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RESEARCH ARTICLE - MEDICAL TECHNIQUES

Association of Fibroblast Growth Factor 23 and Calcium in Chronic Kidney Disease Patients

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Article Info.	Abstract
	Chronic kidney disease (CKD) is a growing international health concern with elevating mortality rate in the world today and it is generally a progressive and irreversible issue. It is defined by changes in kidney shape, function, or both lasting at least three months. Renal disease is commonly associated with Abnormalities of minerals and electrolyte. Levels of Ca change and the FGF23 increase early in CKD. This study was designed to show the Correlation between FGF23 and Ca in chronic kidney disease patients. One hundred blood samples (57males and 43 females) from CKD patients have been gathered from Al-Yarmouk Teaching Hospital, Baghdad Teaching Hospital and Al-Karama Teaching Hospital during the period from December 2021 to March 2022 besides 50 samples as apparently healthy control. The age range in the current study was at 33-75 years for CKD patient and 30-65 years for control. The fibroblast growth factor 23 was screened by an ELISA method and serum Calcium, by cobas c111 analyze. Ca, FGF23 is statistically highly significant at p-value =0.001. The receiver operation characteristic (ROC) curve results revealed that the sensitivity and specificity for FGF23 was 100%. The conclusion of the current study shows that the. FGF 23 was high in all CKD patients and Ca was high in two patients, normal in thirty-seven patients, and decreased in sixty-one patients.

1. Introduction

Kidney failure, is a medical condition when kidney function is less than 15% of normal levels [1]. The kidney failure is classified into 2 types, acute and chronic renal failure (CRF). Acute renal failure (ARF) is a life-threating disease with high mortality percentage, patient may be recover and others cases subsequently develop to CRF. According to recent studies, roughly one in ten persons may have CKD, but young adults are less likely to have it than the general population, where it affects one in fifty. One in two patients with CKD in those over 75 years of age [2]. Reducing kidney function leads to various complications such as water and salt imbalance, anemia, bone weakness, heart disease, hypertension and the accumulation of waste products in the body [3]. Kidney disease is commonly associated with Abnormalities of urea, creatinine, Ca, phosphorus, parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and vitamin D metabolism [4]. FGF 23 is a phosphatonin of 251 amino acids that increases phosphate releasing by lowering phosphorus absorption in the gut by blocking the formation of active vitamin D in the proximal tubules through inhibition of renal 1 alpha hydroxylase, and reducing phosphorus resorption by inhibiting the activity of the Na/P cotransporter type 2 in the proximal convoluted tubules. Decreased active vitamin D encourages the release of PTH, which further encourages the outflow of phosphorus by the kidneys [5]. Traditional paradigms have been challenged by the notion of an osteo-renal axis for controlling phosphorus equilibrium, which is produced by the release of FGF23 by bone [6]. Plasma FGF-23 levels rise throughout the early stages of chronic kidney disease (CKD), suggesting that it is a sensitive biomarker of aberrant renal phosphate processing in humans [7]. Calcium plays a significant function in the bodies in numerous metabolic processes, enzymatic signal that is used in metabolic pathways. The parathyroid hormone (PTH), calcitonin, and calcitriol, which jointly control serum calcium levels, strictly regulate calcium. The hormones PTH and calcitriol (1,25-dihydroxyvitamin D) regulate the absorption of calcium in the digestive system. Physiological levels of total calcium range from 8.5 mg/dl to 10.5 mg/dl (2.12 – 2.62 mmol/L) [8].

2. Materials and Methods

This case-control study was conducted on patients who showed up at AL Yarmouk Teaching Hospital, Baghdad Teaching Hospital and AL karama Teaching Hospital in the time span from December 2021 to March 2022. One hundred of patients with renal failure selected in our study with age (35-75) years were diagnosed as chronic renal failure based on clinical examination by expert nephrologists, laboratory tests, and previous medical reports. These patients' outcomes were contrasted with 50 healthy age (30-65) years as apparently healthy control group without diabetic nephropathy or hypertension, and without a history of kidney disease depending on previous medical reports and laboratory investigation.

Nomenclature			
AKI	Acute kidney injury	CRF	Chronic renal failure
ARF	Acute renal failure	F.E.P	Fishers exact probability
AUC	Area under curve	FGF 23	Fibroblast growth factor 23
Ca	Calcium	PTH	Parathyroid hormone
CKD	Chronic renal failure	ROC	Receiver operating curve

2.1. Statistical analysis

Utilizing the Ch-square(x2) test, the current study's data were examined to compare percentages. The T-test for independent samples was used to compare two numerical variables. A significance level of 0.05 was used for the test. Programs called SPSS v.23 are used to analyze current data.

3. Results and Discussion

A total of 100 blood specimens from (57males and 43 females) were investigated during the study period in addition to 50 samples as control (Table 1). The mean age (years) for patients was 55.07±10.5 versus 48.34±8.15 for control group. Also, the results of age groups in this table observed 33(33%) cases out of 100 were attacked with renal disease in age group (53-62) years, but the high number and percentage 22(44%) in control group was appear in 43-52 years. While the less age group were attacked with the renal disease were the age group >72 years, but in control group at age 63-72 years was 1(2%), this difference was highly significant with p-value ≤ 0.001. Alternatively, the outcomes in this study demonstrated that the male group were more than the female with 57 (57.0%),43 (43.0%) respectively with a male to female ratio of 1:1.3, this difference was non-significant with P-value >0.05.

Table 1 Demographical Picture of studied group

Parametr		Patient (N=100)	Control (N=50)	Sign
Age (Years)	M± SD	55.07±10.5	48.34±8.15	T-test=3.95 P-value≤ 0.001 (H.S)
(33-42)	N (%)	15 (15,0%)	12(24.0%)	F.E.P=20.13
(43-52)	N (%)	24 (24.0%	22 (44,0%)	P-value ≤ 0.001 (H.S)
(53-62)	N (%)	33 (33.0%)	15 (30.0%)	
(63-72)	N (%)	27 (27.0%)	1 (2.0%)	
>72	N (%)	1 (1.0%)	0 (0.0%)	
Gender	Male	57 (57.0%)	25 (50.0%)	Chi-sequare=0.65
N (%)	Female	43 (43.0%)	50.0%)	P-value=0.1 (N.S)

Our study resembles with previous Pakistan study submitted representative by [9] which showed that from 265 patients enrolled for final analysis in this data with a male to female ratio of 1:1.03 (146/121), and another study in India by [10] Showed that the patients' mean age was 42.57 years but this result was lower than our result 55.07±10.5 year. but [11] Showed that (79%) were females and the median age was 58 years old. In addition, [12] from Spain showed that more cases were in females (39.1%) than males (29.6%) with age group (49-67) years. The result in these studies match to our study. The variation with our study depend on the sample size which taken in each study ,geographic distribution , life style different from country to country. It was suggested that a rise in age-related risk factors for developing chronic kidney disease (CKD) could explain the rising prevalence of reduced renal function in older people such as diabetes, hypertension and cardiovascular disease However, GFR decreases with age as a result of various changes the body experiences with aging that affect renal function [13] Because men and women may have renal failure at different times due to variances in hormone levels. Men who have higher testosterone levels may experience decreased renal function. On the other hand, men's kidneys not protected by estrogen, which is higher in women until menopause [14].

Table 2 observed that 61 patients had increased levels of FGF23 >900 in the same time had decreased levels of S.Ca++ <8.6 (mg/dl),Also 37 had normal levels of S.Ca++ 8.6-10 (mg/dl) with high level of FGF23. But only 2 cases had increased levels of S.Ca++ >10 (mg/dl) with increase of FGF23 levels when categorized these parameter according to its cutoff points.

Whereas (42.2%) of participants believed that herd immunity is enough to protect from coronavirus. The highest percentage of the participants (70.5%) answered correctly for awareness of performance work normally after taking the COVID-19 vaccine, (63.7%) of participants answered correctly that the COVID-19 vaccine should provide for all not only for the high-risk group. The majority of participants (70.9%) answered incorrectly that they thought never taken the immunotherapeutic medication with the COVID-19 vaccine. (76.8%) of participants believed that the COVID-19 vaccine should be a personal decision, while (76.9%) believed that they must be adherence to the time of the vaccination. A high percentage of participants (84.2%) was seeing that health care providers must be taken a training course on the COVID-19 vaccine.

Table 2 Distribution the levels of FGF23 according to the cutoff point with S.Ca^{++} among cases

Categorial FGF23 (pg/ml)		Categorial S.Ca^{++} (mg/dl)			Total
		Normal (8.6-10)	Decrease (<8.6)	Increase (>10)	
>900	No.	37	61	2	100
	%	100.0%	100.0%	100.0%	100.0%
Total	No.	37	61	2	100
	%	100.0%	100.0%	100.0%	100.0%

According to previous Iraqi reports [15] 52.07 percent of patients had a decrease in Ca, 1.33 percent had increase in Ca, and 46.6 percent had normal serum Ca levels., with increase FGF23 level. [1] who decided that a restricted normal range is maintained for serum calcium levels and

elevated FGF-23, [16, 17] showed elevated level of calcium and FGF 23 level, also a study by [18] identified that hypercalcemia occurs in AKI and develop through a number of ways, including direct changes in intravascular tone and volume loss from polyuria. Furthermore, nephrocalcinosis, or calcium deposits in the kidneys, can result from persistent hypercalcemia. This findings dissimilarity with our data may be attributed to the difference in sample size, methodology, normal range in different laboratories in multiple countries. In response to a number of circumstances, such as reduced filtration and/or breakdown by the sick kidney, FGF23 levels increase [19]. It has been proposed that decreased glomerular filtration and increased tubular re absorption are proposed mechanisms by which CKD may contribute to hypercalcemia [20].

Table 3 and Fig. 1 Present the area under curve (AUC) for Receiver Operative Curve (ROC) curve analysis for the FGF23 (pg/ml) which were 1.0 among renal disease patients reflecting the great diagnostic power of tests. This table also observed the high value of sensitivity and specificity of the FGF23 with 100% and 100% respectively, with 95% confidence with (p-value≤0.001). [21] reported that the threshold value for FGF23 was 277 pg/mL and that patient serum levels were much higher. The calculated area under the ROC curves was 0.959; the calculated sensitivity and specificity were 94.0 percent and 84.0 percent, respectively (P< 0.001). On the other hand [22] showed that FGF23 has (sensitivity 80%, specificity 78.95%) while [23] patients had high FGF-23. (ROC) curve analysis showed serum FGF-23 has sensitivity 78%, specificity 76%. The current study was higher in sensitivity 100% and specificity 100%, this difference may be due in samples size, the relationship between the parameters that used in this study.

Table 3 ROC test for FGF23 test among studied groups

Area	Cutoff point	Asymptotic 95% Confidence Interval		Sensitivity	Specificity
		L,B	U.B		
1.000	972	1.000	1.000	1.000	1.000

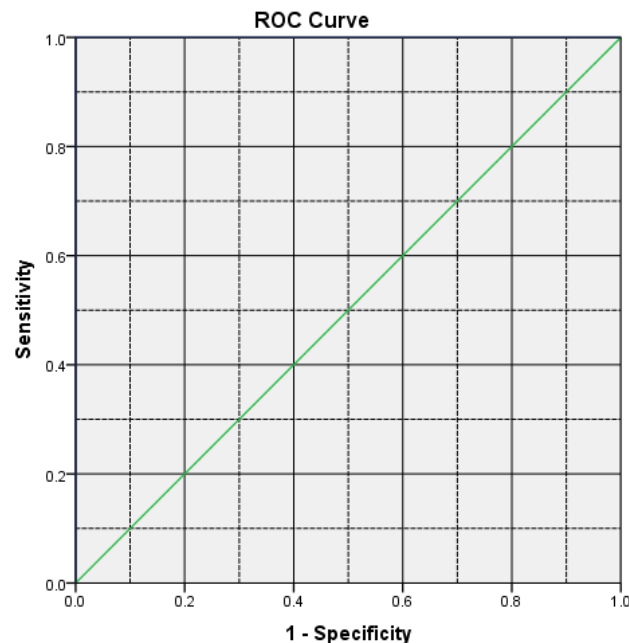(**) Highly Sig. at P<0.01; Non Sig. at P>0.05; C.I.: Confidence Interval; L.B.: lower bound

Fig 1. ROC Curve Chart for the FGF23 marker among studied group (N=150)

4. Conclusion

More kidney disease was found in age group of 53 to 62 year as well as it was being more relevant in the male patients compared to the female ones. FGF 23 was elevated in all kidney patients when correlated with serum Ca.

5. Recommendation

Further analysis in large scale study of chronic renal cases to confirm the results of current study and may contribute to the understanding the function of (FGF 23) for renal damage in CKD disease and Correlation with Calcium.

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Ethical Approval

Ethical approval for this study was granted from the ethical committee of Iraqi Ministry of Health AL-Karkh Directorate of Health (no.123).

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