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Original Research Article

Metabolic Syndrome a Risk Factor of Nephrolithiasis: A Case Control Study

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Abstract:

Background: This study was conducted to determine as to whether metabolic syndrome is a risk factor for nephrolithiasis among patients and whether individual components of metabolic syndrome are risk factors for nephrolithiasis.

Methods: This was a hospital-based case control study conducted among 238 patients who underwent evaluation for the presence of metabolic syndrome at the Department of Urology, Governmental Medical College Alappuzha, over a period of 18 months after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Results: A total of 238 patients were enrolled in the study after counselling and informed consent. 119 had ultrasound-proven nephrolithiasis, and the rest of the patients were controls. All were evaluated for components of metabolic syndrome. The average age of patients was 43.45, waist circumference was 95.01, BMI was 22.82, systolic BP was 129.01, diastolic BP was 79.99, FBS was 91.58, HDL was 49.91 and triglycerides was 151.68. Male predominance was noted with 77.3 percent of participants enrolled in the study. Primary outcome: metabolic syndrome as a risk factor for nephrolithiasis is proven with a p-value of 0.008. Secondary outcomes: obesity and dyslipidemia were proven to be independent risk factors with a p-value <0. 001. However hypertension and diabetes mellitus do not independently increase the risk of nephrolithiasis.

Conclusion: Metabolic syndrome when present acts as a risk factor for nephrolithiasis and components of the syndrome obesity and dyslipidemia are independent risk factors. Hypertension and diabetes mellitus do not form independent risk factors.

Keywords: Metabolic Syndrome, Nephrolithiasis.

Introduction

Urinary stone disease is a common disease affecting mankind, and it has been described since historical times. The lifetime risk of developing stone disease was 1%-15%.[1] It varies between races, geographical areas of living, age,[2] gender, occupation etc. Generally, there is an increased prevalence of stone disease in western countries when compared to south Asian countries, but due to the westernization of culture in these countries, there is an increased incidence of nephrolithiasis. Nephrolithiasis was a polycrystalline aggregate containing various proportions of crystal and organic matrix components. The common nephrolithiasis calculus were calcium oxalate stones, calcium phosphate stones, uric acid stones, calcium magnesium ammonium phosphate stones (triple phosphate stones or struvite stones) and cysteine stones. Due to advances in the investigation modalities for the diagnosis of nephrolithiasis, stone disease is increasingly diagnosed prior to its symptomatic presentation. And also due to the marked advancement in technology, nephrolithiasis is increasingly treated by noninvasive methods like ESWL (Extra Corporeal Shockwave Lithotripsy) and by minimal invasive procedures like PCNL (Percutaneous Nephrolithotomy). These procedures treat nephrolithiasis patients with less morbidity and with good results. Because of the profound morbidity due to the disease and during treatment, the loss of renal function with end stage renal disease in some neglected cases and the increased cost of diagnosis and treatment, there is a shift of focus from treatment to prevention of nephrolithiasis. The development of nephrolithiasis is most likely a multi-factorial process and it is not fully addressed by current theories. Metabolic syndrome[3] is a

complex of medical disorders that when they occur together have clinical significance, like an increased risk of developing cardiovascular disease, cerebrovascular accidents, diabetes mellitus (type 2) and atherosclerosis. There are different definitions for defining metabolic syndrome and they all include the main components: obesity or waist circumference, hypertension, hyperlipidemia and hyperglycemia. The associations of metabolic syndrome with nephrolithiasis were shown by many studies[4] in a defined population. The exact pathophysiology of this association was not clear, but it was shown to be[3] associated with metabolic syndrome patients' urinary constituents like a decrease in urinary PH, increased urinary calcium and uric acid excretion and decreased excretion of urinary citrate which is an important inhibitor of nephrolithiasis.

Rationally we investigate this association in the patient population of our institute with nephrolithiasis and compare it with individuals without nephrolithiasis.

Aims and Objectives

- To find out whether metabolic syndrome is a risk factor for nephrolithiasis among patients attending urology OPD at TDMC
- To find out whether individual components of the metabolic syndrome are risk factors for nephrolithiasis.

Methods

This was a hospital-based case control study conducted among 238 patients who underwent evaluation for the presence of metabolic syndrome at the Department of Urology Governmental Medical College Alappuzha, over a period of 18 months after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Inclusion Criteria

- Patients with ultrasound proven nephrolithiasis

Exclusion Criteria

- Patients with congenital renal abnormalities
- Patients with metabolic bone disorders or taking treatment for osteoporosis
- Patients with gout
- Patients with major debilitating diseases like cancer
- Patients with complications of calculus disease like calculus pyelonephritis, pyonephrosis or perinephric abscess
- Pregnancy

Sample size

Formula

$$n = \frac{Z^{2}_{1-\frac{\alpha}{2}} \left\{ \frac{1}{p_1^{*}\left(1 - p_1^{*}\right)} + \frac{1}{p_2^{*}\left(1 - p_2^{*}\right)} \right\}}{[\ln(1 - \varepsilon)]^2}$$

Where

$$P_1^{*} = \frac{(OR)P_2^{*}}{(OR)P_2^{*} + (1 - P_2^{*})}$$

P_2^{*} : Probability of exposure given disease absent

P_1^{*} : Probability of exposure given disease present

OR : Anticipated odds ratio

ε : Precision

α : Significance level

Study procedure

Patients with ultrasound proven nephrolithiasis after confirmation of the diagnosis were included in the study as cases. Patients' undergone evaluation for the presence of metabolic syndrome. Patients underwent measurements of height, waist circumference, systolic and diastolic blood pressure, their fasting blood was analysed for blood sugar, serum triglycerides and serum HDL cholesterol levels.

These details were entered into proforma and analysed. Controls without evidence of renal calculus disease were included as per inclusion criteria.

Statistical Methods

The data was entered in Microsoft Excel and further statistically analysed using Statistical Package for Social Sciences (SPSS) software version 16.

The categorical variables were summarized using frequencies and proportions. The quantitative data was summarized with mean and standard deviation for normally distributed data.

The statistical significance of association was tested using the Pearson Chi square test for qualitative variables and the strength of association was expressed using the odd's ratio.

Results

Table 1: Demographic Distribution

Descriptive Statistics					
	N	**Minimum**	**Maximum**	**Mean**	**Std. Deviation**
Age	238	18	78	43.45	14.400
Waist Circumference	238	76	118	95.01	8.447
BMI	238	14	29	22.82	2.688
Systolic BP	238	90	190	129.01	22.955
Diastolic BP	238	50	110	79.99	13.445
FBS	238	57	154	91.58	20.695
HDL	238	22	66	49.91	6.573
Triglycerides	238	110	252	151.68	35.181
Uric Acid	238	4.0	9.0	5.887	1.1067
Age Distribution					
			Frequency		Percent
Valid	Male		184		77.3
	Female		54		22.7
	Total		238		100.0
Sex Distribution					

The mean waist circumference in the study group was 96.66 cm, while in the control group it was 93.36 cm. A total of 238 subjects were studied: 184 were male patients and 54 were female patients.

Table 2:

		Frequency	**Percent**
Valid	Absent	172	72.3
	Present	66	27.7
	Total	238	100.0
H/o UTI			
		Frequency	Percent
Valid	Absent	149	62.6
	Present	89	37.4
	Total	238	100.0
Antihypertensives Drugs Intake			

A previous history of UTI was present in 66 patients. Anti-hypertensive intake in the study population; 89 patients in the study population were taking antihypertensives.

Table 3:

		Metabolic Syndrome		**Total**
		Absent	**Present**	
Nephrolithiasis	**Absent**	97	22	119
	Present	79	40	119
Total		176	62	238
Nephrolithiasis versus Metabolic Syndrome Cross tabulation				
Chi-Square Tests				
	Value	DF	Asymp. Sig. (2-sided)	
Pearson Chi-Square	7.067	1	.008	
	Nephrolithiasis		Total	
	Absent	Present		

Obesity	Present	27	48	75
	Absent	92	71	163
Total		119	119	238
Crosstabulation				
Chi-Square Tests				
		Value	DF	Asymp. Sig. (2-sided)
Pearson Chi-Square		8.586	1	.0003

Nephrolithiasis versus metabolic syndrome. Obesity versus nephrolithiasis

Table 4:

		Nephrolithiasis		**Total**
		Absent	**Present**	
Hypertension	**Absent**	60	50	110
	Present	59	69	128
Total		119	119	238
Cross tabulation				
Chi-Square Tests				
		Value	DF	Asymp. Sig. (2-sided)
Pearson Chi-Square		1.690	1	.194
Crosstab				
		Nephrolithiasis		Total
		Absent	Present	
Diabetes Mellitus	Absent	83	83	163
	Present	36	39	75
Total		119	112	238
Chi-Square Tests				
	Value	DF	Asymp. Sig. (2-sided)	
Pearson Chi-Square	.175[a]	1	0.676	

Hypertension versus nephrolithiasis. Diabetes mellitus versus nephrolithiasis.

Table 5:

		Nephrolithiasis		Total
		Absent	Present	
Dyslipidemia	Absent	83	43	126
	Present	36	76	112
Total		119	119	238
Crosstab				
	Value	DF	Asymp. Sig. (2-sided)	
Pearson Chi-Square	26.984	1	<.0001	
Chi-Square Tests				

Dyslipidemia versus nephrolithiasis

Discussion

The purpose of the present study was to determine the association between MetS components and the incidence of nephrolithiasis.

Metabolic Syndrome and Nephrolithiasis

Studies of large patient cohorts have demonstrated the correlation between MetS and the development of kidney stones. West and associates analyzed the United States National Health and Nutrition Examination Survey (NHANES III) and found that patients with MetS had twice the risk of developing a kidney stone based on self-reporting[5] In a longitudinal study of 2132 patients in southern Italy, Rendina and colleagues reported that 50.9% of patients with echographic evidence of nephrolithiasis qualified for a diagnosis of MetS.

Furthermore, after adjusting for age, the occurrence of MetS was associated with echographic evidence of nephrolithiasis (odds ratio 2.0). West and associates[6] reported that the prevalence of kidney stones was 3.7% with no traits, 7.5% with three traits, and 9.8% with five traits.

Similar correlations have been reported in Japan and South Korea. This relationship has also been demonstrated in radiographic screening studies. Jeong and colleagues reported that among almost 35 000 residents of South Korea who were screened with ultrasonography or CT, 2.4% had stones,

13.7% had MetS, and the odds ratio based on imaging for MetS and kidney stones was 1.25.

West et al. reported a graded association between the number of MetS traits present and self-reported kidney stone disease in a cross-sectional study. 1 Rendina et al. also reported that MetS was significantly associated with ultrasonographic evidence of nephrolithiasis. 2 Among the components of MetS, high BP and abdominal obesity were also independently related to nephrolithiasis. In South Korea, recent studies have shown that MetS as well as each trait are risk factors for nephrolithiasis. 3 In males, high BMI, high BP and abnormal glucose metabolism were significant nephrolithiasis factors, whereas in females, nephrolithiasis factors included only high BMI and abnormal glucose metabolism.

In our study, a total of 238 patients were included, as per inclusion criteria. 50 percent of patients had ultrasound proven nephrolithiasis. All patients were evaluated for metabolic syndrome components, a history of previous urinary tract infections, daily fluid intake, and uric acid levels were assessed.

Male patients constitute the majority (77.3%). The mean age was 43.45, with a standard deviation of 14.4. The mean waist circumference was 95.01, with a standard deviation of 8.44. The mean BMI was 22.82, with a standard deviation of 2.688. The mean systolic BP was 129.01 with a standard deviation of 22.95, and the mean diastolic BP was 79.99 with a standard deviation of 13.445. The mean FBS was 91.98, with a standard deviation of 20.695. The mean HDL was 49.91, with a standard deviation of 6.573. The mean triglycerides were 151.68, with a standard deviation of 35.181. The mean uric acid level was 5.887, with a standard deviation of 1.1067.

West et al. demonstrated that having all components of the metabolic syndrome increases the risk of nephrolithiasis by two-fold. In our study, patients with metabolic syndrome also had an increased risk of nephrolithiasis, with a Chi-square test showing a p-value of 0.008 which is significant.

Obesity and Nephrolithiasis

Waist circumference is a quick metric of visceral obesity. The accumulation of adipose tissue increases the release of adipocyte derived inflammatory cytokines which potentiate other factors contributing to MetS.[7] Taylor and associates[8] utilized three large epidemiological prospective cohort studies to examine 4,827 kidney stone incidents.

They showed that body mass index (BMI) and waist circumference, two distinct measures of obesity, were associated with an increased risk of kidney stone formation. Inci and associates[9] found BMI to be significantly higher in stone forming patients. In a study of 84,225 women with no history of kidney stones, Sorensen and colleagues[10] identified a BMI dependent increased risk of incident kidney stones, 25 to 29.9 kg/m2 (1.3 fold), 30 to 34.9 kg/m2 (1.62 fold), and >35 kg/m2 (1.81 fold) as compared to BMI < 25 kg/m2. Body fat may impact kidney stone formation. Increasing visceral adipose tissue, as measured by computed tomography (CT), was reported to be associated with the risk of developing uric acid and calcium oxalate stones.[11] Kidney stone risk has also been shown to be positively correlated with the ratio of visceral to subcutaneous fat tissue and nonalcoholic fatty liver disease.

In our study obesity alone was a significant risk factor for nephrolithiasis with a p-value of <0.001

Dyslipidemia and Nephrolithiasis

Elevated serum triglycerides and low high-density lipoprotein (HDL) levels, components of MetS, negatively influence cardiovascular health. Dyslipidemia has been suggested as an independent risk factor for nephrolithiasis as it is associated with a lower urine pH.[12] The specific disorders contributing to this increased risk have not been defined. Masterson and colleagues[13] in a retrospective study of 52 184 patients demonstrated an association between dyslipidemia and nephrolithiasis, with a hazard ratio of 2.2. While low-density lipoprotein (LDL) and triglycerides were not individually associated with stone formation, low HDL values had a hazard ratio of 1.4.

In our study dyslipidemia was an independent risk factor for nephrolithiasis with a p-value of <.001

Hypertension and Nephrolithiasis

Hypertension, a component of MetS, has a bidirectional association with kidney stone risk. Patients with hypertension have been shown to possess a higher risk for stone development and stone formers are predisposed to develop hypertension compared to the general population.[14,15] The risk of hypertension was higher after a first symptomatic kidney stone event when evaluating Olmstead County data from 2000 to 2011.[16]

However, in our study, hypertension alone was not an independent risk factor for nephrolithiasis with a p-value of 0.194.

Diabetes Mellitus and Nephrolithiasis

In three large cohorts, type 2 diabetes mellitus was a risk factor for developing kidney stones; on multivariate analysis, the relative risk of stone disease in those with diabetes was 1.38 in older women, 1.67 in younger women, and 1.31 in men.[17] Uric acid kidney stone formation has been linked to diabetes. For example, it has been reported

that uric acid stone paitents have a higher prevalence of diabetes as well as glucose intolerance.[18] Furthermore, those with type 2 diabetes mellitus are at an increased risk of uric acid stone formation.[19] Fasting glucose levels assist in detecting insulin resistant diabetes mellitus, a disease with progressive negative systemic effects. Hyperglycemia secondary to insulin resistance leads to the accumulation of advanced glycation end products (AGEs) inducing a pro-inflammatory state and vascular endothelial dysfunction.[20] Insulin resistance is also associated with decreased ammonium production in the proximal tubule resulting in decreased urine pH, the major driver of uric acid stone formation.[21]

However, in our study, diabetes was not an independent risk factor for nephrolithiasis with a p-value of 0.676

Conclusion

Metabolic syndrome is definitely a risk factor for nephrolithiasis and its individual components, obesity and dyslipidemia are independent risk factors. This evidence is corroborative with previous studies. However, hypertension and diabetes were not independent risk factors which is corroborated by previous studies. Hence, more studies are required to reach a conclusion.

Medical management is directed at correcting the underlying metabolic abnormalities of metabolic syndrome as well as those that lead to stone formation, namely low urine volume, hyperuricosuria and low urine pH. It also encompasses the implementation of a robust preventative strategy. It is important to stress patient compliance as a key factor in any preventive strategy. Adequate patient information regarding drinking and dietary recommendations plays a major role. A considerate approach in a dedicated outpatient setting and establishing good communication and a relationship of trust by setting realistic targets with the patient are essential elements to success. Lifestyle and diet modification are the primary approaches, independent of risk factors.

Patients should be encouraged to mobilize regularly, lose weight to achieve a BMI of less than 25 (with respect to age, sex and body habitus) and manage conditions that lead to excessive fluid loss. A fluid intake of 2 to 3 L of neutral pH, clear fluids per day, in order to produce a diuresis of at least 2 L/day is pivotal to stone prevention for all stone formers. A limitation of salt intake of 4 to 5 g/day, animal protein intake up to 1 g/kg BW/day, normal calcium intake of 1 to 1.2 g/day (because of the inverse relationship between dietary calcium and stone formation) and a balanced diet low in fats and carbohydrates and rich in fruit and vegetables constitute the general plan.

A lifelong commitment is necessary and should be explained clearly from the beginning. Appropriate lifestyle and dietary modifications should never be abandoned, even when a pharmacological approach is started. There is recent evidence that a Mediterranean type diet appears to improve the metabolic profile and possibly reverse the effects of metabolic syndrome from five years onwards. The Mediterranean diet emphasizes consumption of olive oil, fruits, vegetables, and seeds, which contain mono- and poly- unsaturated fatty acids, dietary fiber, magnesium, potassium, antioxidant vitamins (i.e., folate, vitamin E), polyphenols, and other phytochemicals that combat oxidative stress, inflammation, and insulin resistance. The beneficial effects of this diet have also been studied relative to lithogenic risk in metabolic syndrome patients and have been found to be substantial. Correction of low urine pH by urine alkalinization is central to preventing recurrent urate stones. Sodium reduction is advised, as well as reduction in animal protein intake and carbohydrates and loss of weight.

Along with alkalinization, the addition of allopurinol is indicated in cases of hyperuricemia or hyperuricosuria (excretion >1.2 g/day). Allopurinol is a xantine-oxidase inhibitor that prevents uric acid production from purine. It is administered orally at doses ranging from 100 to 300 mg per day. Care must be taken when administering allopurinol for prolonged periods. Reported side effects include Steven-Johnson or Lyell syndrome, vasculitis, hepatitis, renal failure and the formation of xanthine stones.

Urological intervention should be considered for increased stone burden that does not respond to preventative and medical therapy and leads to complications such as intractable pain, recurrent urinary tract infections and prolonged obstruction with progressive renal insufficiency.

References

1. Asplin JR, Favus MJ, Coe FL. Nephrolithiasis. In: Brenner BM, ed. Brenner and Rector's the kidney. 5th edn. Philadelphia: Saunders 1996:1893-935.
2. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC. Time trends in reported prevalence of kidney stones in the United States: 1976-1994. Kidney Int 2003;63(5):1817-23.
3. Anderson PJ, Critchley JA, Chan JC, Cockram CS, Lee ZS, Thomas GN, et al. Factor analysis of the metabolic syndrome: obesity vs insulin resistance as the central abnormality. International Journal of Obesity 2001;25(12):1782-8.

4. Sakhaee K, Maalouf NM. Metabolic syndrome and uric acid nephrolithiasis. Semin Nephrol 2008;28(2):174-80.
5. West B, Luke A, Durazo-Arvizu RA, Cao G, Shoham D, Kramer H. Metabolic syndrome and self-reported history of kidney stones: the National Health and Nutrition Examination Survey (NHANES III) 1988–1994. Am J Kidney Dis 2008;51(5):741-7.
6. Grant AM, Baker LR, Neuberger A. Urinary Tamm-Horsfall glycoprotein in certain kidney diseases and its content in renal and bladder calculi. Clin Sci 1973;44:377.
7. Despre´s JP, Lemieux I, Bergeron J, Pibarot P, Mathieu P, Larose E, et al. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. Arterioscler Thromb Vasc Biol 2008;28(6):1039-49.
8. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. JAMA 2005;293(4):455-62.
9. Inci M, Demirtas A, Sarli B, Akinsal E, Baydilli N. Association between body mass index, lipid profiles, and types of urinary stones. Ren Fail 2012;34(9):1140-3.
10. Sorensen MD, Chi T, Shara NM, Wang H, Hsi RS, Orchard T, et al. Activity, energy intake, obesity, and the risk of incident kidney stones in postmenopausal women: a report from the Women's Health Initiative. J Am Soc Nephrol 2014;25(2):362-9.
11. Kim JH, Doo SW, Yang WJ, Song YS, Hwang J, Hong SS, et al. The relationship between urinary stone components and visceral adipose tissue using computed tomography based fat delineation. Urology 2014;84(1):27-31.
12. Torricelli FC, De SK, Gebreselassie S, Li I, Sarkissian C, Monga M. Dyslipidemia and kidney stone risk. J Urol 2014;191(3):667-72.
13. Masterson JH, Woo JR, Chang DC, Chi T, L'Esperance JO, Stoller ML, et al. Dyslipidemia is associated with an increased risk of nephrolithiasis. Urolithiasis 2015;43:49-53.
14. Cappuccio FP, Siani A, Barba G, Mellone MC, Russo L, Farinaro E, et al. A prospective study of hypertension and the incidence of kidney stones in men. J Hypertens 1999;17(7):1017-22.
15. Madore F, Stampfer MJ, Rimm EB, Curhan GC. Nephrolithiasis and risk of hypertension. Am J Hypertens 1998;11(1):45-53.
16. Kittanamongkolchai W, Mara KC, Mehta RA, Vaughan LE, Denic A, Knoedler JJ, et al. Risk of hypertension among firsttime symptomatic kidney stone formers. Clin J Am Soc Nephrol 2017;12(3):476-82.
17. Taylor EN, Stampfer MJ, Curhan GC. Diabetes mellitus and the risk of nephrolithiasis. Kidney Int 2005;68(3):1230-5.
18. Sakhaee K, Adams-Huet B, Moe OW, Pak CY. Pathophysiologic basis for normouricosuric uric acid nephrolithiasis. Kidney Int 2002;62(3):971-9.
19. Pak CY, Sakhaee K, Moe O, Preminger GM, Poindexter JR, Peterson RD, et al. Biochemical profile of stone-forming patients with diabetes mellitus. Urology 2003;61(3):523-7.
20. Nowotny K, Jung T, Hohn A, Weber D, Grune T. Advanced glycation end products and oxidative stress in type 2 diabetes mellitus. Biomolecules 2015;5(1):194-22.
21. Maalouf NM, Cameron MA, Moe OW, Adams-Huet B, Sakhaee K. Low urine pH: a novel feature of the metabolic syndrome. Clin J Am Soc Nephrol 2007;2(5):883-8.