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ORIGINAL ARTICLE

A Biochemical Study of Fibroblast Growth Factor -23 and Phosphorus Metabolism in Adult Patients with Obstructive Renal Failure in Babylon-Iraq

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KEYWORDS

Fibroblast growth factor 23;
Phosphorus;
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ABSTRACT: Complete or partial obstruction to the urine's flow can cause gradual and cumulative kidney damage, and this is what is known as obstructive uropathy (OU). The obstruction could be caused by a problem with one or both ureters, and it could occur close to or far from the bladder neck (such as in the urethra). Multiple research have sought to understand the origins and implications of obstructive uropathy, which is a primary cause of renal failure. Fibroblast growth factor23 (FGF23) Osteocytes and osteoblasts create this phosphaturic hormone, which binds to FGF receptors via the transmembrane protein Klotho. Specifically, FGF23 inhibits sodium/phosphate cotransporters NaPi2a and NaPi2c, which in turn inhibits renal phosphate reabsorption, by targeting the renal proximal tubule and decreasing calcitriol synthesis. FGF23 also inhibits the synthesis and secretion of parathyroid hormones by the parathyroid glands. Calcitriol, phosphate, and parathyroid hormone are all involved in the control of FGF23 at the cellular and molecular levels. More FGF23 is found in rare hereditary and acquired illnesses, but chronic kidney disease is also linked to an increase in FGF23 as a reaction to Hyperphosphatemia. However, Increased levels of FGF23 have been associated to deterioration of chronic kidney disease. Whether FGF23 is linked to renal impairment and an increased risk of death .The study's objective was to take measurements of serum level of Fibroblast growth factor- 23 (FGF-23) and phosphorus in people suffering from obstructive renal failure and healthy control subject and to assess the relation of each of them. The study involved collecting blood samples from 100 volunteers, 50 healthy subjects (38 men and 12 women), (34 men and 16 women) suffering from obstructive renal failure.age was (15 –65) years BMI with (18.5-24.9) Kg m^{-2}. Patients were subjected to Kidney Surgery Department at Hillah Hospital from The period from1st of December, 2020 to 1 of June, 2021. The findings revealed statistically significant variations ($P<0.0001$) in the serum FGF23 level between obstructive renal failure group (501.3±230.89 Pg ml^{-1}) compared with control group (119.63±29.8 Pg ml^{-1}). P = <0.001 for Phosphorus obstructive renal failure group (2.01±0.76 mmol L^{-1}) compared with control group (0.68±0.39 mmol L^{-1}).The results of levels of Hemoglobin& GFR in the of people with obstructive renal disease were significantly lower than healthy people and significantly, as the value of $P<0.05$. The level of occurrence of The Fibroblast growth factore23 & phosphors is higher in patient with obstructive renal failure than those healthy control, The FGF23 could be served as a diagnostic marker in obstructive renal failure patients to predict the possibility to develop chronic kidney disease, The occurrence of obstructive renal disease at a large rate in old age and in men more than women.

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INTRODUCTION

Complete or partial obstruction to the urine's flow can cause gradual and cumulative kidney damage, and this is what is known as obstructive uropathy (OU). The obstruction could be caused by a problem with one or both ureters, and it could occur close to or far from the bladder neck (such as in the urethra). Numerous research projects have sought to understand the origins and implications of obstructive uropathy[1]. Which is a common cause of renal failure. Obstructions of the kidneys are a prevalent medical issue that affects a large number of individuals. Kidney stones (nephrolithiasis) cause the majority of renal blockages[2]. n addition, renal artery stenosis and polycystic kidney disease both contribute to renal blockages, albeit in slightly different ways The presence of renal polyps or tumors is a less prevalent cause of kidney blockage[3].

For older men with benign prostatic hyperplasia or prostate cancer, obstructive uropathy (OU) is a common problem to deal with. It's a term used to describe urinary tract obstructions due to anatomical or functional issues. Chronic kidney disease (CKD) is caused by a blockage in the passage of urine through the kidneys, causing renal injury and damage to the kidney parenchyma. It can present as anything from somewhat disabling to a severe acute renal injury in the elderly, depending on how old the patient is. There is an indication that the kidneys and calyces are distended due to hydronephrosis (OU's other name for it) [4]. Hydronephrosis is more common in the old (>64 years) than in the young (5.1 percent vs. 3.1 percent), particularly in the elderly males (6.2 % in men and 2.9 % in women)[5]. Untreated (or unattended) OU can lead to obstructive kidney disease (ON) (ON). Obstructive nephropathy (ON) can cause chronic kidney disease as well as end-stage renal disease (ESRD). Hydronephrosis and a considerable loss of functional renal parenchyma in the obstructed kidney occur with long-term blockage (greater than 6 weeks). However, even a short-term obstruction might have an impact on renal function. As an example, 57.4% of ESRD patients with UN are above the age of 64, with 73.84% being men. [5]. This endocrine hormone is released from bone and operates on the kidney to induce phosphaturia while inhibiting calcitriol synthesis, making it a key risk factor for kidney disease in the elderly. [6]**.** FGF23 is a glycoprotein with a molecular weight of 32 kDa that belongs to the fibroblast growth factor superfamily (FGF)[7]. It has recently been shown that FGF23 secreted locally can regulate osteoblast mineralization in an autocrine/paracrine way. [8] local secretion of FGF23 has possible paracrine actions in the heart as well [9]. Although FGF23 levels grow to keep phosphate levels stable in chronic renal disease, they are also linked to worse CKD outcomes and increased mortality. [10].

MATERIALS AND METHODS

Prospective case-controlled study. The protocol of this research was given the go-ahead by the scientific committee of Babylon University-College of Medicine, and the agreement of the attendance to Kidney Surgery Department at Hillah Hospital to collect the sample from the patients was approved by the Babylon Health Directorate. This study was conducted on one hundred individuals including fifty patients who had obstructive renal failure and fifty healthy control subjects. The samples were collected from Kidney Surgery Department at Hillah Hospital from1st of December, 2020 to 20 of June, 2021. The criteria of exclusion were patients with History of prolonged use of nephrotoxic drugs, Nephritis, Bone disease, immune disease, Parathyroid disease. The levels of FGF23&PO4 were measured by ELISA technique, whereas the levels of other parameters were measured by colorimetric method according to the manufacturer manual.

Each participant in the trial had a vein puncture to obtain a blood sample of 5ml. After blood clotting, blood samples were placed in sterile test tubes, centrifuged at 3000 rpm for 15 minutes, and the obtained serum was aspirated using a mechanical micropipette and transferred into clean plain tubes with a screw cap that were labeled and stored at -20°C until needed for various investigations.

Detection range for **FGF23** 15.6 -1000 pg mL^{-1} *

RESULTS AND DISCUSSION

General characteristics of studied groups

In this study, 100 participants were taken 50 patients and other healthy people and their ages ranged between (25 – 65) years. Comparison between study groups regarding the age was performed using t-test. There was not statistically significant difference p value (0.340) High incidence of obstructive renal failure in the aged group (61-70 years) as see in then Table 1.

Table 1. Age groups of the obstructive renal failure patients and controls

		Study groups		P value
		Control	Patient	
Age groups	<40 years	8	11	0.340NS
	٪	16.0%	22.0%	
	41-50 years	16	9	
	٪	32.0%	18.0%	
	51-60 years	7	4	
	٪	14.0%	8.0%	
	61-70 years	12	18	
	٪	24.0%	36.0%	
	> 70 years	7	8	
	٪	14.0%	16.0%	
	Total	50	50	
Age (year)		53.77±14.18	57.05±15.21	0.304NS

NS: none statistical significance (p>0.05)

According our study we found more cases of obstructive renal failure in old age that agrees with previous study Asymptomatic OU in the elderly can develop into a serious acute renal damage requiring dialysis [4]. Depending on the severity of the OU. Hydronephrosis is more common in the old (>64 years) than in the young (5.1 percent vs. 3.1 percent), particularly in the elderly males (6.2 percent in men and 2.9 percent in women) [5]. In this study, 50 patients with obstructive renal failure, there were 34 males and 16 females. The percentage of male 68.0% and female 32.0% as shown in Table 2.

Table 2. Gender type of the study groups

		Study groups		P- value
		Control	Patient	
Sex	Female	12	16	0.252NS
	%	24.0%	32.0%	
	Male	38	34	
	%	76.0%	68.0%	
Total		50	50	100

NS: none statistical significance (p>0.05)

Regularly, epidemiological studies of disease prevalence show that obstructive renal failure may occur more often in men, As an example, 57.4% of ESRD patients with UN are above the age of 64, with 73.84% being men. [5].

Measurements of FGF23, PO4, Hb, GFR among three study groups

Comparison among three study groups regarding serum FGF23 level. Cases which have included: obstructive renal failure and control**.** Obstructive renal failure patients had significantly higher serum FGF23 levels (501.3±230.89 Pg mL^{-1}) and control group (119.63±29.8 Pg mL^{-1}). P = <0.001. As see in then Table 3 and Figure 1.

Table 3. Comparison of FGF23, Hb, Po4, and GFR levels between control group and patient group

	Study groups		P -value
	Control	Patient	
Fibroblast growth factor 23 (pg ml^{-1})	119.63±29.8	501.3±230.89	<0.001**
Hemoglobin (mg dL^{-1})	13.48±1.28	10.25±2.44	<0.001**
Phosphorus (mmol L^{-1})	0.68±0.39	2.01±0.76	<0.001**
Glomerular Filtration Rate (mL min^{-1})	97.86±17.98	21.53±11.58	<0.001**

**: High statistical significant difference (p≤0.001)

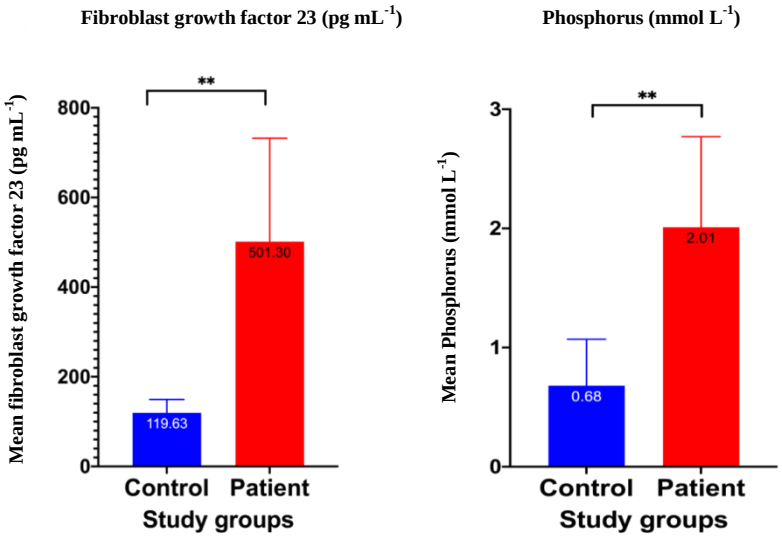

Figure 1. Comparison of FGF23 &Po4 between patient & control groups

PO4 level in obstructive renal failure group (2.01±0.76 mmol L^{-1}) and control group (0.68±0.39 mmol L^{-1}). P = <0.001. as see in then Table 3 and Figure 1.

In our study we found the FGF23 levels was significantly elevated in patients compared to apparently healthy controls. This study agree with Javier A. Neyra[11] whose founds Acute kidney injury (AKI) is a state of high FGF23 [11]. Elevated FGF23 levels have been observed in multiple studies of human AKI [12]. Plasma cFGF23 levels were 5.6-fold higher in patients with AKI versus age-matched patients without AKI [13]. One nephron has to do the work of three when the glomerular filtrate rate is less than 30% of normal in a patient. There is a phosphate load because phosphate intake is kept constant, but the number of glomeruli accessible to filter phosphate is reduced by 30%. There is no increase in serum phosphate levels because the phosphate load promotes FGF23, which reduces tubular absorption by 30%, but a high concentration of phosphate in the tubule causes a decrease in renal Klotho. [14]. Due to the kidney's resistance to the action of FGF23, a low Klotho level produces a rise in FGF23, which in turn causes a drop in calcitriol. [15]. FGF23 and PTH concentrations rising while calcitriol and Klotho levels falling are associated with an increased risk of cardiovascular and other disorders developing. [16] For every 15 percent reduction in the glomerular filtrate rate, it takes six kidneys to perform the same amount of work. This

increases levels of FGF23 and PTH. However, when the phosphate excretion percentage is greater than 60% (in humans), the kidneys are unable to eliminate enough phosphate, resulting in hyperphosphataemia. [14]. Vitamin D production is limited by 1ahydroxylase, an enzyme that is inhibited by FGF23's binding to FGFR1 and FGFR3, which is found on the renal proximal tubular cells. [17]. Furthermore, FGF23 stimulates calcium and sodium reabsorption by acting directly on distal tubular cells. Ca and Pi excretion are reduced when renal function is lost [18]. Only 1% to 2% of the ultrafilterable Ca (ionized and complexed fractions) is excreted in the urine by people with normal renal function. FGF-23, on the other hand, may act to correct the Pi levels and halt the progression of hyperphosphatemia. As a result of this unique response pattern to Ca and Pi retention, FGF-23 is now recognized as the primary hormone involved in the control of Pi levels. While extracellular Ca2+ remains within normal limits, FGF-23 inhibits PTH secretion. [19]. If Pi levels continue to rise, FGF-23's ability to normalize serum Pi will be compromised at some point, and at that point, PTH may begin to rise, resetting the homeostatic system to its previous equilibrium state.Hb level in obstructive renal failure group (10.25±2.44 mg dL^{-1}) and control group (13.48±1.28 mg dL^{-1}). P = <0.001. As see in then Table 3 and Figure 2.

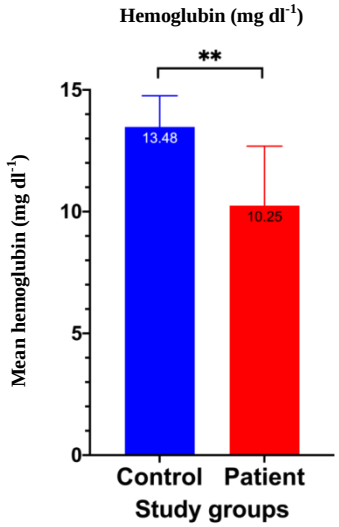

Figure 2. Comparison of Hb between patient & control groups.

The present study found the blood concentration of Hb significantly lower in patients compared with control group and this result agree with (Micarelli et al) [20] Patients with chronic kidney disease (CKD) who have severe anemia are at an increased risk of cardiovascular disease and heart failure. In addition to low erythropoietin production, iron insufficiency, and inflammation all have a role in renal anemia. According to animal and clinical investigations, no link has been shown between high FGF23 levels and renal anemia in the past. An observational research, however, found a negative correlation between high FGF23 levels and hemoglobin levels in 53 CKD patients. [21].

GFR level in obstructive renal failure group (21.53±11.58 mL min^{-1}) and control group (97.86±17.98 mL min^{-1}). P = <0.001. As see in then Table 3 and Figure 3.

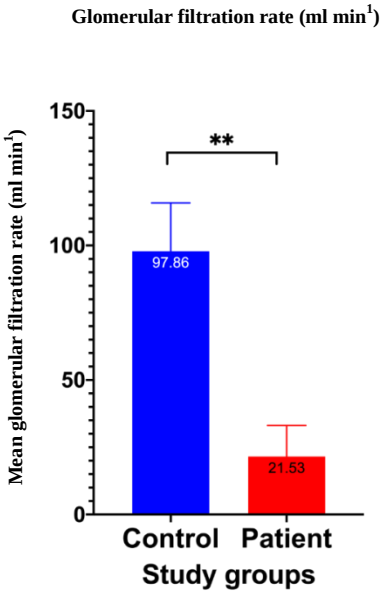

Figure 3. Comparison of GFR between patient & control groups.

The results demonstrated from this study illustrated that the level of GFR in patients lower kthan controls, P-value (<0.001) agreement with Tolani [22]. demonstrated decrease in GFR in patients with obstructive renal disease [22].

Receiver operating characteristic (ROC Test) curve analysis for FGF23 as differentiating patients from control subjects.

FGF23 serum with (AUC=0.954) in patients and CI between (0.903-1.000) in patients, the cut-off point for serum FGF23 = (>198.136).The sensitivity was (92%). specificity was (100%) Tables 4 & 5 and Figure 4.

We show there highly specific which indicates the FGF23 diagnostic for obstructive renal disease &highly sensitive for renal impairment that The AUC is close to one that It can separate the patients from the healthy this study agree with (Rygasiewicz et al) [23].

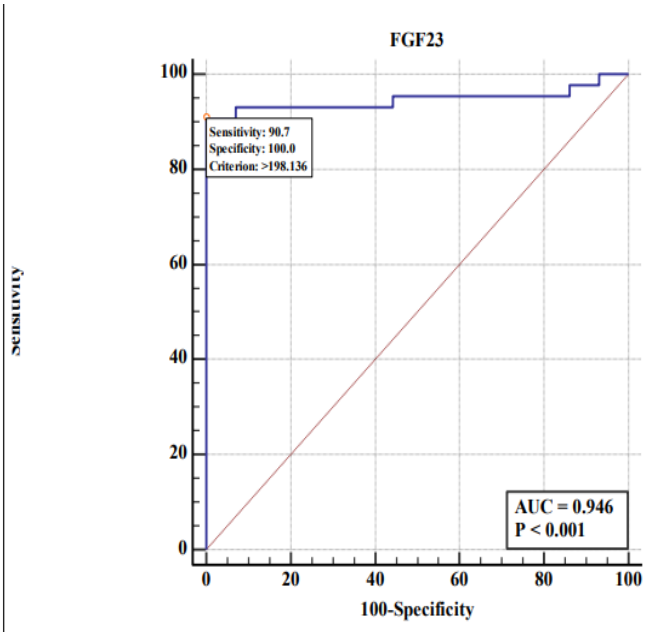

Figure 4. Criterion values and coordinates of the ROC curve analysis for FGF23 as differentiating patients from control subjects.

Table 4. Comparison and Criterion values and coordinates of the ROC curve for FGF23 as differentiating patients from control subjects

Area Under the Curve

Test Result Variable(s): Fibroblast growth factor 23 (pg ml^{-1})				
Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.954	0.026	0.000	0.903	1.000

Table 5. Best discriminative (with maximum sensitivity + specificity values) cut-off values and their criteria of the serum FGF23

		Study groups	
		Control	Patient
Fibroblast growth factor (pg/ml)	< 200 pg ml^{-1})	50	4
	%	100.0%	8.0%
	> 200 (pg ml^{-1})	0	46
	%	0.0%	92.0%
Total		50	50
Effect size			
Sensitivity		92 (81.16-96.85)	
Specificity		100 (92.87-100)	
Positive Predictive Value		100 (92.29-100)	
Negative Predictive Value		92.59 (82.455-97.08)	

CONCLUSIONS

1-The Fibroblast growth factore23 is higher in patient with obstructive renal failure than that healthy control.

2-The phosphors is higher in patient with obstructive renal failure than those healthy control.

3-The FGF23 could be served as a diagnostic marker in obstructive renal failure patients to predict the possibility to develop chronic kidney disease.

4-The occurrence of obstructive renal disease at a large rate in old age

5-The obstructive renal disease occurred at a large rate in men more than women.

6-There was a decrease in Hb and GFR levels in patients compared to healthy people.

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Conflict of interest

The authors declared no conflict of interest.

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