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Evaluation of some biomarkers (phosphorus, Parathyroid hormone, Calcium, vitamin D) in patient's serum with chronic kidney disease (CKD)

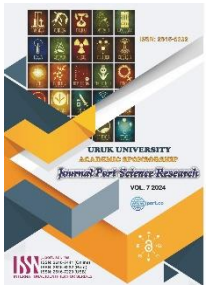
Ola A. Naser[1], Shatha Q .Al-Temimi[2], Hanaa S. Kadhum[1], Mahdi M. Thuwaini*[2] , Nabaa G. Nasser[1], Tabarek N. Abd[1], Nada N. Hassan[1]

[1] *Department of Pathological Analysis, College of Science, Basrah University; Iraq.*

[2]*Department of Medical Laboratories, College of Health and Medical Techniques, Basrah University; Iraq.*

Mahdi.Murshd@stu.edu.iq.

Abstract Background chronic kidney disease (CKD) can be defined as abnormalities either in kidney structure or function by decreasing glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m² for at least 3 months. it is considered to be a major medical problem, especially in developing countries and emerging economies. The study aims to measure biochemical markers (calcium, phosphorus, vitamin D, and PTH) in patients with CKD and healthy control, also finding out the effect of CKD on formation active form of vitamin D. Methods: This study includes (90) individuals (60) patients (30 males and 30 females) and (30) healthy control. The criteria of inclusion were: patients previously diagnosed with chronic kidney disease, In the study population age ranged between (30-70) years old for both groups who visited Al-Basra General Hospital in the province of Basra (The National Hemodialysis Project, artificial kidney Center) through period from November 2022 to February 2023.VIDAS was used to measure parathyroid hormone and vitamin D, while COBAS C111 was used to measure serum phosphorus and calcium levels, for both patients and healthy control groups. The results of the current study have shown that there was a high significant increase ($P < 0.001$) in the levels following biomarkers in CKD patients: PTH and phosphorus, the results also showed that a significant decrease was recorded in levels following biomarkers in CKD patients: serum calcium and vitamin D. There was also a positive relationship between the levels of calcium in patients with CKD and vitamin D while it was recorded that there was a negative relationship between the level of vitamin D with phosphorus and parathyroid hormone levels. In conclusion, the results of the current study have shown that there was a highly significant increase in PTH and phosphorus and a significant decrease in levels of serum calcium and vitamin D.



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Keywords: *CKD, Biomarkers, phosphorus, Parathyroid hormone, Calcium, vitamin D*

1. INTRODUCTION

Chronic kidney disease (CKD) is characterized by a progressive loss of kidney function; decreased kidney function is shown by a glomerular filtration rate (GFR) of less than 60 mL/min per 1·73 m². The gradual and usually persistent deterioration of the kidney's filtration function may last months or years, with health implications. It is considered to be a major medical problem in the world, and a global burden, especially in developing countries and emerging economies (Stevens et al.,2013).

Non-communicable diseases such as CKD are the major cause of death around the world. In 2015, 1.2 million individuals died of renal failure, a 32 percent increase from 2005, in 2016 chronic kidney disease (CKD) caused 1.19 million deaths globally, which has increased by 28.8% from 2006. This made CKD the 11th leading cause of death in 2016, compared with the 13th and 27th in 2013 and 1990, respectively. (Luyckx et al., 2016).

Without access to chronic dialysis, an estimated 2.3–7.1 million individuals with end-stage renal disease died in 2010. In addition, it is estimated that 1.7 million individuals die each year from acute renal damage. (Zhang et al., 2008) As a result, an estimated 5–10 million individuals die each year.

As a result of renal illness. Moreover, the global prevalence of CKD is estimated to be 11-13%, and this number is likely to rise further with the aging population and the increasing prevalence of diabetes. As a result, the global burden of CKD has become a major public health problem in many countries. (Hill et al., 2016).

Diabetic mellitus nephropathy (DMN) and hypertensive nephropathy (HTN), which are complications of diabetes and chronic hypertension, respectively, are the two leading causes

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of CKD. Unlike DMN and HTN, polycystic kidney disease (PKD) is a genetic disorder that causes the uncontrolled growth of numerous cysts in the kidney. (Wilson, 2004).

Patients with chronic kidney disease (CKD) may have cardiovascular or cerebrovascular problems, and their deaths might be attributed to either. Clients with hypertensive and ischemic heart disease, both of which are linked to an increased risk of cardiovascular illness and mortality, often have altered kidney function. (Glassock et al ., 2017).

Incidence, prevalence, and progression of CKD also vary within countries by social determinants of health, possibly through epigenetic influence and ethnicity ،Diabetic nephropathy affects around 30% of diabetic patients, with certain ethnic groups having a higher risk. (Glassock et al., 2017).

End-stage kidney disease (ESKD) refers to the stage of CKD where the kidneys can no longer function on their own, and dialysis or kidney transplant is required. (Yang et al.,2020).

Kidney failure may be caused by the progression of chronic nephropathy or by acute kidney injury (AKI). Kidney failure is associated with the inability to excrete waste products, control serum electrolytes, handle the daily dietary and metabolic acid load, and maintain fluid balance. In addition, kidney failure causes inadequate production of erythropoietin, deranged calcium and phosphorous metabolism, high blood pressure, and accelerated progression of cardiovascular disease (Yang et al.,2020).

The kidneys play an important role in maintaining the balance of calcium and phosphorus. However, it has been observed that kidney failure is associated with disorders in all stages of phosphorus and calcium circulation. A decrease in the glomerular filtration rate (GFR) to a level of less than 60 ml/min/1.73 m2 is associated with a decrease in the phosphorus filtration rate with an increase in the serum level, which in turn leads to stimulation of the secretion of parathyroid hormone (PTH). (Milovanova et al ., 2009).

The PTH hormone prevents the reabsorption of phosphorus, which will return its level in the blood to normal. However, when the glomerular filtration rate falls below 30 mL/min/1.73 m2, this mechanism becomes ineffective, and persistent hyperphosphatemia develops. The latter enhances PTH secretion. Hyperphosphatemia is associated with inhibition of the effect of 1a-hydroxylase in renal proximal tubules and decreased serum 1,25(OH); Dr; Calcitriol level. (Ritter et al., 2006).

Calcitriol deficiency results in calcium absorption disorders in the small intestine; as a result, hypocalcemia develops. Persistent hypocalcemia results in parathyroid glands hyperplasia (PTGH) that is associated with excessive PTH production and secretion. PTH hyper-production and hyperphosphatemia are the manifestations of secondary hyperparathyroidism (SHPT) (Milovanova et al., 2009).

Hypocalcemia, vitamin D deficiency, and hyperphosphatemia develop at the initial stage or renal dysfunction - Chronic Kidney Disease (CKD) III (GFR 60-30 ml/min/1.73 m2); they progress with the increasing severity of renal failure (GFR 29-15 ml/min/1.73 m², CKD IV-V). (Milovanova et al., 2009).

Disorders of calcium and phosphorus balance associated with CKD result in bone diseases, generally called renal osteodystrophy. (Kdigo, 2009).

Diagnosis is commonly made after chance findings from screening tests (urinary dipstick or CKD blood indicators of kidney function, including serum creatinine and blood urea nitrogen), or when symptoms become severe. The best available indicator of overall kidney function is GFR, which is measured either via exogenous markers (e.g., DTPA, iohexol) or estimated using equations. The presence of proteinuria is associated with an increased risk of progression of CKD and death. This increased risk of death rises exponentially as kidney function worsens and is largely attributable to death from cardiovascular disease, although cancer incidence and mortality are also increased. Health-related quality of life is substantially lower for people with CKD than for the general population and falls as GFR declines. (Liano et al. 2016).

for this, the present study aimed to Measurement of biochemical markers (calcium, phosphorus, and vitamin D) in both patients with CKD and healthy individuals, and the extent to which these markers change in the progression of the stages of CKD

2. MATERIALS AND METHODS

The study design includes (90) individuals (60) patients and (30) healthy controls. The criteria of inclusion were: patients previously diagnosed with chronic kidney disease, In the study population age, ranged between (30-70) years old, who visited Al-Basra General Hospital in the province of Basra (The National Hemodialysis Project, artificial kidney Center) through the period from November 2022 to February 2023. The practical study was also carried out in the department of The National Hemodialysis Project, Artificial Kidney Center in AlBasra General Hospital. From each patient and healthy control, the following information was collected age, gender, and sample patient with CKD. For each patient and control the following tests were carried out: serum calcium, serum phosphorus, and Parathyroid hormone, serum Vitamin D (25-hydroxyvitamin D Total) test. The control group consists of (30) healthy people (15 males,15 females) participants matched by age, who have no disease.

2.1. Sample collection

Five milliliters of human blood were obtained from each subject (patients and controls), and transferred to a gel & and clot activator tube. Then allow blood to clot for 10 min. at room

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temperature. Centrifuge at 3000-4000 RPM for 10 min. and the serum was then isolated and deposited at 20 (0C) until it was used.

2.2. Frozen Sample Handling

The frozen serum was thawed at room temperature (20-25 °C) for 2 hours until they were completely thawed and then centrifuged at 3000 RPM for 5 minutes.

2.3. Statistical Analysis

Together, the data of the study is shown as {means, ± standard deviation (SD)} The variations between the groups of the study were established by the Chi-square test, Statistical significance is designated by a value of P < 0.05. All statistical investigations were attained by utilizing IBM SPSS (version 25) for Windows.

3. RESULT AND DISCUSSION

This study includes (90) individuals between ages (30_70), (60) patients divided into (30 males, 30 females) and (30) healthy control (15 Males,15 females) The criteria of inclusion were: patients previously diagnosed with chronic kidney disease, these groups were also divided according to age. The gender and age were matched in the same way for all participants, as shown in Table (1).

Table (1): *Basic characteristics of the participants, according to the number, sex. Values were expressed as mean± SD.*

Characteristics		Control group (n=30)	Patients (n=60)	*P. value
Male	No.	15	30	$1.0^{NS\ **}$
Female	No.	15	30	
Total	No.	30	60	
Age		47.93± 11.5	51.72 ± 11.53	0.14^{NS**}

no. of the patient in comparison to control age subgroup (61_70 yrs.). Conversely, as shown in the same table (2) regarding sex the results appeared there are no significant differences (p=1.00) between study groups (control and patients). The data of the present study shows there isn't a statistical significance difference in the Biomarkers involved study (PTH, phosphorus, calcium, Vitamin D) (p= 0.48, p=0.09, p=0.97, p=0.24) respectively. among age subgroups of patients (30_40 yr, 41_50 yr., 51_60 yr, 61_70 yr.) respectively. Though, according to the age categories we included in this study maximum prevalence occurs in ages>41 years, also we found there was no significant difference in the level of biomarkers including the study and the extent to which these biomarkers (calcium, phosphorus, PTH, and vitamin D) changes depending on the stage of CKD.

Table (2) Demographic and clinical characteristics of study groups (patients and control .Values were expressed as Mean ± SD.

Variables	Age-subgroups	Control		Patients		P-Value
		Freq.	%	Freq.	%	
Age(yrs)	30- 40	9	30.0	15	25.0	0.35 NS
	41 - 50	8	26.7	14	23.3	
	51 -60	8	26.7	15	25.0	
	61 -70	5	16.6	16	26.7	
Mean ± SD		47.93 ± 11.50		51.72 ± 11.53		0.14 NS
Sex	Male	15	50.0	30	50.0	1.00 NS
	Female	15	50.0	30	50.0	

However, according to parameters including study (PTH, Phosphorus, calcium, vitamin D), the data of this study show an increase strong significant difference of PTH and phosphorus in the patient's group in comparison to the control Group (321.20 ± 223.4, 6.04 ±2.05) vs (31.09 ± 8.15, 3.45 ± 0.56) respectively. In addition, the other parameters included in this study (calcium and vitamin D) show decrease a strongly significant difference in the patient Group in comparison to the control Group (8.08 ± 1.32, 13.38 ± 6.00) vs (9.23± 0.68, 24.58 ± 7.90) respectively.

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Table (3) *show significant difference among parameters including study (PTH, Phosphorus, calcium, vitamin D) of patients and control group, values were expressed as Mean ± SD.*

Parameters	Control group (n=30)	Patients Group (n=60)	P. value
	Mean ± SD	Mean ±SD	
PTH	31.93 ± 8.15	321.20± 223.41	<0.001
Phosphorus	3.45 ± 0.56	6.04 ± 2.05	<0.001
Calcium	9.23 ± 0.68	8.08 ± 1.32	<0.001
Vitamin D	24.58 ± 7.90	13.38 ± 6.00	<0.001

The data of the present study shows there isn't statistical significance difference of Biomarkers involved study (PTH, phosphorus, calcium, Vitamin D) (p= 0.48, p=0.09, p=0.97, p=0.24) respectively. among age subgroups of patients (30-40 yr, 41-50 yr, 51-60 yr, 61-70 yr) respectively. Table (4).

Table (4) *show the comparison of biomarkers that involved study among age subgroups, values were expressed as Mean ±SD.*

Parameters		**Age-Sub group**				**P- value**
		(30-40) Y (N=18)	**(41-50) Y (N=40)**	**(51-60) Y (N=18)**	**(61-70) Y (N=4)**	
PTH	**Mean**	**332.19**	**241.76**	**338.24**	**364.43**	**0.48 NS**
	SD	**232.77**	**139.74**	**270.85**	**228.17**	
Phosphorus	**Mean**	**6.83**	**5.01**	**6.41**	**5.84**	**0.09 NS**
	SD	**1.54**	**1.84**	**2.29**	**2.18**	
Calcium	**Mean**	**8.16**	**8.01**	**8.17**	**7.99**	**0.97 NS**
	SD	**1.47**	**1.67**	**1.16**	**1.06**	
Vitamin D	**Mean**	**11.19**	**12.97**	**15.62**	**13.68**	**0.24 NS**
	SD	**5.03**	**5.18**	**6.50**	**6.71**	

Ns; not significance

4. DISCUSSION

In our study, we found CKD patients to be associated with a decrease in several vitamin D metabolites. were positively correlated with calcium concentration and negatively correlated with PTH and phosphorus concentrations. The presence of vitamin D deficiency in the general population and in patients with CKD has been estimated, this clinical problem has always been seen as large in our country, Low vitamin D is observed in the general population due to low intake of vitamin D in the diet and inadequate exposure to sunshine. However, in the case of CKD patients with hypovitaminosis D, other factors affect them. First, most patients with CKD have restricted protein and caloric intake, so vitamin D is relatively low. Second, many CKD patients have limited outdoor physical activities with reduced exposure to sunlight. Finally, greater loss of urinary vitamin D metabolites occur in patients with overt proteinuria. In addition, 1-alpha hydroxylase activity decreases due to reduced function of renal mass and an elevation in circulating FGF-23 levels, which potently suppress 1-alpha hydroxylase expression.

Also, we found e phosphorus levels significantly increased (p< 0.001) in patients with CKD compared to the control Group due to progressively loss of the ability to excrete phosphorus. Other results obtained by Nadkarni and Uribarri were similar to these results in finding elevated phosphorus levels among chronic kidney patients (Nadkarni and Uribarri, 2014) There are many valid factors for chronic hyperphosphatemia in dialysis patients, including the following: phosphate elimination during a single hemodialysis session is only 800 mg to 1,000 mg. As a result, dialysis three times a week is insufficient to eliminate the required daily intake of phosphorus (1,000 mg/d) for dialysis patients.

Calcium levels significantly decreased (p<0.001) in CKD patients compared to a control group, that this decrease in serum calcium could be due to an increase in serum phosphorous, because serum calcium and phosphorous concentrations have an inverse relationship, and any increase in one will result in a decrease in the other. Also, calcium concentrations were positively correlated with 25(OH)D concentrations, because 25(OH)D is metabolized to 1,25(OH)2D, which then positively influences intestinal calcium absorption and subsequently serum calcium concentrations. Another study, agreed with this result when they found a highly significant positive correlation between serum vitamin D and Ca (P< 0.0001). (Narayanasamy et al., 2019).

Also, PTH concentrations significantly increase (p< 0.001) in CKD patients compared to the control group. As well as, the Results of this study agreed with the findings of **(Al- Jasim and Yaseen, 2017)** who stated that PTH was highly significantly

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increased (P<0.001) in the sera of CKD patients compared with the control group. However, in CKD, there is a reduction in calcium receptor expression in vascular smooth muscle cells. Consequently, this leads to a decrease in calcium levels in serum indicating a relationship between PTH and calcium levels in chronic kidney disease. Parathyroid glands release higher concentrations of PTH in response to a low level of calcium blood. In this regard, PTH is the most important hormone that contributes to the regulation of phosphate in the kidney.

5. CONCLUSION

The results of the current study have shown that there was a highly significant increase in PTH (p<0.001) and phosphorus (p<0.001) and a significant decrease in levels of serum calcium (p<0.001) and vitamin D. in CKD patients compared with healthy subjects. All these changes were age-independent. Alterations of PTH, vitamin D, and minerals should be corrected, because these biochemical changes increase cardiovascular risk, increased mortality, and progression of CKD, in addition to other adverse effects.

Declarations

Ethical approval: Not applicable.
Consent to participate: Not applicable.
Consent for publication: Not applicable.
Competing interests: The authors declare no competing interests.
Source of findings: self-findings.

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