Association of Different Biochemical and Hemodynamic Characteristic with Type 2 Diabetes Mellitus and Hypertension in Nephrolithiasis Patients

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ABSTRACT

Background

Although Nephrolithiasis is a common condition caused by a wide variety of metabolic or environmental disturbances, its being one of the major factor of morbidity. Incidence of kidney stone disease (KSD) is highly affected by metabolic disorders and change in blood pressure and glucose.

Objective

To find out association of different biochemical and hemodynamic parameters with various glycemic status and hypertension in kidney stone disease.

Method

A cross sectional study was conducted in patients diagnosed as nephrolithiasis by using re¬nal ultrasonography and underwent nephrectomy between January 2019 to January 2021 in Shahid Dharmabhakta National Transplant Centre (SDNTC). A total of 100 subjects with 60 male and 40 females were enrolled. Glycemic status was categorized based on criteria of American Diabetes Association (ADA) and hypertension was defined as BP ≥ 140/90 mm Hg in right arm supine position. All biochemical and hemodynamic profile was carried out following standard protocol.

Result

Out of 100 patients enrolled, pre-diabetes accounted for 31% followed by diabetes (4%). However, hypertension comprised of 66% in total subjects. Serum urea, cholesterol and triglyceride level were found to be increased by 84.6%, 67.7% and 64.7% respectively in diabetes followed by increase of 3.9%, 19.5% and 3.1% respectively in prediabetes when compared to normal glycemic condition in nephrolithiasis subjects. Serum fasting blood glucose, creatinine and uric acid level was observed significantly higher ($p=0.003$, $p=0.004$, $p < 0.001$ respectively) in hypertensive patients. Duration of hospital stay was also seen positively correlated with hypertension.

Conclusion

Not only diabetes, prediabetes also manifests the increased risk of kidney stone disease along with hypertension. There is significant impairment in renal function and lipid profile based on diabetes mellitus and hypertension. Early identifying these systemic diseases, different biochemical and hemodynamic parameters and proper treatment accordingly may minimize risk and prevent serious complication in these patients.

KEY WORDS

Diabetes mellitus, Hypertension, Nephrolithiasis

INTRODUCTION

Nephrolithiasis is being increasing throughout the globe and is found to be closely associated with gender, ethnicity, age factor and transition to present sedentary lifestyle.[1] It is considered as one of the responsible factor for morbidity. It was reported that at the age of 75 years, around 10% men followed by 5% women develop kidney stone.[2-5] Most of studies have been conducted to show the association of nephrolithiasis with different metabolic disorder components like hypertension, hyperglycemia and diabetes mellitus. Kidney stone disease (KSD) not only enhance the risk of other comorbidity but in fact leads to final stage of renal disorder. Type 2 diabetes mellitus is a systemic metabolic disease caused due to insulin resistance that in turn causes alteration in formation of renal ammonium and finally contributes to formation of kidney stones.[6-8] Apart from diabetes mellitus (DM), nephrolithiasis is also seen in close association with hypertension. Although the main mechanism behind hypertension is still in doubt, different experimental study yet provide evidence to support hypertension as a causative factor that amplify risk of kidney stone. Tibblin was first of them to explain the association in 1965.[9] Risk of hypertension is increased by 1.24-1.96 in nephrolithiasis patient in contrary to normal ones.[10-16] Review by Cupisti et al. also supported the close link of hypertension with incidence of kidney stone.[17] Thus, recognizing such systemic disease at right time will minimize the risk of forming kidney stone and recurrent stones as well.

METHODS

A hospital based descriptive cross-sectional study was conducted over a period of 2 years commencing from January 2019 to January 2021 in Shahid Dharmabhakta National Transplant Centre (SDNTC). Hundred patients who have been diagnosed with nephrolithiasis based on ultrasonography and undergone nephrectomies were included in this study whereas patients with other causes of kidney disease were excluded. Post- operative outcomes were also recorded. The ethical committee approval was obtained with the research reference number 77/78. Glycemic status, prediabetic (100-125 mg/dl), diabetic (≥ 126 mg/dl) and normal (< 100 mg/dl), was categorized based on criteria of American Diabetes Association (ADA) and hypertension was defined as BP ≥ 140/90 mmHg in right arm supine position. Different socio-demographic characteristics of the patients like age, sex, ethnicity, dietary habits, alcohol intake, pulse rate and blood pressure were noted. eGFR was calculated by Cock Croft Gault (CG) equation. Serum level of calcium, phosphorous, lipid profile, renal function test, and hemoglobin were measured by using standard protocol.

The sample size was determined as follows: $n=(Z^{\wedge 2}\ PQ)/D^{\wedge 2} = (1.96)^2 \times 0.07 \times 0.93 / (0.0025)^2 = 100$

Where, n = sample size, Z = critical value = 1.96, P = prevalence of nephrolithiasis = 7%, Q = without disease (1-P), D = allowance error (5%)

All the data from cases were fed in Microsoft office 2010, MS Excel and then analyzed by Statistical Package for Social Service (SPSS) for window version; SPSS 22, Inc., Chicago, IL. The data was expressed in terms of percentage frequency and tested by chi-square test; the median values were compared by Man Whitney U test and association of variables with Spearman's correlation. P-value < 0.05 was considered to be statistically significant.

RESULTS

Table 1 shows the association of different biochemical and hematological variables with FBG and BP of nephrolithiasis patients. The serum urea level was seen significantly increased in all 4 cases (100%) in diabetic subjects as compared to 6 cases (19.3%) in prediabetes followed by 10 cases (15.4 %) in normal subjects (p < 0.001). Similarly, increased cholesterol and TG were observed in all cases 4 (100%) in FBG ≥ 126 mg/dl as compared to 100-125 mg/dl with 35.4% and 54.8% cases respectively and <100 mg/dl blood glucose level with 32.3% and 35.3% cases respectively (p=0.024, p=0014). Moreover, lower HDL level was observed in 3 cases (75%) and higher diastolic pressure with 3 cases (75%) was observed in diabetic as compared to prediabetes and normal cases (p=0.004, p=0.047). Regarding hypertension, serum creatinine level was found significantly increased in 7 cases (20.6%) with BP ≥ 140/90 as compared with < 140/90 (p=0.004).

Table 2 illustrates the median (IQR) of biochemical parameters, hemodynamic variables and outcome of surgery with FBG and BP of Nephrolithiasis patients. In comparison of DM with prediabetes and normal cases, the median age of diabetic subjects was 54 years with an interquartile range (IQR) of 48-58 years followed by 38-56 years in prediabetes and least IQR of 30-50 years in normal FBG cases (p=0.006). Man Whitney U test shows statistically significant difference in FBS, HbA1c, urea, creatinine, uric acid and eGFR among these three groups (<0.001, 0.019, 0.004, 0.004, 0.008, <0.001) respectively. Serum TC, TG and LDL were statistically different in FBS ≥ 126 in comparison to 100-125 (prediabetic) and <100 (normal) cases (0.003, < 0.001, < 0.001 respectively.)

In subjects with hypertension, there was significant increase in fasting blood glucose level with IQR 97-108 in cases with BP ≥ 140/90 (p= 0.003). Serum uric acid was observed significantly higher in BP ≥ 140/90 mmHg as compared to < 140/90 mm Hg (p < 0.001).

The spearman's correlation shows significant negative correlation in nephrolithiasis cases between serum urea, creatinine, sodium, TC, TG and LDL with estimated GFR whereas FBG was found positively correlated with serum

Table 1. **Association Biochemical parameters and Hemodynamic variables with FBG and BP in Nephrolithiasis**

Biochemical & Hemodynamic variable		FBG level (mg/dl)			p-value	BP (mm/Hg)		p-value
		≥126 (n=4)	100-125 (n=31)	<100 (n=65)		≥140/90 (n=34)	<140/90 (n=66)	
HbA1c (%)	Normal (<5.7)	2	19	53	0.057	24	50	0.371
	High (≥5.7)	2	12	12		10	16	
Urea (mg/dl)	Normal	0	25	55	<0.001	26	54	0.351
	High>40	4	6	10		8	12	
Crea (mg/dl)	Normal	3	28	59	0.659	27	61	0.004
	High > 1.3 (M) / >1.1(F)	1	3	6		7	4	
T.C (mg/dl)	Normal	0	20	44	0.024	24	40	0.383
	High≥200	4	11	21		10	26	
TG (mg/dl)	Normal	0	14	42	0.014	17	39	0.404
	High≥150	4	17	23		17	27	
LDL (mg/dl)	Normal	1	22	32	0.063	22	33	0.204
	High>130	3	9	33		12	33	
HDL (mg/dl)	Normal	1	14	49	0.004	19	45	0.273
	Low <35	3	17	16		15	21	
Hb (g/dl)	Normal	4	30	64	0.823	32	66	0.113
	Low≤10	0	1	1		2	0	
SBP (mm Hg)	Normal	2	18	50	0.114	8	62	<0.001
	High≥140	2	13	15		26	4	
DBP (mm Hg)	Normal	1	15	45	0.047	1	60	<0.001
	High≥90	3	16	20			6	

Abbreviation: HbA1c-Glycated Hemoglobin (%), Crea-Creatinine, T.C-Total Cholesterol, TG-Triglycerides, LDL-Low Density Lipoprotein, HDL-High Density Lipoprotein, Hb-Hemoglobin, SBP-Systolic Blood Pressure, DBP-Diastolic Blood Pressure. Results obtained from Chi-square test. P-value <0.05 considered statistically significant and indicated bold.

phosphorous, uric acid, TG and LDL ($p < 0.05$). Likewise, in nephrolithiasis cases, there was positive correlation between HbA1c with TC, TG and phosphorous level ($p < 0.05$). Systolic blood pressure and diastolic blood pressure were found to be positively correlated with TG and hospital stay ($p < 0.05$).

DISCUSSION

In our study, approximately 31% and 4% of total kidney stone patients were prediabetes and diabetes respectively. Most of the study depicted positive association of DM with nephrolithiasis but still there is little explanation about the inconsistent link with prediabetes.[18] One of the accepted mechanisms behind it is insulin resistance that alters ammonium formation by disturbing use of glutamine subsequently.[19-23] Our study also addressed the relative incidence of kidney stone in subjects diagnosed with metabolic disorder (35%) and is supported by many epidemiological studies conducted in western countries. However, diabetes mellitus caused due to nephrolithiasis is uncommon.[24-29] The distribution of nephrolithiasis is found to be higher in male subjects (60%). Likewise, significant increase in uric acid ($p = 0.008$) with metabolic disorder is also seen in kidney stone patients. Such findings are also observed consistent with some study conducted by Romero, Ramello, Lien, Gutman and Yu.[1,30-32] Diabetes mellitus is one of the common causes of renal dysfunction.[33] In congruence with a study done in the Olmsted country population where patients with nephrolithiasis and chronic kidney disease were found frequently in hyperglycemic cases.[34-36] The present research discovered that serum urea and creatinine level were increased in nephrolithiasis subjects with elevated fasting blood glucose level, which is approximately 1.25 times higher than normal. This was followed by a decrease in eGFR by 1.1 times. In context of nephrolithiasis, HbA1c levels can indicate the severity and control of underlying diabetes. Higher HbA1c levels reflect poorer glycemic control and suggest an increased risk of stone formation. The present study has also soon diabetic and prediabetic cases with more HbA1c level with derangement in some renal and lipid profiles.

Few studies were conducted to find out association of kidney stone with renal function. Obstructive nephropathy, infection, and inflammation along with metabolic disorders mainly diabetes mellitus and hypertension has shown contributory factor behind nephrolithiasis.[35-39] In some studies, it was observed that stone deposited in loop of Henle causes interstitial inflammation resulting impairment in renal function.[40-42] The present study has shown uric acid level was positively correlated with increased blood sugar.

Table 2. Median (IQR) of Biochemical parameters, Hemodynamic variables and outcome of surgery with FBG and BP in Nephrolithiasis subjects (N=100)

	Blood Glucose (mg/dl)			p-value	Blood Pressure (mm Hg)		p-value
	≥126 (n=4)	100-125 (n=31)	< 100 (n=65)		≥ 140/90 (n=34)	< 140/90 (n=66)	
Age (yrs)	54 (48-58)	50 (38-56)	38 (30-50)	0.006	43 (34-53)	43 (30-52)	0.458
FBG	156 (146-183)	108 (102-111)	94 (89-98)	<0.001	101 (97-108)	96 (89-100)	0.003
HbA1c	6.5 (5-8.7)	5 (5-6)	5 (5-5.1)	0.019	5 (5-6)	5 (5-5.2)	0.450
Urea	48 (43-160)	37 (31-40)	34 (31-38)	0.004	34 (31-40)	35 (31-39)	0.945
Crea	1.5 (1-6.5)	1 (1-3.5)	1(0.5-1)	0.004	1 (1-2.8)	1 (1-2.3)	0.144
Na+	139 (137-140)	136 (135-138)	138 (135-139)	0.191	137 (135-138)	138 (135-138)	0.903
K+	4 (4-4.7)	4 (4-4.4)	4 (4-4.5)	0.440	4 (4-4.3)	4 (4-4.2)	0.115
T.Ca++	8 (8-8.3)	8 (8-8.2)	8 (8-8.1)	0.486	8 (8-8.1)	8 (8-8.4)	0.665
PO4---	4.5 (4-5)	4(4-5)	4(4-4.5)	0.303	4(4-5)	4 (4-4.8)	0.103
UA	5 (5-6.5)	5(4-5)	4(4-5)	0.008	5(4-5.2)	4(4-5)	0.008
T.C	278 (254-289)	196 (164-215)	187 (168-205)	0.003	187 (161-208)	192 (168-212)	0.310
TG	196 (175-211)	152 (132-165)	145 (135-154)	<0.001	151 (135-166)	146 (134-158)	0.111
LDL	167 (111-193)	132 (65-142)	64 (41-99)	<0.001	91 (40-140)	73 (54-120)	0.353
HDL	33(32-48)	48(38-56)	39(35-51)	0.054	43(35-52)	41(35-52)	0.726
eGFR	163 (82-187)	200 (180-215)	214 (200-230)	<0.001	210 (196-218)	212 (200-230)	0.681
Hb	13(11-15)	12(12-13)	13(12-14)	0.710	12(11-13)	13(12-14)	0.004
PR	75(67-78)	72(68-85)	74(68-80)	0.807	75(69-85)	72(68-80)	0.064
SBP	130 (112-140)	130 (120-140)	120 (120-133)	0.342	140 (137-142)	120 (120-130)	<0.001
DBP	90 (82-97)	90 (80-90)	80 (80-90)	0.075	90 (90-98)	80 (74-86)	<0.001
Size	43.5 (19.5-53.2)	16 (14-35)	18 (15-29.5)	0.566	20 (14.7-32.7)	16 (15-35.2)	0.630
D. Sur.	90 (42-165)	67 (46-86)	69 (48-92)	0.561	67 (46-90)	69 (47.5-92)	0.639
Hos. Stay	2 (1-4.5)	1 (1-2)	2 (1-4)	0.412	1 (1-3)	1.5 (1-4)	0.336

Abbreviation: Age (yrs)-Age (years), FBG-Fasting Blood Glucose (mg/dl), HbA1c-Glycated Hemoglobin (%), Crea-Creatinine (mg/dl), Na+ -Sodium (mmol/L), K+-Potassium (mmol/L), T.Ca++-Total Calcium (mg/dl), PO4----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-Dystolic Blood Pressure (mm Hg), D. Sur.-Duration of Surgery (Minutes), Hos. Stay-Hospital Stay (days). Results obtained from Kruskal-Wallis for FBG and Man Whitney for BP. P-value < 0.05 considered statistically significant and indicated bold.

Table 3. Spearman's Correlation of Biochemical parameters, Hemodynamic variables and outcome of Nephrolithiasis (N=100)

Variables	Sys. BP	Dias. BP	PR	Hb	FBG	HbA1c	eGFR
Urea	-.139	-.077	.089	-.009	.207*	-.055	-.356*
Creatinine	-060	.020	-.123	.099	.099	-.131	-.367*
Sodium	-.161	.046	-.040	.095	-.011	-.065	-.275*
Potassium	.021	.126	.003	-.132	.139	.018	.009
Calcium	-.070	-.043	-.185	.094	-.151	-.008	-.019
Phosphorus	.174	.143	.057	-.020	.300*	.408*	.024
Uric acid	.136	.278*	.076	-.122	.244*	.078	-.090
T. Cholesterol	-.075	-.126	-.142	.029	.123	.320*	-.246*
Triglyceride	.206*	.118	.035	-.034	.222*	.260*	-.378*
LDL	.112	.019	.008	-.036	.320*	.129	-.276*
HDL	.182	-.004	-.017	-.094	.065	-.241*	-.040
Size	-.038	.006	-.131	.066	.068	.051	.616
Duration of Surgery	-.033	-.060	.068	.001	-.015	-.008	-.012
Hospital Stay	.024	-.202*	-.072	-.118	.004	-.032	.020

Results obtained were Spearman's correlation (ρ) value where *p-value <0.05 considered statistically significant and indicated bold.

Under normal circumstances, uric acid dissolves in the blood, passes through the kidneys, and is excreted in urine. However, when there is an excess of uric acid or if the urine becomes too acidic in infections or diabetes mellitus, it can crystallize and form uric acid stones.

In contrast to prior investigations, a substantial link between dyslipidemia and nephrolithiasis was observed in these participants. The elevated levels of certain lipids, particularly TC, TG and LDL-C have been shown to be associated with diabetes mellitus cases and increased risk of kidney stone formation. Though full mechanism is not still understood, but it may be related to the impact of lipid abnormalities on various physiological processes, including inflammation, oxidative stress, and urinary excretion of stone-forming substances.[43] In the present study there was a significant increase in fasting blood glucose level showing insulin resistance and further affecting vascular system leading to elevated blood pressure in kidney stone patients.[11,44]

High uric acid levels can contribute to endothelial dysfunction, which refers to impaired function of the cells lining the blood vessels. This dysfunction can lead to vasoconstriction and increased resistance to blood flow, contributing to elevated blood pressure. Like our investigation, some cohort studies conducted in China, Japan, and Bangladesh found a favorable connection between serum uric acid levels and hypertension.[45-50]

Elevated blood pressure can alter kidney function, leading to changes in urine composition and reduced urine volume. These factors can promote the formation of kidney stones. Individuals with diabetes may have altered urine composition, including increased excretion of calcium and oxalate, which are major components of kidney stones. Moreover, poorly controlled blood glucose levels can lead to dehydration, concentrated urine and reduced urinary flow, all of which increase the risk of stone formation.

It is important that the biochemical and hemodynamic characteristics can vary among individuals depending on the severity and control of diabetes mellitus, hypertension, and nephrolithiasis. Hence, long term randomized control trial can be studied in those patients including medication use, lifestyle and other comorbidities which can influence these characteristics. By addressing these factors, healthcare providers aim to reduce the risk of recurrent kidney stone formation, minimize cardiovascular complications, and promote overall health and well-being in patients with nephrolithiasis.

CONCLUSION

Hypertension, metabolic disorder, and renal impairment are found to be significantly associated with each other in kidney stone disease. Early detection of these diseases with periodic investigation of different hemodynamic and biochemical parameters can make it easy to avoid serious complications in handling and treating nephrolithiasis.

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