ISSN: 0067-2904

Influence of Phosphatidyl Inositol (4,5) Bisphosphate,5-Phosphatase (PIP2), in Patients With Kidney Stones and Renal Failure

Shatha Shakir Ahmed, Luma Hassan Alwan Al Obaidy*
Department of Biology, College of Science for Women, University of Baghdad, Baghdad, Iraq

Received: 4/2/2025 Accepted: 27/5/2025 Published: 30/5/2026

Abstract

Phosphatidylinositol 4,5-bisphosphate (PIP2) is an essential lipid involved in metabolic processes. It is integral to the cell membrane of all animal and plant cells and acts as a second messenger in various signaling pathways. Still, its hydrolysis can lead to increased calcium levels and kidney stones. The study aims to investigate the role of PIP2 enzyme levels in patients with renal failure and kidney stones. The enzyme-produced amount was measured by enzyme-linked immunosorbent assay (ELISA). Peripheral whole-blood samples were collected in gel tubes from eighty patients (40 with kidney stones and 40 with renal failure), and 40 were healthy individuals. The results of urea, creatinine, and uric acid levels were significantly different between renal failure patients (140.35±41.45, 8.70±3.22, 8.43±1.47) and the control group (27.07±7.21, 0.70±0.26, 4.53±0.94), with a *p*-value of 0.001. Uric acid levels in kidney stone patients were also significant (6.30±1.39) with a *p*-value of 0.001. The findings revealed significant differences in PIP2 levels among patients with kidney stones (6.63±1.40) and renal failure (9.13±1.76) compared to the control group (1.87±0.94), with *p*-values of 0.001 and 0.02, respectively. Serum Ca^{2+} levels also showed significant differences (9.55±1.63, 8.19±1.11) compared to the control group (9.47±0.28) with *p*-values of 0.94 and 0.001, respectively. To confirm the results of the *p*-value. Effect Size (Cohen's d) was conducted, and confidence intervals (95% CI) were calculated for all parameters, and the results were consistent with the *p*-value. This study demonstrated that PIP2 and vitamin D3 play distinct roles in Ca^{2+} homeostasis, underscoring their potential role in disease pathology.

Keywords: Calcium; Kidney Stone; Renal Failure; PIP2; Vitamin D3.

تأثير فوسفاتيديل إينوسيتول (4,5) ثنائي الفوسفات، 5-فوسفاتيز(PIP2) في مرضى حصوات الكلى والفشل الكلوي

شذى شاكر أحمد، لمى حسن علوان العبيدي*
قسم علوم الحياة، كلية العلوم للبنات، جامعة بغداد، بغداد-العراق

الخلاصة:

فوسفاتيديلينوسيتول 4،5-ثنائي الفوسفات (PIP2) هو احد الدهون الأساسية التي تشارك في العمليات الأيضية. وهو جزء لا يتجزأ من الغشاء الخلوي لجميع الخلايا الحيوانية والنباتية، ويعمل كناقل ثانوي في مسارات الإشارات المختلفة. ومع ذلك، يمكن أن يؤدي تحلله المائي إلى ارتفاع مستويات الكالسيوم وتكوين حصوات الكلى. تهدف الدراسة إلى دراسة دور مستويات إنزيم PIP2 لدى مرضى الفشل الكلوي وحصوات

*Email: lumaha-bio@csw.uobaghdad.edu.iq

الكلى. قُيست الكمية المنتجة بواسطة الإنزيم باستخدام اختبار الممتز المناعي المرتبط بالإنزيم(ELISA) جُمعت عينات دم كامل محيطية في أنابيب هلامية من ثمانين مريضًا (40 منهم مصابون بحصوات الكلى و40 مصابون بالفشل الكلوي)، وكان 40 فرداً أصحاء. أظهرت نتائج مستويات اليوريا والكرياتينين وحمض اليوريك اختلافًا كبيرًا بين مرضى الفشل الكلوي (140.35±41.45، 8.70±3.22، 8.43±1.47) ومجموعة الاصحاء (27.07±7.21، 0.70±0.26، 4.53±0.94)، بقيمة احتمالية 0.001. كما أظهرت مستويات حمض اليوريك لدى مرضى حصوات الكلى اختلافًا كبيرًا (6.30±1.39) بقيمة احتمالية 0.001. وكشفت النتائج عن اختلافات كبيرة في مستويات PIP2 بين مرضى حصوات الكلى (6.63±1.40) والفشل الكلوي (9.13±1.76) مقارنةً بمجموعة الاصحاء(1.87±0.94)، بقيمة احتمالية 0.001 و0.02 على التوالي. أظهرت مستويات Ca^{2+} في المصل فروقًا معنوية (9.55±1.63، 8.19±1.11) مقارنةً بمجموعة الاصحاء (9.47±0.28)، حيث بلغت قيم 0,94p و0.001 على التوالي. ولتأكيد نتائج قيمة p. تم تحديد حجم التأثير (كوهين د)، وحُسبت فترات الثقة (95% CI) لجميع الاختبارات، وكانت النتائج متوافقة مع القيمة الاحتمالية. أظهرت هذه الدراسة أن PIP2 وفيتامين D3 يلعبان أدوارًا مميزة في توازن الكالسيوم، مما يؤكد دورهما المحتمل في إحداث المرض.

1. Introduction

Phosphatidylinositol (4,5)-bisphosphate (PIP2) and phosphatidylinositol (3,4,5)-trisphosphate (PIP3) constitute less than 1% of membrane phospholipids. They regulate a broad spectrum of biological processes, including membrane signal transduction, endocytosis, exocytosis, remodeling of the cytoskeleton, and ion channel regulation [1]. The IP3 and its receptors (IP3Rs) are expressed in nearly all animal cells in a tissue-specific manner to regulate intracellular calcium (Ca^{2+}) release from the endoplasmic reticulum, governing specific cell functions such as muscle contraction, neurotransmitter release, and glucose metabolism [2,3].

Kidney Disease: Improving Global Outcomes (KDIGO) defines chronic kidney disease (CKD) as abnormalities in kidney structure or function that have been present for at least three months and impact a person's health. CKD is categorized according to its cause: Albuminuria is classified as (A1–A3), and glomerular filtration rate (GFR) is classified as (G1–G5) and abbreviated as (CGA) [4]. Prolonged CKD is marked by impaired kidney function, leads to the accumulation of toxic substances in the body, and poses significant global health challenges. Contributing factors include hypertension, diabetes mellitus [5-7], and obstructive kidney stones, which may progress to renal failure if untreated [8]. Beyond their filtration role, kidneys are integral to vitamin D3 metabolism, converting it to its active form, calcitriol, essential for Ca^{2+} absorption [9]. Insufficient vitamin D_3 impairs Ca^{2+} absorption, leading to low serum Ca^{2+} levels and increased urinary Ca^{2+} salt supersaturation, predisposing individuals to kidney stone formation. The resulting secondary hyperparathyroidism, driven by elevated parathyroid hormone (PTH) levels, exacerbates bone demineralization and associated bone disorders in renal failure patients.

Central to the regulation of Ca^{2+} homeostasis is the Phosphoinositide 3-Kinase (PI3K)/Akt cascade, involving the enzyme Phosphatidylinositol (4,5)-Bisphosphate 5-Phosphatase (PIP2), encoded by the Oculocerebrorenal syndrome of Lowe (OCRL) gene [10,11]. Mutations in this gene, initially linked to Lowe syndrome, affect ocular, neurological, and renal systems [12]. PIP2, the most abundant member of the phosphoinositide family, is characterized by a distinctive inositol head group enabling reversible phosphorylation, generating seven unique phosphorylated derivatives [13].

PIP2's critical cellular roles include modulating adhesion, motility, membrane fluidity, and ion channel regulation, particularly in Ca^{2+} signaling [14,15]. Hydrolyzed by phospholipase C (PLC), PIP2 generates diacylglycerol (DAG) and inositol triphosphate (IP3), the latter elevating cytosolic Ca^{2+} levels via endoplasmic reticulum release. If inadequately regulated,

persistent Ca^{2+} elevation may lead to urinary supersaturation and kidney stone formation [15]. Dysregulation of this pathway contributes to metabolic and cellular dysfunctions characteristic of renal failure. This study aims to investigate the PIP2 levels and their influence on vitamin D3 and Ca^{2+} balance in patients with recurrent kidney stones and end-stage chronic kidney disease (ESCKD).

2. Subjects and Methods

2.1 Sampling

The study aimed to evaluate the PIP2, vitamin D3, and calcium levels in patients suffering from recurrent kidney stones and end-stage kidney failure (G5) and with a GFR of less than 15 ml/min per 1.73 m^2. To minimize the variation among patients [3]. Samples were obtained from 80 patients 40 were diagnosed with recurrent kidney stones, distributed among 24 males and 16 females (20-66) years old, and 40 patients were diagnosed with end-stage kidney failure, also distributed among 28 males and 12 females between (5-66) years old, and 40 healthy individuals (20 males and 20 females) between (5-67) years old. These samples were taken from patients who visit the following hospitals in Baghdad: Baghdad Teaching Hospital-Iraqi Dialysis Center, Abu Ghraib General Hospital/Al-Mustafa Kidney Dialysis Center, Al Karama Teaching Hospital, Al-Imam Al-Kazemin Medical City Hospital/ Al-Jawadin Dialysis Center, Yarmouk Teaching Hospital/ Al-Shifa Dialysis Center. The diagnosis was performed by specialist physicians in the Dialysis Unit in the hospitals mentioned above. The control group comprised 40 healthy individuals, 20 males and 20 females aged 5 to 67. The data collection period spanned from November 2023 to March 2024. Both patients and control participants were subjected to kidney ultrasound and X-ray to confirm the presence or absence of kidney stones. General urine examination and biochemical analysis for renal function investigation were performed for patients and control participants as a routine hospital investigation. The kidney stones were collected from the patients and subjected to semi-quantitative colorimetric analysis [16]. Data not shown in this study.

2.2 Excluded Criteria

The exclusion criteria were patients who were diagnosed with autoimmune disorders, diabetes, hypertension, thalassemia, hemophilia, HIV, hepatitis B and C, or coronavirus, and none of the participants had cancer or underwent radiation therapy or chemotherapy. Individuals who experienced severe bleeding, kidney-related accidents, or kidney impairment as a result of receiving lengthy treatment were also excluded. The participants provided consent through a questionnaire and were registered with the Iraqi Ministry of Health. The questionnaire included age, sex, diet, smoking, and family history.

2.3 General urine examinations

Urine samples (10-30 mL) were collected from patients and control participants. The samples were subjected to macroscopic examination including (the color, oder, specific gravity, pH, albumin, and glucose), then 10 mL was centrifuged at 1500 rpm for 10 minutes of each, were subjected to microscopic examination including (lymphocyte count, RBC count, epithelial cells count, crystals types and cast), [17], the results are not shown in this study.

2.4 Blood Sample Processing

Peripheral whole-blood samples were collected in gel tubes and allowed to clot for 15–20 minutes. The samples were centrifuged at 4000 rpm for 10 minutes to separate the serum. The serum was transferred to clean, sterile Eppendorf tubes and stored at -20 °C until analysis.

2.5 Enzyme Assay

The concentration of the Phosphatidylinositol (4,5) Bisphosphate, 5-phosphatase (PIP2) enzyme was quantified using the Enzyme-Linked Immunosorbent Assay (ELISA) technique, following the manufacturer's instructions (Sun Long, China). Absorbance (O.D.) was measured at 450 nm using a Microtiter Plate Reader (Human, USA) with a sensitivity of 0.06 ng/mL and a detection range of 0.3–20 ng/mL.

2.6 Biochemical Analysis for kidney functions, calcium, and vitamin D_3

This included investigating serum uric acid, urea, and creatinine in hospital laboratories for both patient and control participants. Additionally, serum vitamin D3 (Elecsys® Vitamin D total III, Roche Diagnostic, Ref. Code: 09038116190, Germany) and Ca^{2+} (Calcium Gen.2, Roche Diagnostic, Ref. Code: 05061504190, Germany) levels were measured using a biochemical automated analyzer (Cobas e411, Roch Diagnostics, Germany) according to the manufacturer's instructions.

2.7 Statistical analysis

Statistical analyses were conducted using OriginPro (2024, USA) software. The effect of various factors on study parameters was assessed through descriptive statistics, tests of normality (Shapiro-Wilk), and tests of equality of variances (Levene's), within the framework of Analysis of Variance (ANOVA), to determine statistical differences. A chi-square test was applied to compare percentages between groups. Statistically significant differences were determined at p-values < 0.05 and 0.01.

3. Results:

The distribution of samples according to sex was studied in the control and patient groups. The kidney stone patients group included 24 (60%) males and 16 (40%) females, and the renal failure patients group also included 28 (70%) males and 12 (30%) females. The healthy group registered in this study was 20 (50%) males and 20 (50%) females, as shown in Figure 1.

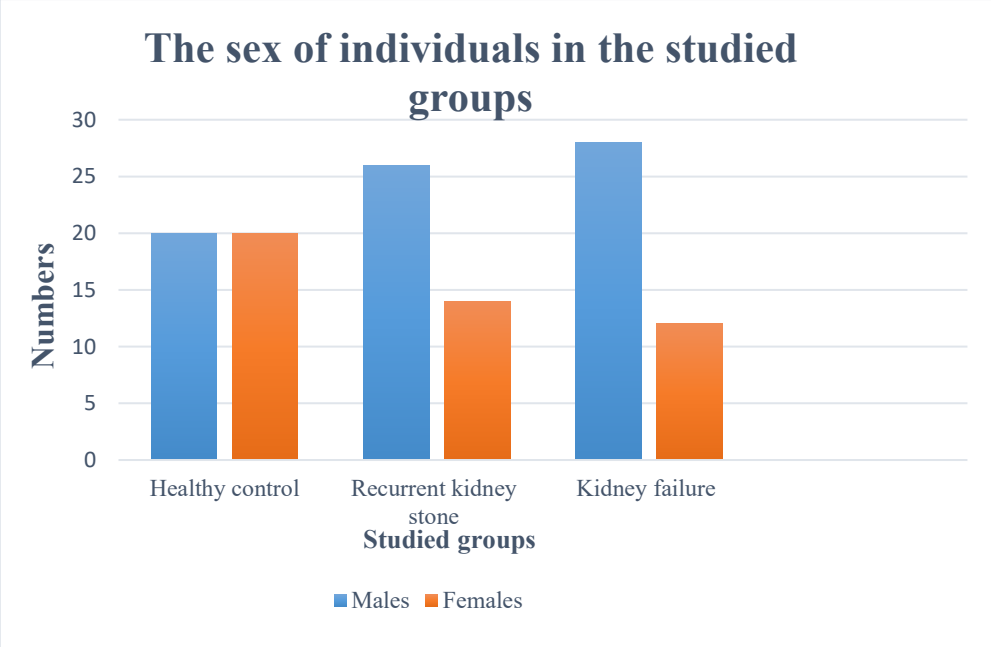

Figure 1: The sex on individuals in the studied groups.

The distribution of samples according to age was divided into 4 age groups: 1-19, 20-39, 40-59, and 60-79 years old. The highest prevalence of kidney stones was 19 patients (47.5%) in the age group (40-59) years old, while the highest prevalence of renal failure was 21 (52.5%) in the age group (1-19) years old, compared with the ages of the control group, as explained in Figure 2.

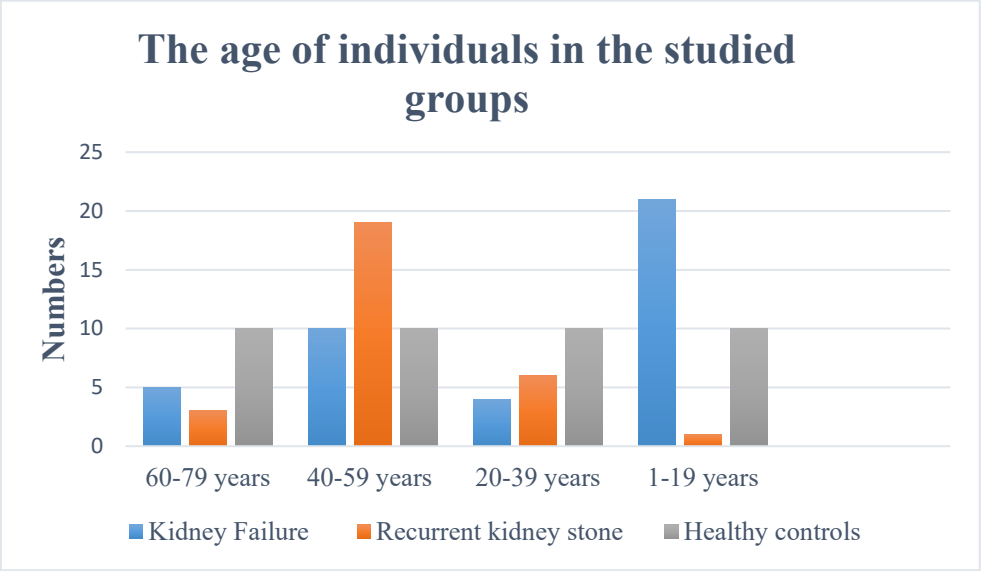

Figure 2: The age of the individuals in the studied groups.

3.1 Kidney function tests

The results show no significant difference in serum urea and creatinine levels between kidney stone patients (33.04±11.42, 0.99±0.61) and the control group (27.07±7.21, 0.70±0.26), with *p*-values of 0.54 and 0.77, respectively. Still, as Table 1 shows, uric acid levels significantly increased in kidney stone patients (6.30 ± 1.39) compared to the control group (4.53±0.94) ($p = 0.001$).

There were significant increases in serum urea, creatinine, and uric acid levels in the renal failure patient group (140.35±41.45, 8.70±3.22, 8.43±1.47) when compared to the control group (27.07±7.21, 0.70±0.26, 4.53±0.94), with $p = 0.001$, as shown in Figures 3,4, and 5, respectively.

To confirm the results of the *P*-value, Cohen's difference test was conducted, and confidence intervals (95% CI) were calculated for these tests, and the results were consistent with the *P*-value, as shown in Table 1.

Table 1: Comparison of renal function tests (mg/dL) among the study groups.

Renal Function Tests (mg/dl)	Groups	Mean ± SD	Comparison Between Groups		95% CI for Cohen's d Lower	Upper	Cohen's d	*P*-value
Urea	Control	27.07 ± 7.21	Control [a]	Kidney stone [a]	-0.78	0.31	-0.24	**0.54 N.S.**
	Kidney stone	33.05 ± 11.42		Kidney failure [b]	-5.4	-3.6	-4.5	**< 0.001*** **
	Kidney Failure	140.36 ±41.45	Kidney stone [b]	Kidney failure [b]	3.4	5.13	4.26	**< 0.001*** **
Creatinine	Control	0.70 ± 0.26	Control [a]	Kidney stone [a]	-0.7	0.39	-0.15	**0.77 N.S.**
	Kidney stone	0.99 ± 0.61		Kidney failure [b]	-5.08	-3.36	-4.22	**< 0.001*** **
	Kidney Failure	8.70 ± 3.22	Kidney stone [b]	Kidney failure [b]	3.22	4.91	4.07	**< 0.001*** **
Uric Acid	Control	4.53 ± 0.94	Control [a]	Kidney stone [c]	-1.96	-0.79	-1.38	**< 0.001*** **
	Kidney stone	6.30 ± 1.39		Kidney failure [b]	-3.75	-2.3	-3.03	**< 0.001*** **
	Kidney Failure	8.43 ± 1.47	Kidney stone [c]	Kidney failure [b]	1.05	2.25	1.65	**< 0.001*** **

Different letters indicate significant differences; similar letters indicate no significance, $P < 0.001^{***}$ Significant**,** N.S. =(Non-significant).

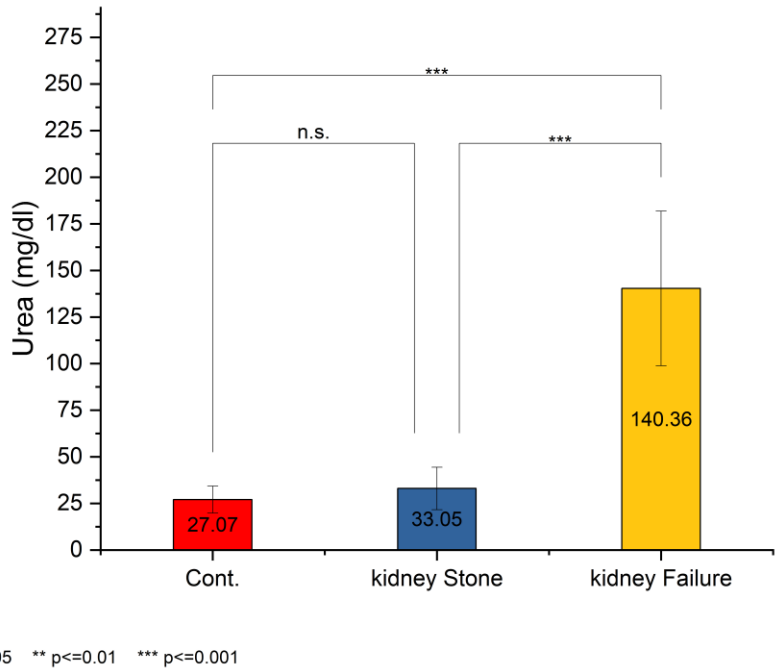

Figure 3: Comparison of serum urea levels (mg/dl) among the study groups.

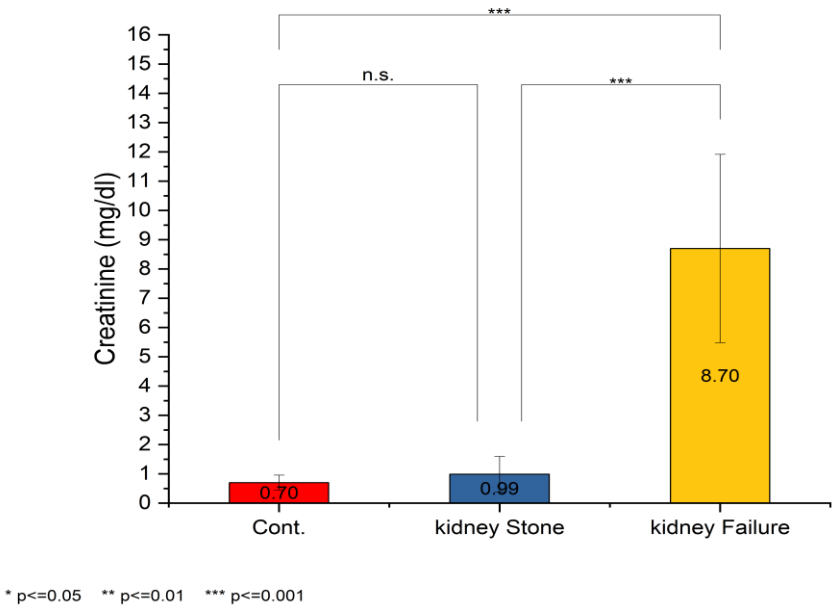

Figure 4: Comparison of serum creatinine levels (mg/dl) among the study groups.

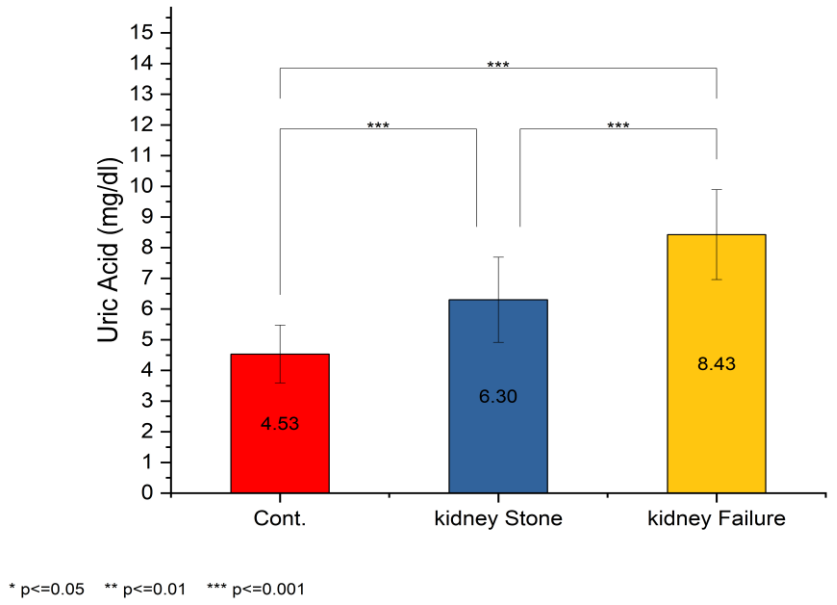

Figure 5: Comparison of serum uric acid levels (mg/dl) among the study groups.

3.2 Measurement of calcium, vitamin D3, and PIP2 enzyme concentration in patients' serum

There was a significant increase in serum Ca^{2+} levels in kidney stone patients (9.55±1.63) and renal failure patients (8.19±1.11) compared to the control group (9.47±0.28), with *p*-values of 0.94 and 0.001, respectively.

It was found that serum vitamin D3 decreased more in renal failure patients (12.65±5.56) than in kidney stone patients (16.88±5.15) and the control group (19.69±5.72); however, this was not significant, as shown in Table 2.

Additionally, serum PIP2 levels in kidney stone patients (6.63±1.40) and renal failure patients (9.13±1.76) were significantly higher than those in the control group (1.87±0.94), with *p*-values of 0.001, as shown in Figures 6,7, and 8, respectively. Cohen's test also confirmed the results of the *p*-value, as shown in Table 2.

Table 2: Comparison of serum calcium, vitamin D3, and PIP2 enzyme levels (mg/dl) among the study groups

Parameters (mg/dl)	Groups	Mean ± SD	Comparison Between Groups		95% CI for Cohen's d Lower Upper	Cohen's d	*P*-value
Calcium (Ca^{2+})	Control	9.47 ± 0.28	Control [a]	Kidney stone [a]	-0.62 0.47	-0.07	**0.94 N.S.**
	Kidney stone	9.55 ± 1.63		Kidney failure [b]	0.54 1.68	1.11	**< 0.001*** **
	Kidney Failure	8.19 ± 1.11	Kidney stone [b]	Kidney failure [b]	-1.76 - 0.61	-1.18	**< 0.001*** **
Vitamin D	Control	19.69 ± 5.72	Control [a]	Kidney stone [a]	-0.04 1.06	0.51	**0.06 N.S.**
	Kidney stone	16.88 ± 5.15		Kidney failure [b]	0.70 1.86	1.28	**< 0.001*** **
	Kidney Failure	12.65 ± 5.56	Kidney stone [b]	Kidney failure [b]	-1.33 - 0.21	-0.77	**< 0.001*** **
PIP2 Enzyme	Control	1.87 ± 0.94	Control [a]	Kidney stone [c]	-4.15 - 2.62	-3.38	**< 0.001*** **
	Kidney stone	6.63 ± 1.40		Kidney failure [b]	-6.14 - 4.18	-5.16	**< 0.001*** **
	Kidney Failure	9.13 ± 1.76	Kidney stone [c]	Kidney failure [b]	1.16 2.39	1.78	**< 0.001*** **

Different letters indicate significant differences, and similar letters indicate no significant differences, $P < 0.001^{***}$, highly Significant difference, N.S. (Non-significant).

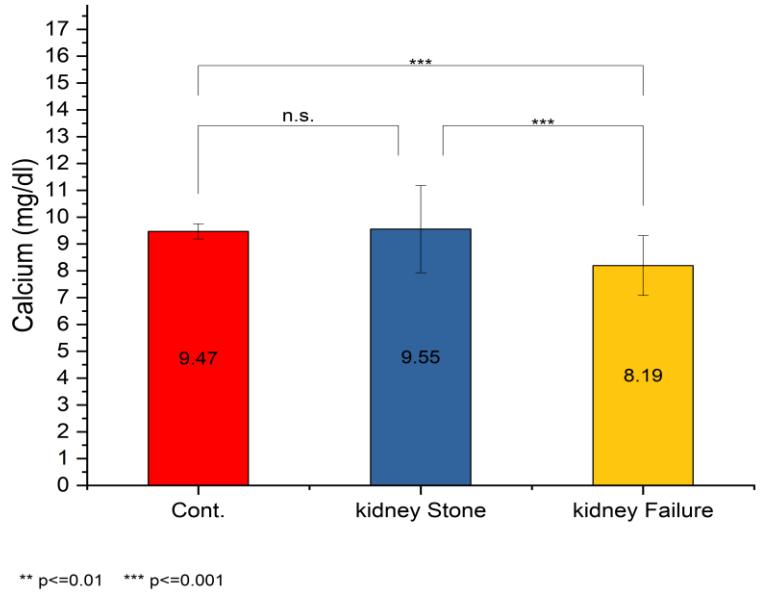

Figure 6: Comparison of serum calcium (Ca^{2+}) levels (mg/dl) among the study groups.

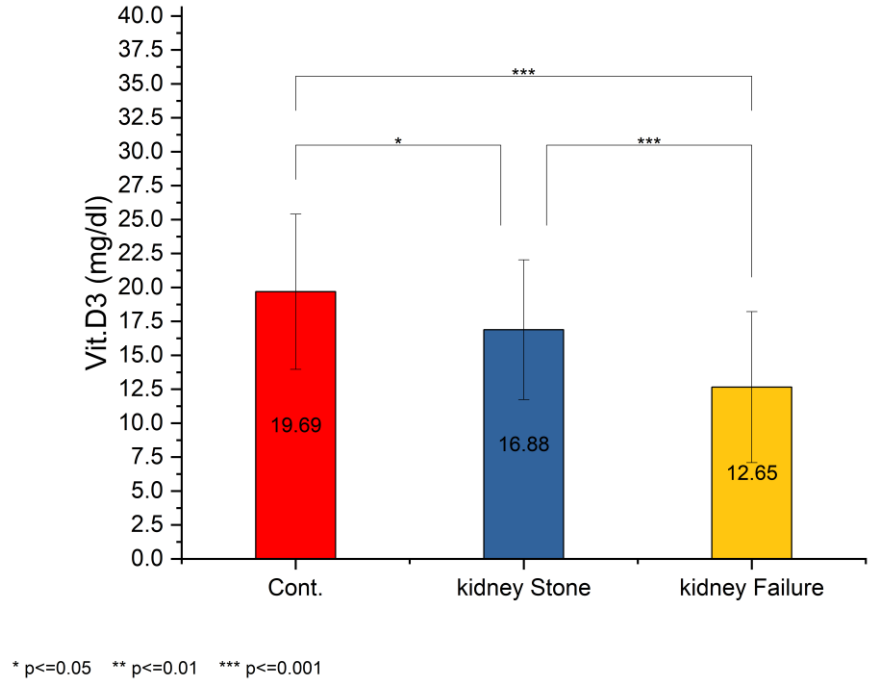

Figure 7: Comparison of serum vitamin D3 levels (mg/dl) among the study groups.

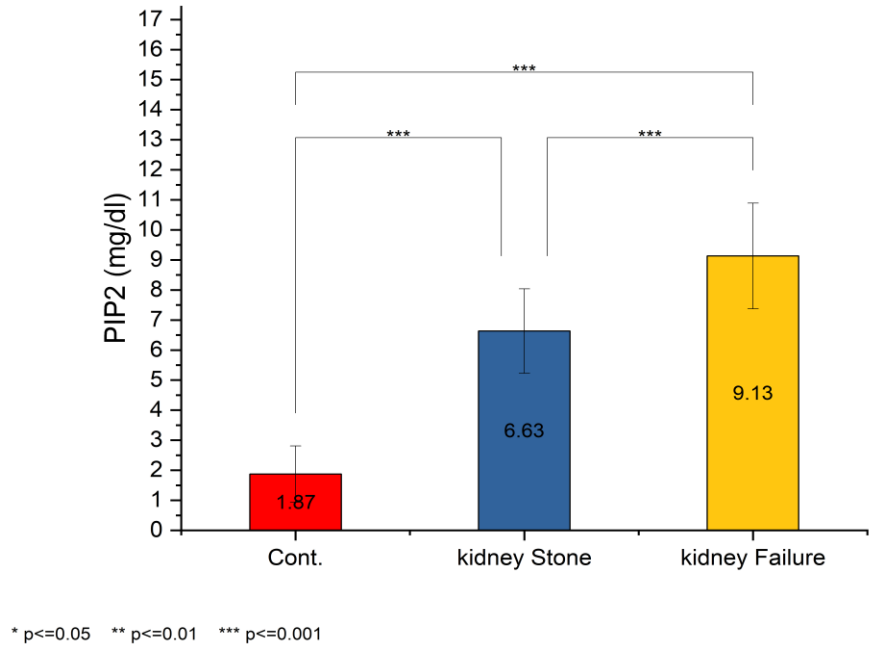

Figure 8: Comparison of serum PIP2 enzyme levels (mg/dl) among the study groups.

4. Discussion

Kidney diseases, also known as renal diseases, encompass a wide range of conditions that affect the structure and function of the kidneys and impact various age groups, particularly adults over 30. However, younger populations can also be affected, especially those with underlying risk factors such as diabetes, hypertension, or genetic predispositions.

This study included 120 participants, including 40 healthy individuals, 40 patients with renal failure, and 40 with kidney stones. According to sex, the males were the highest in both patients' groups; in kidney stones, there were 24 (60%) males, and in renal failure, there were 28 (70%) compared with 14 (40%) and 12(30%) females in both groups, respectively. Globally, it was proved that CKD is more prevalent in females than males, but mortality rates are higher in males than in females with kidney diseases [18]. In the Middle East, mortality rates are the highest in women for reasons related to socioeconomic, cultural norms, and complementary family essentialities [19].

In this study, it was found that the prevalence of renal failure in the age group 1-19 years was the highest compared with other age groups. In children and adolescents, kidney failure is related to congenital kidney disease and urinary tract, including large ranges of anomalies such as cystic/hereditary/congenital disorders, vasculitis, focal segmented glomerulosclerosis, renal hypoplasia/dysplasia, Wilms tumor, hematological anomalies, congenital obstructive uropathies, systemic lupus erythematosus and unspecified with renal failure [20].

In adults, it was believed that testosterone worsens CKD in men due to its effect on eGFR outcomes. Moreover, high serum testosterone induces cellular apoptosis and proinflammation by producing reactive oxygen species, which may cause cell damage [21]. On the other hand, estrogen may have a protective role against the deterioration of kidney parenchyma in females at reproductive age through several mechanisms, including vasodilation of kidney tubes, production of nitric acid, mitigation of inflammatory responses, and ischemia mediators. Also, estrogen protects women of reproductive age from kidney stones by increasing citrate levels and reducing urinary calcium excretion [22]. Lifestyle factors such as diet, physical activity, and substance use (e.g., smoking and alcohol) may further account for these differences, as well as genetic factors influencing kidney disease may also be differentially expressed in males and females [23]. The highest prevalence of kidney stones was detected in 47.5% of 25 patients aged 40-59 years, potentially due to increased metabolic activities that lead to elevated calcium and oxalate excretion. Age is a risk factor for kidney stones in stone-former individuals, as it was previously recognized that the incidence of kidney stones is higher in older men than in women. It's often associated with cardiovascular, bone fractures, diabetes, and chronic kidney diseases, and vice versa, and these systemic health conditions lead to kidney stones as well as metabolic disorders that affect calcium metabolism and thyroid hormone balance [24].

Blood urea, serum creatinine, and uric acid were significantly elevated compared to controls in patients with kidney stones and kidney failure, indicating impaired filtration capacity. Elevated urea levels result from reduced kidney function, while increased creatinine levels reflect decreased GFR [25,26]. The pathophysiology mechanism of CKD demonstrated that the injury in proximal tubule epithelial cells (PTECs) and the inflammatory processes due to elevated oxidative stress may be the reason behind the decline in GFR [27]. Moreover, the high uric acid levels in recurrent kidney stone patients may indicate systemic metabolism dysregulation worsened by dietary habits and lifestyle [28,29].

Vitamin D3 deficiency was observed across all groups, with the lowest levels in kidney failure patients. This deficiency impairs calcium-phosphorus homeostasis, contributing to bone demineralization and stone formation [30,31]. The PIP2 enzyme plays a crucial role in the complex network in releasing intracellular Ca^{2+} mediated by the activation of vitamin D receptor (VDR), which may explain the elevated levels of PIP2 and the decline of serum calcium in the studied patients. Although not directly linked to kidney stone formation, it may

influence ion channel activity and Ca^{2+} balance, potentially contributing to stone formation and kidney dysfunction [32,33].

5. Conclusions

This study demonstrated that PIP2 and vitamin D3 play distinct roles in Ca^{2+} homeostasis. Significant differences in PIP2 enzyme levels were observed between kidney stone and renal failure patients compared to the control group, underscoring their potential role in disease pathology.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Ethical Clearance

The Institutional Scientific Committee at the University of Baghdad approved this study (88784 on 29/11/2023) according to the Declaration of Helsinki for human studies, which is consistent with the instructions of the Iraqi Ministry of Health and Environment.

References

[1] M. Katan and S. Cockcroft, "Phosphatidylinositol (4, 5) bisphosphate: diverse functions at the plasma membrane," *Essays in biochemistry,* vol. 64, no. 3, pp. 513-531, 2020.

[2] K. A. Woll and F. Van Petegem, "Calcium-release channels: structure and function of IP3 receptors and ryanodine receptors," *Physiological Reviews,* vol. 102, no. 1, pp. 209-268, 2022.

[3] U. Ahumada-Castro, G. Bustos, E. Silva-Pavez, A. Puebla-Huerta, A. Lovy, and C. Cárdenas, "In the right place at the right time: regulation of cell metabolism by IP3R-mediated inter-organelle Ca^{2+} fluxes" *Frontiers in cell and developmental biology*, vol. 9, p. 629522, 2021.

[4] P. E. Stevens, S. B. Ahmed, J. J. Carrero, B. Foster, A. Francis, R. K. Hall, W. G. Herrington, G. Hill, L. A. Inker, and R. Kazancıoğlu, "KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease," *Kidney international,* vol. 105, no. 4, pp. S117-S314, 2024.

[5] F. Mallamaci and G. Tripepi, "Risk Factors of Chronic Kidney Disease Progression: Between Old and New Concepts," *Journal of Clinical Medicine,* vol. 13, no. 3, pp. 678, 2024.

[6] M. A. Escobar Vasco, S. H. Fantaye, S. Raghunathan, and C. Solis-Herrera, "The potential role of finerenone in patients with type 1 diabetes and chronic kidney disease," *Diabetes, Obesity and Metabolism,* vol. 26, no. 10, pp. 4135-4146, 2024.

[7] K. Balawender, E. Łuszczki, A. Mazur, and J. Wyszyńska, "The Multidisciplinary Approach in the Management of Patients with Kidney Stone Disease—A State-of-the-Art Review," *Nutrients,* vol. 16, no. 12, pp. 1932, .2024

[8] Y. D. Molla, G. M. Getahun, and M. A. Assefa, "Giant bladder stone a rare cause of renal failure, a case report," *International Journal of Surgery Case Reports,* vol. 105, pp. 108085, 2023.

[9] Q. Yuan, B. Tang, and C. Zhang, "Signaling pathways of chronic kidney diseases, implications for therapeutics," *Signal transduction and targeted therapy,* vol. 7, no. 1, pp. 182, 2022.

[10] J. H. Lee, J. Lee, and D. H. Suh, "A Case of Hidradenitis Suppurativa in a Genetically Confirmed Lowe Syndrome Patient," *Annals of Dermatology,* vol. 35, no. Suppl 2, pp. S314, 2023.

[11] H. Chen, C. Lu, Y. Tan, M. Weber-Boyvat, J. Zheng, M. Xu, J. Xiao, S. Liu, Z. Tang, and C. Lai, "Oculocerebrorenal syndrome of Lowe (OCRL) controls leukemic T-cell survival by preventing excessive PI (4, 5) P2 hydrolysis in the plasma membrane," *Journal of Biological Chemistry,* vol. 299, no. 6, 2023.

[12] L. Gianesello, D. Del Prete, F. Anglani, and L. A. Calò, "Genetics and phenotypic heterogeneity of Dent disease: the dark side of the moon," *Human genetics,* vol. 140, no. 3, pp. 401-421, 2021.

[13] K. Mandal, "Review of PIP2 in cellular signaling, functions and diseases," *International journal of molecular sciences,* vol. 21, no. 21, pp. 8342, 2020.

[14] S. Li, C. Ghosh, Y. Xing, and Y. Sun, "Phosphatidylinositol 4, 5-bisphosphate in the Control of Membrane Trafficking," *International Journal of Biological Sciences,* vol. 16, no. 15, pp. 2761, 2020.

[15] D. J. Tóth, J. T. Tóth, A. Damouni, L. Hunyady, and P. Várnai, "Effect of hormone-induced plasma membrane phosphatidylinositol-5 ,4 bisphosphate depletion on receptor endocytosis suggests the importance of local regulation in phosphoinositide signaling," *Scientific Reports,* vol. 14, no. 1, pp. 291, 2024.

[16] W. Panich, S. Nak-On, M. Sabaijai, A. Raksaman, C. Puttharugsa, T. Tejangkura, and T. Chontananarth, "Evaluation of semi-quantitative colorimetric assays based on loop-mediated isothermal amplification indicators by using image analysis," *Analytical Biochemistry,* vol. 688, pp. 115481, 2024.

[17] M. Katica, N. H. Ahmed, A. Salkić, A. Mukača, A. Bašić, and E. Dervišević, "The role of organic urine sediment analysis in the monitoring of renal diseases," *Journal of Advances in VetBio Science and Techniques,* vol. 4, no. 1, pp. 40-50, 2019.

[18] A. Francis, M. N. Harhay, A. Ong, S. L. Tummalapalli, A. Ortiz, A. B. Fogo, D. Fliser, P. Roy-Chaudhury, M. Fontana, and M. Nangaku, "Chronic kidney disease and the global public health agenda: an international consensus," *Nature Reviews Nephrology*, pp. 1-13, 2024.

[19] G. G. García, A. Iyengar, F. Kaze, C. Kierans, C. Padilla-Altamira, and V. A. Luyckx, "Sex and gender differences in chronic kidney disease and access to care around the globe." pp. 101-113, 2022.

[20] J. S. VanSickle, and B. A. Warady, "Chronic kidney disease in children," *Pediatric Clinics of North America,* vol. 69, no. 6, pp. 1239-1254, 2022.

[21] J. V. Zhao and C. M. Schooling, "The role of testosterone in chronic kidney disease and kidney function in men and women: a bi-directional Mendelian randomization study in the UK Biobank," *BMC Medicine,* vol. 18, pp. 1-10, 2020.

[22] M. Farahmand, F. Ramezani Tehrani, D. Khalili, L. Cheraghi, and F. Azizi, "Endogenous estrogen exposure and chronic kidney disease; a 15-year prospective cohort study," *BMC Endocrine Disorders,* vol. 21, pp. 1-8, 2021.

[23] D. A. A. M. Alzubaidy and L. H. A. Al Obaidy, "GRHPR gene variations in Iraqi patients infected with calcium oxalate kidney stones," *Baghdad Science Journal*, vol 21, no. 8, pp. 2531-2550, 2024.

[24] L. Moftakhar, F. Jafari, M. Ghoddusi Johari, R. Rezaeianzadeh, S. V. Hosseini, and A. Rezaianzadeh, "Prevalence and risk factors of kidney stone disease in population aged 40–70 years old in Kharameh cohort study: a cross-sectional population-based study in southern Iran," *BMC urology,* vol. 22, no. 1, pp. 205, 2022.

[25] H. T AL-Ani, and M. Q. Al-Lami, "Evaluation of some Biochemical and Hematological Parameters in Patients with Chronic Kidney Disease," *Journal of the Faculty of Medicine Baghdad,* vol. 66, no. 2, pp. 154-161, 2024.

[26] L. Muglia, M. Di Dio, E. Filicetti, G. I. Greco, M. Volpentesta, A. Beccacece, P. Fabbietti, F. Lattanzio, A. Corsonello, and G. Gembillo, "Biomarkers of chronic kidney disease in older individuals: navigating complexity in diagnosis," *Frontiers in Medicine,* vol. 11, pp. 1397160, 2024.

[27] S. Lopez-Giacoman and M. Madero, "Biomarkers in chronic kidney disease, from kidney function to kidney damage," *World journal of nephrology,* vol. 4, no. 1, pp. 57, 2015.

[28] N. R. Silva, C. E. T. Gonçalves, D. L. N. Gonçalves, R. M. M. Cotta, and L. S. da Silva, "Association of uric acid and uric acid to creatinine ratio with chronic kidney disease in hypertensive patients," *BMC nephrology,* vol. 22, pp. 1-8, 2021.

[29] S. S. Salih and J. H. Yenzeel, "Evaluation of thyroid hormones and some biochemical variables in patients with chronic kidney disease," *Iraqi Journal of Science*, vol.61, no.5, pp. 985-992, 2020.

[30] R. H. Hamid and R. M. K. AL-Jumaily, "Immunological Role of IL-3, IL-22 and Some Physiological Markers in Iraqi Patients with Chronic Kidney Disease," *Ibn AL-Haitham Journal For Pure and Applied Sciences,* vol. 37, no. 3, pp. 42-49, 2024.

[31] M. Mehta and D. S. Goldfarb, "Vitamin D and kidney stones," *Feldman and Pike's Vitamin D*, pp. 619-624: Elsevier, 2024.

[32] M. Ningoo, L. D. Plant, A. Greka, and D. E. Logothetis, "PIP2 regulation of TRPC5 channel activation and desensitization," *Journal of Biological Chemistry*, vol. 296, 2021.

[33] K. Mandal, "Review of PIP2 in cellular signaling, functions and diseases," *International journal of molecular sciences,* vol. 21, no. 21, pp. 8342, 2020.