Rising Incidence of Hyperuricemia in Patients with Urolithiasis

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Abstract

Background: Uric acid nephrolithiasis is the leading cause of kidney stones in developed countries, and it usually indicates a systemic biochemical/metabolic imbalance; however, hyperuricemia is frequently employed as an accompanying feature of gout and is associated with urolithiasis.

Objective: To determine the rising incidence of hyperuricemia in patients with urolithiasis at Liaquat National Hospital Karachi.

Methods: The cross-sectional study was conducted from January to July, 2024 at the Department of Urology, Liaquat National Postgraduate Medical Centre Karachi, Pakistan. The patients 18-65 years of age and either gender diagnosed with urolithiasis were recruited and explored for serum uric acid levels. Predesigned proforma was used for data collection while frequency (percentage) and mean ± SD were calculated for qualitative and quantitative variables.

Results: 320 individuals with urolithiasis were studied, and hyperuricemia was detected in 197 (61.5%) patients. The statistical significance was observed for hyperuricemia by age (p=0.03), gender (p<0.001), diabetes mellitus (p<0.001), smoking (p<0.001), obesity (p<0.001), hypertension (p<0.001), family history urolithiasis (p=0.04) and anatomical location of the stone (p=0.04). The frequency and proportions observed were male as 59.7%, female at 40.3%, urban and rural as 48.8% and 51.2%, smoking 53.1%, hypertension 50.9%, diabetes mellitus 55.6%, obesity 56.6%, family history of hyperuricemia and urolithiasis as 51.2%, and 60.6% and anatomical location of stone as right 50.9% and left 49.1%.

Conclusion: The hyperuricemia has been observed in patients with urolithiasis.

Keywords: *Urolithiasis, kidney stone, renal stone, uric acid, calculi, and hyperuricemia.*

INTRODUCTION

Nephrolithiasis, a highly challenging condition, impacts approximately 1 in 11 people globally and imposes a substantial strain on the healthcare system [1, 2]. Nephrolithiasis affects between 1.1% and 19.1% of Asian people [3]. Pakistan is situated in the Afro-Asian stone belt, an area known for its elevated prevalence of kidney stones. The occurrence of nephrolithiasis in Pakistan varies from 7.4 cases per 100,000 in the northern regions to 200 cases per 100,000 in the southern regions [3, 4]. The lifetime prevalence of recurring renal stones varies from 10-75%, resulting in end-stage kidney damage in between two and three percent of these individuals [5]. Urological therapies have significantly reduced the number of chronic kidney disease (CKD) cases caused by repeated kidney stone formation [6]. Nevertheless, although being a reversible cause, late treatment in Pakistan still contributes to 8-10% of CKD cases [7]. Furthermore, conducting a thorough analysis of the chemical makeup of the kidney stone is crucial for effectively treating the root reasons and preventing future occurrences. Unfortunately, this step is often overlooked in developing nations [8-10].

Hyperuricemia occurs when the body's uric acid metabolism is abnormal, either owing to excessive production or insufficient excretion. When the concentration of uric acid exceeds a specific level, it can lead to the formation of kidney stones. During gout, the renal systems of patients can be affected by soluble uric acid and urate crystals. Gout is primarily due to hyperuricemia, which refers to elevated levels of urate in the blood serum that exceed its solubility limit. Multiple investigations have indicated that the occurrence of urolithiasis in individuals with gout was greater compared to the general population [11]. Nevertheless, gout and urolithiasis have overlapping risk factors, including hypertension, diabetes, and obesity [12, 13]. Furthermore, the current knowledge does not definitively establish whether hyperuricemia alone is independently linked to the possibility of developing coincidental urolithiasis [14]. Thus far, the majority of research related to urolithiasis has only involved individuals with gout, except for those with subclinical hyperuricemia. A study conducted by Deng H, *et al.* reported hyperuricemia in urolithiasis as 16.87% [15]. Another research study found that 14% of patients with urolithiasis had hyperuricemia [16]. A research study by Perumal KR, *et al.* observed hyperuricemia in urolithiasis as 29.54% (13 out of 44) [17]. A study by Ahmad I, *et al.* revealed that 29.5% of patients with urolithiasis had hyperuricemia [18].

It is very reasonable to believe that SUA levels play an important role in the independent association between nephrolithiasis and joint pain in a high-risk population. However, hyperuricemia is often used as an accompanying symptom of joint pain to explore its association with nephrolithiasis. Furthermore, it is

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predicted that the risk of nephrolithiasis can be higher in patients with nonspecific joint pain. Moreover, the high-risk population could be different according to these demographic factors.

The goal of the study was to investigate the magnitude of hyperuricemia in individuals with urolithiasis. Multiple international investigations have demonstrated a correlation between hyperuricemia and urolithiasis. Nevertheless, our regular practice does not include a recommendation for screening urolithiasis in hyperuricemia patients, and vice versa, because there is little evidence available. The study's findings would assist urologists in evaluating the impact of the condition, offering valuable information for modifying screening protocols in these patients, ultimately leading to early detection of urolithiasis. Furthermore, utilizing the discovered information, urologists can formulate ways to manage hyperuricemia and its associated problems.

PATIENTS AND METHODS

The cross-sectional study of six months was carried out at the urology ward, Liaquat National Hospital Karachi from January to July, 2024, following approval from the ethical review committee of the institute. The inclusion criteria were patients of age 18-65 years, either gender presented with urolithiasis while the exclusion criteria were the patients with a history of renal diseases, myeloproliferative or lymphoproliferative disorders, chronic infection, and having history of alcohol use. The quantity for the target population was determined using the WHO sample size tool. By taking the prevalence of hyperuricemia in patients with urolithiasis from the previous study 29.5%, [17] the 5% margin of error and 95% CI, the required estimated population for this study was 320.

The urolithiasis was considered as the patient presented with severe pain in either of the lower back, hematuria, and nausea/vomiting confirmed on ultrasound, shown echogenic foci, acoustic shadow, CT kidney ureter and bladder (CT-KUB)/CT abdomen and color comet-tail artifact or twinkle artifact on Doppler while the diagnostic tests vary according to the presentation of the patient parallel to the journey of exploration & utilization of tests as per patient.

Hyperuricemia was labeled when serum uric acid concentration was>7.0 mg/dL in males and >6.0 mg/dL in females [19].

Diabetes mellitus was considered when the patients had a documented history of diabetes mellitus for at least one year and were on oral hypoglycemic agents or insulin for at least the last six months either uncontrolled or controlled.

The hypertension was evident in a history of hypertension and on medication for at least six months either uncontrolled or controlled.

Obesity was estimated through body mass index (BMI) measured by using the formula as weight in kilograms/ height in meters. Weight was measured by using the digital weighing machine in light clothes and height was measured by using wall wall-mounted scale without shoes and a cap.

Smoking was classified into two categories smoker and non-smoker.

All eligible patients who had urolithiasis and met the inclusion criteria were enrolled in the research study using a consecutive sampling method in the urology outpatient department. Before enrollment, complete details of the study were explained to the patient by the principal investigator, and informed consent was taken. The baseline demographic and clinical details such as age, gender, residence, family monthly income, height, weight, BMI, comorbid (diabetes, hypertension), smoking, family history of hyperuricemia, and family history of urolithiasis were taken and noted in a predesigned proforma. All patients underwent ultrasound KUB for the confirmation of urolithiasis. After confirming the diagnosis of urolithiasis, a 5cc venous blood sample was taken by a phlebotomist using an aseptic technique and sent to the hospital laboratory for the assessment of uric acid levels. The outcome variable *i.e.* hyperuricemia was labeled as per cutoff values.

The data was processed by SPSS version 24. Mean ± standard deviation was computed for normally distributed data while median with inter-quartile (IQR) for non-normal data, whereas the normality of data was evaluated by the Shapiro Wilk test. Qualitative variables such as gender, residence, diabetes, hypertension, smoking, family history of hyperuricemia, family history of urolithiasis, anatomical location of stone, and hyperuricemia were presented as frequency and percentage. However, quantitative variables such as age, height, weight, BMI, family monthly income, number of stones, size of stone, and uric acid level were presented as mean and SD or median (IQR). The stratification was done for age, gender, residence, family monthly income, diabetes, hypertension, smoking, family history of hyperuricemia, number of stones, size of the stone, anatomical location of the stone, and family history of urolithiasis while the post-stratification Chi-square/Fisher exact test was used and the p-value ≤0.05 was taken as statistically significant.

RESULTS

During a span of six months, a total of 320 patients with urolithiasis, ranging from 18 to 65 years and of either gender, sought treatment at the urology ward at Liaquat National Hospital Karachi. The median (IQR) for the age of the overall population and number of stones is 57 years and 3 cm while the demographical and clinical parameters of the study population are shown in Table **1** while the mean ±SD for age (years), height, weight, BMI, number of stone and its size and

Table 1: The demographical and clinical parameters of study population.

Parameter	Frequency	Percentage
Age (yrs)		
18-29	40	12.5
30-39	83	25.9
40-49	85	26.6
50-59	71	22.2
60-65	41	12.8
Gender		
Male	191	59.7
Female	129	40.3
Residence		
Urban	156	48.8
Rural	164	51.2
Smoking		
Yes	170	53.1
No	150	46.9
Hypertension		
Yes	163	50.9
No	157	49.1
Diabetes Mellitus		
Yes	178	55.6
No	142	44.4
Obesity		
Yes	181	56.6
No	139	43.4
Family History of Hyperuricemia		
Yes	164	51.2
No	156	48.8
Family History Urolithiasis		
Yes	194	60.6
No	126	39.4
Anatomical Location of Stone		
Right kidney	163	50.9
Left kidney	157	49.1
Site o Renal Stone		
Kidney Stones	187	58.4
Upper ureteric stones	80	25.0
Lower ureteric stone	53	16.5
Hyperuricemia		
Yes	197	61.5
No	123	38.4

serum uric acid are presented in Table **2** whereas the median (IQR) for age (yrs), serum uric acid (mg/dL) and BMI (kg/m2) observed as 56.00, 9.00 and 30.00. Hyperuricemia was observed in 181 (56.6%) obese individuals of which 120/181 (66.2%) had a BMI (30-34) while 61/181 (33.7%) had a BMI (35-40) respectively. The stratification of hyperuricemia according to age, gender, residence, diabetes mellitus, smoking, obesity, hypertension, family history of hyperuricemia, family history of urolithiasis, and anatomical location of the stone is presented in Table **3**. The statistical significance was observed for hyperuricemia by gender (p<0.001), age (p=0.030), diabetes mellitus (p<0.001), smoking (p<0.001), obesity (p<0.001), hypertension (p<0.001), family history urolithiasis (p=0.040) and anatomical location of the stone (p=0.04) while statistical non-significance have been observed for hyperuricemia in accordance residence (p=0.25) and family history of hyperuricemia (p=0.81) respectively.

Table 2: The mean ±sd for quantitative variables of the study population.

Quantitative Variables	Minimum	Maximum	Mean ± SD
Weight (kg)	60.0	95.5	81.13± 8.75
Height (m)	1.3	1.8	1.65±0.05
BMI (kg/m^2)	24.0	35.0	30.85 ± 2.52
Stone size (cm)	0.5	3.2	2.96 ±0.75
Serum uric acid level (mg/dL)	6.2	10.5	9.75 ± 1.93

DISCUSSION

Urolithiasis is a widespread condition in contemporary life, with a high prevalence globally occurring at 7-13% in the USA, 5-9% in the European continent, and 1% in Asia

Table **3**: The distribution of hyperuricemia in the study population.

Variables	Hyperurecemia		p-value
	Yes n(%)	No n(%)	
Age			
18-29 years	28(14.2)	12(9.8)	0.030
30-39 years	53(26.9)	30(24.4)	
40-49 years	59(29.9)	26(21.1)	
50-59 years	39(19.8)	32(26.0)	
60-65 years	18(9.1)	23(18.7)	
Gender			
Male	132(67)	59(48)	<0.001
Female	65(33)	64(52)	
Residence			
Urban	101(51.3)	55(44.7)	0.250
Rural	96(48.7)	68(55.3)	
Diabetes mellitus			
Yes	142(72.1)	36(29.3)	<0.001
No	55(27.9)	87(70.7)	
Smoking			
Yes	135(68.5)	35(28.5)	<0.001
No	62(31.5)	88(71.5)	
Obesity			
Yes	136(69)	45(36.6)	<0.001
No	61(31)	78(63.4)	
Hypertension			
Yes	121(61.4)	42(34.1)	<0.001
No	76(38.6)	81(65.9)	
Family History of Hyperuricemia			
Yes	102(51.8)	62(50.4)	0.810
No	95(48.2)	61(49.6)	
Family History of Urolithiasis			
Yes	128(65)	66(53.7)	0.040
No	69(35)	57(46.3)	
Anatomical Location of Stone			
Yes	109(55.3)	54(43.9)	0.040
No	88(44.7)	69(56.1)	
Size of Stone			
≤1 cm	84(42.6)	40(32.5)	0.050
2-3 cm	54(27.4)	49(39.8)	
≥3 cm	59(29.9)	34(27.6)	

according to prior research. In addition, the prevalence and incidence of kidney stones are continuously increasing on a global scale [20]. Moreover, urolithiasis is a common clinical systemic illness that has a strong correlation with an increased risk of high blood pressure, persistent kidney damage, end-stage renal disease (ESRD), and other adverse renal consequences [21]. It has been connected to bone loss/fractures, diabetes type 2, and metabolic syndrome. It also increases the risk of developing cardiovascular disease and ischemic stroke [22]. It is a chronic illness that occurs 50% of the time in 5-10 years and 75% of the time in 20 years [23]. The risk of developing chronic renal disease will be significantly increased and renal function will be significantly reduced in cases with recurrent urolithiasis [24].

Urinary crystals of uric acid tend to hinder the function of urinary inhibitors, hence promoting the formation of urinary stones. Several prior studies conducted in Pakistan have demonstrated that stone formers (SF) have higher average levels of serum uric acid compared to non-stone formers (NSF) [25, 26]. According to reports, 31% of stone formers have shown hyperuricemia, [27] while hyperuricemia has also been found in 61.5% of participants in the current series. According to the former study, there may be a link between high serum uric acid levels and the occurrence of stones. A multi-ethnic cohort was studied in the southwest region of China to investigate the association between nephrolithiasis prevalence and hyperuricemia [28]. The findings demonstrated an independent correlation between urolithiasis and hyperuricemia. Moreover, it was discovered that the risk of kidney calculi in both men and women was dose-response related to the level of serum uric acid (SUA). Even after taking into consideration any confounding variables, this link held significance. This suggests that even in those without gout symptoms, having high serum uric acid (SUA) levels is a distinct risk factor for kidney calculus, with greater vulnerability in men [28].

A study from Korea found that SUA levels were independently and moderately associated with an increased risk of nephrolithiasis in healthy adult men, and a relationship was observed in men, specifically between SUA reaching 300 μmol/L and the risk of developing nephrolithiasis [29], which is consistent with our view that elevated SUA is an independent risk factor for nephrolithiasis. The current set of observations also found a correlation between SUA levels and kidney stones in both men and women, with varying proportions. This correlation may be attributed to the gender and age distribution of the individuals. Prior research has indicated that the occurrence of hyperuricemia in women rises as they get older, and there is an association between age and levels of serum uric acid (SUA) in women [30]. Additionally, animal experiments have suggested that estrogen might have a beneficial effect on hyperuricemia by enhancing the elimination of serum uric acid (SUA) through the kidneys. The geographical and human disparities between Korea and China are significant and cannot be disregarded [31, 32]. The presence of both high uric acid and urolithiasis is affected by factors such as eating habits, lifestyle changes, lipid disorders, diabetes mellitus, hypertension, obesity, and cardiovascular disease. The current series also takes into account the potential influence of these factors when examining the association between hyperuricemia and urolithiasis.

The variable rates of alcohol and tobacco consumption between the genders as well as the unique anatomical and physical structure of the urinary tract may be the cause of the different incidence of urolithiasis among males and females. The disparity may be attributed to the fact that androgens promote the production of oxalate, whereas estrogen enhances the elimination of citric acid in urine [33]. The variations in the occurrence of kidney stones may be attributed to disparities in food patterns and variations in water quality across different locations. Moreover, the major sources of drinking water for residents vary and include the following main sources: purified water & groundwater. Verifying these circumstances necessitates the utilization of more precise measurement devices and more advanced experimental methods. Pathophysiology and molecular biology studies have shown that uric acid (UA) can trigger the release of reactive oxygen species (ROS) from vascular smooth muscle cells or allow UA transport proteins to enter endothelial cells. Nitric oxide (NO) availability is decreased as a result of this process, which also causes inflammatory processes, oxidative stress (OS), and dephosphorylation of endothelial-type nitric oxide synthase (eNOS) and such cascades could be the triggering factor [34]. Endothelial injury plays an important role in the development of nephrolithiasis [35]. It is reasonable to know that inflammation, reactive oxygen species (ROS) generation, and the occurrence of oxidative stress (OS) contributed to the development of nephrolithiasis [36]. Furthermore, human epidemiological studies have discovered a correlation between levels of serum uric acid (SUA) and microalbuminuria, which serves as a biomarker for endothelial dysfunction [37]. Endothelial dysfunction is a recently recognized systemic pathological state characterized by an imbalance in the key endothelial processes. It plays a crucial role in the initiation of several metabolic disorders like hypertension and hyperlipidemia [38]. Endothelial dysfunction has been proposed as an intermediary clinical characteristic connecting urolithiasis and cardiovascular disease. Additionally, it has been demonstrated that nephrolithiasis can contribute to the development of hypertension. This finding aligns with the current study, which suggests a relationship between urolithiasis and hypertension. However, a multidisciplinary approach is required to fully understand the precise mechanism behind their association.

The current research study found hyperuricemia in 136 (69.0%) obese adults. It has been documented that obesity is connected with various co-morbidities that enhance the incidence of kidney stones. Individuals with a body mass index (BMI) of ≥40 kg/m2 have a higher risk of developing diabetes and hypertension compared to adults who are not fat [39]. These comorbidities have been demonstrated to be associated with kidney stone formation and can cause specific alterations in both the overall functioning of the body and specific organs, ultimately leading to the development of kidney stones.

In the present series, hyperuricemia was observed among 142 (72.1%) individuals with diabetes mellitus while it has been known that kidney crystallization is a complex process influenced by several factors and is connected to other disorders. Insulin resistance, a significant component in diabetes type 2 mellitus (DM), is closely associated with the development of uric acid stones [40]. Insulin resistance can lead to a decrease in the generation of ammonium in the kidney, causing a decrease in urine pH. This creates an environment that is conducive to the creation of uric acid stones [41].

The present study demonstrated that hyperuricemia has been observed among 135 (68.5%) subjects having a history of smoking while in the research study conducted by Kim SK *et al.* a notable discrepancy in serum uric acid levels was observed based on smoking status. Smokers exhibited elevated serum uric acid levels compared to individuals who had never smoked [42]. Cigarette smoke contains more than 4,000 substances known to be antigenic, cytotoxic, mutagenic, and carcinogenic. Many of these substances produce significant physiologic effects on the human body and can harm almost every organ. It has been posited by some authors that trace elements such as magnesium, zinc, aluminum, iron, and copper may have a role in lithogenesis but this contention is still under debate. Probably some of them may contribute crystal nucleation of stone components. Thus, the concentration of these trace elements and heavy metals in body tissues is elevated in cigarette smokers.

The present cross-sectional study just concerned with a screening of the patients present with a kidney stone to evaluate their uric acid level and didn't concentrate on analyzing the stone composition although in the study by Rana MN, *et al.* [43] and Rizvi SA, *et al.* [44] the urate was observed in 26.9% and 40% respectively.

When evaluating patients who may have a stone occurrence, it is important to gather a detailed medical history. This should include asking about any underlying diseases that are known to be linked to crystal formation, such as gastrointestinal issues, particularly those involving malabsorption and diarrhea. Other conditions that should be considered are those with high cell turnover, like cancer or myeloproliferative disorders, as well as genetic disorders associated with elevated levels of uric acid in the urine and insulin resistance. It is important to get a thorough family history to see if the specified illnesses and nephrolithiasis are present. In less developed nations, patients often refrain from seeking medical counsel for extended periods. The delay may result in a higher incidence of struvite stones in underdeveloped countries, as well as increased urate concentration in mixed stones. Urolithiasis remains a prevalent clinical ailment in Pakistan, affecting both males and females. However, its prevalence has been decreasing in recent times due to improved living standards. Urolithiasis may be caused by several factors, but structural abnormalities and metabolic diseases play a significant role. Thus, In Pakistani adults, hyperuricemia is associated with an increased risk of developing nephrolithiasis and therefore needs to be treated timely. The study observed the directly proportional association of serum uric acid and urolithiasis and recommended the screening of uric acid levels in individuals present with renal stones or among subjects having a history of joint pain as far as preventive measures are concerned whereas the study has some limitations, first, the study was the single centered, short duration and conducted on limited population thus unable to reflect and represents the whole population and second, the study spared the 24-hour urinary uric acid level.

CONCLUSION

The hyperuricemia was detected in 197 (61.5%) patients with urolithiasis. Thus, hyperuricemia is associated with an increased risk of developing nephrolithiasis, and before reaching the diagnostic criteria for hyperuricemia, the risk of nephrolithiasis rises with the increase in SUA. This suggests that controlling SUA levels may be significant for the prevention of nephrolithiasis. However, the study only reflects a small and particular target population, and being a cross-sectional study is inadequate to strengthen the possible association between uric acid level and renal stone formation. To more clearly determine the impact of blood uric acid levels on kidney stone formation, more research is required. Furthermore, additional research is needed to validate, confirm, and clarify these findings.

LIST OF ABBREVIATIONS

BMI	Body Mass Index
CKD	Chronic Kidney Disease
DM	Diabetes Mellitus
eNOS	Endothelial-Type Nitric Oxide Synthase
ESRD	End-Stage Renal Disease
HTN	Hypertension
IQR	Interquartile Range
KUB	Kidneys, Ureters, and Bladder
LNH	Liaquat University Hospital
NSF	Nonstone Formers
OS	Oxidative Stress
ROS	Reactive Oxygen Species
SUA	Serum Uric Acid

UA Uric Acid
WHO World Health Organization

ETHICS APPROVAL

Ethical approval was obtained from the ethical review Board of Liaquat National Hospital Karachi (Ref. Letter No: App # 0969-2023-LNH-ERC, dated Jan-04-2024). All the procedures performed in the study involving human participants followed the ethical standards of the institutional and/or national research committee and the Helsinki Declaration.

CONSENT FOR PUBLICATION

The written /informed consent was taken from the participants.

AVAILABILITY OF THE DATA

The data set may be acquired from the corresponding author upon a reasonable request.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

Sumaiya Noor: Contributions to conception and design, acquisition of data, and interpretation of data.

Seerat Ul Uroos: Drafting the article and sharing expert opinion and experience in finalizing the manuscript.

Waqas Ahmed: Contributed in conception and interpretation of data and give expert view.

Sana Khurshid: Collection and acquisition of data, analysis, and interpretation of data and making it suitable for final revision.

Ali Raza: Acquisition of data, grammatical and topographical revision.

Iqbal Shahzad: Revision & topographical correction of the manuscript.

Syed Farhan Ahmed: Final revision of the manuscript and rephrasing the appropriate scientific terminologies.

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