – 267) |
| **HbA1C** | Mean ±SD | 9.6 ±1.9 |
| **Free Urine Analysis** | n (%) | 50 (100) |
| **eGFR (ml/min/1.73m$^2$)** | Mean ±SD | 87.4 ±19.3 |
| **Early renal impairment** | n (%) | 22 (44) |
| **FGF23 (Pg/mL)** | Mean ±SD | 62 ±16 |

eGFR: Estimated Glomerular Filtration Rate, Alb/Creat ratio: Albumin to Creatinine Ratio, HbA1C: Glycated Hemoglobin, FGF23: Fibroblast Growth Factor 23, SD: Standard Deviation, n: Number.

**Table 3:** General and clinical comparison between patients with and without early renal impairment

| | | **Early renal impairment** | | |
|---|---|---|---|---|
| | | **Yes (n = 22)** | **No (n = 28)** | **P-value** |
| **Age (years)** | Mean ±SD | 15.2 ±1.5 | 12.8 ±2.5 | **<0.001*** |
| **Sex** | | | | |
| Males | n (%) | 12 (54.5) | 14 (50) | 0.749 |
| Females | n (%) | 10 (45.5) | 14 (50) | |
| **Weight (kg)** | Mean ±SD | 52 ±9 | 46 ±15 | 0.107 |
| **Weight centile (%)** | Median (range) | 43 (3 - 88) | 51 (4 - 96) | 0.184 |
| **Height (cm)** | Mean ±SD | 154 ±9 | 149 ±13 | 0.071 |
| **Height centile (%)** | Median (range) | 9 (0.5 - 38) | 24.5 (0.4 - 87) | **0.006*** |
| **BMI (kg/m$^2$)** | Mean ±SD | 21.3 ±3.1 | 20.4 ±3.9 | 0.557 |
| **SBP (mmHg)** | Mean ±SD | 117 ±5 | 111 ±6 | 0.684 |
| **DBP (mmHg)** | Mean ±SD | 75 ±6 | 70 ±6 | 0.525 |
| **SBP centile (%)** | Mean ±SD | 77 ±11 | 68 ±14 | 0.143 |
| **DBP centile (%)** | Mean ±SD | 82 ±9 | 72 ±16 | **0.007*** |
| **Diabetes duration (years)** | Mean ±SD | 9.8 ±2.6 | 7.5 ±1.9 | **0.191** |
| **Insulin dose (unit/kg)** | Mean ±SD | 1.15 ±0.29 | 1.01 ±0.25 | **0.583** |
| **Compliance to diet** | | | | |
| **Good** | n (%) | 5 (22.7) | 17 (60.7) | **0.007*** |

| | | | |
|---|---|---|---|
| **Poor** | n (%) | 17 (77.3) | 11 (39.3) |

BMI: Body Mass Index, SD: Standard Deviation, SBP: Systolic Blood Pressure, IU: International Units, DBP: Diastolic Blood Pressure, n: Number, *: Significant P-value.

**Table 4**: Laboratory investigations between the studied groups

| | | Early renal impairment | | |
|---|---|---|---|---|
| | | **Yes (n = 22)** | **No (n = 28)** | **P-value** |
| **Urea (mg/dL)** | Mean ±SD | 27 ±4 | 26 ±6 | 0.091 |
| **Creatinine (mg/dL)** | Mean ±SD | 0.81 ±0.11 | 0.67 ±0.13 | 0.161 |
| **Serum phosphorus (mg/dL)** | Mean ±SD | 4.9 ±0.5 | 3.7 ±0.7 | **<0.001*** |
| **HbA1C** | Mean ±SD | 10.4 ±2 | 9 ±1.5 | **0.009*** |
| **eGFR (ml/min/1.73m$^2$)** | Mean ±SD | 78.9 ±11.7 | 94.1 ±21.6 | **0.003*** |
| **FGF23 (Pg/mL)** | Mean ±SD | 76 ±10 | 51 ±11 | **<0.001*** |

Data were presented as Mean ±SD (Standard deviation), FGF23: Fibroblast Growth Factor 23, eGFR: Estimated Glomerular Filtration Rate, HbA1C: Glycated Hemoglobin, SD: Standard Deviation, n: Number, *: Significant P-value.

**Table 5:** Univariate and stepwise multivariate logistic regression analyses to predict early renal impairment.

| | **Univariate** | | **Multivariate** | |
|---|---|---|---|---|
| | **OR (95% CI)** | **P-value** | **OR (95% CI)** | **P-value** |
| **Age (years)** | 1.742 (1.219 - 2.489) | **0.002*** | - | - |
| **Height centile (%)** | 0.943 (0.903 - 0.985) | **0.009*** | - | - |
| **Poor diet compliance** | 5.255 (1.501 - 18.391) | **0.009*** | - | - |
| **DBP centile** | 1.065 (1.011 - 1.122) | **0.017*** | 1.18 (0.991 - 1.405) | 0.063 |
| **Phosphorus (mg/dL)** | 48.804 (5.696 - 418.145) | **<0.001*** | - | - |
| **HbA1C** | 1.597 (1.111 - 2.295) | **0.011*** | 5.529 (1.035 - 29.547) | **0.046*** |
| **eGFR (ml/min/1.73m$^2$)** | 0.924 (0.867 - 0.985) | **0.015*** | - | - |
| **FGF23 (Pg/mL)** | 1.257 (1.102 - 1.433) | **0.001*** | 1.414 (1.056 - 1.894) | **0.02*** |

OR: Odds Ratio, CI: Confidence Interval, IU: International Units, DBP: Diastolic Blood Pressure, HbA1C: Glycated Hemoglobin, eGFR: Estimated Glomerular Filtration Rate, FGF23: Fibroblast Growth Factor 23, *: Significant P-value.

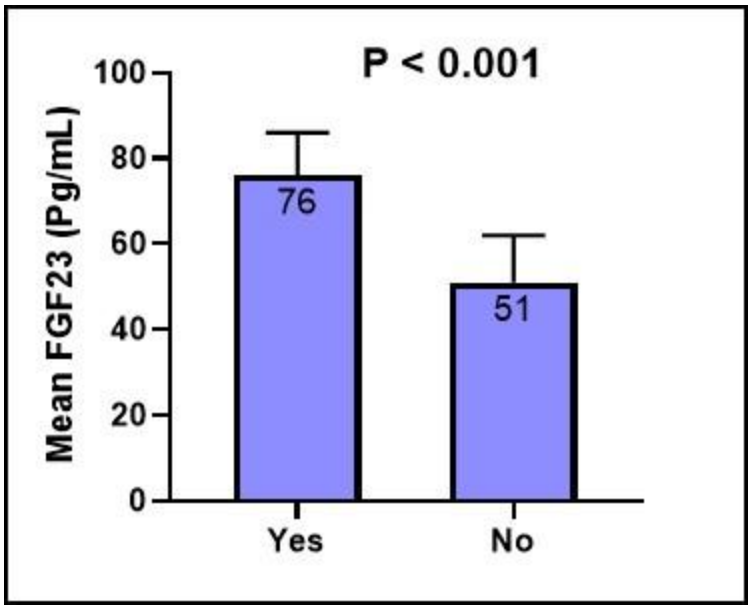


**Figure 1: Mean serum FGF23 (Pg/mL) according to the early renal impairment status**

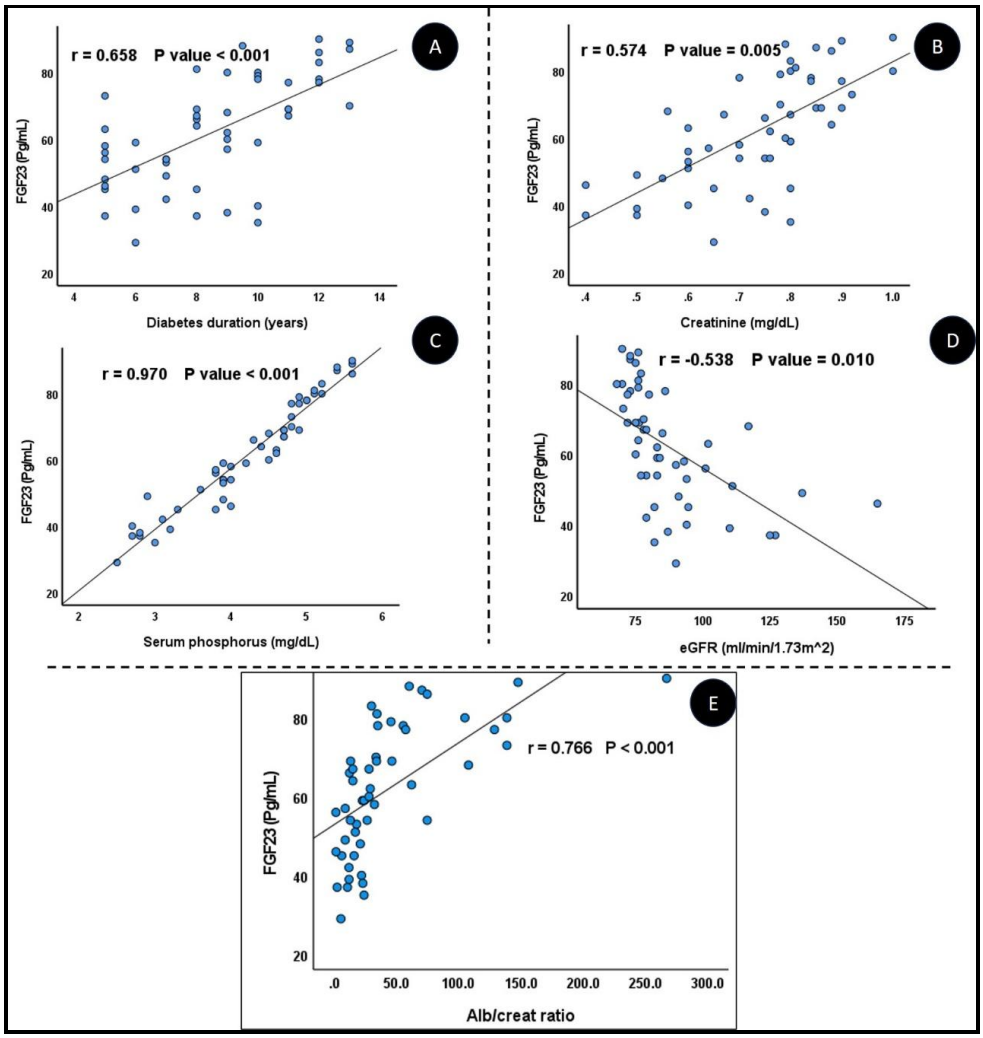


**Figure 2**: Correlation between serum FGF23 (Pg/mL) and A) diabetes duration (years), B) creatinine (mg/dL), C) serum phosphorus (mg/dL), D) eGFR (ml/min/1.732), and E) albumin/create ratio.

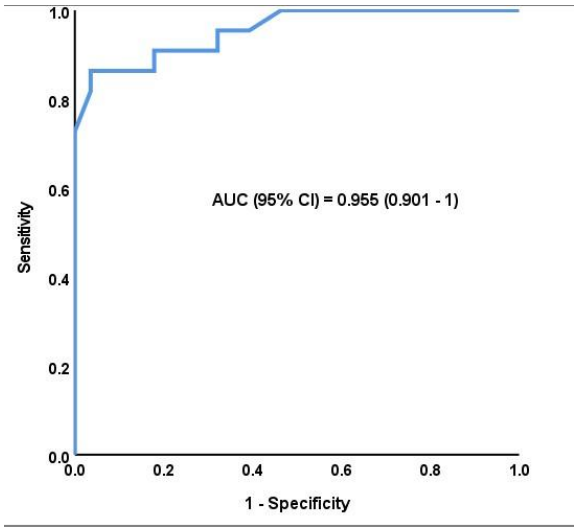


**Figure 3:** ROC analysis of serum FGF23 to predict early renal impairment.

## Discussion

T1DM is a common chronic condition in children, often leading to complications such as DKD, a major cause of morbidity, mortality, and ESRD. While DKD typically progresses from albuminuria to declining GFR, some cases exhibit GFR decline without albuminuria, indicating possible early tubular injury. FGF23, a key regulator of phosphate metabolism, has been linked to early renal dysfunction and may serve as a potential early biomarker [(8)].

However, FGF23 levels may be influenced by multiple physiological variables including dietary phosphate intake, bone turnover, vitamin D levels, and circadian rhythm. These factors may introduce variability and must be considered when interpreting FGF23 as a biomarker in clinical settings. Standardization of testing protocols and incorporation of these variables into future studies is essential to enhance clinical utility [(9-11)].

In this study, children with early renal impairment were markedly older and had a lower height centile relative to those without impairment, suggesting a link between growth retardation and early kidney dysfunction. No substantial variations were observed between groups regarding sex, weight, weight centile, or SBP. However, DBP centile was higher in early renal impairment group. These findings align with Mamilly et al. [(12)] , who reported older age in T1D cases relative to controls, and Elmeazawy et al. [(13)], who found higher DBP in children with early DN.

In this study, children with early renal impairment had a longer duration of diabetes and markedly elevated serum phosphorus and HbA1c levels relative to those without impairment, suggesting an

association between poor glycemic control, altered phosphate metabolism, and kidney dysfunction. These findings are consistent with Elmeazawy et al. [13], who reported substantially higher HbA1c levels in T1DM cases with DN relative to those without.

Regarding HbA1c, Arnold et al. [14] investigated its predictive value for renal outcomes independent of diabetes status in a cohort of 19,285 individuals, regardless of baseline CKD or diabetes presence. Their findings identified HbA1c as a significant determinant of CKD development, reporting a hazard ratio of 1.18 (95% CI: 1.16–1.21; P < 0.001). Additionally, Hernandez et al. [15] explored the relationship between HbA1c levels and CKD in a cohort of 2,270 adults. Their analysis revealed that each one-percentage-point increase in HbA1c was associated with a 30% higher likelihood of CKD. These results imply that the relationship observed between diabetes and CKD is mediated by HbA1c levels, as evidenced by odds ratio (OR = 1.3; 95% CI: 0.99–1.6; P = 0.05).

In the present study, FGF23 levels exhibited a notable inverse correlation with eGFR, suggesting that elevated FGF23 concentrations are associated with reduced renal function and may serve as a potential early biomarker for kidney impairment. This aligns with findings by Abdel-Azeez et al. [16], who reported substantially elevated FGF23 levels and reduced eGFR in T2DM cases compared to controls, supporting its role in early detection of DN.

During the initial phases of CKD, FGF23 levels progressively increase as a compensatory mechanism to regulate serum phosphate levels. However, sustained elevations in FGF23 ultimately contribute to the pathogenesis of bone disease in these cases [17]. An association has been observed between elevated FGF23 levels and incidence of ESRD. Research involving participants with early-stage CKD demonstrated that increased FGF23 concentrations were predictive of a higher risk of all-cause mortality and progression to ESRD [18, 19].

Regarding FGF23, Isakova et al. [20] evaluated FGF-23 as a risk factor for adverse outcomes in cases with CKD including 3879 participants and found that elevated FGF23 was independently associated with markedly higher risk of ESRD among participants with an estimated GFR between 30 and 44 mL/min/1.73 m2 (HR, 1.3; 95% CI, 1.04-1.6). In addition, Takashi et al. [21] showed notable association between FGF23 and eGFR (β= -0.141, P value= 0.037) indicating the value of FGF23 for prediction of renal impairment. Furthermore, Fliser et al. [19]. included 227 non-diabetic cases with CKD in their study hypothesing that FGF23 is a predictor of CKD progression and found that adjusting for all variables in addition to age and gender, c-terminal FGF23 (OR= 1.014 (95%CI: 1.005 to 1.024, P value= 0.002), and intact FGF23 (OR=

1.061 (95%CI: 1.018 to 1.106, P value =0.005) remained significant predictors for progression of CKD.

In a study conducted by A Kamel et al. [22], serum FGF23 was investigated as an early biomarker for diagnosis of renal osteodystrophy in pediatric cases with CKD. The findings revealed that FGF23 levels were markedly elevated in CKD cases compared to controls (532.5 pg/mL vs. 124.9 pg/mL, $P < 0.0001$). Additionally, the GFR was markedly reduced in CKD group relative to controls ($22.9 \pm 20.2$ vs. $114.4 \pm 9.9$ mL/min/1.73 m², $P < 0.0001$).

Consistent with our findings on reduced eGFR in early renal impairment, Maahs et al. [23] reported that adults with T1DM experienced substantially greater declines in eGFR over six years relative to non-diabetic controls. In contrast, Ledeganck et al. [24] found no substantial variation in eGFR between T1DM children and controls, which may be due to variations in age group or study methodology, highlighting the complexity of early renal changes in diabetes.

In this study, serum FGF23 levels showed a strong positive correlation with diabetes duration, serum creatinine, and phosphorus levels, indicating its association with prolonged disease and declining renal function. Similarly, Abdel-Azeez et al. [16] reported a borderline notable correlation between FGF23 and diabetes duration and a notable negative correlation with eGFR. Takashi et al. [21] also found FGF23 to be negatively associated with eGFR and positively with serum phosphate, further supporting its link to early renal impairment, though they observed no substantial correlation with diabetes duration.

In comparison to other early renal biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and cystatin C, FGF23 has the advantage of being associated with both phosphate metabolism and tubular injury [25]. However, studies suggest that a combination of markers may enhance diagnostic sensitivity for early renal impairment, and comparative studies are warranted [26, 27].

In our study, ROC curve analysis revealed that serum FGF23 is a highly accurate predictor of early renal impairment, with a cutoff value >67 pg/mL demonstrating strong sensitivity and specificity, supporting its role as a reliable early biomarker. Similarly, Dohuim et al. [28] reported excellent diagnostic performance for FGF23 in predicting kidney damage, with a cutoff ≥59,735 pg/mL yielding over 90% sensitivity, specificity, and overall accuracy, further validating its clinical utility.

Consistent with our findings, A Kamel et al. [22] identified a cutoff value of 159.7 pg/mL for FGF23 in predicting CKD, yielding a sensitivity of 85%, specificity of 90%, accuracy of 80%, NPV of 75%,

PPV of 94.4%, and an AUROC of 0.837, with a statistically significant P value of 0.0001.

This study has some limitations. Its cross-sectional design limits causal inference between FGF23 levels and early renal impairment. The small sample size may affect generalizability. The study also lacks control group Renal impairment was assessed by albumin/creatinine ratio rather than biopsy, the diagnostic gold standard. Additionally, factors such as phosphate intake, vitamin D status, and genetic influences on FGF23 were not accounted for.

## Conclusion

In conclusion, FGF23 is a sensitive and specific early biomarker for renal impairment in children with T1DM, offering potential for earlier diagnosis and intervention before irreversible kidney damage occurs.

## References

1. Muntean C, Starcea IM, Banescu C. Diabetic kidney disease in pediatric patients: A current review. World J Diabetes. 2022;13:587-99.
2. Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clin J Am Soc Nephrol. 2017;12:2032-45.
3. Wang N, Zhang C. Oxidative Stress: A Culprit in the Progression of Diabetic Kidney Disease. Antioxidants (Basel). 2024;13.
4. Mizdrak M, Kumrić M, Kurir TT, Božić J. Emerging Biomarkers for Early Detection of Chronic Kidney Disease. J Pers Med. 2022;12.
5. Jüppner H. Phosphate and FGF-23. Kidney Int Suppl. 2011;79:S24-7.
6. Leifheit-Nestler M, Haffner D. How FGF23 shapes multiple organs in chronic kidney disease. Mol Cell Pediatr. 2021;8:12.
7. Metwalley KA, Farghaly HS, Gabri MF, Abdel-Aziz SM, Ismail AM, Raafat DM, et al. Midkine: utility as a predictor of early diabetic nephropathy in children with type 1 diabetes mellitus. Journal of Clinical Research in Pediatric Endocrinology. 2021;13:293.
8. Lin Y-C, Chang Y-H, Yang S-Y, Wu K-D, Chu T-S. Update of pathophysiology and management of diabetic kidney disease. Journal of the Formosan Medical Association. 2018;117:662-75.
9. Vervloet MG, van Ittersum FJ, Büttler RM, Heijboer AC, Blankenstein MA, ter Wee PM. Effects of dietary phosphate and calcium intake on fibroblast growth factor-23. Clin J Am Soc Nephrol. 2011;6:383-9.
10. Nordholm A, Egstrand S, Gravesen E, Mace ML, Morevati M, Olgaard K, et al. Circadian rhythm of activin A and related parameters of mineral metabolism in normal and uremic rats. Pflügers Archiv-European Journal of Physiology. 2019;471:1079-94.
11. Quarles LD. Role of FGF23 in vitamin D and phosphate metabolism: implications in chronic kidney disease. Exp Cell Res. 2012;318:1040-8.
12. Mamilly L, Mastrandrea LD, Mosquera Vasquez C, Klamer B, Kallash M, Aldughiem A. Evidence of early diabetic nephropathy in pediatric type 1 diabetes. Front Endocrinol. 2021;12:669954.
13. Elmeazawy R, El Shall S, AbdElsamea MZ, Emara MH. Systemic immune-inflammatory index and systemic inflammation response index in predicting renal impairment in children with type 1 diabetes mellitus. Gaz Egypt Paediatr Assoc. 2024;72:49.
14. Arnold F, Kappes J, Rottmann FA, Westermann L, Welte T. HbA1c-dependent projection of long-term renal outcomes. J Intern Med. 2024;295:206-15.
15. Hernandez D, Espejo-Gil A, Bernal-Lopez MR, Mancera-Romero J, Baca-Osorio AJ,

Tinahones FJ, et al. Association of HbA1c and cardiovascular and renal disease in an adult Mediterranean population. BMC Nephrol. 2013;14:1-7.

16. Abdel-Azeez HA, Eldeeb SAMM, Atef DM, Abd Elfatah AH, Kamel LM. Fibroblast Growth Factor 21 and 23 as Biomarkers for Early Stage Diabetic Nephropathy in Type 2 Diabetic Patients. ZUMJ. 2024;30:2465-74.
17. Musgrove J, Wolf M. Regulation and Effects of FGF23 in Chronic Kidney Disease. Annu Rev Physiol. 2020;82:365-90.
18. Marthi A, Donovan K, Haynes R, Wheeler DC, Baigent C, Rooney CM, et al. Fibroblast Growth Factor-23 and Risks of Cardiovascular and Noncardiovascular Diseases: A Meta-Analysis. J Am Soc Nephrol. 2018;29:2015-27.
19. Fliser D, Kollerits B, Neyer U, Ankerst DP, Lhotta K, Lingenhel A, et al. Fibroblast growth factor 23 (FGF23) predicts progression of chronic kidney disease: the Mild to Moderate Kidney Disease (MMKD) Study. J Am Soc Nephrol. 2007;18:2600-8.
20. Isakova T, Xie H, Yang W, Xie D, Anderson AH, Scialla J, et al. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. Jama. 2011;305:2432-9.
21. Takashi Y, Maeda Y, Toyokawa K, Oda N, Yoshioka R, Sekiguchi D, et al. Fibroblast growth factor 23 and kidney function in patients with type 1 diabetes. PLoS One. 2022;17:e0274182.
22. A Kamel A, S ElHamshary A, R AbdelGwad E, A Elsayed R. Serum fibroblast growth factor 23 as an early biomarker for detection of renal osteodystrophy and progression of chronic kidney disease in children. BJAS. 2022;7:109-17.
23. Maahs DM, Jalal D, Chonchol M, Johnson RJ, Rewers M, Snell-Bergeon JK. Impaired renal function further increases odds of 6-year coronary artery calcification progression in adults with type 1 diabetes: the CACTI study. Diabetes Care. 2013;36:2607-14.
24. Ledeganck KJ, den Brinker M, Peeters E, Verschueren A, De Winter BY, France A, et al. The next generation: Urinary epidermal growth factor is associated with an early decline in kidney function in children and adolescents with type 1 diabetes mellitus. Diabetes Res Clin Pract. 2021;178:108945.
25. Kurpas A, Supeł K, Idzikowska K, Zielińska M. FGF23: A Review of Its Role in Mineral Metabolism and Renal and Cardiovascular Disease. Dis Markers. 2021;2021:8821292.
26. Lu Z, Ni W, Wu Y, Zhai B, Zhao Q, Zheng T, et al. Application of biomarkers in the diagnosis of kidney disease. Front Med (Lausanne). 2025;12:1560222.
27. Lopez-Giacoman S, Madero M. Biomarkers in chronic kidney disease, from kidney function to kidney damage. World J Nephrol. 2015;4:57-73.
28. Dohuim AHE, Ghazy MAEM, Nosair NAA, Hussien AK. Correlation linking fibroblast growth factor 23 in circulation (FGF-23) and serum aldosterone levels in different stages of chronic kidney disease. The Egyptian Journal of Internal Medicine. 2025;37:46.

**To cite this article**: Eman A. Mohammed, Amira O. Abdel Ghaffar, Mohamed K. Salamh, Effat H. Assar, Naema H. Zeriban · Serum FGF23 as an Early Biomarker of Renal Impairment in Children with Type 1 Diabetes. BMFJ XXX, DOI: 10.21608/bmfj.2025.397804.2499