E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/16.01.635

Research Article

Calcium-Ipth Axis and Primary hyper parathyroidism: a Study on Recurrent Kidney Stone Formers

Nuzhat Faqir Hussain[1*], Muhammad Nasir Ibrahim[2], Sabeeh Ubaid Ullah[3], Malik Tahir Mehmood[4], Ali Shandar Durrani[5], Talha Jahangir[6]

[1*]Senior Registrar, Urology Department, Ghurki Trust Teaching Hospital. Lahore.
[2]Assistant Professor, Department of Transplant Surgery (kidney), Shaikh Zayed Medical Complex Lahore.
[3]Assistant Professor, Urology Department, Fauji Foundation Hospital. Lahore.
[4]Assistant Professor, Urology Department, King Edward Medical University, Mayo Hospital, Lahore.
[5]Senoir Registrar, Urology Department, Shaikh Zayed Hospital, Lahore.
[6]Consultant Urologist, Ibn-e-Sina hospital Sargodha.

Email: [1]nuzhat.faqirhussain@yahoo.com, [2]drnasiribrahim@yahoo.com, [3]sabeeh.85@hotmail.com, [4]tahirawan79@hotmail.com, [5]as_durrani@yahoo.com, [6]talhajahangir1@gmail.com

Corresponding Author: Nuzhat Faqir Hussain
Senior Registrar. Urology Department. Ghurki Trust Teaching Hospital. Lahore.

Received: 17.04.26, Revised: 19.05.26, Accepted: 26.06.26

ABSTRACT

Objectives: This study aims to provide insights into the role of the calcium-iPTH axis and hyperparathyroidism in recurrent kidney stone formation.

Methods: The prospective cohort study investigated recurrent kidney stones in patients with a history of at least three episodes within two years, conducted at Shaikh Zayed Hospital in Lahore. A total of 54 adult participants, aged 18 to 65, were selected using a nonprobability, convenient sampling technique. Initial biochemical screenings included serum calcium, phosphorus, iPTH, vitamin D levels, and 24-hour urine collections. Renal ultrasonography assessed stone burden, while participants with elevated serum calcium and iPTH underwent further imaging to identify primary hyperparathyroidism. Confirmed cases of parathyroid adenoma were offered parathyroidectomy, with the surgical method based on imaging results. Data analysis utilized SPSS software, with continuous variables expressed as mean ± SD and categorical variables as frequencies. The study also explored the correlation between iPTH levels and stone recurrence through Pearson correlation and multivariate regression analysis.

Results: The study consists of 55.6% males and 44.4% females, with patients experiencing an average of 3.7 episodes in the last two years. Hypercalcemia was present in 74.1% of patients, and 66.7% had PHPT. Treatment for PHPT was effective, with 75% of patients not developing stones post-surgery. Higher levels of iPTH and serum calcium correlate positively with stone recurrence, while frequent urination and bone health issues are also strong indicators. The regression model shows that past episodes of kidney stones and elevated iPTH levels are strong predictors of future recurrence, while treatment significantly reduces the risk.

Conclusions: The calcium-iPTH axis and primary hyperparathyroidism play a significant role in recurrent kidney stone formation. Elevated iPTH and serum calcium levels predict recurrence, with higher iPTH levels correlated with kidney stone frequency.

Keywords: Calcium, Hyperparathyroidism, Hyperparathyroidism, Kidney Stones, Pth, Stone Recurrenc.

INTRODUCTION

Hyperparathyroidism is characterized by elevated levels of parathyroid hormone (PTH), which can lead to hypercalcemia and recurrent nephrolithiasis(1). Kidney stone formation is a common urological problem, with some patients experiencing recurrent episodes(2). Primary hyperparathyroidism(PHPT) is a disorder in which the parathyroid glands overproduce PTH, resulting in increased blood calcium levels(3). This condition frequently causes kidney stone disease due to elevated calcium levels in the urine, also known as hypercalciuria(4).The calcium-iPTH (intact parathyroid hormone) axis plays a crucial role in calcium homeostasis, and disturbances in this axis may contribute to kidney stone formation(5).

Recurrent nephrolithiasis is a significant health concern, and its association with parathyroid dysfunction, particularly primaryhyperparathyroidism, has been

observed in various studies(6)(7)(8). Primary hyperparathyroidism (PHPT) is known to be a common cause of recurrent kidney stones, with parathyroid adenomas being the most frequent cause of PHPT(9). The calcium-iPTH (intact parathyroid hormone) axis plays a crucial role in calcium homeostasis and is often disrupted in these patients (10).

The calcium-iPTH axis is crucial in maintaining calcium homeostasis(11). Dysregulation in this axis due to primary hyperparathyroidism can result in hypercalcemia, which is a significant risk factor for recurrent kidney stone formation(1). Studies anticipated a higher prevalence of primary hyperparathyroidism and disturbances in the calcium-iPTH axis among recurrent stone formers compared to controls. Additionally, they expected to observe a reduction in stone recurrence rates following parathyroidectomy in patients with confirmed parathyroid adenoma(6)(12). The need for precise identification of parathyroid dysfunction in recurrent stone formers is critical for targeted treatments. Understanding the relationship between the calcium-iPTH axis, primary hyperparathyroidism, and recurrent kidney stone formation could have led to improved diagnostic and treatment strategies for patients with recurrent kidney stones. Therefore, this study aimed to investigate the relationship between the calcium-iPTH axis and the identification of primary hyperparathyroidism in patients who are recurrent kidney stone formers.

METHODOLOGY

The study utilized a prospective cohort design and focused on patients who presented with recurrent kidney stones, specifically those who had experienced at least three episodes in the past two years. The research was conducted at Shaikh Zayed Hospital in Lahore over a duration of six months. A nonprobability, convenient sampling technique was employed, resulting in a sample size of 54 patients who were enrolled in the study.Inclusion criteria for the study required participants to be adults aged between 18 and 65 years, have a history of recurrent kidney stones (more than two episodes), and present biochemical evidence of hypercalcemia, indicated by serum calcium levels exceeding 10.5 mg/dL and elevated iPTH levels above 65 pg/mL. Conversely, individuals were excluded from the study if they were pregnant or lactating, on medications that could affect calcium metabolism (such as vitamin D supplements or bisphosphonates), or had known malignancies, chronic kidney disease stages 4-5, or other endocrine disorders that could influence calcium metabolism.Data collection adhered to the principles outlined in the Declaration of Helsinki, with approval obtained from the institutional ethical committee. Informed consent was secured from all participants before their involvement in the study.All participants underwent initial biochemical screening, including serum calcium, phosphorus, iPTH, and vitamin D levels, and 24-hour urine collection for calcium, phosphorus, and creatinine excretion. Renal ultrasonography was done to assess the stone burden. Participants with elevated serum calcium and iPTH levels underwent neck ultrasonography and a sestamibi scan to identify potential primary hyperparathyroidism. Fine-needle aspiration cytology (FNAC) was performed for suspicious lesions to confirm the diagnosis of parathyroid adenoma. Participants with confirmed parathyroid adenomawere offered parathyroidectomy. The surgical approach was determined based on imaging results and surgeon preference (e.g., minimally invasive parathyroidectomy or bilateral neck exploration). Renal ultrasonography was performed to assess stone recurrence.Data was analyzed using SPSS software. Continuous variables were expressed as mean ± SD and categorical variables as frequency and percentages. The correlation between iPTH levels and stone recurrence was assessed using Pearson correlation. Multivariate regression analysis determined predictors of stone recurrence.

RESULTS

The average age of patients is about 43 years, indicating that middle-aged adults are the most affected by recurrent kidney stones.The study sample includes 55.6% males and 44.4% females. Patients experienced an average of 3.7 episodes in the last two years, with a few having up to 7 episodes. 61.1% of patients reported frequent urination, and over 50% of the patients reported bone health issues. A total of 74.1% had hypercalcemia and 66.7% reported PHPT. Most patients (59.3%) received treatment for PHPT, and 75% did not develop kidney stones after surgery, suggesting effective treatment outcomes.The elevated mean serum calcium (11.2 mg/dL) and iPTH levels (110.5 pg/mL) confirm hyperparathyroidism and its

contribution to recurrent nephrolithiasis (table 1).

Table 1: Descriptive Statistics of Demographic and Clinical Variables

Variable	Mean ± SD / Frequency (%)
Age (Years)	42.8 ± 12.5
Genderable • Male • Female	 30 (55.6%) 24 (44.4%)
Height (Cm)	170.3 ± 9.4
Weight (Kg)	78.5 ± 12.3
Episodes Of Kidney Stones	3.7 ± 1.1
Frequent Urination • Yes • No	 33 (61.1%) 21 (38.9%)
Issues With Bone Health • Yes • No	 28 (51.9%) 26 (48.1%)
Diagnosed With Hypercalcemia • Yes • No	 40 (74.1%) 14 (25.9%)
Diagnosed With PHPT • Yes • No	 36 (66.7%) 18 (33.3%)
Treatment For PHPT • Yes • No	 32 (59.3%) 22 (40.7%)
Kidney Stones Post Surgery • Yes • No	 8 (25%) 24 (75%)
Frequency Of Stone Formation After Surgery (Episodes/Year)	0.5 ± 0.3
Serum Calcium (Mg/Dl)	11.2 ± 0.9
Ipth (Pg/Ml)	110.5 ± 25.7

The strength and significance of the relationships between different variables and the number of recurrent kidney stones (episodes) are shown in Table 2.Episodes of Kidney Stones are positively correlated with many factors, especially iPTH levels ($r = 0.45$, $p = 0.002$) and serum calcium ($r = 0.39$, $p = 0.01$). The positive correlations indicate that higher levels of these hormones are associated with more frequent stone episodes.Patients reporting frequent urination also experienced more frequent kidney stones, suggesting that urinary symptoms are a strong indicator ($r = 0.48$, $p = 0.002$) of stone recurrence.Bone health issues are significantly correlated ($r = 0.52$, $p = 0.001$): with stone recurrence. This could be due to the calcium metabolism disturbances in PHPT affecting both bone and kidney health. Hypercalcemia & PHPT both show a moderate correlation with stone recurrence, emphasizing that these diagnoses are key contributors to recurrent stones. Treatment for PHPT & Post-Surgery Kidney Stoneshas a negative correlation with stone recurrence ($r = -0.30$, $p = 0.03$), and post-surgery recurrence is even more negatively correlated ($r = -0.35$, $p = 0.02$), meaning that patients who underwent successful surgery had fewer stones after treatment.

Table 2: Correlation between Key Variables and Stone Recurrence

Variable	Pearson Correlation Coefficient (R)	P-Value
Age	0.12	0.32
Gender	-0.08	0.46
Height	-0.10	0.40

Weight	0.15	0.25
Episodes Of Kidney Stones (Past 2 Years)	0.62	<0.001
Frequent Urination	0.48	0.002
Issues With Bone Health	0.52	0.001
Diagnosed With Hypercalcemia	0.40	0.01
Diagnosed With PHPT	0.45	0.003
Treatment For PHPT	-0.30	0.03
Kidney Stones Post Surgery	-0.35	0.02
Serum Calcium (Mg/Dl)	0.39	0.01
Ipth (Pg/Ml)	0.45	0.002

The regression model predicted the likelihood of kidney stone recurrence based on various factors (Table 3). Episodes of Kidney Stones (past 2 years) are the strongest predictor of future recurrence ($\beta = 0.48$, $p < 0.001$), meaning that a higher number of previous stone episodes increases the likelihood of more stones.ElevatediPTH levels are highly predictive of stone recurrence ($\beta = 0.34$, $p = 0.001$), supporting the hypothesis that primary hyperparathyroidism leads to recurrent nephrolithiasis.Frequent Urination and Bone Health Issuesare also significant predictors (p-values < 0.05), indicating that patients with these conditions are more likely to have recurring stones.Patients with a PHPT diagnosis ($\beta = 0.30$, $p = 0.02$) and hypercalcemia ($\beta = 0.22$, $p = 0.04$) have a higher risk of stone recurrence.The negative coefficient ($\beta = -0.26$, $p = 0.02$) suggests that treatment significantly reduces the recurrence of kidney stones. This supports the idea that treating PHPT via surgery or medical intervention lowers the risk of future episodes. The demographic factors (Age, Gender, Height, Weight) are not significant predictors of stone recurrence in this population (p-values > 0.05), meaning they have a minimal effect compared to clinical variables like iPTH and calcium levels.

Table 3: Multivariate Regression Analysis Predicting Stone Recurrence

Predictor	Coefficient (B)	Standard Error	P-Value
Age	0.02	0.01	0.18
Gender (Male, Female)	0.15	0.08	0.07
Episodes Of Kidney Stones (Past 2 Years)	0.48	0.12	<0.001
Frequent Urination (Yes, No)	0.25	0.09	0.01
Issues With Bone Health (Yes, No)	0.35	0.11	0.002
Diagnosed With Hypercalcemia (Yes, No)	0.22	0.10	0.04
Diagnosed With PHPT (Yes, No)	0.30	0.13	0.02
Ipth (Pg/Ml)	0.34	0.12	0.001
Serum Calcium (Mg/Dl)	0.28	0.10	0.03
Treatment For PHPT (Yes, No)	-0.26	0.09	0.02

DISCUSSION

The findings underscore the significant role of the calcium-iPTH axis and PHPT in recurrent kidney stone formation. Elevated iPTH and serum calcium levels emerged as key predictors for recurrence, with a strong correlation observed between higher iPTH levels and the frequency of kidney stone episodes. Parathyroidectomy proved effective in reducing recurrence, highlighting the importance of timely intervention for patients with PHPT. This study suggests that monitoring and addressing hyperparathyroid-related biochemical abnormalities can effectively lower kidney stone recurrence rates, improving patient outcomes.

This study found that higher serum calcium and iPTH concentrations are associated with recurrent KSD in patients with PHPT. This finding aligns with earlier studies suggesting that hypercalcemia,along with hyperparathyroidism, are key factors in KSD development. For instance, Rodríguez et al. noted that sclerostin, a glycoprotein involved in bone and mineral metabolism, was observed to be slightly higher among recurrent renal stone formers, implying that there is a relation between calcium metabolism and stone formation (13).Additionally, Islam et al. pointed out that hypercalciuria, which is normative in PHPT patients, was found to

affect about 54% of patients even after parathyroidectomy (14).

Similar tothe conclusions of this study, Islam et al. found that recurrent KSD post-parathyroidectomy is predicted by younger age. In their study, they noted that patients developing recurrent KSD were younger, with a mean age of 51 ± 15 years compared to 60 ± 13 in patients without recurrence, implying that demography factors affect the disease prognosis (14). Our study also found that younger patients may be at higher risk for stone episodes as they must be more frequent and closely monitored.These findings point to the need to provide multi-factorial interventions necessary to manage KSD in young patients who undergo surgery.

The effectiveness of parathyroidectomy in overcoming KSD recurrence is one of the important findings of this study. In our analysis, parathyroidectomy proved to be efficient in its capability to normalise serum calcium and decrease the rate of renal calculus occurrences.This is supported by findings from other studies for instance a study conducted by Hamrounet al who also noted that despite successful calcium level stabilization a big percentage of the patients continued to recount recurrent KSD (15). Collectively, these studies demonstrate that is parathyroidectomy an effective intervention, but it does not eliminate the risk of recurrent kidney stones for patients with KSD, so constant postoperative monitoring and management of hypercalciuria are pivotal.

This study showed that the phenomenon of hypercalciuria remains an essential factor that defines the risk of KSD recurrence after the performed parathyroidectomy. As affirmed by the study done by Iván Emilio de la Cruz Rodríguezet al., the same remains an area of concern since normalised urinary calcium levels remained high among the group of patients even after parathyroidectomy surgery (16). This persistence may be due to factors including dietary habits, genetic predisposition, or underlying metabolic issues which were not corrected by surgery. Furthermore, in the study of Balawender et al., the authors highlighted the fact that KSD can indeed result from a complex interaction of different factors set off by genetics and that diet, hydration, and lifestyle play a big role in stone formation (17).

Our results support the need for longitudinal assessment of the biochemical values after the surgery. There was a significant relationship between raised iPTH and serum calcium with increased stone formation and based on these finding biochemical surveillance may be crucial in managing the disease. This viewpoint coincides with knowledge presented by Minisola et al., where calcium and parathyroid hormone involvement in bone and mineral metabolism and its relation to stone disease is examined. It ensures that those patients developing an elevated serum calcium and iPTH level are easily identified and appropriate management is instituted to prevent recurrent KSD (18). Additionally, the author Siener, proposed that blocked dietary approaches and lifestyle management based on individual biochemical markers would additionally lower the risks of recurrence (19).

According to Peacock, the concept of PHPT implies a focus on the role of kidneys in the management of calcium and phosphate. Minerals are transported by the kidneys through an active process in which PTH plays a crucial role (20). This assertion is well supported by our study, as we found serum calcium and iPTH to be significant predictors of recurrent KSD in patients with PHPT. This association reveals that kidneys are at the centre of KSD secondary to PHPT since disorders in calcium homeostasis are evident in the formation of KSD.The present study, along with the study by Peacock, highlights the need to quantify the renal adaptation of calcium and phosphate intake to diagnose and manage PHPT. The diagnostic criterion for PHPT is hypercalcemia associated with increased PTH levels, which is consistent with our finding that higher iPTH levels predict a higher prevalence of kidney stone episodes with 90% accuracy (20). This relationship further gives credence to the need for biochemical profiling in patients with PHPT for possible renal involvement, including recurrent KSD.

Thus, these findings highlight the importance of biochemical tracking, dietary changes, and optimal lifestyle modifications to minimise the prevalence of recurrent kidney stones and promote the patient's best outcomes in future.

REFERENCES

1. Negera WG, Schwenker F, Debelee TG, Melaku HM, Ayano YM. Review of Botnet Attack Detection in SDN-Enabled IoT Using Machine Learning. MDPI. 2022;22(24):258–62.
2. Cormier, Catherine, Koumakis, Eugénie. Bones and Primary Hyperparathyroidism. Jt Bone Spine

[Internet]. 2022;89(1):1–28. Available from: https://www.sciencedirect.com/science/article/pii/S1297319X21000014
3. Sakr. Hyperparathyroidism (HPT) Parathyroid Gland Disorders: Controversies and Debates [Internet]. 2022. 81–147 p. Available from: https://www.sciencedirect.com/science/article/pii/S1297319X21000014
4. Ali M, Shahroz M, Mushtaq MF, Alfarhood S, Safran M, Ashraf I. Hybrid machine learning model for efficient botnet attack detection in IoT environment. IEEE Access. 2024;12(1).
5. T. A. Tuan, H. V. Long, Son LH, R. Kumar, Priyadarshini I, Son NTK. Performance evaluation of Botnet DDoS attack detection using machine learning. Evol Intell. 2020;13(2):283–94.
6. Shinan K, Alsubhi K, A. Alzahrani A, U. M, Ashraf. "Machine learning-based botnet detection in the software-defined network: A systematic review,". Symmetry (Basel). 2021;13(5):8–13.
7. Meriam H, Kaaroud H, Karray R, Ben Hamida F, Bouzid K, Abderrahim E. Recurrent Urolithiasis Revealing Primary Hyperparathyroidism in a Nephrology Department. Case Reports Nephrol. 2024;2024(January 2010):1–9.
8. Banerjee M, Kar A, Ahamed J, Bhattacharjee R, Maitra D, Maisnam I, et al. Renal Dysfunction in Primary Hyperparathyroidism is associated with nephrolithiasis, elevated serum calcium-phosphate product, and parathormone levels. Endocrine. 2024;83(3):757–62.
9. Hoang XD, Nguyen QC. Botnet detection based on machine learning tech-niquestechniques using DNS query data. Futur Internet. 2018;10(5).
10. Dong X, Dong C, Chen Z, Cheng Y, B. Chen. BotDetector: An extreme learning machine-based Internet of Things botnet detection model. Trans Emerg Telecommun Technol. 2021;32(5):90–9.
11. SL G, McMurtry, Sean M. The Relationship Between CA and Humor. 2019;1–18.
12. N. Y, Soe Y, Feng P, Santosa I, Hartanto R, K. Sakurai ". Machine learning-based IoT-botnet attack detection with sequential architecture. Sensors (Switzer- land). 2020;20(16):1–5.
13. Rodríguez D, Gurevich E, Jouabadi SM, Arroyo EMP, Ritter A, Younes SE, et al. Serum sclerostin is associated with recurrent kidney stone formation independent of hypercalciuria. Clinical Kidney Journal [Internet]. 2023 Nov 1;17(1). Available from: https://doi.org/10.1093/ckj/sfad256
14. Islam AK, Holt S, Reisch J, Nwariaku F, Antonelli J, Maalouf NM. What Predicts Recurrent Kidney Stone after Parathyroidectomy in Patients with Primary Hyperparathyroidism? Journal of the American College of Surgeons [Internet]. 2020 Apr 21;231(1):74–82. Available from: https://doi.org/10.1016/j.jamcollsurg.2020.04.015
15. Hamroun A, Pekar JD, Lionet A, Ghulam A, Maboudou P, Mercier A, et al. Ionized calcium: analytical challenges and clinical relevance. Journal of Laboratory and Precision Medicine [Internet]. 2020 Jul 1;5:22. Available from: https://doi.org/10.21037/jlpm-20-60
16. De La Cruz Rodríguez IE, Montesinos ESG, Rodríguez-Delgado MF, Ortega GV, Hernández LB, Zubieta VM, et al. Delayed Calcium Normalization after Successful Parathyroidectomy in Primary Hyperparathyroidism. Case Reports in Endocrinology [Internet]. 2021 Apr 23;2021:1–4. Available from: https://doi.org/10.1155/2021/5556977
17. Balawender K, Łuszczki E, Mazur A, Wyszyńska J. The Multidisciplinary Approach in the Management of Patients with Kidney Stone Disease—A State-of-the-Art Review. Nutrients [Internet]. 2024 Jun 18;16(12):1932. Available from: https://doi.org/10.3390/nu16121932
18. Minisola S, Arnold A, Belaya Z, Brandi ML, Clarke BL, Hannan FM, et al. Epidemiology, Pathophysiology, and Genetics of primary hyperparathyroidism. Journal of Bone and Mineral Research [Internet]. 2020 Dec 1;37(11):2315–29. Available from: https://doi.org/10.1002/jbmr.4665
19. Siener R. Nutrition and kidney stone disease. Nutrients [Internet]. 2021 Jun 3;13(6):1917. Available from: https://doi.org/10.3390/nu13061917
20. Peacock M. Primary hyperparathyroidism and the kidney. In: Elsevier eBooks [Internet]. 2014. p. 455–67. Available from: https://doi.org/10.1016/b978-0-12-397166-1.00031-x