Original Article

Does urinary metabolic assessment in idiopathic calcium nephrolithiasis matter? A matched case control study among Indian siblings

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ABSTRACT

Objective: To identify the differences in urinary profile of a stone former and the matched member of the family.

Patients and Methods: This prospective case-control study was conducted from April 2006 to January 2008. Forty-one matched pairs from one geographic region were recruited. Renal/ureteric idiopathic calcium nephrolithiasis in patients of 18 years and above were included as cases. Controls were of the same gender and first-degree relative with no urolithiasis or history. They were living together at least for the last 5 years and consuming minimum of two out of three major meals together per day. For cases and controls besides fluid intake, ambulatory serum analysis for calcium, phosphorus, uric acid, albumin-globulin ratio, sodium, potassium and bicarbonate was done. Ambulatory 24-hour urinalysis was done for urinary volume, calcium, phosphorus, oxalate, uric acid, citrate, magnesium, creatinine and urinary pH was measured. For controls X-ray and USG-Kidney-Ureter-Bladder was done to rule out stone disease. The statistical analysis was done using Mc-Nemar test.

Results: Of the 41, 31 cases (76%) were first-time stone formers. No statistical difference was found for 24-hour urinary calcium ($P = 0.68$), oxalate ($P = 0.68$), citrate ($P = 0.45$) and urinary volume ($P = 0.14$). All pairs had normal 24-hour urinary magnesium, uric acid and urinary pH.

Conclusions: The urinary biochemical profile of idiopathic calcium nephrolithiasis was similar to the appropriately matched family member. It appears that an independent intrinsic factor may possibly be present and responsible for stone disease. The usefulness of urinary metabolic evaluation is seems to be of doubtful significance.

Key words: Metabolic assessment, urinary biochemical profile, urolithiasis

INTRODUCTION

A significant progress has been made in the diagnosis and management of urolithiasis but many aspects of it is remains to be elucidated. We still wonder why in a family some form stones while others do not, though they are living in the same environment, consuming the same diet and inherit the same sets of genes.

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Many physiological and metabolical derangements, based on the theory of urinary supersaturation, have been implicated in the etiology of renal stone formation. Since the development of simple ambulatory method to identify the underlying urinary metabolic cause, a 24-hour urinary biochemical profile is considered as an integral part for the selection of appropriate intervention to prevent urinary stone recurrences.[1] Still the significance of the urinary biochemical profile, magnitude of its clinical effects and efficacy of selective treatment remains to be defined.[2-4]

This study was carried out to determine the significance of urinary profile in stone formers compared to appropriately matched sibling as a control from the same family.

PATIENTS AND METHODS

This was a matched case-control study, conducted from April 2006 to January 2008. Institutional review board approval was acquired. Informed consent was obtained from subjects before enrollment in the study. Those patients who were

18 years and above, and had renal/ureteric stones with normal renal function were included as cases. Patients with bladder stone, endocrine, anatomical abnormality of urinary tract, history of bowel disease or resection, medication or disease predisposing to stone formation were excluded from the study. Controls were 18 years or older, of same gender as of the patient, and first-degree relative (full sibling) of patients. They were living in the family with the stone former in the same house at least for last 5 years and consuming minimum of two out of three similar major meals together. Dietary matching was done with the help of the Dietary Department of our institution. Controls did not have urolithiasis or history of urolithiasis. Controls with endocrine abnormality, history of bowel disease or resection, medication and diseases associated with stone formation were excluded from the study. Of the 1400 urolithiasis patients evaluated at our center during the study period, 450 were from Tamil Nadu i.e., from one geographical region. Of these 450 patients, 41 matched pairs were recruited for this study using the above-mentioned inclusion and exclusion criteria. A thorough history and clinical examination pertaining to urolithiasis was performed for both cases and controls and subsequently they underwent serum and urinary evaluation. For controls upper tract evaluation, with USG and X-ray Kidney-Ureter-Bladder region, was done to rule out urolithiasis.

Parameters in cases and controls

Serum analysis was done for calcium, phosphorus, uric acid, albumin–globulin ratio, sodium, potassium and bicarbonate. Twenty-four hour urinary analysis was done for calcium, oxalate, uric acid, citrate, magnesium, and creatinine.

Urinary volume and urinary pH was also recorded on an ambulatory basis. The reference laboratory value and normal ranges for the various test parameters used in our center are shown in [Table 1].

Urinary collection

Ambulatory 24-hour urinary analysis was done on two consecutive days. The first 24-hour urinary collection for analysis of urinary calcium and oxalate was done in a container with 10 ml of 6 mmol of hydrochloric acid to prevent precipitation of calcium and oxalate salts and also prevents oxidation of ascorbic acid to oxalate. The second day collection for urinary pH, uric acid, citrate, magnesium and creatinine was done in a container with 10 ml of 0.3 mmol of sodium-azide to prevent bacterial growth. Urinary volume was calculated averaging the urinary volume collected on the two consecutive days. There was no dietary restriction and 24-hour urinary samples were collected while on their regular diet at home. Urinary 24-hour sample collection was done before any intervention for urolithiasis. Urinary abnormalities studied were hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia and hypomagnesuria. All the serum and urinary parameters were measured on Olympus auto-analyzer (model: μ-16) machine using calorimetric method except the urine pH, measured by pH electrode and serum sodium and potassium, measured by ion selective electrode [ISE] method.

Statistical analysis

Data was analyzed using SPSS 15.0 software. All continuous variables were summarized using mean and standard deviation, while the categorical variables were summarized using frequencies and percentages. The value of each urinary constituent was compared using Mc-Nemar test, to test the difference between cases and their matched controls. P value < 0.05 was considered as statistically significant. All the P-values were two tailed.

RESULTS

The mean age of the cases and controls was 38.5 years (18-69 years) and 37.6 years (18-78 years), respectively. Out of 41 matched pairs, 26 (63%) were male and 15 (37%) were females. Thirty-one cases (76%) were first-time stone former and the rest had recurrence (24%).

Serum parameters

No significant difference was found between affected and unaffected siblings for serum calcium ($P = 0.18$), phosphorus ($P = 0.10$), uric acid ($P = 0.15$), A-G ratio ($P = 0.51$), potassium ($P = 0.51$) and serum bicarbonate ($P = 0.26$). Only serum sodium was found to be higher in unaffected controls ($P = 0.01$) [Table 2].

Urinary biochemical profile

Among cases the common urinary abnormality in this

Table 1: Laboratory values for serum and urinary parameters

Ambulatory normal serum values	
Calcium	8.3-10.2 mg/dl
Phosphorus	2.5-4.6 mg/dl
Uric acid	4.0-7.0 mg/dl
Albumin-globulin ration	1.0-1.8
Sodium	35-145 mEq/L
Potassium	3.5-5.0 mEq/L
Bicarbonate	22-29 mmol/L
Ambulatory 24 hr urinary values	
Low urinary volume	≤1500 ml
Hypercalciuria	>300mg for male; >250mg for females
Hyperoxaluria	>40mg
Hyperuricosuria	>700 mg
Hypocitraturia	<250 mg
Hypomagnesuria	<3mmol
Urinary creatinine	1-2 gm
Urinary pH	5.5-6.5

geographic area was hypocitraturia (22%), hypercalciuria (20%) and hyperoxaluria (12%). All of the cases and controls were found normal for ambulatory 24-hour urinary magnesium and urinary pH. All the cases were normal for urinary uric acid level but one of the controls was found to be hyperuricosuric. Overall in 20 cases (49%) and 15 controls (37%) there was single or multiple 24-hour urinary parameter abnormality.

On comparing 24-hour urinary profile between individual case and their control for urinary volume, calcium, oxalate and citrate we found the following.

Table 2: Average serum parameters for cases and controls

Parameters	Cases (Mean ± SD)	Controls (Mean ± SD)	*P*-value
Calcium (mg/dl)	9.23 ± 0.43	9.10 ± 0.39	0.18
Phosphorus (mg/dl)	3.93 ± 0.68	4.17 ± 0.63	0.10
Uric acid (mg/dl)	5.0 ± 1.05	4.8 ± 1.13	0.15
A:G ratio	1.34 ± 0.23	1.37 ± 0.25	0.51
Sodium (mEq/L)	138.7 ± 2.4	140.2 ± 2.4	0.01
Potassium (mEq/L)	4.24 ± 0.42	4.19 ± 0.32	0.51
Bicarbonate mmol/L	26.0 ± 2.30	26.5 ± 1.77	0.26

Ambulatory urinary volume

Urinary volume of 1500 ml or less was considered abnormally low in cases and controls.

In this study, there were 12 discordant pairs (case and control had different urinary volume). There were 9 (75%) pairs where the control had low urinary volume and 3 (25%) other pairs where the cases had low urinary volume [Table 3a].

Ambulatory 24-hour urinary calcium

Out of 41 matched pairs, only eight cases were hypercalciuric. Of these eight cases, five of their matched controls were also found to be hypercalciuric. Three controls had hypercalciuria though their cases were normal for urinary calcium. In this analytical study there were six discordant pairs. Three pairs where the controls had hypercalciuria, the cases were normal for urinary calcium and three pairs where the cases had high urinary calcium the controls were normocalciuric [Table 3b].

Ambulatory 24-hour urinary oxalate

Five cases had hyperoxaluria and high urinary oxalate was also seen in two of their matched controls. Three controls had hyperoxaluria though their cases were normal for urinary oxalate [Table 3c]. Similar to the urinary calcium,

Table 3: Urinary volume and biochemical profile among matched case and control pairs

a: Low and normal urinary volume among matched case and control pairs

	Controls		Total	*P*-value
	Low volume	Normal volume		
Cases				0.14
Low volume *n* = 08	05	03	08	
Normal volume *n* = 33	09	24	33	
Total	14	27	41	

b: Hypercalciuria and normal urinary calcium among matched case and control pairs

	Controls		Total	*P*-value
	Hypercalciuria	Normal urinary calcium		
Cases				0.68
Hypercalciuria *n* = 08	05	03	08	
Normal urinary calcium *n* = 33	03	30	33	
Total	08	33	41	

c: Hyperoxaluria and normal urinary oxalate among matched case and control pairs

	Controls		Total	*P*-value
	Hyperoxaluria	Normal urinary oxalate		
Cases				0.68
Hyperoxaluria n=05	02	03	05	
Normal urinary oxalate *n*= 36	03	33	36	
Total	05	36	41	

d: Hypocitraturia and normal urinary citrate among matched pairs

	Controls		Total	*P*-value
	Hypocitraturia	Normal urinary citrate		
Cases				0.45
Hypocitraturia *n* = 09	04	05	09	
Normal urinary citrate *n* = 32	02	30	32	
Total	06	35	41	

there were six discordant pairs, three pairs where the controls had hyperoxaluria but the cases were normal and three pairs where the cases were hyperoxaluric but the controls were normal for urinary oxalate.

Ambulatory 24-hour urinary citrate

Out of 41 matched pairs, only nine cases were hypocitraturic. Of these nine cases, four of their matched controls were also found to have hypocitraturia. Two controls had hypocitraturia though their cases were normal for urinary citrate. In this study there were seven discordant pairs. There were five pairs where the cases were exposed to the risk factor (hypocitraturia) but the controls were normal for urinary citrate and two pairs where the controls had low urinary citrate but cases were normal [Table 3d].

DISCUSSION

The understanding of the mechanism of idiopathic calcium nephrolithiasis is still controversial. Although the supersaturation theory is simple and attractive, we are unable to establish clear-cut cause-effect relationship between metabolic, physicochemical abnormalities and stone formation.

Observational studies have shown urinary parameters as a risk factor in stone formers. Twenty-four hour urinary profile made possible the diagnostic separation and classification of urolithiasis. The ability to distinguish the underlying physiological disturbances allowed the application of a selective treatment program on the basis of specific physiological derangement. On the basis of urinary profile, studies have shown that the numbers of metabolical abnormalities are more in stone formers[5] or that there is improvement in urinary profile after dietary manipulation,[6] but definite evidence of dietary modification in stone prevention is lacking.[7] The drawback in most of the case-control studies in literature is selection of control as healthy volunteers from general population for comparison with the stone formers. On analyzing our data we found 37% of controls had abnormal urinary profile inspite of the fact that they do not have stone disease thus emphasizing the role of control selection from within the family.

In the present study, we have selected controls from the same family, first-degree relative and same gender as of the patient. They were living in the family with the stone former in the same house at least for last 5 years and consuming minimum of two out of three similar major meals together. On comparing these matched controls with their individual cases we found no statistical difference for 24-hour urinary biochemical profile between them. Literature also shows that individual urinary risk factors do not reliably predict the subsequent course of stone disease.[8,9]. Similar to our study, for more common type of stone namely calcium oxalate, Kavanagh *et al*., did not found significant differences in supersaturation between stone formers and those that do not form stone.[10] Thus none of the indices developed to date possess straightforward applicability with sufficient predictive power to be useful to the clinician in making treatment decisions in usual clinical settings.

Julka *et al*. have analyzed and found an underlying urinary abnormality in 86% high risk recurrent renal calculus patients among them hypocitraturia (77%) was most common.[11] In our set of patients the overall urinary abnormality was seen in 49% of case, among them hypocitraturia was most common (22%). In these cases 76% were first time and 24% were recurrent stone formers. It is shown that protocol-based 24-hour urinary metabolic evaluation reveals more number of urinary biochemical profile abnormality in recurrent urolithiasis.[5,11] When we analyzed our data, besides 49% cases, 37% of the controls also had abnormal urinary biochemical profile. Although the presence of these abnormality may suggest the possibility that family member are at high risk of stone formation in future but the definite evidences are lacking.[8-10] In our study the controls never had stones inspite of the abnormal biochemical profile though they were together for 5 or more years.

With a family history of stone disease, Curhan *et al*.[12] found that the risk of becoming a stone former is more than two and a half times. This higher risk is thought to be due to a combination of genetic predisposition as well as similar environmental exposures.[13]. But Alberto *et al*.[8] did not notice family history as a risk factor for urolithiasis. Similarly in our study we have not noticed increased risk of urolithiasis in appropriately selected controls from the same family. While a number of genetic factors have been clearly associated with rare forms of nephrolithiasis, the information regarding genetic contribution for the common forms of stone disease is still limited.

This study is unique from other studies in the selection of strictly matched controls within the family of a stone former as we have chosen both cases and controls from the same family having similar environmental conditions and set genetic pattern. We had the advantage of joint families, which is unique in Indian culture. In this study we also tried to nullify the effect of environment, by limiting the study to a geographic area i.e., from Tamil Nadu. This study has limitation of less number of recruitment of subjects but one should acknowledge that with the above-mentioned criteria recruitment of strictly matched controls was difficult.

CONCLUSIONS

Although urometabolic evaluation can stratify a stone former into various metabolic abnormal categories, in our study we have found that the urinary biochemical profile of idiopathic calcium nephrolithiasis was similar to the appropriately

matched family member. It appears that an independent intrinsic factor may possibly be present and be responsible for stone disease and our study does question the usefulness of metabolic evaluation as a routine in the evaluation of stone disease and subsequent correction of these anomalies.

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