https://doi.org/10.46389/rjd-2024-0049
www.jrdiabet.ro
Rom J Diabetes Nutr Metab Dis
2024; Volume 31, Issue 1, pages 49-57

STUDY OF THE CAUSES OF PARATHYROID HORMONE IMBALANCE AND SOME BIOCHEMICAL PARAMETER IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Rana Ayad Al-jumaili*[1], Essam Fadel Al-Jumaili[1]
Institute of Genetic Engineering and Biotechnology for Postgraduate Studies, University of Baghdad

Abstract

Parathyroid hormone (PTH) is produced and secreted by the parathyroid glands and acts on the kidneys and bones. It's the main factor regulating the homeostasis of serum calcium and phosphate levels. In this study, we evaluated several biochemical indicators of kidney function in patients with chronic kidney disease and mineral disorders. We tested the level of total calcium, phosphorus, parathyroid hormones, and vitamin D3. In patients with chronic kidney disease and treated by regular hemodialysis. The sample collation was performed at the Medical City Dialysis Center and Iraqi Dialysis Center in Medical City from October 2022 until April 2023. The study showed that the level of PTH, vitamin D3, Ca and PO4 was highly significant (($p \leq 0.0001$) increase in patients with Chronic Kidney Disease (CKD) in comparison with controls .

There was a correlation between PTH levels and each (calcium, phosphor and vitamin D3) in CKD patient groups. This study showed that the increase in PTH levels leads to a decrease in total calcium levels and an increase in phosphor levels in patients with chronic kidney disease.

Keywords: Parathyroid hormones, Vitamin D3, Calcium, Phosphor, Chronic kidney disease

Introduction

The kidneys are a vital organ responsible for filtering blood and removing waste from the body. As a result, they play a crucial role in the transportation and disposal of nanoparticles inside the body[1]. Kidney disease is a worldwide health issue that has significant mortality rates and socioeconomic consequences. It encompasses conditions such as acute kidney injury (AKI), chronic kidney disease (CKD), diabetic nephropathy (DN), and lupus nephritis (LN)[2]. CKD is a broad term encompassing various illnesses that impact the structure and function of the kidneys[3, 4]. CKD is widely acknowledged as a significant worldwide health issue, as it plays a substantial role in causing illness and death. [5]. Its is a patho-physiologic process with multiple etiologies, resulting in the inexorable attrition of Nephron number and function and frequently leading to end-stage renal disease (ESRD) [6]. Chronic kidney disease–bone mineral disorder (CKD-MBD) encompasses several interconnected problems, such as low calcium levels (hypocalcemia), high phosphorus levels (hyperphosphatemia), insufficient vitamin D (hypovitaminosis D), and increased levels of parathyroid hormone (PTH). [7]PTH is primarily made and produced by the parathyroid main cells of the parathyroid glands in response to a decrease in circulating calcium levels. Numerous conditions, such as insufficient PTH or vitamin D production, PTH resistance, and others, can lead to hypocalcemia[8,9].

In the kidney, PTH plays two primary roles. The mechanism of action involves the up-regulation of TRPV5, a calcium transporter located on the tubular epithelium in the thick ascending

loop of Henle, distal convoluted tubule (DCT), and collecting ducts. This up-regulation facilitates the reabsorption of calcium. In addition, PTH attaches to specific locations in the proximal tubule, inhibiting phosphate reabsorption. Secondary hyperparathyroidism is a multifaceted condition that arises when chronic renal disease advances. The accumulation of phosphorus and the decrease in calcium and vitamin D levels prompt the production and release of parathyroid hormone, as well as the pace of growth of parathyroid cells[10]. Hypocalcemia and hyperphosphatemia are significant stimuli for releasing PTH. The excessive production of PTH characterises secondary hyperparathyroidism (SHPT) due to parathyroid hyperplasia triggered by factors such as low calcium levels, high phosphorus levels, or reduced levels of active vitamin D[11,12]. Calcium ions (Ca^{2+}) play a crucial role as a widespread and essential intracellular messenger, participating in various cellular and biological activities. Alterations in the extracellular Ca^{2+} concentration can disturb the regular cellular processes and the physiological functioning of these systems[13]. It is crucial for adequately functioning the heart, kidneys, bones, and nervous system. The majority of the calcium present in the body is stored in the bones in the form of calcium-phosphate complexes.

Calcium gives the bones strength and structure and acts as a dynamic reservoir to regulate calcium levels within and outside cells. Calcium is vital in various activities, including intracellular and extracellular signalling, nerve impulse transmission, and muscle contraction[14,15]. The two main hormones regulating calcium levels are PTH and 1,25-dihydroxy vitamin D (1,25D). The secretion of PTH is increased by low levels of calcium in the blood (hypocalcemia) and decreased by high levels of calcium (hypercalcemia). The primary factor is the diminished production of 1,25-dihydroxy vitamin D in the renal system, which directly promotes the release of PTH and indirectly affects calcium absorption in the intestines. Furthermore, there is a decrease in calcium release from the bone due to diminished responsiveness of the bone to PTH in combination with a shortage of calcitriol[16]. Phosphate is a vital nutrient for living organisms as it is a constituent of high-energy molecules such as AMP, ADP, and ATP. It is also crucial for maintaining the helical structure of nucleic acids like RNA and DNA. Phosphate is crucial in the mineralization process[17]. It is a constituent of high-energy molecules such as AMP, ADP, and ATP and is crucial for the helical structure of nucleic acids like RNA and DNA. Additionally, it serves as a crucial regulator in blood and urine, aiding in maintaining a balanced acid-base equilibrium. Due to its extensive involvement in nearly all molecular and cellular processes, alterations in serum Pi levels and equilibrium can have significant and adverse consequences. The equilibrium of Pi levels in the body is regulated through Pi absorption from the gut, release from bone, and elimination through the kidneys. The majority of phosphorus (Pi) in the body, around 85%, is found in bone, whereas only a tiny fraction, about 1%, exists as free Pi in extracellular fluids. The extracellular quantities of inorganic phosphate (Pi) in humans range from 0.8 to 1.2 mM. In plasma or serum, Pi is present in both its monovalent (H2PO4-) and divalent (HPO4-2) forms [17].

Materials and Methods

study design

The sample collation was place in the Medical City Dialysis Centre and the Iraqi Dialysis Centre, both located in the Medical City. The blood sample collection and practical activities for this study spanned from October 2022 to April 2023. The study had a total of 50 patients, including females and men, ranging in age from 20 to 69 years. (50) Control participants, whose ages ranged from 20 to 69 years, were selected to match the age of the patients. The blood sample was placed in a gel tube and allowed to coagulate at a temperature of 37 ºC for a duration of 30 minutes. Subsequently, the mixture underwent centrifugation at a speed of 4000 revolutions per minute for a duration of 10 minutes in order to isolate the serum.

Methods and Biochemical Determinations

The BioMéreux Vidas system was utilised for the analysis of PTH and 25(OH)D hormones. This method use the ELFA (Enzyme-Linked fluorescence Assay) technology, which is an immuno-enzymological technique that detects fluorescence in two stages. This method enables the visualisation of an antigen-antibody interaction by generating a coloured reaction. The reaction is facilitated by an enzyme that is linked to the antibody and acts on a substrate. The resultant analytical signal is the intensity of light that is directly proportional to the concentration of the drug being measured in the sample. Calcium and phosphorus levels were quantified using ROSCH/ (Cobas c111) using flame atomic absorption spectrophotometry (FAAS). FAAS functions by utilising the heat from a flame to separate the element from its chemical bonds, leading to the creation of unexcited or ground-state atoms.

Statistical analysis

The SAS (2018) programme was utilised to identify the impact of various factors on the research parameters through statistical analysis. The Least Significant Difference (LSD) test, which is a part of the Analysis of Variance (ANOVA), was employed to compare the means in a statistically significant manner. The chi-square test was utilised to determine the statistical significance of comparing percentages at the 0.05 and 0.01 probability levels. Estimate of Odd ratio and CI in this study [18].

Results

This study showed that the average age of the patient group was (47.24 ±1.84) years table (1), which was similar to the average age of the healthy control group (44.72 ±2.79) years. Age-matched between the patients and the control group. The lack of substantial differences indicates that the research sample is homogeneous. The biochemical parameters and clinical characteristics of kidney function from the whole CKD groups and the control group are shown in (table 2) parathyroid hormones, vitamin D3, Total calcium and phosphor were comparable between the CKD group and control group. The study showed that the mean total calcium for the patient's group was (8.54 ±0.14), and there was a highly significant decrease in the CKD group when compared with the control group ($p \leq 0.0001$) Table (2) and Figure (1).

Discussion

The present study investigated the lower calcium in CKD patients in the present study, similar to Numerous studies [20, 21]. Who found the levels of calcium in the CKD group were lower and

there is a highly significant difference between the study groups. Also, a study by[22] revealed that 55.7% of patients with CKD exhibited abnormal calcium levels. another study by [23] found that (P<0.0001) in circulating concentration of total calcium in patients (8.06±0.18 mg/dL) as compared to controls (10.15±0.23 mg/dL). As CKD advances, calcium levels tend to decrease, and there is an increased reliance on a positive gradient to maintain a neutral camouflage in intestinal calcium absorption. This is because calcium can be absorbed and lost across the gastrointestinal tract. As shown in Table (2) and Figure (2), phosphorus level was highly significant ($p \leq 0.0001$) increase in patients (5.64 ±0.18 mg/dl) with CKD in comparison with control group(3.79 ±0.11 mg/dl) This result agrees with [24], in Karbala city found that a significant increase (P<0.05) in concentrations of phosphorus level in kidney failure groups when compared with healthy people and study by [25] in Baghdad city found that phosphorus level was highly significant ($p \leq 0.01$) increase in patients (4.69 ± 0.12 mg\dl) with CKD in compare with control group (3.85 ± 0.07 mg\dl).

A study by [26], examined serum phosphate levels and associated factors in individuals with CKD. The findings demonstrated that serum phosphate levels in American CKD patients (CRIC) were markedly elevated compared to those in Chronic Kidney Disease-Japan (CKD-JAC) patients, irrespective of the stage of CKD. This discovery implies that there could be differences in phosphate measurements across different countries, which in turn may result in changes in cardiovascular risk among individuals with CKD.

The level of PTH showed a highly significant (($p \leq 0.0001$) increase in patients with CKD (695.92 ±49.36 pg/ml) in comparison with controls (31.96 ±1.74 pg/ml), as shown in table (2) and figure (3). PTH levels were elevated in CKD patients. These findings are compatible with [22, 25, 27], who found higher evolution PTH among CKD patients and control PTH has proved valuable as a marker of CKD and is frequently assayed for this reason [28]. When the calcium level drops, the parathyroid gland releases PTH, which increases calcium reabsorption in the collection duct, distal convoluted tube, and ascending loop of Henley. Additionally, the PTH enhances the kidneys' production of vitamin D3, which promotes calcium absorption through the intestine. Osteoclasts that take part in the release and reabsorption of free calcium are activated by PTH [29. 30]. Table (2) and figure (4) showed a highly significant decrease in vitD3 levels($p \leq 0.0001$) in patients with CKD (11.98 ±0.79 mg/dl) compared with a control group (20.38 ±2.31 mg/dl). This study agrees with Numerous studies [31], which found that vitD3 level was significantly lower in CKD groups. According to [32], 97% of hemodialysis patients had insufficient levels of VitD3, [33], , showing that patients undergoing chronic hemodialysis lack vitD3, and only 4% had a level within the range considered normal by the KDOQI guidelines. Furthermore , study by [34], has substantiated that Vitamin D plays a crucial role in regulating calcium and phosphate balance inside the body .a study by [35] found that (97.33%) of ckd patient have vit D deficiency and (2.33%) of patient were normal Additionally, it exerts various impacts on the cardiovascular system, central nervous system, endocrine system, immunological system, and cellular differentiation and proliferation, extending beyond its effect on bone health. The primary factor is a decrease in the production of 1,25-dihydroxyvitamin D in the kidney, which directly stimulates the release of parathyroid

hormone (PTH) and also indirectly affects the absorption of calcium in the intestines. Furthermore, there is a decrease in calcium release from the bone because the bone becomes less responsive to parathyroid hormone (PTH) when there is a shortage of calcitriol[16, 36].

Table 1: Comparison between study group in age

Group	**No**	**Mean ±SE of Age (year)**
Control	50	44.72 ±2.79
CDK	50	47.24 ±1.84
LSD value	---	6.773 NS
P-value	---	0.613
NS: Non-Significant.		

Table 2: Characteristics of study subject

Variable	**CKD Mean ± SE**	**Control Mean ± SE**	**LSD value**	**P-value**
Age	47.24 ±1.84	44.72 ±2.79	6.773 NS	0.613
PTH (pg/ml)	695.92±49.36	31.96±1.74	127.31 **	0.0001
Vit.D_3(mg/dl)	11.98 ±0.79	29.38 ±2.31	4.236 **	0.0001
Ca (mg/dl)	8.34 ±0.14 b	9.59 ±0.10 a	0.435 **	0.0001
PO_4 (mg/dl)	5.64 ±0.18 a	3.79 ±0.11a	0.584 **	0.0001

Means having with the different letters in same column differed significantly, * (P≤0.05), ** (P≤0.01).

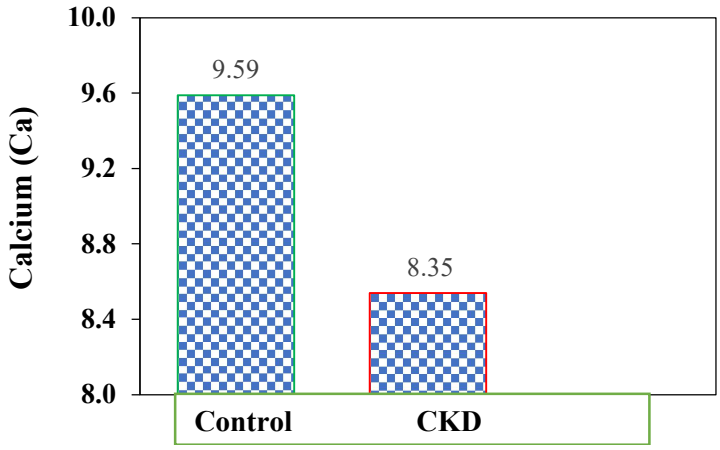

Figure 1: Comparison between patient and control group in CA

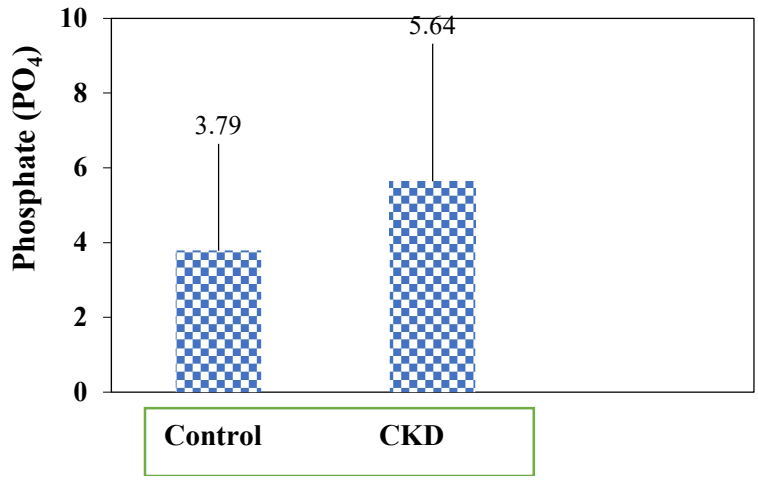

Figure 2: Comparison between patient and control group in PO_4

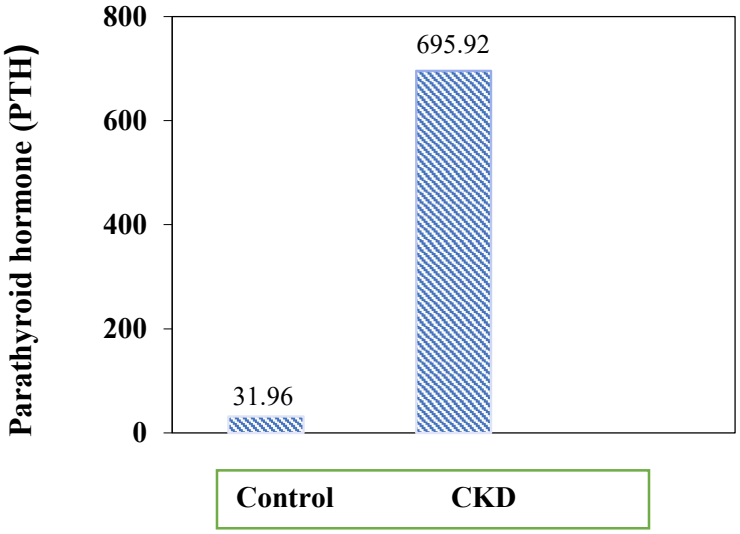

Figure 3: Comparison between patient and control group in PTH

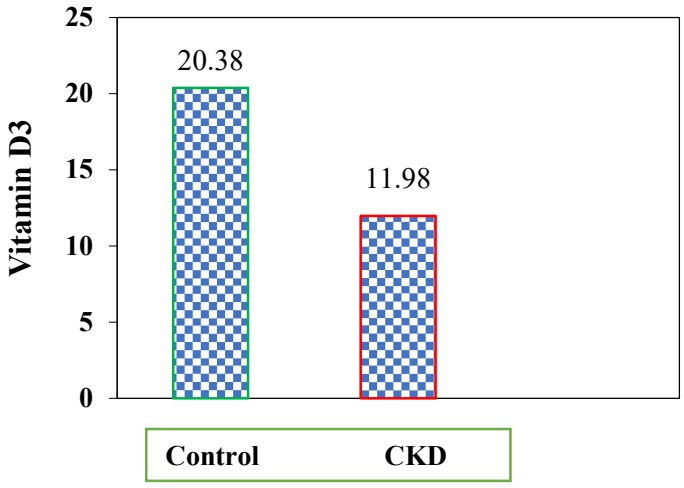

Figure 4: Comparison between patient and control group in D3

Conclusions:

PTH and phosphorus had a linear, statistically significant association. And there was no statistically significant association between calcium and PTH, in CKD patients, A problem with vitamin D activation in the kidneys causes hypocalcemia and hyperphosphatemia.

Reference

1. Du B, Yu M, Zheng J. Transport and interactions of nanoparticles in the kidneys. Nature Reviews Materials. 2018;3(10):358-74.
2. Wei W, Zhao Y, Zhang Y, Jin H, Shou S. The role of IL-10 in kidney disease. International Immunopharmacology. 2022;108:1089.17
3. Romagnani P, Remuzzi G, Glassock R, Levin A, Jager KJ, Tonelli M, et al. Chronic kidney disease. Nature reviews Disease primers. 2017;3(1):1-24.
4. Maranduca MA, Clim A, Pinzariu AC, Statescu C, Sascau RA, Tanase DM, et al. Role of arterial hypertension and angiotensin II in chronic kidney disease. Experimental and Therapeutic Medicine. 2023;25(4):1-5.
5. Gonçalves LED, Andrade-Silva M, Basso PJ, Câmara NO. Vitamin D and chronic kidney disease: Insights on lipid metabolism of tubular epithelial cell and macrophages in tubulointerstitial fibrosis. Frontiers in Physiology. 2023;14:499.
6.. Al-Taiee, T. A. K., and Al-Shammaa, N. M. (2018). Effect of Anti Diuretic Hormon (ADH) in Kidney Function on Post Hemodialysis End Stage Renal Failure Disease (ESRD) Iraqi Patients. *Iraqi Journal of Science*, 1372-1377.
7. Albayati, A. S., and Al Jowari, S. A. (2023). Comparison of Allele Frequency of Uromodulin Gene rs13333226 and rs13333144 in a Sample of Iraqi Patients on Dialysis. *Iraqi Journal of Science*, 536-545.
8. Hakami Y, Khan A. Hypoparathyroidism. Parathyroid Disorders. 2019;51:109-26.
9. Sachan S, Moya CG, Voigt B, Köhn M, Balbach J. The pro-sequence of parathyroid hormone prevents premature amyloid fibril formation. FEBS letters. 2023;597(7):995-1006.
.10 Rodríguez-Ortiz ME, Rodríguez M. Recent advances in understanding and managing secondary hyperparathyroidism in chronic kidney disease. F1000Research. 2020;9.
11. Muppidi V, Meegada SR, Rehman A. Secondary hyperparathyroidism. 2020.
12. Alexander RT, Dimke H. Effects of parathyroid hormone on renal tubular calcium and phosphate handling. Acta Physiologica. 2023;238(1):e13959.
13. Ranieri M. Renal Ca2+ and water handling in response to calcium sensing receptor signaling: Physiopathological aspects and role of CaSR-regulated microRNAs. International Journal of Molecular Sciences. 2019;20(21):5341.
14. Portillo MR, Rodríguez-Ortiz ME. Secondary hyperparthyroidism: pathogenesis, diagnosis, preventive and therapeutic strategies. Reviews in Endocrine and Metabolic Disorders. 2017;18:79-95.
15. Vakiti A, Anastasopoulou C, Mewawalla P. Malignancy-related hypercalcemia. 2018.
16. Cunningham J, Locatelli F, Rodriguez M. Secondary hyperparathyroidism: pathogenesis,

disease progression, and therapeutic options. Clinical Journal of the American Society of Nephrology. 2011;6(4):913-21.
17. Hernando N, Gagnon K, Lederer E. Phosphate transport in epithelial and nonepithelial tissue. Physiological reviews. 2021;101(1):1-35.
18. Jacquillet G, Unwin RJ. Physiological regulation of phosphate by vitamin D, parathyroid hormone (PTH) and phosphate (Pi). Pflügers Archiv-European Journal of Physiology. 2019;471:83-98.
19. SAS S. Statistical Analysis System, User's Guide. Statistical. Version 9. SAS Inst Inc Cary NC USA. 2012.
20. Hruska KA, Sugatani T, Agapova O ,Fang Y. The chronic kidney disease—Mineral bone disorder (CKD-MBD): Advances in pathophysiology. Bone. 2017;100:80-6.
21. Meri MA, Al-Hakeem AH, Al-Abeadi RS, Mahdi DM. Study of the changes of some biochemical parameters of patients with renal failure. Bulletin of National Institute of Health Sciences. 2022;140(3):2925-33.
22. Kumar S, Jha PR, Bavishi N, Pathak KJ. Study of evaluation and correlation of calcium and phosphorus in chronic kidney disease with reference to parathyroid hormone. 2020.
23. Balaky, H. M., Mustafa, A. J., and Ismail, P. A. (2023). Clinical significance of Osteoprotegerin, Vitamin D, Obestatin and some biochemical variables in Kidney failure Patients. *Iraqi Journal of Pharmaceutical Sciences (P-ISSN 1683-3597 E-ISSN 2521-3512)*, *32*(1): 59-66.
24. Alsaedi ANN, Al-Asady HMK, Najm TA, AL-Nasrawi WS, editors. Study of some physiological and biochemical parameters in patients with chronic renal failure in Holy Karbala. AIP Conference Proceedings; 2023: AIP Publishing.
25 Salih, S. S., and Yenzeel, J. H. (2020). Evaluation of Thyroid Hormones and Some Biochemical Variables in Patients with Chronic Kidney Disease. *Iraqi Journal of Science*, 985-992..
26. Fujii N, Hamano T, Hsu JY, Imai E, Akizawa T, Nitta K, et al. A comparative study of serum phosphate and related parameters in chronic kidney disease between the USA and Japan. American journal of nephrology. 2022;53(2-3):226-39.
27. Shardlow A, McIntyre NJ, Fluck RJ, McIntyre CW, Taal MW. Associations of fibroblast growth factor 23, vitamin D and parathyroid hormone with 5-year outcomes in a prospective primary care cohort of people with chronic kidney disease stage 3. BMJ open. 2017;7(8):e016528.
28. Nwosu IF, Ibeson CE, Olawoye A, Kyaw H, Kumar K, Odigwe C, et al. Interpretation of Parathyroid Hormone Levels in Renal Impairment. Cureus. 2022;14(6.(
29. Yu E, Sharma S. Physiology, calcium. 2018.
30. Spiardi R, Geara AS. Normal Regulation of Serum Calcium. Hypercalcemia: Clinical Diagnosis and Management. 2022:1-17.
31. Jouda J, Ibrahim RK, Herez MS. Vitamin D 3, parathyroid hormones, and calcium levels in patients with hypothyroidism and chronic kidney disease and the relationship between them. EurAsian Journal of Biosciences. 2020;14(1.(

32. González EA, Sachdeva A, Oliver DA, Martin KJ. Vitamin D Insufficiency and Deficiency in Chronic Kidney DiseaseA Single Center Observational Study. American journal of nephrology. 2004;24(5):503-10.
33. Marinelli AM, Pistolesi V, Rossi V, Battista M, Buono A, Della F. Deficit severo di 25-OH Vitamina D in emodialisi cronica. G Ital Nefrol. 2014;31(5):1724-5590.
34. Bouillon R. Extra-skeletal effects of vitamin D. Vitamin D in Clinical Medicine. 2018;50:72-88
35. Mohamed, S. H., Athab, A. M., mohammed Ali, N. K., and Latif, I. I. (2019). Mineral Derangement and Bone Diseases in Uremic Patients on hemodialysis in Ibn-Sina Hemodialysis Center/Diyala. *Diyala Journal of Medicine*, *17*(1), 60-76.
36. Mohammed, A., & Patil, D.H. (2018). A Study on Correlation Between Serum Creatinine, Estimated Glomerular Filtration Rate (EGFR), Calcium, Phosphorus, Uric Acid, Vitamin D , Parathyroid Hormone, and Alkaline Phosphatase in Patients with Chronic Kidney Disease.

