BIOCHEMICAL AND HEMODYNAMIC CHARACTERIZATION OF NEPHROLITHIASIS PATIENTS VISITING NATIONAL TRANSPLANT CENTRE, BHAKTAPUR, NEPAL

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ABSTRACT

In present scenario, nephrolithiasis (renal stones) are more prevalent and highly related with morbidity worldwide. The aim of the study is to associate different biochemical and hemodynamic parameters of renal stones and to see post-operative outcomes. Hundred patients from January 2019 to January 2021 having renal stone in ultrasonography at Shahid Dharmbhakta National Transplant Centre Bhaktapur are included in the study. All variables are measured following the standard protocol. Nephrolithiasis was found to be frequent in male population (60%) who has a habit of regular alcohol intake (65%, p=0.009) and mixed dietary habit (mostly non-vegetarians) (92%, p= 0.042). Calcium oxalate either solely (21%) or mixed type (41%) were higher in proportion. The most common dyslipidemia in recurrent cases were hypercholesterolemia and increased LDL (p<0.001). The significant increase in serum urea (p=0.006) and creatinine (p=0.004) signify decrease in eGFR (p=0.007). Serum creatinine with IQR (1-2.5 mg/dl) was noticed significantly higher in others stone group V in contrast to mixed calcium containing stones group IV. Hydronephrosis was seen in 96% of patient, 7% developed post-operative complication comprising 57% haematuria, 28.5% wound infection and 14.5 % chest infection. Biochemical and hemodynamic parameters should be incorporated in nephrolithiasis to rule out risk of dyslipidemia, chronic kidney disorder and stratify the risk group based on stone composition.

KEYWORDS

Biochemical, chronic kidney disorder, hemodynamics, nephrolithiasis, types of stone

***Received on**: February 10, 2022*
***Accepted for publication**: August 20, 2022*

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DOI: https://doi.org/10.3126/nmcj.v24i4.50577

INTRODUCTION

Nephrolithiasis is defined as the accumulation of crystals in the pelvicalyceal system of kidney.[1] Renal stone is increasing significantly and is considered as one of the major cause of morbidity.[2] It was reported that in the United States, more than 5% of adults were found to be affected with stone diseases and the incidence rate has been increasing in the course of 30 years irrespective of gender, based on survey conducted by National Health and Nutrition Examination Surveys.[3] The main principle behind stone formation is super saturation of urine with materials depending on type of stone present.[4] Calcium stones are dominant, seen in both adults and children, and are alsofound in association with different metabolic disorders.[5] Although formation of renal stone are affected by environmental conditions and dietary habits, inheritance from family also plays a significant role.[6,7] These can be best explained in idiopathic stone formation.[8-10] Kidney stones are frequently seen in male in contrary to female and even types of stones seen vary according to gender.[10] Most stones less than 5 mm pass on itself by giving simple medication without any urosurgical intervention but larger stones may need endoscopic surgery for removal. In recurrent cases, special investigation followed by review and intervention is required.[11] On biochemical examination of stones, calcium oxalate are found to be dominant and often seen mixed with calcium phosphate stones.[12] The present study took an opportunity to associate the different biochemical and hemodynamic parameters of nephrolithiasis to observe any possibilities for improving medical intervention.

MATERIALS AND METHODS

A cross-sectional study was carried out in Shahid Dharmabhakta National Transplant Centre Bhaktapur, SDNTC between January 2019 and January 2021. A total of 100 patients including 60 male and 40 female diagnosed as nephrolithiasis in ultrasonography, visiting in OPD of SDNTC for treatment were enrolled. Patients with other cause of renal impairment were excluded. Per Cutaneous Nephrolithotomy (PCNL), Retrograde Intrarenal Surgery (RIRS), Uretro Renoscopy Lithoplast (URSL) were performed as a mode of surgery on the view of clinical correlation to patients. The demographic factors including previous history of stone and post-operative outcomes were also analysed. The ethical committee approval was obtained with the research reference number 77/78. All the biochemical estimations were carried out in Johnson and Johnson Vitros 350 fully automated analyzer. Kidney stone after surgery was kept in 10% formalin before its analysis. The stones were first examined for physical characteristics. As most of the stones were mixtures and consist of several layers so were pulverized. Fifty (50) mg of stone powder was mixed with 10dropsof 1.65 M HCl to form a reaction mixture used to test for Calcium, Ammonium, Cystine, Phosphate, Carbonate, Magnesium, Uric acid, and Oxalate using standard protocols. The category of stone was than categorized as:

1. Calcium Carbonate ($CaCO_3$)
2. Calcium Oxalate (CaC_2O_4)
3. Calcium Phosphate [$Ca_3(PO_4)_2$]
4. Mixed (Ammonium/Oxalate/ Phosphate with Calcium)
5. Others (Ammonium/Magnesium/Uric acid)

The sample size was determined as follows:

$$n = \frac{z^2PQ}{D^2}$$

$$= (1.96)^2 \times 0.07 \times 0.93/(0.05)^2 = 100$$

Where, n = sample size, Z = critical value = 1.96, P = prevalence of nephrolithiasis = 7%, Q = without disease (1-P), D = allowance error (5.0%).

Statistical analysis: All the data analysis were carried out by using Statistical Package for Social Service (SPSS) for window version; SPSS 22, Inc., Chicago, IL. Mann-Whitney U test was used to compare different hematological and biochemical parameters with history and number of stones present while Kruskal-Wallis test was employed to compare sub groups of stones with the datas. $P < 0.05$ was considered statistically significant.

RESULTS

Table 1 shows general characteristics of nephrolithiasis subjects based on gender. Male and female patients accounted for 69% and 31% respectively in alcoholics while in non alcoholics it was found to be 43% and 57% respectively, with a statistical significance (p=0. 009). Likewise, mixed diet in male and female occupied 61% and 39% whereas vegetarian was 50% in each group. However, presence of single stone (59% in male followed by 41% in female) and occurrence in ureter (57%) were seen dominant followed by kidney (53% in right kidney). Oval shaped and mixed stones

Table 1: General Characteristics of the Nephrolithiasis subjects based on gender

Variables		Total (n=100)	Gender	
			Male (n=60)	Female (n=40)
Alcohol, n (%)	No	35	15(43)	20(57)
	Yes	65	45(69)	20(31)
Dietary habit, n (%)	Mixed	92	56(61)	36(39)
	Veg	8	4 (50)	4(50)
Number of stones, n (%)	Single	88	52(59)	36(41)
	Multiple	12	8(67)	4(33)
Shape of stone, n (%)	Elliptical	4	2(50)	2(50)
	Mixed	1	1(100)	0(0)
	Oval	37	24(65)	13(35)
	Round	13	8(62)	5(38)
	Spherical	26	17(65)	9(35)
	Staghorn	19	8(42)	11(58)
Types of stone, n (%)	$CaCO_3$	2	0	2 (100)
	CaC_2O_4	21	13(61.9)	8 (38.1)
	$Ca_3(PO_4)_2$	5	2(40)	3(60)
	Mixed	41	25(61)	16(39)
	Other	31	20(64.5)	11(35.5)
Occurrence zone, n (%)	Kidney	43	26(60)	17(40)
	Ureter	57	34(60)	23(40)
Hydronephrosis, n (%)	No	4	4 (100)	0 (0)
	Yes	96	56(58)	40(42)
Presence of Stone in kidney, n (%)	Bilateral	19	13(68)	6(32)
	Left	28	16(57)	12(43)
	Right	53	31(58)	22(42)

were found more frequently (37% and 41% respectively) than others in both male and female. Calcium oxalate (CaC_2O_4) stones were seen in 61.9% male. Hydronephrosis were seen in 96% of total population enrolled.

Variation in different biochemical and hemodynamic parameters on the basis of previous history and number of stones is described in Table 2. Man Whitney U test shows statistically significant difference in fasting blood glucose (p=0.006), serum urea (p=0.006), serum creatinine (p =0.004), total cholesterol level (p <0.001), LDL (p <0.001), and eGFR (p =0.007) in subjects with previous history of stone when compared with new cases. However, serum creatinine, total cholesterol, triglyceride, and LDL were found to be higher in patients with multiple stone in contrast to single ones with no any statistical significance.

Table 3 illustrates comparison of different biochemical and hemodynamic characteristics on the basis of various stones present. On comparison, fasting sugar level, urea, sodium and calcium level (median, 100mg/dl, 39mg/dl, 139mg/dl and 8.5mg/dl respectively) were seen slightly higher in subjects with $CaCO_3$ stone. Uric acid, eGFR, and SBP (5mg/dl, 214ml/min, 130mm Hg, respectively) were increased in condition with CaC_2O_4 while triglyceride and HDL level with IQR, (147-174mg/dl) and (36-52mg/dl) was seen higher in $Ca_3(PO_4)_2$ group. Total cholesterol with median of 196mg/dl and LDL with 98mgldl were slightly higher in other case. However no any statistical significance was observed. In contrast, serum creatinine level was also found significantly increased in later group with IQR range of (1-2.5mg/dl).

Results after nephrolithiasis surgery were discussed in Table 4. Out of 100 subjects enrolled, 90% needed insertion of double J (DJ)stent in which, male population accounted for 61% (n=55). Out of total cases, 7% developed post-operative complication. Hematuria was found dominant (n=4) followed by wound infection and chest infection (n=2, n=1 respectively). 71.4% of post-operative complications were seen in male. The median size of stone recovered from surgery was significantly larger in female (18mm) with interquartile range of (15-35 mm). Duration of surgery and hospital stay was with median of 67 min and 1 day (IQR 1.0 -3.75 days) irrespective of gender.

Table 2: Biochemical and Hemodynamic characterization of Nephrolithiasis subjects based on previous history and number of stones

Variables Median (IQR)	Previous History of stone		p-value	Number of Stones		p-value
	Yes (n= 23)	No (n=77)		Single (n=81)	Multiple (n=19)	
Age (yrs)	43 (28-54)	43 (32-52)	0.52	43 (33-54)	44 (26-52)	0.301
FBG	102 (97-111)	96 (89-101)	**0.005**	97 (89-104)	99 (92-109)	0.324
HbA_{1c}	5.3 (5.2-5.7)	5.2 (5.1-5.4)	0.085	5.3 (5.1-5.5)	5.2 (5-5.6)	0.743
Urea	39 (34-45)	34 (30-38)	**0.007**	35 (31-39)	33 (26-40)	0.295
Crea	1.1 (0.9-1.4)	0.8 (0.6-1.1)	**0.004**	0.9 (0.6-1.1)	1 (0.7-1.2)	0.678
Na^+	138 (136-139)	138 (135-138)	0.58	137 (135-138)	138 (136 -140)	0.058
K^+	4 (4-5.2)	3.9 (3.7-4.1)	0.81	3.9 (3.7-4.1)	4.1 (3.9-4.3)	**0.021**
$T.Ca^{++}$	7.9 (7.6-8.1)	8.1 (7.9-8.3)	**0.028**	8.1 (7.8-8.3)	8 (7.8-8.4)	0.884
PO_4^{---}	4.2 (3.8-4.8)	4 (3.7-4.6)	0.455	4 (3.7-4.6)	4.2 (3.8-4.5)	0.982
UA	4.5(3.9-5.1)	4.3 (3.9-5.1)	0.597	4.4 (3.9-5.1)	4.3(3.7-5.1)	0.986
T. C	219 (196-250)	187 (164-200)	**<0.001**	188 (164-208)	199 (187-236)	0.072
TG	152 (136-168)	145 (133-158)	0.066	145 (134-157)	152 (138-165)	0.096
LDL	133 (65-160)	68 (40-110)	**<0.001**	78 (45-123)	73 (58-134)	0.565
HDL	45 (35-52)	40 (35-52)	0.307	42 (35-52)	41 (35-51)	0.898
eGFR	198 (178-215)	210 (200-230)	**0.005**	210 (197-226)	206 (191-231)	0.898
Hb	12.5 (11-14)	12 (12-14)	0.544	12.5 (11.5-13.4)	14 (12.5-14.5)	**0.025**
PR	73 (68-85)	72 (68-80)	0.869	76 (68-81)	72 (68-80)	0.677
SBP	120 (120-140)	130 (120-140)	0.287	130 (120-140)	120 (112-137)	0.225
DBP	80 (80-90)	80 (80-90)	0.768	80 (80-90)	80 (72-90)	0.527

Abbreviation: Age (yrs)–Age (years), FBG-Fasting Blood Glucose (mg/dl), HbA_{1c}-Glycated Hemoglobin (%) Crea-Creatinine(mg/dl), Na^+ -Sodium (mmol/L), K^+-Potassium (mmol/L), $T.Ca^{++}$-Total Calcium (mg/dl), PO_4^{---}-Phosphorus (mg/dl), UA–Uric Acid (mg/dl), T.C-Total Cholesterol (mg/dl), TG-Triglycerides (mg/dl), LDL-Low Density Lipoprotein (mg/dl), HDL-High Density Lipoprotein (mg/dl), eGFR –estimated Glomerular Filtration Rate (ml/min), Hb-Hemoglobin (g/dl), PR-pulse rate (/min), SBP-Systolic Blood Pressure (mm Hg), DBP-Diastolic Blood Pressure (mm Hg). Results obtained from Man Whitney U test. P-value <0.05 considered statistically significant, and indicated bold

Table 3: Biochemical and Hemodynamic characterization of Nephrolithiasis subjects based on types of stone

Variables Median (IQR)	Types of stone					p-value
	$CaCO_3$ (n=2)	CaC_2O_4 (n=21)	$Ca_3(PO_4)_2$ (n=5)	Mixed (n=41)	Others (n=31)	
Age (yrs)	38 (NA)	47 (33-56)	34 (29-55)	40 (31-51)	46 (33-56)	0.413
FBG	100 (NA)	96 (81-99)	98 (93-105)	98 (92-109)	99 (92-107)	0.217
HbA_{1c}	5 (NA)	5 (5-5.5)	5 (5-6)	5 (5-6)	5 (5-5.5)	0.263
Urea	39 (NA)	34 (33-37)	36 (22-41)	35 (26-40)	35 (31-40)	0.630
Crea	1 (NA)	1 (0.1-1)	1 (1-1.1)	1 (1-1.8)	1 (1-2.5)	**0.009**
Na^+	139 (NA)	138 (136-139)	138 (135-140)	136 (134-138)	136 (135-139)	0.366
K^+	4 (NA)	4 (4-4.5)	4 (4-4.8)	4 (4-5)	4 (4-4.6)	0.290
$T.Ca^{++}$	8.5 (NA)	8 (8-8.2)	8 (8-8.2)	8 (7.5-8)	8 (7.7-8.1)	0.104
PO_4^{---}	4 (NA)	4 (4-4.5)	4 (4-4.5)	4 (4-5)	4 (4-5)	0.553
UA	4 (NA)	5 (4-5)	4 (2-5.5)	4 (4-5)	4 (4-5)	0.570
T.C	195 (NA)	190 (180-200)	188 (157-212)	187 (159-215)	196 (180-210)	0.903
TG	131 (NA)	147 (135-159)	164 (147-174)	146 (133-158)	145 (134-165)	0.298
LDL	60 (NA)	40 (40-150)	87 (64-145)	78 (57-133)	98 (64-134)	0.149
HDL	43 (NA)	45 (35-53)	51 (36-52)	40 (32-52)	40 (37-56)	0.748
eGFR	195 (NA)	214 (200-234)	205 (197-231)	205 (197-231)	202 (186-230)	0.433
Hb	11.5 (NA)	13 (12-15)	12 (11-13.5)	12 (12-13)	13 (12-14)	0.217
PR	68 (NA)	80 (72-84)	78 (72-89)	72 (68-80)	72 (68-80)	0.077
SBP	125 (NA)	130 (120-140)	130 (125-138)	120 (120-135)	120 (120-140	0.374
DBP	75 (NA)	90 (80-90)	80 (74-90)	80 (80-90)	80 (80-90)	0.440

Abbreviation: Age (yrs)–Age (years), FBG–Fasting Blood Glucose (mg/dl), HbA_{1c}–Glycated Hemoglobin (%), Crea–Creatinine(mg/dl), Na^+–Sodium (mmol/L), K^+–Potassium (mmol/L), $T.Ca^{++}$–Total Calcium (mg/dl), PO_4^{---}-Phosphorus (mg/dl), UA–Uric Acid (mg/dl), T.C–Total Cholesterol (mg/dl), TG–Triglycerides (mg/dl), LDL–Low Density Lipoprotein (mg/dl), HDL–High Density Lipoprotein (mg/dl), eGFR–estimated Glomerular Filtration Rate (ml/min), Hb–Hemoglobin (g/dl), PR–pulse rate (/min), SBP–Systolic Blood Pressure (mm Hg), DBP–Diastolic Blood Pressure (mm Hg). $CaCO_3$–Calcium Carbonate,CaC_2O_4–Calcium Oxalate, $Ca_3(PO_4)_2$–Calcium Phosphate Mixed (oxalate & phosphate), Others (cystine/ammonium phosphate). Results obtained from Kruskal-Wallis test. P–value <0.05 considered statistically significant, and indicated bold

Table 4: Outcome of Nephrolithiasis Surgery based on Gender

Variables		Total(n=100)	Gender		p-value
			Male (n=60)	Female (n=40)	
Nephrostomy tube	No	90	55(61%)	35(39%)	0.361
	Yes	10	5(50%)	5(50%)	
Any post operative complications	Chest infection	1	1(100%)	0(0%)	0.533
	Hematuria	4	2(50%)	2(50%)	
	Wound infection	2	2(100%)	0 (0%)	
	No	93	55(59%)	38(41%)	
Median (IQR)	Size (mm)	18 (15-34)	17(14-34)	18(15-35)	**<0.001**
	Duration of surgery (mins)	67(46-90)	67(46-90)	68(48-90)	0.776
	Hospital stay (days)	1(1-3.75)	1(1-3.75)	1.5(1-3.75)	0.679

DISCUSSION

Nephrolithiasis is frequently encountered as one of the common kidney disease and is increasing throughout the globe.[13] Renal stones are seen prevalent in patients with mixed diet rather than vegetarian diet. Naya *et al*[14] also discovered incorporation of animal protein and fat in diet is positively correlated with risk of nephrolithiasis. Out of 100 patients enrolled, male accounted for 60% while 40% were female. This is supported by the study of Curhan *et al*[15] and Faiza *et al.*[16] The recurrence rate was found to be 23% with previous history of stone that was around half of the result seen in the study of Daudon *et al.*[17] In our study, serum urea and creatinine level were found significantly higher directing to the possibility of CKD in recurrent cases as that of Sigurjonsdottir *et al*[18] and Vupputri *et al.*[19] Estimated GFR was also observed lower in patients with previous history of stone in comparison to new cases. The finding was similar to the study of the Third National Health and Nutrition Examination survey.[20] In contrary, no any significant association was found with number of stones recovered and stone recurrence unlike a recent Canadian cohort study.[21] But similar results were seen in finding of Sigurjonsdottir *et al.*[18] Stone recurrence was found to be associated with hypercholesterolemia group. But surprisingly there was no association with elevated triglyceride level in contrast to some study.[22] Our study also shows hyperglycemia contributing for prevalence of nephrolithiasis mostly in recurrent cases. Liu *et al*[23] also showed close relationship between diabetes and urolithiasis, in one of his review article. Furthermore, regarding composition of stone removed, calcium oxalate was dominant covering 21% followed by mixed stone 41%. Similar results were also seen in previous reports in China.[24,25] Serum creatinine level was seen significantly higher in group V with struvite and uric acid. This implies that patient with calcium containing stones are at low risk of developing renal impairment and CKD as compared to later groups.[26] It can be explained by chronic recurrent urinary tract infection leading to rapid deterioration of renal function in case of struvite stone,[27,28] whereas uric acid stones are closely associated with metabolic disorder that may cause CKD.[27,29,30] However, eGFR was seen slightly lower in calcium containing stones unlike some clinical studies.[26] The pragmatic way to prevent the recurrence of renal calculi after a single episode is to analyze chemical composition of stone. The surgical procedures for stone removal are applied to a patient who has been diagnosed with large renal calculi and failure of medical expulsive therapy. Some study has shown 4-50% renal stone recurrence, so patient should be counseled on risks of recurrence on their first visit of stone treatment.[31] Hence, stone analysis plays an important role in the outcome of renal stone management. In present study the median size of stone was observed to be statistically differing between male and female. However, post-operative complications, insertion of DJ stent, duration of surgery and hospital stay remain statistically non significant for both gender. The main limitations of the study were a relatively small sample size, no clear differentiation of stone types in the group "others" and recurrent cases were not properly defined.

Apart from different metabolic disorder, our study shows that composition of stones do affect renal function test leading to high risk of CKD. Thus, examination of stone should be carried out thoroughly and the vulnerable group should be treated on time to avoid recurrence which can prevent the further serious complication.

ACKNOWLEDGEMENT

We would like to thank all participants who had undergone various modalities of treatment for removal of stones. My immense thanks to the surgeon and the technologist, SDNTC, whoever is directly or indirectly involved during surgery.

Conflict of interests: None

Source of research fund: None

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