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ASSESSMENT OF FIBROBLAST GROWTH FACTOR 23 AS AN EARLY PREDICTOR IN CHRONIC KIDNEY DISEASE PATIENTS

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ABSTRACT

Fibroblast growth factor -23 (FGF23) was initially identified as the causative factor of autosomal dominant hypophosphatemic rickets ,further studies confirmed that FGF 23 is predominantly expressed in the osteocytes and osteoblasts of bone1 . (FGF23) is an endocrine hormone that regulates phosphate and vitamin D homeostasis. FGF23 is synthesized and secreted by bone cells, mainly osteocytes and plays a role as a phosphatonin (a phosphate regulating protein). FGF23 inhibits phosphate reabsorption in the renal tubule and promotes phosphaturia by down-regulating sodium-phosphate co-transporters. As kidney function decreases in chronic kidney disease (CKD) patients, FGF23 increases progressively in order to regulate phosphate homeostasis2 .This study will include two groups : group 1 patient with chronic kidney disease (CKD) in different CKD stages according to estimated glomerular filtration rate (eGFR) .group 2 healthy persons with no chronic kidney disease. Both groups investigated for (creatinine, phosphorus, total and ionized calcium, albumin PTH hormone,FGF23 and eGFR was calculated). Key words : CKD, FGF23,fibroblast growth factor -23, eGF

1-INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem affecting 5-10% of the world population. Etiological causes of impaired kidney function are typically hypertension, diabetes, polycystic kidney disease and various inflammatory and systemic disorders.[1]

CKD is defined according to kidney disease outcomes quality initiative (KDOQI) guidelines as kidney damage of 3 or more months duration caused by structural or functional abnormalities with or without a decreased estimated glomerular filtration rate (eGFR). Pathological markers, abnormalities in the blood or urine, or imaging tests, may reveal kidney dysfunction. CKD may also be defined as a persistently low (eGFR) of less than 60 ml/min/1.73m2 for 3 or more months, with or without identifiable kidney damage.[2]

CKD is a progressive, most often irreversible, and associated with multiple disorders and adverse outcomes. This is particularly true in regard to the risk of cardiovascular disease and cardiovascular events, which increases with worsening renal function. More than 50% of deaths in patients with end-stage renal disease (ESRD) are due to cardiovascular complications. Any degree of kidney dysfunction not just the most severe can hasten the onset and progression of cardiovascular disease, and dramatically worsen prognosis.[3]

The two main causes of chronic kidney disease are diabetes and high blood pressure, which are responsible for up to two-thirds of the cases. Diabetes causes damage to many organs in body, including the kidneys and heart, as well as blood vessels, nerves and eyes. High blood pressure (hypertension) if uncontrolled, or poorly controlled, high blood pressure can be a leading cause of heart attacks, strokes and chronic kidney disease.[4]

Other conditions that affect the kidneys are Glomerulonephritis, inherited diseases, polycystic kidney disease, Lupus, repeated urinary infections and obstructions caused by problems like abnormally shaped ureters, stones, tumors or an enlarged prostate gland in men.[4]

Glomerular filtration rate (GFR) is used to measure the level of kidney function and determine the stage of kidney disease. GFR represents the flow rate of produced urine per unit area (normal >100 ml /min/1.73 m2), and corresponds to the percent of kidney function available.

The degree of renal deficiency can be divided into five CKD stages according to the (eGFR) level [1]

I-Stage 1, GFR _90 mL/min/1.73 m2: kidney damage with normal

or high GFR (slightly diminished kidney function).

II Stage 2, GFR 60-89 mL/min/1.73 m2: mild reduction in GFR with kidney damage.

III. Stage 3, GFR 30-59 mL/min/1.73 m2: moderate reduction in GFR.

IV. Stage 4, GFR 15-29 mL/min/1.73 m2: severe reduction in GFR.

V. Stage 5, GFR <15 mL/min/1.73 m2: established kidney failure or

permanent renal replacement therapy (RRT).[1]

Stage 3 CKD should be split into two subcategories defined by:

- GFR 45–59 ml/min/1.73 m2 (stage 3A) (Mildly to moderately decreased GFR)
- GFR 30–44 ml/min/1.73 m2 (stage 3B).(Moderately to severely decreased GFR).5

Fibroblast growth factors (FGFs) comprise a family of polypeptides that share a common core region containing approximately 120 highly conserved amino acid residues, with variable flanking N- and C-terminal residues.1

FGF family members are now defined as humoral factors which have FGF homology region characterized by β-trefoil structure. FGF23 was identified as the last member of FGF family and belongs to the FGF19 subfamily as well as FGF19 and FGF21. FGF23 is produced as a peptide with 251 amino acids by bone .There is a signal peptide with 24 amino acids, and the secreted FGF23 protein consists of 227 amino acids which is approximately 32-KD.[6]

Fibroblast growth factor-23 (FGF23) is an endocrine hormone that regulates phosphate and vitamin D homeostasis. FGF23 is synthesized and secreted by bone cells, mainly osteocytes and plays a role as a phosphatonin (a phosphate regulating protein). FGF23 inhibits phosphate reabsorption in the renal tubule and promotes phosphaturia by down-regulating sodium-phosphate co-transporters. It decreases renal production of 1,25 (OH)2D by inhibiting 1α-hydroxylase and up-regulating 24-hydroxylase in the proximal tubule. FGF23 also acts on the parathyroid gland to inhibit parathyroid hormone (PTH) secretion. PTH increases the uptake of phosphate from bone and up-regulates 1α-hydroxylase, leading to increased vitamin D activation and enhanced phosphate reabsorption in the intestine. As kidney function decreases in chronic kidney disease (CKD) patients, FGF23 increases progressively in order to regulate phosphate homeostasis .2

2- OBJECTIVES

The study is a cross sectional study. Patients will be recruited from the dialysis unit at Portfouad General Hospital in Portsaid city. The study will include 2 groups:

1-Patients group:

50 CKD patients in different CKD stages and it splits to two sub groups according to (eGFR) values to:

a- Severe and kidney failure CKD stages patient.

b- Mild and moderate CKD stages patient.

Inclusion criteria:

25 male and female patients who have received maintenance hemodialysis (HD) in Portfouad general hospital age between (18 – 80 years).

Exclusion criteria:

Patients will be excluded from the study if they have tumour induced osteomalacia or patients with fibrous dysplasia.

2- Control group:

25 volunteer patients with no chronic kidney disease from outpatient Portfouad General Hospital Clinic.

3. METHODOLOGY

5mL of blood will be withdrawn from the patients in EDTA tubes and plain tubes will be used and samples (in plain tube) will be allowed to clot at room temperature before centrifugation for 15 minutes at 1000 ×g. Serum will be removed and stored at -20°C.

Laboratory work will be performed at Suez Canal University Hospital Lab in Ismailia

•Both patients and control groups investigated for (creatinine, phosphorus, total and ionized calcium, albumin ,PTH hormone,FGF23 and eGFR was calculated)

By (CKD-EPI) equation)

eGFR =141× min(SCr/k, 1) α× max(SCr/k,1) -1.209×0.993age×1.018 (if female) × 1.159 (if black), where k is 0.7 for females and 0.9 for males, α is(-0.329) for females and(-0.411) for males, min indicates the minimum of SCr/k or 1, and max indicates the maximum of SCr/k or 1.

4- STATISTICAL DESIGN

Quantitative variables were calculated as mean ± standard deviation (SD). P value lower than 0.05 was considered statistically signifi¬cant. The distribution

of quantitative data were assessed by one sample Shapiro-Wilk test.Association between variables was assessed by Spearman's correlation coefficient . Statistical analysis was conducted by SPSS version 24.and MedCalc Version 17.8 softwares.

5- RESULTS

-Mild and moderate CKD stages patients.

Table(1):Demographic data of the studied groups

Groups	Age (years)	Male	Female
Group b	53±10	19(76.0%)	6(24.0 %)
Control group	41.8±12.26	8 (32.0 %)	17 (68.0 %)

-We label male as (1) and female as (0)

Table(2):Control group data results

NO	Age	gender	eGFR	Creat	FGF23	PTH	T.Calc	I.Clciun	Ph	alb
1	45	0	105.0	0.7	29.11	30.5	8.8	4.1	3.8	4.7
2	36	0	95.0	0.8	30.56	28.6	9.1	4.8	3.2	3.5
3	39	0	109.0	0.7	37.94	52.0	8.7	4.3	3.1	4.2
4	38	0	94.0	0.8	39.72	57.8	9.2	4.9	3.4	3.4
5	55	1	96.0	0.9	56.11	48.2	9.3	4.3	3.2	4.8
6	56	0	97.0	0.7	45.44	26.9	10.0	5.3	3.7	3.5
7	32	0	98.0	0.8	33.61	24.8	8.6	4.3	4.0	4.0
8	42	1	105.0	0.9	35.60	37.4	9.2	4.8	3.8	4.2
9	58	0	100.0	0.6	38.60	46.4	8.4	4.4	4.7	3.8
10	30	1	114.0	0.9	32.80	49.7	9.3	4.8	3.9	4.3
11	27	0	119.0	0.7	67.60	35.8	8.7	4.6	4.3	4.2
12	28	0	118.0	0.7	34.50	38.2	8.9	4.8	4.0	4.1
13	27	0	125.0	0.6	39.00	40.5	9.2	4.9	3.9	3.8
14	29	0	100.0	0.8	28.90	33.6	9.0	4.7	4.3	3.9
15	48	0	102.0	0.7	30.70	37.6	9.3	4.8	3.9	4.2
16	53	1	97.0	0.9	63.90	42.8	9.5	4.9	4.1	4.4
17	62	0	93.0	0.7	35.00	39.6	9.1	4.6	3.7	3.9
18	27	0	101.0	0.8	36.80	28.8	9.7	4.8	3.5	4.3
19	59	1	98.0	0.8	38.00	36.5	9.3	4.7	4.2	3.8
20	44	1	104.0	0.9	32.40	37.9	9.5	4.8	3.9	3.7
21	57	1	99.0	0.8	34.80	41.6	9.7	5.0	4.3	3.8
22	32	0	98.0	0.8	35.90	43.7	9.3	4.8	3.8	4.0
23	55	1	96.0	0.9	57.60	32.5	9.6	5.0	3.5	3.9
24	42	0	91.0	0.8	34.80	29.4	8.8	4.8	4.0	4.1
25	25	0	120.0	0.7	36.40	39.8	9.0	4.7	3.9	3.8

Table (3)group (b) of mild and moderate CKD patients result data:Egfr(30-89 mL/min/1.73 m²

NO	Age	gender	eGFR	Creat	FGF23	PTH	T.Calc	I.Clciun	Ph	alb
1	75	1	32.0	2.0	48.06	49.20	8.7	4.5	4.7	3.8
2	48	0	33.0	1.78	49.72	27.60	9.1	4.9	4.6	3.4
3	50	1	38.0	2.00	75.83	19.30	8.7	4.2	4.8	4.4
4	62	1	41.0	1.75	45.28	39.70	8.9	4.5	3.9	3.9
5	65	1	36.0	1.90	51.39	44.90	8.6	4.5	4.7	3.6
6	56	1	51.0	1.51	74.44	34.10	10.6	4.9	4.0	4.8
7	65	1	48.0	1.50	63.33	14.60	8.0	4.3	3.0	3.5
8	43	0	47.0	1.38	66.11	13.90	8.8	4.3	4.4	4.3
9	63	1	48.0	1.53	61.94	32.10	10.4	5.0	3.4	4.4
10	42	0	47.0	1.39	50.83	32.90	10.1	4.9	4.1	4.3
11	44	0	46.0	1.40	43.61	34.90	9.1	4.6	4.3	4.0
12	46	0	68.0	1.00	38.33	45.90	9.0	4.3	3.7	4.5
13	35	1	87.0	1.10	40.00	31.70	10.5	5.1	4.5	4.4
14	42	1	76.0	1.18	32.78	33.50	10.0	4.9	4.2	4.3
15	38	1	65.0	1.46	44.72	31.60	9.5	4.7	3.6	4.1
16	48	1	71.0	1.20	88.89	32.60	9.2	4.8	4.0	3.6
17	65	1	34.0	1.98	78.90	66.50	8.7	4.4	4.8	3.9
18	69	1	33.0	2.00	92.50	40.90	9.1	4.5	3.9	4.1
19	59	1	54.0	1.41	33.25	23.40	9.8	4.8	3.2	4.2
20	48	1	57.0	1.43	37.80	25.80	9.6	4.6	4.5	4.5
21	46	0	60.0	1.10	57.40	45.90	9.0	4.5	3.9	4.2
22	56	1	63.0	1.26	49.30	39.50	8.7	4.6	3.5	4.4
23	54	1	38.0	1.95	68.40	35.70	9.2	4.6	4.3	3.8
24	51	1	32.0	2.30	76.20	46.70	8.8	4.5	4.1	3.9
25	62	1	50.0	1.48	46.80	28.20	9.6	4.9	3.4	4.0

In group (b) of mild and moderate CKD patients FGF23 showed highly significance positive correlation with creatinine,.FGF23 showed significance Negative correlation with eGFR.

Table4: Correlation Coefficient by Spearman's rho group(b)

Test	eGFR	creatinine
FGF23	-.485-*	.516**
Significance level(p)	P<0.05	P<0.01

We compared FGF23 medians between group (b) of CKD and control group using Mann-Whitney U Test and we found statistical significance difference between both groups (p<0.01)

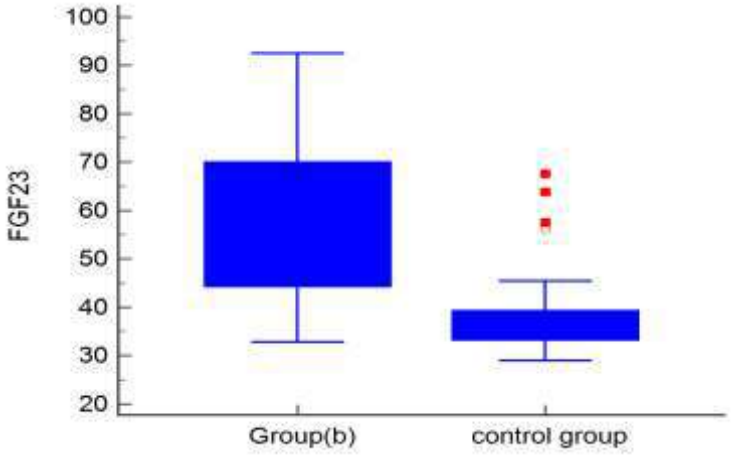


Fig (1) comparison between FGF23 medians in group (b) and control group

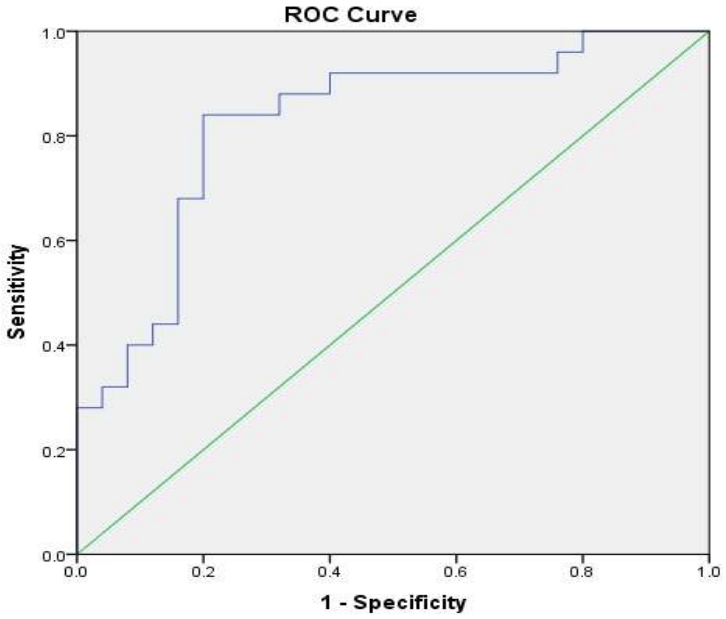
We calculated sensitivity and Specificity of FGF 23 as a biomarker for group (b) of CKD patients and compare the Sensitivity and specificity of FGF23 to those of eGFR and Creatinine as golden standards using ROC curve analysis and determine the cut off value .

Table (5) sensitivity and Specificity of FGF 23(Group)(b)

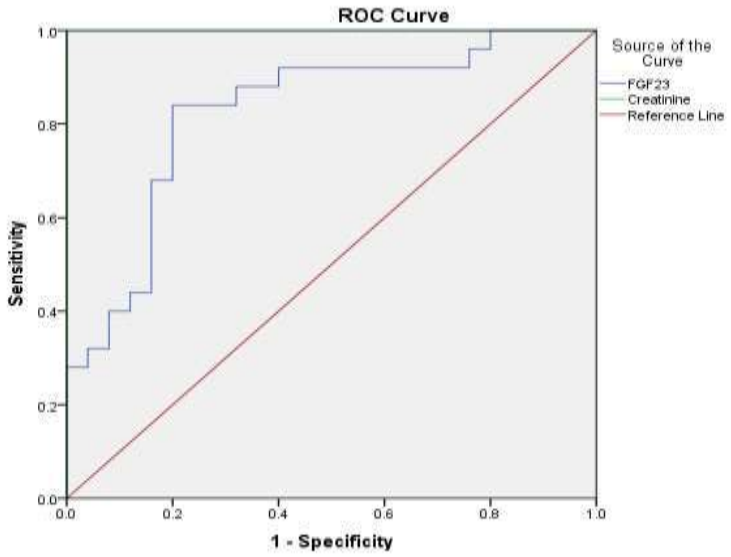
Statistic	Value
Sensitivity	84.0 %
Specificity	80.0 %
Area under the ROC curve (AUC)	0.826
Significance level P	<0.01
Optimum cut off point	>39.7

Table (6):Comparison of Sensitivity and specificity of FGF23 to eGFR and Creatinine (Group (b)

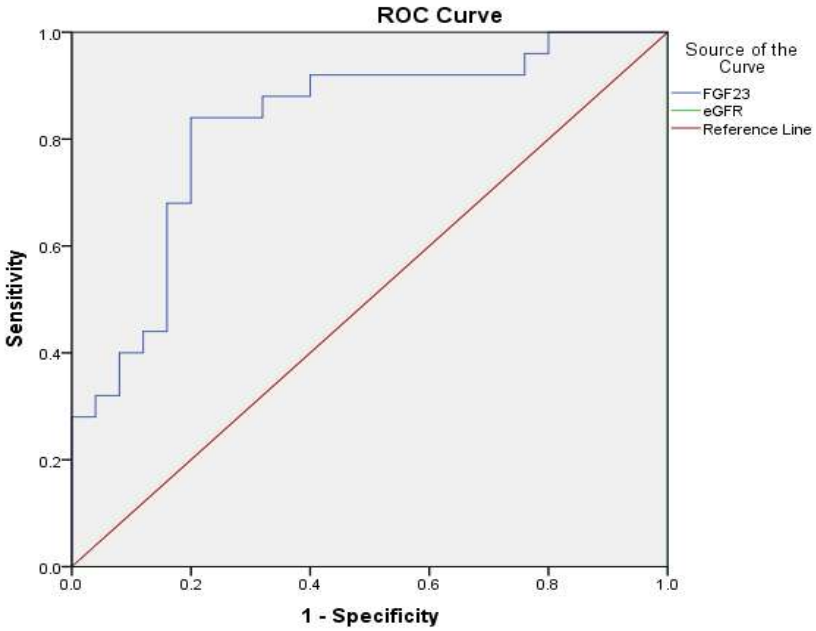
Variable	AUC	Sensitivity	Specificity
FGF23	0.826	84.0%	80.0%
eGFR	1.000	100.0 %	100.0 %
Creatinine	1.000	100.0 %	100.0 %



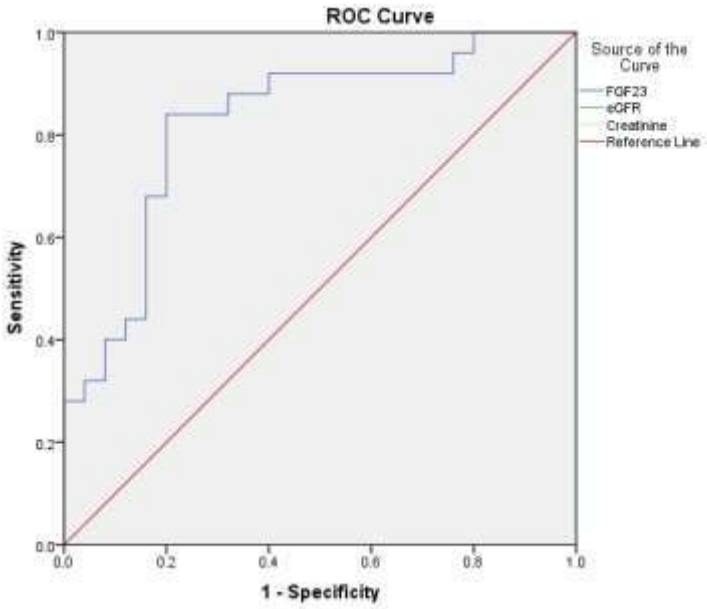
Fi g(2) FGF23 ROC curve group(b)



Fig(3) ROC curve of FGF23 andCreatinine group (b)



Fig(4)ROC curve of FGF23and eGFR group (b)



Fig(5) ROC curve of FGF23,eGFR andCreatinine group(b)

6-DISCUSSION

Fibroblast growth factor 23is a about 30 kD protein secreted by osteocytes and osteoblasts. It was discovered in 2000 as a circulating factor found in excess in hypophosphataemic patients with tumour-induced osteomalacia.[7]

The kidney is the main regulatory organ for maintenance of phosphate balance. When phosphate balance is positive, the reabsorption of filtered phosphate in the kidney proximal tubules is diminished leading to increased phosphaturia and lowering of serum phosphate levels and vice versa. The renal reabsorption of phosphate is regulated by Sodium-Phosphate co-transporters NPT_2a and NPT_2c in the proximal epithelial cells.[1]

Intestinal uptake of Phosphate is stimulated by vitamin D, the movement of phosphate into and out of bone mineral is regulated by vitamin D and parathyroid hormone (PTH), and PTH causes renal phosphaturia by decreasing the number of NPT_2a co-transporters on the apical surface of the proximal tubular cell .Hyperphosphatemia usually occurs as a result of renal failure and reduced ability of the kidney to excrete a phosphate excess.[1]

Fibroblast growth factor (FGF)-23 is a recently founded as a regulator of calcium–phosphate metabolism. Whereas other known FGFs mainly act in a paracrine manner, FGF-23 has

significant systemic effects as endocrine hormone . Together with its cofactor Klotho, FGF-23 enhances renal phosphate excretion in order to maintain serum phosphate levels within the normal range. Klotho is a 130-kDa protein transmembrane b-glucuronidase capable of hydrolyzing steroid glucoronides. FGF-23 exerts its biological effects through activation of FGF receptors (FGF-Rs) in a Klotho dependent manner, as a Klotho/FGF-R complex binds toFGF-23 .[8]

FGF23 induces phosphaturia by decreasing phosphate reabsorption in the proximal tubule through down regulation of sodium-phosphate co-transporters FGF23 reduces circulating

levels of calcitriol by inhibiting renal 1-α hydroxylase and stimulating 24-hydroxylase,

which catalyzes the initial step in vitamin D degradation; and FGF23 inhibits secretion of parathyroid hormone (PTH). These effects are dependent on the presence of klotho, which is highly expressed in the kidney and the parathyroid glands and acts as a co-receptor for FGF23 by markedly increasing the affinity of FGF23 for combine with FGF receptors.[9]

The aim of this study is to determine the sensitivity and specificity of serum Fibroblast Growth Factor 23 (FGF 23) as biomarker in different stages of CKD patients and to assess FGF 23 as an early predictor of kidney disease progression.

Sensitivity is the ability of a test to correctly classify an individual as diseased in another way is the proportion of people with disease who will have a positive result(true positive rate).[10]

Specificity is The ability of a test to correctly classify an individual as disease- free in another way is the proportion of people without the disease who will have a negative result(true negative rate).[10]

The gold standard is the best single test (or a combination of tests) that is considered the current preferred method of diagnosing a particular disease. All other methods of diagnosing this disease, including any new test, need to be compared against this gold standard.[10]

In our study group (b) of CKD patients, FGF23 showed significant negative correlation with eGFR. FGF 23 showed significant positive correlation with Creatinine .

In our study FGF23 showed high sensitivity 84.0% and high specificity 80.0% as a biomarker for CKD in group (b) moderate and mild CKD patients compared to eGFR and Creatinine as golden standards. whereas the area under the ROC curve (AUC) =0.826 and the cut off points > 39.7

Our results are in harmony with those of **(Seiler, S., Heine, G. H., & Fliser, D. 2009).** Among various parameters of calcium–phosphate metabolism, FGF-23 levels were a significant independent predictor of CKD progression, defined as doubling of serum creatinine and/or terminal renal failure.[8]

Our results are in agreement with **(Jüppner, H., Wolf, M., & Salusky, I. B. 2010).** who reported that Circulating FGF-23 levels are elevated in patients with CKD stages 2 and 3, (mild and moderate CKD)that is before there is a critical reduction in functioning nephrons, increased FGF-23 levels in these early CKD stages are associated with increased fractional excretion of phosphate, making it likely that enhanced FGF-23 secretion helps to maintain normal phosphate level despite a reduction in nephron mass.[11]

Our results are opposed to those of **(Yaghoubi, F., *et al.* 2016).** as their study showed that there are not any significant correlation between FGF23 and level of calcium and phosphorus also they reported The correlation between GFR of all patients (37.59 ± 11.21 cc/min) and serum FGF23 was not significant (P = 0.11). We categorized GFR into three groups in patients with following prevalence. Group 1 with GFR of 45-59 = 24 cc/min (29.6%), group two with GFR of 30-44 = 34(42%) and group 3 with GFR of 15-29 cc/min = 22 (27.2%). None of the groups had correlation with FGF23 (P > 0.05) which showed disagreement to our results.[12]

7-CONCLUSION

Fibroblast growth factor-23 (FGF23) is an endocrine hormone that regulates phosphate metabolism and vitamin D homeostasis . FGF23 concentrations increase markedly and gradually with renal function efficiency decrease. FGF23 represents a promising biomarker for CKD Progression . there are still some questions unanswered such as the sensitivity of FGF23 as a CKD progression biomarker comparing to cystatin C .

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