Clinical Research

Stone recurrence among Indonesian kidney stone formers: a comprehensive analysis of genetic polymorphism, demographic, and clinical factors

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ABSTRACT

BACKGROUND The recurrence rate of kidney stone disease (KSD) can exceed 50% within 5 years. This study aimed to investigate factors associated with stone recurrence based on single nucleotide polymorphisms (SNPs) of the calcium-sensing receptor (CaSR) rs1801725 and rs1042636, demographic, and clinical profiles.

METHODS We collected data on the demographic and clinical characteristics of 80 adult kidney stone formers from April 2021 to September 2022, including peripheral blood samples, morning and 24-hour urine, and 7-day water intake records. Real-time polymerase chain reaction was used to evaluate SNP. Comparisons were made between patients with recurrent and first-time stones.

RESULTS 41% of 80 patients have experienced stone recurrence. Recurrent stone formers exhibited significantly higher 24-hour urine calcium excretion (p = 0.03) and lower serum calcium levels (p = 0.019) than first-time stone formers. Hypocitraturia (100%), low urine volume (78%), and hyperoxaluria (55%) were the main abnormalities of all patients. No significant differences were found in CaSR gene polymorphisms and other demographic, biochemical, or clinical parameters.

CONCLUSIONS Recurrent stone formers had higher 24-hour urine calcium excretion and lower serum calcium levels. Other risk factors and CaSR polymorphisms may insignificantly affect KSD recurrence.

KEYWORDS genetic polymorphism, Indonesia, kidney stone, metabolic, recurrence, risk factors

Over the years, the incidence and burden of kidney stone disease (KSD) have increased globally.[1] The prevalence of KSD in Asia is approximately 1–19.1% and seems to be greater in Stone Belt regions, such as Southeast America, North Africa, Middle East and Southeast Asia, and the Northeast region of Australia, due to the impact of the hot climate on renal stone formation.[2] Moreover, the recurrence rate of KSD is high, ranging from 0.9–94% within 5 years period.[3,4] The pathophysiology of KSD involves a complex physiochemical process within the kidney.[5] This process results from multiple causes, including genetic, biochemical, medical, socioeconomic, dietary habits or nutritional, and other environmental risk factors.[6] A recently published meta-analysis of 53 articles on risk factors for KSD recurrence revealed that 12

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risk factors were associated with stone recurrence. Nevertheless, the authors found that the follow-up period was heterogeneous, and publication bias existed for some risk factors, which may have affected the interpretability of the data.[7]

A twin study of genetic involvement in KSD found that the heritability of kidney stones is approximately 46–57%.[8] Several studies have also found a correlation between single nucleotide polymorphisms (SNPs) and KSD,[9] although the results in the literature have been inconsistent. Genes involved in calcium metabolism, such as the calcium-sensing receptor (CaSR), are among the most studied gene polymorphisms associated with KSD and are frequently observed in Asian populations.[10] However, genetic polymorphisms reported to increase susceptibility or recurrence vary among different regions and ethnicities.[11,12] A meta-analysis by Atmoko et al[13] found that different polymorphisms were associated with an increased risk of kidney stone recurrence in Asians than in Caucasians. This underlines the fact that ethnicity and the multifactorial nature of KSD may explain the differences in genetic and SNP variants.[13]

Despite Indonesia being one of the most populous countries in the Stone Belt area, no study has thoroughly assessed of KSD recurrence. Many previously published articles from Indonesia were focused more on the surgical management of kidney stones. Therefore, a significant knowledge gap exists in the basic and clinical analyses of kidney stones. Improved preventive intervention strategies for patients can be developed with the assistance of risk factors for KSD recurrence. This study aimed to investigate the differences in CaSR variant rs1801725 and rs1042636 gene polymorphisms, demographic, and clinical profiles between first-time and recurrent patients with kidney stones in the Indonesian population. The findings of this study fill the gap in the literature and serve as a foundation for preventive measures against KSD recurrence.

METHODS

Study population

The study was conducted at the Cipto Mangunkusumo Hospital, Jakarta, Indonesia, between April 2021 and September 2022. The study protocol conformed to the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia (No: KET-544/UN2.F1/ETIK/PPM.00.02/2020). The inclusion criteria included patients aged ≥18 years and meeting the diagnostic criteria for KSD based on ultrasonography, computed tomography (CT) scan, kidney, ureter, and bladder X-ray imaging. Those who met the inclusion criteria were consecutively recruited after providing informed consent. Patients were excluded if they refused to provide informed consent or had a horseshoe kidney, solitary kidney, medullary sponge kidney, polycystic kidney, congenital vesicoureteral reflux, neurogenic bladder, kidney cancer, pyonephrosis, a history of struvite stones, used urinary catheter or nephrostomy. This study included 80 patients who fulfilled the inclusion criteria and provided informed consent.

Baseline data, including body mass index (BMI), waist circumference (WC), and blood pressure, were retrieved during the screening process. All participants were Indonesian residents, and BMI was classified based on the Asia-Pacific cut-off criteria.[14] High WC was defined as ≥80 cm for females and ≥90 cm for males.[15] Patients with at least two symptomatic episodes or new stones after treatment were classified in the recurrence group, while the rest were classified into the first-time stone group. Education levels were classified as follows: high education level for those who completed senior high school or higher, intermediate level for those who completed junior high school, and low education level for those who completed only elementary school or had no formal education.

From each participant, an 8 ml of venous blood sample was collected for biochemical and genotyping analyses. Hypercalcemia, high serum creatinine levels, and hyperglycemia were defined as >10.2 mg/dl, >1.3 mg/dl, and >200 mg/dl, respectively. A cut-off of >6 mg/dl or >7.2 mg/dl was used for hyperuricemia in women and men, respectively. First-voided morning urine samples were collected to measure inflammatory cytokine gene expression. They were also required to collect their 24-hour urine samples using the S-Y Easy Fold 24hr Urine Collector (Shih-Yung Medical Instrument Co., Taiwan) without additional preservatives and store them in the refrigerator. The cut-off values for interpretation were <2,000 ml/day for low urine volume, hypercalciuria >250 mg/day for females and >300 mg/day for males, hyperoxaluria >40 mg/day, hyperuricosuria >750 mg/day, hypomagnesuria <60 mg/day, and hypocitraturia <300 mg/day.[16,17]

Finally, all participants were asked to complete a validated self-administered 7-day fluid record (Liq.In7) to evaluate total daily water and beverage intake.[18] All data were collected and managed using the Research Electronic Data Capture (REDCap®, USA) database hosted at Universitas Indonesia.[19]

Biochemical analyses

Blood samples were analyzed to determine random blood glucose (RBG), serum uric acid, and serum calcium levels using an Abbott Architecht Chemistry Analyzer (Abbott Diagnostics, USA). Creatinine levels were assessed using isotope dilution gas chromatography-mass spectrometry. Urine pH was determined using a pH paper strip, with acidic urine defined as a pH <5.5. The 24-hour urine excretion of calcium, oxalate, uric acid, magnesium, and citrate was estimated using a colorimetric assay kit (BioVision, USA).

Genotyping

Genomic DNA was extracted from whole blood samples using the QIAamp DNA Blood Mini Kit (QIAGEN, Netherlands). The quantity and quality of the extracted DNA were measured at 260 and 280 nm using a NanoDrop spectrophotometer (Thermo Fisher Scientific, USA). Genotyping of SNPs was performed using the 7500 Fast and 7500 Real-Time PCR Systems (Thermo Fisher Scientific). TaqMan GTXpress Master Mix and SNP genotyping assays (Thermo Fisher Scientific) were used to detect alleles present in the samples.

Statistical analysis

Data were presented as means and standard deviations, or medians and interquartile ranges for continuous variables, whereas categorical variables were presented as proportions. Statistical comparisons were performed using an independent *t*-test or the Mann–Whitney *U* test for continuous variables. All data analyses were completed using SPSS software version 25.0 (IBM Corp., USA), with $p<0.05$ indicating statistical significance. Genotypic, dominant, and recessive genotyping models were used to analyze the association of genes with KSD recurrence.

RESULTS

Demographic and clinical characteristics

This study examined 80 patients, including 33 (41%) with recurrent stones and 47 (59%) with first-time stones. The patients' ages ranged from 46 to 63 years, with a median age of 55 years. The proportions of office employees, shift workers, individuals with multiple stones, individuals with a family history of KSD, individuals with overweight obesity, and individuals with a large WC were higher among recurrent stone formers than among first-time stone formers. However, none of the differences in these proportions were statistically significant (Table 1). Average water consumption was low, with a mean of approximately 1,837 (539) ml for all participants.

Biochemical characteristics

Recurrent stone formers exhibited significantly elevated 24-hour urine calcium excretion ($p = 0.03$), although their serum calcium levels were low ($p = 0.019$). They also presented higher RBG levels, 24-hour urine oxalate, uric acid, citrate excretion, and magnesium excretion. The main abnormalities found in all participants were hypocitraturia (100%), low urine volume (78%), and hyperoxaluria (55%), with comparable proportions of single-type abnormalities between the groups. The results of the biochemical analysis are shown in Table 1.

Gene polymorphism and kidney stone recurrence

We investigated SNPs in the CaSR variants rs1801725 and rs1042636 genes, and their distributions were comparable between recurrent and first-time stone formers based on genotyping, dominant, and recessive models (Table 2).

DISCUSSION

Without preventive measures, the relapse rate of KSD is estimated to be 10–23% per year, 50% within 5–10 years, and 75% within 20 years after the first occurrence.[15] In this study, 41% of the participants had recurring stones, which is consistent with the rate reported in the literature.[7] A good proportion of patients with KSD recurrence in this study can be rationalized, as this study was mostly conducted on patients with complex cases in a national referral hospital.

This study aligns with a previous study that failed to find any association between sex and KSD recurrence,[20] despite the finding that patients with recurring and first-time stones were predominantly male. In contrast, Daudon et al[21] found that KSD recurrence was more common in men, based on an analysis of almost

Table 1. Demographic, clinical, and biochemical features of the subjects

Characteristics	Recurrent stone former (N = 33)	First-time stone former (N = 47)	*p*
Demographic and clinical features			
Sex, n (%)			0.272
Male	17 (52)	30 (64)	
Female	16 (48)	17 (36)	
Age (years), median (IQR)	55.0 (46.5–63.0)	55.0 (46.0–60.0)	0.604*
Degree of education, n (%)			
High	18 (55)	20 (43)	0.578
Intermediate	10 (30)	19 (40)	0.804
Low	5 (15)	8 (17)	0.557
Occupation, n (%)			0.883
Office employees	16 (48)	22 (47)	
Non-office employee	17 (52)	25 (53)	
Shift worker, n (%)			1.000
Yes	1 (3)	0 (0)	
No	32 (97)	47 (100)	
Multiple stones, n (%)			0.141
Yes	23 (70)	25 (53)	
No	10 (30)	22 (47)	
Family history of KSD, n (%)			0.089
Yes	12 (36)	9 (19)	
No	21 (64)	38 (81)	
BMI (kg/m^2), median (IQR)	26.3 (23.15–29.5)	26.7 (22.3–28.9)	0.856*
BMI classification, n (%)			0.513
Overweight–obese	26 (79)	34 (72)	
Underweight–normal	7 (21)	13 (28)	
WC (cm), mean (SD)	96.91 (13.3)	95.17 (12.39)	0.681
WC classification, n (%)			0.931
High	25 (76)	36 (77)	
Normal	8 (24)	11 (23)	
Daily water intake (ml), mean (SD)	1,866 (541)	1,817 (543)	0.694
Biochemical features			
Serum calcium (mg/dl), mean (SD)	8.77 (0.55)	9.14 (0.77)	**0.019**
High, n (%)	0 (0)	2 (4)	0.999
Serum uric acid (mg/dl), median (IQR)	6.4 (4.9–7.95)	6.7 (6.0–8.6)	0.122*
High, n (%)	13 (39)	25 (53)	0.225
Serum creatinine (mg/dl), median (IQR)	1.0 (0.9–1.4)	1.1 (0.75–1.55)	0.453*
High, n (%)	10 (30)	14 (30)	0.960
RBG (mg/dl), median (IQR)	102 (91.5–149.5)	99 (81–134.0)	0.214*
High, n (%)	5 (15)	2 (4)	0.110
24-hour urine volume (ml), median (IQR)	1,450 (975–2,025)	1,300 (950–1,800)	0.577*
High, n (%)	24 (73)	38 (81)	0.394
Urine calcium (mg/24 hour), median (IQR)	101.2 (52.96–168.88)	62.09 (41.85–107.39)	**0.03***
High, n (%)	2 (6)	0 (0)	0.999

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Table 1. (Continued)

Characteristics	Recurrent stone former (N = 33)	First-time stone former (N = 47)	*p*
Urine oxalate (mg/24 hour), median (IQR)	65.53 (33.45–165.7)	48.63 (25.5–105.71)	0.276*
High, n (%)	18 (55)	26 (55)	0.945
Urine uric acid (mg/24 hour), median (IQR)	49.27 (26.12–75.83)	37.31 (24.27–72.67)	0.639*
High, n (%)	0 (0)	0 (0)	NA
Urine magnesium (mg/24 hour), median (IQR)	65.47 (43.61–92.58)	79.7 (45.48-109.35)	0.195*
High, n (%)	15 (45)	14 (30)	0.154
Urine citrate (mg/24 hour), median (IQR)	11.59 (7.49–19.73)	8.15 (2.41–18.21)	0.121*
High, n (%)	33 (100)	47 (100)	NA
Urine pH, median (IQR)	6.0 (5.25–6.5)	6.0 (6.0–6.0)	0.917*
High, n (%)	8 (24)	9 (19)	0.584
Abnormal biochemical indices			
UTI, n (%)			0.536
High	9 (27)	10 (21)	

BMI=body mass index; IQR=interquartile range; KSD=kidney stone disease; NA=not available; RBG=random blood glucose; SD=standard deviation; UTI=urinary tract infection; WC=waist circumference

*Mann–Whitney test

The cut-off values for interpretation were >10.2 mg/dl for hypercalcemia; >750 mg/day for hyperuricosuria; >1.3 mg/dl for high serum creatinine levels; >200 mg/dl for hyperglycemia; <2,000 ml/day for low urine volume; >250 mg/day or >300 mg/day for hypercalciuria in women and men, respectively; >40 mg/day for hyperoxaluria; >6 mg/dl or >7.2 mg/dl for hyperuricemia in women and men, respectively; <60 mg/day for hypomagnesuria; <300 mg/day for hypocitraturia; and pH <5.5 for acidic urine

17,000 participants. It was previously hypothesized that estrogen in women might reduce calcium receptor expression, crystal binding capacity, and adenosine triphosphate in renal tubular cells, creating a protective environment against KSD.[22] Nevertheless, temporal data have shown increased KSD incidence among females in recent years, particularly among adolescents.[23]

This study had a median age of 55 years, supporting the finding of Widyasmara et al[24] that the peak incidence of kidney stones in Indonesia occurs between 51 and 60 years. Moreover, Trinchieri et al[20] reported no age differences between patients with one stone recurrence and those with first-time stones, which contrasts with a study by Li et al,[25] who reported that patients aged <20 years had higher rates of multiple stone recurrences. This study did not include patients aged <18 years, which may explain why the ages of the patients in the two groups were comparable. Moreover, no age data on the beginning of kidney stone formation was available; therefore, patients in the recurrent group may have had their first kidney stone occurring at a much younger age.

In this study, there were more participants with intermediate-to-higher education levels than those with low education levels in both groups. Additionally, more than 40% of the participants were office workers. Sedentary occupations lead to a higher risk of kidney stones, particularly for those with low water intake habits due to limited access to water or sanitary toilets.[26] Nevertheless, based on our findings, neither educational status nor occupation correlated with KSD recurrence.

This study suggests that a family history of KSD and multiple renal stones were more common in the recurrence group, although the difference was not statistically significant. This finding aligns with some related research[20,27] but contrasts with the meta-analysis findings by Wang et al[7] in 2022, which identified family history as a significant recurrence risk. Recurrence intervals were notably shorter in patients with a family history.[7] One study also showed that patients with multiple stones had a greater risk of recurrence than those with a single stone.[28] The difference in the results may stem from the smaller sample size compared to earlier studies.

Clinical factors, particularly hydration levels, can affect kidney stone recurrence. A previous study in Indonesia showed that most adults met their fluid intake recommendations, averaging over 2,000 ml/day.[29] However, the patients with kidney stones in our study only consumed approximately 1,837 (539) ml

Table 2. Association of CaSR SNP genotype to stone recurrence

SNP	Model	Genotype	Recurrent stone former, n (%) (N = 33)	First-time stone former, n (%) (N = 47)	*p*
CaSR rs1801725	Genotypic	TT	0 (0)	2 (4)	0.999
		GT	5 (15)	12 (26)	0.229
		GG	28 (85)	33 (70)	1.00
	Dominant	GT + TT	5 (15)	14 (29.8)	0.136
		GG	28 (85)	32 (70.2)	1.00
	Recessive	TT	0 (0)	2 (4)	0.999
		GG + GT	33 (100)	45 (96)	1.00
CaSR rs1042636	Genotypic	GG	10 (30)	14 (30)	0.355
		AG	18 (55)	20 (43)	0.169
		AA	5 (15)	13 (28)	1.00
	Dominant	AG + GG	28 (85)	34 (72)	0.269
		AA	5 (15)	13 (28)	1.00
	Recessive	GG	10 (30)	14 (30)	0.960
		AA + AG	23 (70)	33 (70)	1.00

CaSR=calcium-sensing receptor; SNP=single nucleotide polymorphism

daily, leading to a low urine volume. Compared with first-time stone formers, recurrent stone formers had significantly greater daily water intake and 24-hour urine volume, supporting a previous study that found lower urine volume was more common in first-time stone formers.[30] A daily urine output of 2.5 liters is recommended to reduce KSD risk.[31]

Metabolic syndrome is also linked to kidney stone recurrence risk, with factors such as low urine pH and high excretion of oxalate, uric acid, and phosphate often observed in individuals with high BMI.[32] Obesity also correlates with high stone recurrence risk.[33] However, this study found no significant differences in BMI or WC between the two groups. A chronic hyperglycemic state is associated with KSD formation, and the severity of diabetes is a key predictor of recurrence among patients with KSD and type 2 diabetes mellitus (DM).[34,35] Insulin resistance in DM leads to decreased renal ammonium production and decreased urinary pH, thus creating a favorable environment for uric acid stone formation.[36]

This study revealed that hypocitraturia, low urine volume, and hyperoxaluria were the most common abnormalities. Notably, 4% of our patients had hypercalcemia, 6% had hypercalciuria, and none had hyperuricosuria. We agree with a recent systematic review of 28 articles that concluded hyperoxaluria and hypocitraturia are common in non-Western countries.[37] In contrast, a higher incidence of hypercalciuria is found in Western countries.[37] These differences in disease risk may be attributed to various dietary patterns and nutritional compositions, and ethnicity may also contribute to these differences in disease risk.[38]

Despite a lower rate of hypercalciuria, we found that higher urine calcium excretion was significantly and independently associated with KSD recurrence, which is consistent with the findings of Hong et al.[39] According to the univariate analysis, patients in the recurrent stone group also had lower serum calcium levels, which could be associated with KSD if coupled with calcium loss in the kidney. Despite this discovery, the recurrent and first-time stone formation groups showed similar rates of hypercalciuria and hypercalcemia. Therefore, although urine calcium excretion levels did not fall in the hypercalciuria group, patients with high–normal levels should be cautioned about the possibility of stone recurrence. Urine supersaturation resulting from calcium excretion puts patients at a risk of stone formation. This is important because a previous study revealed that calcium oxalate is the most common stone component in the Indonesian population, followed by uric acid.[24]

Hypomagnesuria is also significantly associated with kidney stone recurrence. Magnesium prevents KSD by inhibiting calcium oxalate crystallization, which

is enhanced when combined with citrate and acidic urine.[40] Increased dietary magnesium intake is also associated with a reduced risk of KSD.[41] Future studies are needed to determine the role of magnesium supplementation in KSD recurrence.

Although 48% of our patients had hyperuricemia, none had hyperuricosuria. Similarly, several previous studies have shown that hyperuricemia is not associated with hyperuricosuria.[42,43] Therefore, hyperuricemia should not be used as a predictive factor for hyperuricosuria, considering that patients with normal serum urate levels may be overlooked during treatment. However, the evaluation of serum urate concentration still needs to be considered in patients with a history of arthropathy or gout.

CaSR gene, located in chromosome 3q13.3–21, can express the tubular cells protein in thick ascending limbs to regulate calcium reabsorption by inhibiting paracellular uptake of calcium, resulting in hypercalciuria.[44] A previous study found that a variant of the minor T allele in CaSR rs1801725 and the minor G allele in rs1042636 significantly increased the risk of KSD in Eastern India and the Egyptian population.[11,45] Furthermore, a combination of GT + TT genotypes in rs1801725 results in significantly higher serum calcium levels.[11] This result agrees with several other studies that found the association of a minor T allele in SNP rs1801725 to serum calcium level.[46] In contrast, rs1801725 was not correlated with an increased risk of KSD among the Chinese population.[47] This study has found no significant correlations between CaSR (rs1801725 and rs1042636) and kidney stone recurrence using any models. This study is the first to analyze CaSR SNPs associated with KSD recurrence in Indonesia. The small sample size, lack of healthy controls, and different genetic and phenotypic backgrounds may explain these findings. Therefore, it is premature to draw firm conclusions about the role of SNPs in KSD recurrence.

This study has some limitations. Due to a small patient cohort, ultrasound and kidney, ureter, and bladder X-ray, which are less sensitive than CT, were used. Other limitations include the lack of stone composition, comparative analysis with a control group, and failure to consider participant morbidities and medications. Future research should include case-control studies for a more comprehensive risk factor analysis to validate the current research findings.

Our study provides the groundwork for future studies on kidney stone pathophysiology, particularly in the Indonesian context. This study has significant implications for many beneficiaries, including clinicians, patients, and policymakers. Clinicians and patients will benefit from better guidance on personalized and effective kidney stone prevention and treatment strategies. Policymakers can use these insights to develop public health initiatives to reduce kidney stone recurrence.

In conclusion, recurrent stone formers had higher 24-hour urine calcium excretion and lower serum calcium levels. An insignificantly higher proportion of risk factors, such as occupation type, family history of KSD, and obesity, was found; however, no difference was found in CaSR polymorphisms (rs1801725 and rs1042636) between the recurrent and first-time stone groups. Given the small sample size and the complexity of KSD recurrence, this finding cannot be generalized to larger or different populations. Further studies with larger sample sizes are needed.

Conflict of Interest

Agus Rizal Ardy Hariandy Hamid is the editor-in-chief of this journal but was not involved in the review or decision-making process of the article.

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