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Evaluation of Intact Fibroblast Growth Factor- 23 (FGF-23) as Predictors of Bone Integrity in Patients with Chronic Kidney Disease

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Abstract

Back ground:

Chronic kidney disease is an international public health problem affecting 5–10% of the world population. Newly discovered humoral factors- fibroblast growth factor -23 (FGF-23), that are involved in phosphate and vitamin D homeostasis. Elevated levels of the phosphate-regulating hormone fibroblast growth factor- 23 have been linked to greater risk of fractures, especially among individuals with chronic kidney disease (CKD). Therefore, this study was aimed to evaluate FGF23 as a predictor for bone loss and fractures in patients with chronic kidney disease.

Methods:

A case control study; involved (184) participates: 129 patients that meet inclusion criteria and 55 healthy individuals as control group. Serum intact FGF-23 level was measured using an enzyme-linked immunosorbent assay kit. Immune assay (Roche Cobas E411) and spectrophotometry (Roche Cobas C311) techniques were used to analysis other parameters.

Results:

The current study showed significant differences ($p< 0.05$) in the BMI (26.8), uric acid (4.34), urea (28.18), creatinine (0.76), phosphorus (3.42), calcium (9.12), vitamin D (31.55), albumin (4.30), alkaline phosphatase (74.49), bone specific alkaline phosphatase (1.83), parathyroid hormone (33.51), GFR (88.15) and intact FGF- 23 (133.3) of control group in comparison with BMI (24.1), uric acid (6.53), urea (139.4), creatinine (7.69), phosphorus (6.309), calcium (8.813), vitamin D (15.14), albumin (3.79), alkaline phosphatase (120.2), bone specific alkaline phosphatase (11.85), parathyroid hormone (153.7), GFR (19.47) and intact FGF- 23 (390.1) of CKD patients; respectively. The results of this study were shown no significant differences between CKD patients and healthy control, regarding to ages ($P =0.07$) and gender ($P =0.629$). Whereas, showed significant decreases of vitamin D, albumin, calcium levels inpatients, when compared to the control group.

Conclusion:

The current study demonstrated that FGF- 23 was good noninvasive biomarkers for prediction of bone turnover, risk stratification and assessment disease severity in chronic kidney diseases- Metabolic bone disorder.

Keywords:

CKD, bone disease, fibroblast growth factor- 23, FGF- 23, vitamin D, bone ALP.

The inhibitory effect on phosphate reabsorption from the urine is the main activity of FGF-23 on mineral metabolism that led to its identification as a hormone. FGF23 also inhibits the kidney's ability to produce the vitamin D hormone 1,25-dihydroxyvitamin D3 [1,25(OH)2D3], (Agoro et al. 2020). Illnesses characterized by elevated blood levels of FGF- 23 cause renal phosphate depletion and unacceptably low levels of circulating 1,25(OH)2D3, (Luft 2021). Current thinking holds that either the impaired mineralization of the extracellular matrix, which may be detected by matrix-embedded bone cells through a putative sensing mechanism that may involve FGF receptors, or the excessive osteocytic and osteoblastic FGF- 23 secretion in both diseases (Hameed Mohamed et al. 2019). Circulating FGF- 23 is elevated in patients with chronic kidney disease, and can reach blood levels as high as 1,000-fold above the normal range, (Mace, Olgaard, and Lewin 2020). Even though very high levels of intact FGF- 23 in the blood may aid to maintain normophosphatemia in the early stages of CKD, serum phosphate levels normally rise as the disease progresses. Therefore, the phosphaturic activity of FGF-23 is unable to reduce hyperphosphatemia in more advanced CKD when renal function is compromised (Haussler et al. 2021).

Additionally, it has been demonstrated that osteoblasts and osteocytes in human bone express FGF- 23 at significant levels. FGF- 23 is not membrane-bound, in contrast to the majority of FGFs. Due to this, it behaves more like a hormone than an adhesion molecule or cell surface receptor (Agoro et al. 2020). There is some evidence to suggest that FGF- 23 is the most accurate marker for predicting CKD worsening. In order to treat CKD patients with certain kinds of phosphate binders like sevalamer and titrate this medication using FGF-23 concentrations to assist avoid the development of CKD-related complications, many clinical studies are under underway (Haffner et al. 2019).

Materials and Methods

A case- control study was included (184) participates: 129 patients (65 males and 64 females), who attended to Nephrology Center, Al-Basra Teaching hospital, Basra, Iraq; in addition to 55 healthy individuals as control group. Their ages range were from 17-75 years. The samples were collected throughout the period from March 2022 to December 2022. Statistical analysis was conducted using SPSS version 25.0. Statistical results are considered significant if $P<0.05$.

Results and discussion.

The anthropometric data were illustrated in table (1). The current study was demonstrated significant difference in BMI ($p< 0.05$) between patients (24.1) and control (26.8). Because of the impaired capacity to digest food, decrease in appetite and the increased requirement for energy, chronic renal disease can induce weight loss. This could result in malnutrition (Ammirati 2020). This finding of this study was in-agreement with (Koppe, Fouque, and Kalantar-Zadeh 2019).

The means serum uric acid (6.53 mg/dl), urea (139.4 mg/dl), and creatinine (7.69 mg/dl) in patients

were significantly higher ($p< 0.05$) than the means of uric acid (4.34 mg/dl), urea (28.18 mg/dl), and creatinine (0.76 mg/dl) in the control. These findings were consistent with (Nonso et al. 2019), (Hafez et al. 2021) and (Kameda et al. 2020).

Since blood calcium and phosphorous concentration are inversely related, Table1. Serum calcium concentration was significantly low ($P<0.05$) in renal failure patients (8.81) than control. Mohamed et al. 2019, reported that the majority of patients (52%) with stage 5 chronic renal disease had hyperphosphatemia and hypocalcemia. Because the kidneys are unable to produce the active form of vitamin D (1,25-dihydroxycholecalciferol), which is necessary for calcium absorption in the gut, the change in vitamin D synthesis caused by renal failure may be the likely reason of the drop in blood calcium levels (Janoušek et al. 2022). According to the current study, vitamin D3 levels are considerably lower in CKD patients than in healthy control (15.14 vs. 31.55), this finding agreed with (Kawarazaki et al. 2011).

The current study, also revealed that there was a highly significant increase ($P< 0.01$) in the alkaline phosphatase (120.2) and bone ALP (11.85) of CKD patients, when compared to alkaline phosphatase (74.49) and bone ALP (1.83) of control; respectively. This result was in agreement with (Wally 2016). It has been demonstrated that BALP is a sensitive and trustworthy biomarker of bone metabolism (Staykova et al. 2018). Since several research show a link among ALP and accelerated morbidity and mortality. The link of circulating BALP with mortality has frequently been pronounced in patients with advanced CKD. As end result, several pathways might hyperlink ALP to mortality, and strategies that relate circulating BALP to an accelerated chance of mortality could be precise to advanced CKD (Nizet et al., 2020).

FGF23's foremost physiological effects include inducing phosphaturia by means of reducing sodium-phosphate co-transporter luminal expression within the proximal tubule, lowering systemic 1,25-dihydroxyvitamin D stages by means of directly inhibiting renal 1-hydroxylase and inducing catabolic 24-hydroxylase, and inhibiting parathyroid hormone (PTH) secretion (Wolf, 2012).

Beginning in early CKD, fibroblast growth issue 23 stages progressively rise, possibly as a physiological reaction to preserve normal blood phosphate stages or a right phosphorus balance. Increased FGF- 23 can be linked to mortality and CKD development, in line with recent investigations. FGF- 23 is growing as an ability biomarker that, at the least, may be used to decide which CKD patients could benefit maximum from in depth treatment of disrupted phosphorus metabolism (Isakova et al., 2011).

Numerous go-sectional studies confirmed that CKD sufferers have higher FGF-23 stages than healthful human beings. Studies that tested FGF-23 in juvenile CKD populations came up with comparable findings. Despite variations in the right stage of CKD at which FGF-23 stages first became significantly multiplied, better FGF-23 on a non-stop scale become constantly linked to better serum phosphate, higher fractional excretion of phosphate, lower predicted glomerular filtration fee (eGFR), and decrease levels of 1,25-dihydroxyvitamin D, independent of eGFR. The latter showed that reduced 1,25-dihydroxyvitamin D ranges in progressive CKD were usually as a result of inhibition via FGF-23 instead of inadequate renal mass. Animal experiments that administered neutralizing anti-FGF-23 antibodies completely restored 1,25-dihydroxyvitamin D tiers without converting the severity of CKD (Mac et al. 2020).

Table 1 Comparison of the anthropometric and biochemical markers between chronic kidney diseases patients and control.

Variables		Control (n=55) Mean ± SD	CKD (n=129) Mean ± SD	P. value
Age (years)		44.16 ± 13	46.89 ± 13.24	0.07
Gender	Male, n (%)	25, (45.45%	65, (50.39%)	0.629
	Female, n (%)	30, (54.55%)	64, (49.61%)	
	Total, n (%)	55, (100%)	129, (100%)	
BMI (kg/m2)		26.8 ± 3.74	24.1 ± 3.18	<0.0001

Uric Acid (mg/dl)	4.344 ± 0.6218	6.539 ± 2.055	<0.0001
Urea (mg/dl)	28.18 ± 8.953	139.4 ± 64.59	<0.0001
Creatinine (mg/dl)	0.76 ± 0.22	7.69 ± 0.75	<0.0001
Hb (g/dl)	12.78 ± 1.869	9.486 ± 1.832	<0.0001
Ferritin (ng/ml)	134.6 ± 28.38	470.3 ± 50.2	<0.0001
Phosphorus (mg/dl)	3.427 ± 0.7106	6.309 ± 1.941	<0.0001
Calcium (mg/dl)	9.125 ± 0.6114	8.813 ± 0.9576	<0.0001
Vit. D (ng/ml)	31.55 ± 4.801	15.14 ± 3.149	<0.0001
Albumin (g/dl)	4.30 ± 0.492	3.79 ± 0.651	<0.0001
ALP (IU/L)	74.49 ± 13.72	120.2 ± 21.02	<0.0001
Bone ALP (ng/ml)	1.838 ± 0.209	11.85 ± 0.86	<0.0001
Magnesium (mmol/L)	0.9320 ± 0.1574	0.9505 ± 0.2111	0.056
PTH (pg/ml)	33.51 ± 6.782	153.7 ± 40.5	<0.0001
FGF 23 (ng/ml)	133.3 ± 31.12	390.1 ± 51.4	<0.0001
e-GFR (mL/min/1.73m2)	88.15 ± 2.889	19.47 ± 10.04	<0.0001

SD: standard deviation; n: number; CKD: chronic kidney diseases, significant at p< 0.05.

Comparison of chronic kidney disease patients according to gender.

As shown in Table (2), there were no significant differences (p. value >0.05) in the means values of all parameters between patients and control according to gender.

Table 2 Comparison between pateints and control according to gender.

Variables	Males with CKD (n=65) Mean ± SD	Females with CKD (n=64) Mean ± SD	P. value
Age (years)	49.75±13.26	47.98±12.68	0.128
BMI (kg/m^2)	24.01±2.823	24.12±3.532	0.8546
Uric Acid (mg/dl)	6.652±2.538	6.425±1.419	0.5312
Urea (mg/dl)	147.5±23.15	131.2±24.90	0.153
Creatinine (mg/dl)	7.905±1.392	7.488±1.028	0.620
Hb (g/dl)	9.668± 2.105	9.302± 1.499	0.258
Ferritin (ng/ml)	508.5±30.7	431.5±40.6	0.066
Albumin (g/dl)	3.695±0.6221	3.887±0.6705	0.093
Phosphorus (mg/dl)	6.046±2.077	6.577±1.768	0.120
Calcium (mg/dl)	8.782±0.9531	8.844±0.9686	0.717
Vit. D (ng/ml)	14.66±1.784	15.63±1.508	0.372
ALP (IU/L)	123.6±17.01	116.7±16.00	0.588
Magnesium (mmol/L)	0.9531±0.2207	0.9478±0.2027	0.888
PTH (pg/ml)	133.7±21.3	158.1±51.5	0.313
FGF 23 (ng/ml)	378.3±37.9	402.0±44.9	0.343
e-GFR (mL/min/1.73m^2)	21.29±1.99	17.63±1.197	0.077

SD: standard deviation, n: number, significant at p < 0.05.

3 Comparison of chronic kidney disease patients according to the duration of disease.

The mean values of biochemical parameters among patients with chronic renal disease according to duration of CKD were shown no significant differences (P. value >0.05), Table (3).

Table 3 Comparison of biochemical markers among patients with chronic kidney disease according to the duration of CKD.

Variables	CKD < 1 Year (n=60) Mean ± SD	CKD >1 Year (n=69) Mean ± SD	P. value
Age (years)	48.97±8.92	45.09±7.44	0.0971
BMI (kg/m^2)	24.41±3.124	23.76±3.225	0.2482
Uric Acid (mg/dl)	6.783±2.450	6.328±1.626	0.2108
Urea (mg/dl)	140.3±22.50	138.6±18.66	0.8763
Creatinine (mg/dl)	7.082±1.135	8.235±1.355	0.1698
Hb (g/dl)	9.550±1.816	9.430±1.857	0.7131
Ferritin (ng/ml)	437.7±47.5	498.7±51.5	0.1475
Albumin (g/dl)	3.711±0.5661	3.859±0.7141	0.2001
Phosphorus (mg/dl)	6.230±1.868	6.379±2.013	0.6663
Calcium (mg/dl)	8.797±0.9667	8.827±0.9564	0.8606
Vit. D (ng/ml)	15.52±1.958	14.81±1.336	0.5198
ALP (IU/L)	113.3±12.22	125.3±13.27	0.3517
Magnesium (mmol/L)	0.9370±0.2265	0.9622±0.1977	0.5015
PTH (pg/ml)	142.1±10.5	163.8±12.1	0.4176
FGF 23 (ng/ml)	378.3±39.0	400.3±43.6	0.3816
Bone ALP (ng/ml)	11.63±1.19	12.03±1.02	0.8511
e-GFR (mL/min/1.73m^2)	20.47±2.49	18.61±2.563	0.2961
Urea (mg/dl)	140.3±22.50	138.6±18.66	0.8763
Creatinine (mg/dl)	7.082±1.135	8.235±1.355	0.1698

n: number, SD: standard deviation, significant at $p < 0.05$.

4 Identification of risk of CKD by multivariable logistic regression analysis for all Patients.

Multiple logistic regression was performed for all patients to predict risk of CKD. The were high odd ratios of some parameters, Table (4).

Table 4 Identification of risk of CKD by multivariable logistic regression analysis for all Patients.

Variables	Regression coefficient	Standard error	Odds ratio	95% CI	P value
Age (years)	0.03328	0.0127	1.034	1.009 - 1.061	0.0072
BMI (kg/m^2)	-0.2263	0.0519	0.7975	0.716 - 0.879	<0.0001
Uric Acid	1.873	0.3026	6.510	3.802 - 12.54	<0.0001
Hb (g/dl)	-0.8636	0.1280	0.4216	0.320 - 0.530	<0.0001
Ferritin (ng/ml)	0.03752	0.006	1.038	1.027 - 1.055	<0.0001
Albumin (g/dl)	-1.460	0.324	0.2321	0.118 - 0.424	<0.0001
Phosphorus (mg/dl)	1.829	0.299	6.230	3.699 - 12.09	<0.0001
Calcium (mg/dl)	-0.4307	0.196	0.6501	0.436 - 0.946	0.0243
Vit. D (ng/ml)	-0.4114	0.066	0.662	0.568 - 0.742	<0.001
ALP (IU/L)	0.0321	0.006	1.033	1.020 - 1.047	<0.0001
Magnesium (mmol/L)	0.49	0.837	1.632	0.324 - 8.84	0.5560
FGF 23 (ng/ml)	0.053	0.011	1.054	1.036 - 1.082	<0.0001

Bone ALP (ng/ml)	1.066	0.197	2.904	2.073 - 4.521	<0.0001
e-GFR (mL/min/1.73m^2)	-0.270	0.100	0.763	0.563 - 0.872	<0.001
Urea (mg/dl)	0.145	0.854	1.156	0.956 - 1.265	<0.001
Creatinine (mg/dl)	19.31	11.31	2.444	2.001 - 2.98	<0.001

Conclusion:

CKD is induced bone abnormalities; proper diagnosis of the actual underlying skeletal problems helps to prevent future bone loss and fractures. There were significant decreases in each of calcium, vitamin D, albumin, estimated GFR in patient with CKD. While, there were significant increases in uric acid, urea, creatinine, ferritin, phosphorus, alkaline phosphatase, bone alkaline phosphatase, parathyroid hormone and intact FGF-23. These parameters are noninvasive biomarkers for prediction of bone turnover, risk stratification, assessment disease severity and beginning of the proper treatment course, which are crucial in achieving better patient outcomes in CKD patients.

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