

# Phosphate metabolism in kidney donors- a cross sectional study

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## Abstract

**Aim:** 1] To study the changes in phosphate metabolism in kidney donors

2] To study the correlation of albuminuria, fractional excretion of phosphorous [FE Pi] and estimated glomerular filtration rate [eGFR] with fibroblast growth factor 23 [FGF 23] in kidney donors

3] To study the early tubule interstitial injury in the remnant kidney of donors by measuring urine transforming growth factor beta [TGF beta] levels.

**Materials and methods:** A cross sectional study in which kidney donors with 1 year or more after donation were included. 69 kidney donors with a mean duration of 5.86 years after kidney donation were studied. Serum phosphate level, fractional excretion of phosphorous [FE Pi] and serum levels of parathyroid hormone were measured. Plasma levels of FGF 23 were measured by a second generation enzyme linked immune sorbent assay [ELISA]. Renal function was assessed by estimated glomerular filtration rate [eGFR] and degree of albuminuria. Urine levels of transforming growth factor beta [TGF beta] were measured by ELISA.

A hypothesis that in kidney donors with reduced nephron number, the single nephron excretion of phosphorous will be increased to maintain normal phosphorous homeostasis and that this increase in single nephron phosphorous excretion may be mediated by FGF 23 was proposed. Testing of this hypothesis was done by studying the correlation between parameters of phosphorous metabolism, FGF 23 and the renal function of the donors.

**Results.** 1] The mean eGFR was 70.36 mL/min/ 1.73m<sup>2</sup>. 52.2% of donors had moderate increase in albuminuria [microalbuminuria]

2] Serum phosphorous, fractional excretion of phosphorous and serum PTH levels were in the normal range. FGF 23 levels were in the normal reference range and showed no correlation with FE pi, eGFR or albuminuria

3] Urine TGF beta levels were undetectable in all the donors.

**Discussion:** Normal phosphorous homeostasis is maintained in kidney donors. There were no correlation between FE pi and FGF 23 levels. Kidney donors maintained a stable renal function. A significant number of donors had moderately increased albuminuria. No evidence for early tubulointerstitial changes were seen kidney donors as measured by urine TGF beta levels.

## **Phosphate metabolism in kidney donors- a cross sectional study**

### **Introduction**

A normal adult excrete about 1 gram of phosphate in urine per day. Assuming that humans have about 1 million nephrons phosphate excretion per nephron is estimated to be 0.5 microgram/nephron/day<sup>[1]</sup>

Fibroblast growth factor 23 [FGF 23] is a 251 amino acid protein produced by osteoblasts involved in phosphate metabolism<sup>[2]</sup>. FGF 23 exerts phosphaturic action at the proximal tubule by inhibiting the sodium dependent phosphate transporters<sup>[3]</sup>. It also inhibit intestinal phosphate absorption by inhibition of 1 alpha hydroxylase which decreases the 1, 25 [OH] 2 D3 production, the active form of vitamin D<sup>[4]</sup>

In healthy adults FGF 23 levels increase in response to a dietary phosphate load resulting in increased urine phosphorous excretion. FGF 23 can also be regulated by restriction of phosphate intake. FGF 23 regulates urinary phosphate excretion according to dietary phosphate intake and thus maintains stable phosphorous level.<sup>[5][6]</sup>

Kidney donors have reduced nephron number by 50% and have a significant decrease in GFR. The single nephron phosphate excretion is likely to be more than 1 microgram/ nephron/day. FGF 23 levels are likely to increase in kidney donors to increase the single nephron phosphate excretion and to maintain normal serum phosphate levels<sup>[7][8]</sup>.

When the number of intact nephrons are less, the phosphate excretion per single nephron increases in response to a phosphate load. Dietary phosphate load increases the amount of phosphate excreted per nephron and can induce tubular damage. A positive correlation exists between phosphate excretion per nephron and histological renal damage characterized by interstitial edema, infiltration, fibrosis, tubular atrophy and tubular dilation. Individuals with reduced nephron number should reduce dietary phosphate intake to prevent tubular damage<sup>[1]</sup>

The effect of increased phosphate excretion on tubular cells is believed to be due to calcium phosphate crystal formation [nucleation] and formation of calciprotein particles at the proximal tubular lumen. These particles exert oxidative stress and cause tubular epithelial cell damage<sup>[1]</sup>

Whether the increased phosphate excretion per nephron in kidney donors lead to tubular cell damage is not known. Reduced phosphate in diet may be an effective way to maintain good renal function and to prevent renal dysfunction in kidney donors

Follow-up studies of living organ donors have not reported increased cardiovascular and all-cause mortality, but results may have been confounded by selection bias in the control groups. In most studies, controls were selected from the general population, which includes adults with medical conditions that would make them ineligible for kidney donation. Analysis with a longer follow-up time may be necessary to examine the possible impact of living donor nephrectomy<sup>[9]</sup><sup>[10]</sup>. One recent study has suggested that kidney donors are at increased long-term risk for ESRD, cardiovascular, and all-cause mortality compared with a control group of non-donors who would have been eligible for donation<sup>11</sup>.

In chronic kidney diseases [CKD] circulating FGF 23 levels gradually increases with declining renal function which may begin at a very early stage and is most pronounced in patients with advanced CKD.

Higher FGF 23 levels in CKD may reflect a physiological compensation to stabilize serum phosphate level as the number of intact nephrons declines. FGF 23 has been described as an early marker of chronic kidney disease and to predict the progression of mild to moderate kidney disease<sup>9</sup>. FGF 23 is an independent predictor of 1 year mortality in patients on hemodialysis and a significant independent predictor of CKD progression<sup>[12]</sup><sup>[13]</sup>

Urine TGF beta is a marker of marker of fibrotic changes in kidney and has emerged as an early marker of renal damage<sup>[18]</sup><sup>[19]</sup>

**The hypothesis:** Kidney donors have 50 % less number of nephrons compared to a normal person. To maintain a normal phosphorous homeostasis the phosphorous excretion of each of the remaining nephrons should increase so that single nephron phosphorous excretion increases in response to a phosphorous load. This increase in single nephron phosphorous excretion is likely mediated by an increase in FGF 23 level which is a physiological regulator of phosphorous metabolism. The FGF 23 has been found to be an early marker of chronic kidney disease [CKD] and is found to be associated with progression of CKD. The excess tubular excretion of phosphorous is also found to be associated with tubular injury.

To test this hypothesis the correlation of the variables involved in the phosphate metabolism with renal parameters and urine TGF beta was analyzed in this study

## **Aim of the study**

- 1] To study the changes in the phosphate metabolism in kidney donors
- 2] To study the correlation of albuminuria, estimated glomerular filtration rate [eGFR] and fractional excretion of phosphorous [FE Pi] with fibroblast growth factor 23 [FGF 23] in kidney donors
- 3] To study the early tubulointerstitial changes in the remnant kidney of the donor by measuring urine transforming growth factor beta [TGF beta] levels

## **Materials and methods**

The study was conducted in the Department of Nephrology government medical college Kozhikode. The study was designed as a cross sectional study in which kidney donors who had completed 1 year or more after kidney donation were included. The kidney donors included in the study were evaluated by detailed history and physical examination. The following parameters were measured in each donor.

### **Parameters of phosphorous metabolism**

1. Serum phosphate and serum calcium levels.
2. Fractional excretion of Phosphorous was calculated from the serum phosphorous, serum creatinine, urine phosphorous and urine creatinine values from the formula
$$\frac{\text{Urine po}_4 \times \text{Serum creatinine}}{\text{Serum po}_4 \times \text{Urine creatinine}}$$
3. TMP/ GFR was calculated from the fractional excretion, and normalized for age and gender
4. Serum PTH
5. Plasma levels of Fibroblast growth factor 23 [FGF 23] were measured by a second generation enzyme linked immune sorbent assay [ELISA] as per the protocol described by the manufacturer [Immunotopics Inc]

### **Parameters of renal function**

1. Estimated glomerular filtration rate [eGFR] by the CKD EPI formula
2. Measuring urine albumin creatinine ratio [ACR]
3. Urine levels of transforming growth factor beta [TGF beta] by a second generation ELISA technique as per the protocol described by the manufacturer [ DRG TGF b 1 EIA 1864]

## **Statistical analysis**

Mean values, and standard deviations (SDs) were calculated using conventional methods. Student's t-test and chi square were used for comparison between groups. Pearson's correlation coefficients were calculated. Two-tailed P-values were used and values less than 0.05 were taken as significant.

**Ethical consideration:** Each volunteer was informed about the study. He/ she was explained the purpose of study and his right to quit at any time without having to give the reasons. Patient's information is dealt with confidentiality. Any abnormality detected during screening of healthy subjects was appropriately managed.

## **Results**

### **1. Demographic Data**

69 kidney donors meeting the inclusion criteria were enrolled in the study. 17 [24.6%] were males and 52 [75.4%] females. Age of the study population ranged between 30 and 70 years. The mean age was 50.36 years. 44.9 percentages of them were below 50 years of age and 55.1 percentages above 50 years. [Table. 1]. The age at the time of kidney donation varied between 23 to 60 years. The mean age at the time of donation was 44.67 years [Table 2]. The mean duration after kidney donation was 5.86 years. It ranged from 1 to 17 years [Table 3].

### **2. Renal Function tests**

The mean estimated glomerular filtration rate [eGFR] measured by the CKD EPI formula was 70.36 mL/min/ 1.73 m<sup>2</sup> [42.2-111 mL/min/1.73 m<sup>2</sup>]. 72.5 percentage had eGFR between 60 to 90 mL/min/ 1.73 m<sup>2</sup>. The eGFR of 18.8 percentage were between 30 to 60 mL/min/1.73 m<sup>2</sup> [Table 4]

The correlation of the estimated GFR with the duration of kidney donation was analyzed by Chi square test. The eGFR was not found to have any correlation with the duration of Kidney donation [p value 0.876]. A higher percentage of donors who had donated their kidneys 4 to 6 years back had a eGFR between 30 to 60 mL/min/1.73 m<sup>2</sup> [27.3%] compared to others [18.8%]. But this finding did not have a statistical significance. The eGFR was lower in donors in the higher age group [0.043]. The eGFR was found to be lower in those who had a higher age at the time of donation [p value 0.05].

**Albuminuria:** Moderately increased albuminuria [microalbuminuria] was seen in 36 participants [52.2%]. No significant correlation was found between the presence of proteinuria

and the duration after donation [p value 0.611]. Also there was no correlation between the age of the donor and the microalbuminuria [p value 0.165].**[Table 5]**

**Urine TGF Beta:** urine samples of all donors were tested with Enzyme Linked Immuno Sorbent Assay [[ELISA] for the presence of TGF beta. The test was performed as per the protocol described by the manufacturer [DRG® TGF-β1 ELISA (EIA-1864). None of the samples had detectable levels of TGF beta

### **3. Hypertension and Dyslipidaemia**

11 donors [15.9%] had new onset hypertension. The prevalence of hypertension was higher in those with longer duration after donation**[Table 6]**. 25% of those with 7 to 9 years after donation and 23.1% of those with 10 or more years after donation had hypertension compared to the average prevalence of 15.9%. But this difference did not amount to statistically significant levels [p value 0.555]

16 [23.2%] had developed dyslipidaemia after kidney donation. No correlation could be seen between the duration of donation and development of dyslipidaemia [p value 0.910]

### **5. Markers of Phosphate metabolism**

61[88.4%] of the donors had normal serum phosphate levels [2.5-4.5 mg/dL] The mean value was 3.717 and the values ranged between 1.9 and 7.5 mg/dL.**[Table 7]**

2 [2.9%] had serum phosphate levels below the normal range and 6 [8.7%] had the levels above the normal range. The prevalence of higher serum phosphate levels was more when the duration after donation was between 4 and 9 years. But the same relationship was not observed when the duration was more than 10 years. The Pearson Chi square test could not find a significant correlation between the duration after donation and the serum phosphate levels [p value 0.563].Serum Calcium levels were within normal limits in 95.7% of patients

The serum parathyroid hormone [PTH] levels of the donors ranged between 16.4 pg/dL and 129.6 pg/dL. The mean serum level was 56.268pg/dL.Normal serum levels [10 -65pg/dL] were seen in 49 [71%] of the donors. 20 [29%] had a PTH level above 65 pg/dL [Table 8]

The serum PTH levels did not correlate with the duration after kidney donation [p value 0.581] or with the age of the donor. There were no significant correlation between serum PTH and serum Phosphate levels [p value 0.287]. PTH levels also did not have any correlation with eGFR [p value 0.268]

The fractional excretion of Phosphorous in the urine [FE Pi] was found to be in the normal range [5 to 20 %] in 56 [81%] of the donors. 4 had a higher fractional excretion [ $> 20\%$ ] [Table 9].

The fractional excretion [FE Pi %] showed a correlation with the serum phosphorous in that those with lower serum phosphorous had a higher FE Pi [pvalue 0.028]. Fractionalexcretion of Phosphorous [FE Pi %] also showed a positive correlation with eGFR. These findings may only reflect the mathematical equation used for calculating the FE Pi, which takes into account the serum phosphorous and GFR.

There were no correlation between the duration since donation [p value 0.594], donor age [0.955] or the PTH levels [p value 0.216] and the fractional excretion of Phosphorous [Table 12]

### **Human Fibroblast Growth Factor 23 [FGF 23]**

The FGF 23 levels were measured in the plasma using a second generation Enzyme Linked Immuno Sorbent Assay [ELISA]. The procedure was done according to the manufacturer's instruction [Immunotopics Inc] The mean value was 18.1 RU/mL. The plasma levels ranged between 5.7RU/mL and 52.5 RU/mL. All the values obtained were within the normal reference range [ $< 100$  RU/mL].

FGF 23 levels were compared among groups of kidney donors with different duration after donation. The mean FGF 23 levels were higher in those donors who were 4 to 6 years after kidney donation compared to those who were 1 to 3 years after donation [p value 0.056] . However this positive correlation was not found to continue who were more than 7 years after donation. In fact in this group the FGF 23 levels were comparable to those who had donated kidneys 1 to 3 years back. As previously noted, the percentage of donors with higher serum phosphate levels were more in the group of 4 to 10 years [not statistically significant]. The significance of this observation is not understood. [Table 10]

Correlation of the FGF 23 levels with FE Pi and serum PTH was analyzed by the Pierson correlation. No significant correlation was observed in between these variables [Table 11&12] No correlations were observed between the FGF 23 levels, albuminuria or estimated GFR [eGFR]. [Table 13 & 14]

## **Discussion**

Earlier studies from transplant centres have revealed that in the short term kidney function recovers to ~70% of pre-donation GFR [2] and that there is no accelerated loss of kidney function among donors . Moreover, the incidence of end-stage renal disease (ESRD) is typically found to be between 0.2 and 0.6% among large donor populations, which is comparable

to that of the general population<sup>10</sup>. Kidney donation is associated with an increase in proteinuria, as well as a rise in blood pressure (BP) greater than that attributable to normal aging. These factors are associated with an increased risk for cardiovascular and all-cause mortality in the general population. One recent study has suggested that kidney donors are at increased long-term risk for ESRD, cardiovascular, and all-cause mortality compared with a control group of non-donors who would have been eligible for donation<sup>11</sup>.

In this study, majority of the donors had an estimated glomerular filtration rate [eGFR] more than 60 mL/min/1.73 m<sup>2</sup>. 13 donors [18.8%] had eGFR between 30 to 60 mL/min/ 1.73m<sup>2</sup>. Similar observations were made in previous studies also<sup>10, 16</sup>. It is also possible that the equations used for estimating GFR [CKD EPI or MDRD] underestimate the true GFR<sup>17</sup> especially when the eGFR is less than 60 mL/min/1.73m<sup>2</sup>. The eGFR was significantly lower with older age at the time of kidney donation. This could be because younger donors exhibit a capacity for hyperfiltration that remains for several years, whereas renal function declines in the elderly. This observation may suggest that age per se should constitute a more pronounced selection criterion for potential kidney donors.

Moderately increased albuminuria [microalbuminuria] was observed in 36 [52.2%] donors. Compared to some of the previous studies the prevalence of microalbuminuria was higher in this study. [Hassan N. Ibrahim, Robert Foley<sup>10</sup> 11.5%; Ingela Fehrman-Ekholm<sup>17</sup> 21%]. None had overt proteinuria. The microalbuminuria could be a marker of the ongoing hyperfiltration. However there was no correlation with the estimated GFR, the duration after donation, age or the presence of cardiovascular risk factors like hypertension and dyslipidaemia

15.9% of the donors had developed hypertension post kidney donation. The prevalence of hypertension was found to be higher with longer duration after donation. 23.2% had dyslipidemia. The percentage of donors who developed hypertension is lower compared to other studies. The development of hypertension could be a function of the advancing age and could be similar to that of the general population<sup>13</sup>. Screening of the donors for hypertension and dyslipidaemia and their optimal treatment may be beneficial in improving cardiovascular outcome in this population.

The parameters of phosphate metabolism were found to be within the normal range in the study population. The serum phosphate levels and fractional excretion of phosphorus [FE Pi] were comparable to the values described for normal individuals. There were no correlations between these variables with the duration post donation.

The FGF 23 levels remained normal in the kidney donors. FGF 23 levels showed no correlation with the serum phosphate levels, fractional excretion of phosphorus, duration after kidney donation or the estimated GFR [eGFR].

In a previous study, the FGF 23 levels were found to be high after the first week of kidney donation<sup>15</sup>. The reasons for this rise was thought to be an increased Pi load on the kidney, a delayed effect of the initial increase in PTH secretion or accumulation due to decreased renal clearance. The FGF 23 levels were found to return to normal levels by 3 to 6 months after kidney donation as the GFR improved<sup>15</sup>.



The hypothesis that FGF 23 may be increased in kidney donors who have reduced nephron numbers so as to maintain normal phosphorous homeostasis could not be proved in this study. Most of the kidney donors in this study population had normal parameters of phosphate metabolism and FGF 23 levels.

FGF 23 has been described as an early marker of chronic kidney disease and to predict the progression of mild to moderate kidney disease<sup>7</sup>. In the study by Danilo Fliser et al<sup>9</sup> found a significant inverse correlation between glomerular filtration rate and FGF23 levels (p value 0.001). The authors proposed that FGF23 can be a potential uremic toxin in addition to being a physiologic regulator of phosphate balance. An alternative interpretation for the high FGF 23 levels was that FGF23 levels represent the overall burden of phosphate loading. They had also proposed FGF23 as a valuable surrogate parameter to indicate more distal sequelae of the deranged mineral metabolism<sup>7</sup>.

Such an observation was not made in the present study. Kidney donors had normal FGF 23 levels and had no correlation with the estimated GFR [eGFR]

Urine TGF beta was measured as a marker of early tubular injury, which showed no detectable levels in any of the samples. Thus early evidence of tubulointerstitial injury was not demonstrated in this study.

To summarize, the kidney donors did not show any significant alteration in the phosphate metabolism or in the renal function over a mean duration of 5.86 years after kidney donation. The FGF 23 and the urine TGF beta levels used as early markers of renal dysfunction showed no abnormalities. The fact that significant proportion of donors developed microalbuminuria and hypertension underscores the importance of screening of this population for effective treatment of cardiovascular risk factors.

## **Conclusions**

1. Phosphorous homeostasis is maintained in kidney donors
2. There is no correlation between fractional excretion of phosphorous [FE Pi] and fibroblast growth factor 23 [FGF 23]
3. 50% of the kidney donors developed albuminuria and 15 % of donors developed hypertension
4. There are no evidence for early tubulointerstitial injury in the kidney donors based on urine transforming growth factor beta [TGF beta ] levels

## Tables

Table. 1 Age distribution

Age	Number [%]
30-39	7 [10]
<b>40-49</b>	<b>24 [34.8]</b>
<b>50-59</b>	<b>27 [39.1]</b>
60-69	9 [13]
70 and above	2 [2.9]

M: F 1:3

Mean age 50.36 years [45% <50 years, 55% > 50 years]

Table. 2 age at donation

Age at donation	Number [%]
20-29	3 [4.3]
30-39	14 [20.3]
<b>40-49</b>	<b>31 [44.9]</b>
50 and above	21 [30.4]

Mean age at donation: 44.61 years [range 23-60]

Table. 3 years since donation

Years after donation	Number [%]
<b>1-3</b>	<b>22 [31.9]</b>
<b>4-6</b>	<b>22 [31.9]</b>
6-9	12 [17.4]
10 and above	13 [18.8]

Mean duration: 5.86 years [range 1- 17]

Table. 4 eGFR

eGFR[ml/min/1.73m <sup>2</sup>	Number [%]
30- 59	13 [18.8]
<b>60- 89</b>	<b>50 [72.5]</b>
90 and above	6 [8.7]

Mean eGFR 70.36 mL/min/1.73 m<sup>2</sup>

Table .5 microalbuminuria

Years since donation	Microalbuminuria [%]
1-3	10[45.5]
4-6	13[59.1]
7-9	6[50]
10 and above	7 [53.8]
<b>Total</b>	<b>36 [52.2]</b>

52% had microalbuminuria  
No correlation with yrs since donation

[P value 0.611]

Table.6 hypertension

Prevalence of hypertension 15.9%

Higher prevalence with longer duration

[p value 0.555]

Years since donation	Hypertension [%]
1-3	13.6
4-6	9.1
<b>7-9</b>	<b>25</b>
<b>10 and above</b>	<b>23.1</b>

Table .7 serum phosphorous

Years since Donation	PO4 < 2.5 [%]	PO4 2.5-4.5 [%]	PO4 >4.5 [%]
1-3	1[4.5]	21[95.5%]	0
4-6	1[4.5]	18 [81.8%]	3 [13.6]
7-9	0	10 [83.3%]	2 [16.7]
10 and above	0	12 [ 92.3%]	1[7.7]
Total	2 [2.9]	<b>61 [88.4%]</b>	6[8.7]

Table. 8 PTH

Duration since Donation	PTH 10-65	PTH >65
1-3	14	8
4-6	18	4
7-9	8	4
10 and above	9	4
<b>Total</b>	<b>49 [71%]</b>	<b>20 [29%]</b>

71% had normal PTH and 88.4% had normal PO4 levels

Table 9 FE Pi

Duration since donation	< 5 [%]	5-20 [%]	>20 [%]
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1-3	0	21[95.5]	1[4.5]
4-6	4[18.2]	16[72.7]	2 [9.1]
7-9	4 [33.3]	7 [58.3]	1 [8.3]
10 and above	1 [7.7]	12[92.3]	0
Total	9 [13]	<b>56[81.2]</b>	4[5.8]

81% FE Pi in the normal range. No correlation between the FE Pi levels and the duration after kidney donation [p value 0.581]

Table 10 FGF 23

Years since donation	No	Mean RU/mL	SD
1-3	22	15.47	3.06
4-6	22	21.90	11.05
7-9	12	15.15	4.88
10 and above	13	17.72	11.7

The mean level of FGF 23 level was 18.1 RU/mL. The values ranged between 5.75 and 52.5 RU/mL. There were no correlation between the FGF 23 levels and the duration after kidney donation.

Table. 11 Correlation between age, eGFR and albuminuria

		Age	Yrs since donation	Age at donation
eGFR	Pearson correlation	-0.244	-0.057	-0.235
	sig [2 tailed]	<b>0.043</b>	0.644	<b>0.051</b>
ACR	Pearson correlation	0.169	0.156	0.077
	sig [2 tailed]	0.165	0.202	0.529

eGFR was lower in donors in the higher age group [p value 0.043] and with higher age at the time of donation [p value 0.05]. No significant correlation between albuminuria and age of the donor or duration after donation [p value 0.611]. No correlation between eGFR and ACR [Pierson correlation -0.055; p value 0.655]

Table. 12 Correlation between FE Pi, PTH and serum PO4

		PTH	PO4
FE Pi	Pierson correlation	0.151	-0.265
	sig [2 tailed]	0.216	0.028

Fractional excretion of phosphorous did not correlate with PTH levels. FE Pi showed correlation with serum PO4 levels.

Table 13. Correlation of FGF 23 with FE Pi

	FEPi
FGF 23Pearson Correlation	0.049
Sig. (2-tailed)	0.687

Table 14 correlation of FGF 23 with PTH

	PTH
FGF 23Pearson Correlation	0.01
Sig. (2-tailed)	0.992

There were no statistically significant correlation either between FGF 23 and FE Pi or between FGF 23 and PTH

Table 15 correlation of FGF 23 with eGFR

	eGFR
FGF 23Pearson Correlation	-0.051

Sig. (2-tailed)	0.680
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Table 16. Correlation of FGF 23 with Albuminuria

		ACR
FGF 23	Pearson Correlation	0.115
	Sig ( 2 tailed)	0.348

FGF 23 did not show significant correlation with eGFR or Albuminuria

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