Original Article

Protocol-based metabolic evaluation in high-risk patients with renal stones in North India

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ABSTRACT

Context: Renal calculus disease has a lifetime recurrence rate of 80%. Protocol-based metabolic evaluation in high-risk subjects for recurrent renal stones reveals abnormalities in a large subset of subjects. However, such information is not available in Indian subjects. **Aims:** To evaluate the abnormalities by a protocol-based metabolic evaluation in patients at a high risk for recurrent renal stones. **Settings and Design:** Prospective, academic tertiary care center. **Materials and Methods:** Fifty North Indian patients (38 males and 12 females; mean age 38 ± 10.2 years) with recurrent or bilateral renal stones were evaluated. All subjects underwent a protocol-based evaluation involving estimation of serum total calcium, phosphorus, creatinine, albumin, iPTH, $25(OH)D_3$, $1,25(OH)_2D_3$, and a calcium load test. Estimation of daily urinary excretion of volume, oxalate, calcium, uric acid, and citrate, and urinary acidification studies were performed. **Statistical Analysis Used:** Descriptive statistics and *t*-test. **Results:** An underlying disorder was detected in 48 (96%) patients. Almost half had two or more metabolic abnormalities. The metabolic abnormalities detected were: Hypercalciuria 26 (52%) patients, renal hypercalciuria 16 (32%), absorptive hypercalciuria 6 (12%), unclassified hypercalciuria 4 (8%), hyperoxaluria 27 (54%), hyperuricosuria 9 (18%), distal renal tubular acidosis 4 (8%; 2 complete and 2 partial), primary hyperparathyroidism 3 (6%), and hypocitraturia 14 (n=18, 77%). In two patients, the etiology could not be detected. **Conclusions:** Protocol-based metabolic evaluation reveals metabolic abnormalities in majority of patients with nephrolithiasis. The spectrums of metabolic abnormalities are different in Indian subjects as compared to the western population.

Key words: Hypercalciuria, India, metabolic evaluation, renal stones

Introduction

Renal calculus disease (RCD) has a lifetime recurrence rate of 80%[1] and 20% develop mild renal insufficiency.[2] Metabolic evaluation in RCD in western countries has shown at least one identifiable and treatable metabolic abnormality in more than 90% of subjects.[3-6] Selective medical treatment reduces the new stone formation rate by 95%.[5] Environmental, genetic, and dietary factors have been implicated in the pathogenesis of RCD and can vary from region to region.[7,8] There are limited data regarding the metabolic evaluation in Indian subjects.[9-12] We studied the metabolic profile in North Indian patients at high risk for recurrent renal stone formation.

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Materials and Methods

From January 2003 to January 2004, we prospectively evaluated 50 consecutive patients with RCD (mean age 38 ± 10.2 years; M/F: 38/12). Demographic and clinical characteristics are given in Table 1. Inclusion criteria were patients with recurrent RCD, bilateral renal stones, and stones in the solitary kidney. Patients who were on pharmacologic doses of vitamin D, calcium, antacids, and vitamin C, and those with recent urologic intervention [extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL)] were evaluated after 1 month of stopping drugs or intervention, respectively. Subjects with active urinary tract infection

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Table 1: Clinical profile of the patients (*N*=50)

Age of presentation	38 ± 10.2 years (range: 19–58)
Mean age of diagnosis of RCD	31 ± 8.69 years
Sex distribution (male/female)	38/12
Family history (first degree)	5 (10%)
Interventions	21 (PCNL, ECSWL, ureteroscopy), 2 nephrectomies
Bilateral stones	35
Recurrence time (years)	
Median (range)	3.5 (1–10)
Patients with recurrent stones	28
Number of episodes	
Median (range)	3 (1–5)
Stone in solitary kidney	2

(UTI) were evaluated after appropriate treatment. Subjects with impaired renal functions (serum creatinine > 1.5 mg%) were excluded.

Protocol-based metabolic evaluation

A protocol-based metabolic evaluation was carried out in all the subjects. On the first visit, a detailed history regarding the age of first stone formation, frequency of renal colic, kidney involved, number and size of stones, and intervention done was elicited. A detailed diet history with emphasis on intake of calcium, oxalate, and meat intake was taken in the form of a food frequency questionnaire. Fasting blood samples for serum total calcium, phosphorous, albumin, creatinine, and alkaline phosphatase, and a morning freshly voided urine sample for pH were collected on two different days and analyzed. All patients with urine samples with pH >5.5 without UTI were further investigated for RTA. An ammonium chloride loading test was performed in all patients with a normal basal arterial pH to diagnose partial RTA. Two 24-h urine samples, preferably one on a week day and another on a holiday, were collected for analysis of creatinine, oxalate (oxalate oxidase, Sigma), citrate, uric acid, calcium, and phosphorous. Patients who lived outstation were admitted to ensure completeness of collection. Subsequently, the patients were prescribed a metabolic diet (calcium 400 mg/day, sodium 100 mmol/day and oxalate <50 mg/day for 10–14 days). On the second visit, blood samples for serum intact parathyroid hormone (PTH; IRMA, Diagnostic systems Laboratories, Webster, TX, USA), 25(OH)D_3, and 1,25,$(OH)_2D_3$ (RIA, Diasorin, Stillwater, MN, USA) were collected in chilled tubes kept on ice. Calcium load test was done with 1g elemental calcium (calcium carbonate 2.5 g) for adults. Urine sample was collected over 2 h in fasting state for urinary calcium: Creatinine ratio. Subsequently, elemental calcium 1 g (tab Shelcal™ 500, 2 tablets) was administered with water and urine sample was collected over the next 4 h for urinary calcium:creatinine ratio. A fasting calcium: Creatinine ratio of >0.11 and post load ratio of >0.22 was considered diagnostic of fasting hypercalciuria and post-absorptive hypercalciuria, respectively.[4]

The patients were classified on the basis of the metabolic abnormalities into the following categories: Absorptive hypercalciuria type 1 and 2, renal hypercalciuria, resorptive hypercalciuria (primary hyperparathyroidism), hyperoxaluria, hypocitraturia, hyperuricosuria, RTA, and low urine volume calculus. Absorptive hypercalciuria type 1 was diagnosed as those with normocalcemia, normophosphatemia, hypercalciuria (>200 mg/day) on calcium restricted diet, normal fasting urinary calcium <0.11 mg GF, elevated calciuric response to an oral calcium load (>0.2 mg GF) and normal to suppressed iPTH. Absorptive hypercalciuria type 2 was diagnosed like that of type 1, except normal urinary calcium (<200 mg/day) on calcium restricted diet. Renal hypercalciuria included patients with high fasting and post load urinary calcium, while absorptive hypercalciuria included patients with normal fasting urinary calcium:creatinine ratio on a calcium restricted diet and a high urinary calcium:creatinine ratio following calcium load. The diagnostic criteria for various metabolic abnormalities were: Hypercalciuria (24-h urine calcium >4 mg/kg), hyperoxaluria (24-h urine oxalate >44 mg/kg), hyperuricosuria (24-h urine uric acid excretion: Males >850mg/day, females >750 mg/day), hypocitraturia (24-h urine citrate <320 mg/day), distal renal tubular acidosis (urine pH >5.5 with non-anion gap metabolic acidosis), and low urine output (24-h urine volume <1500 ml/day).

All analyses were performed using SPSS version 10.0 for windows. Descriptive statistics were computed for all biochemical variables for each of the diagnostic categories. A two-tailed *P* value <0.05 was regarded as significant.

Results

Of the 50 patients, 48 (96%) had at least one identifiable metabolic risk factor. Almost 50% of them had two or more metabolic abnormalities. The metabolic abnormalities were hypocitraturia (77%), hyperoxaluria (54%), hypercalciuria (52%), hyperuricosuria (18%), RTA (8%), primary hyperparathyroidism (6%), and low volume (6%). In two patients, no metabolic abnormality was found [Table 2].

Hypercalciuric renal calculus disease

The hypercalciuric patients were subdivided on the basis of the calcium load test into the categories of renal hypercalciuria (32%) and absorptive hypercalciuria type 2 (12%) [Table 3]. Patients with renal hypercalciuria had significantly earlier age of onset (*P*<0.038) and a higher fasting urinary Ca:Cr ratio (*P*<0.0001) compared to patients with absorptive hypercalciuria. Serum 1,25$(OH)_2D_3$ levels were higher, though statistically insignificant, in renal hypercalciuria group. None

of the patients had type 1 absorptive hypercalciuria. Only 4 (8%) patients with hypercalciuria could not be classified into any of the categories and were labeled as unclassified hypercalciuria. Three subjects (two males and one female, age 45 ± 5.5 years) had PHPT presenting as renal stone disease and did not have bony pain or proximal weakness. All these subjects had elevated corrected total serum calcium (11.68 ± 0.3 mg/dl), phosphorus (2.7 ± 1.3 mg/dl), alkaline phosphatase (180 ± 36 IU/l), and iPTH (median 249 pg/ml, range 113–519 pg/ml).

Table 2: Classification of metabolic abnormalities in subjects with renal calculus disease

Metabolic abnormality	Occurring alone *n* (%)	Occurring with multiple diagnosis *n* (%)	Total incidence: Single and multiple diagnosis *n* (%)
Renal hypercalciuria	6 (12)	10 (20)	16 (32)
Absorptive hypercalciuria type II	1 (2)	5 (10)	6 (12)
Unclassified	1 (2)	3 (6)	4 (8)
Primary hyperparathyroidism	2 (4)	1 (2)	3 (6)
Hyperoxaluria	6 (12)	21 (42)	27 (54)
Hypocitraturia (n= 18)	2 (11)	12 (66)	14 (77)
Hyperuricosuria	-	9 (18)	9 (18)
RTA	3 (6)	1 (2)	4 (8)
Low volume RCD	1 (2)	2 (4)	3 (6)
No diagnosis	2 (4)	-	2 (4)

Table 3: Hypercalcuria: Comparison of renal and absorptive hypercalciuria type II

	Renal hypercalciuria	Absorptive hypercalciuria type II
Number of patients	16	6
Mean age of onset (years, mean ± SD)	26.1 ± 8.5*	37.6 ± 8.7
Sex distribution (male/female)	12/4	5/1
Serum corrected total calcium (mg/dl, mean ± SD)	9.2 ± 0.74	9.10 ± 0.52
Serum phosphorous (mg/dl, mean ± SD)	3.4 ± 0.65	3.7 ± 0.447
Serum iPTH (pg/ml)	46 (18–128)	36 (8–108)
Serum 25(OH)D_3 (ng/ml) (median, range)	12.6 (3.7–100)	16.3 (7–34)
Serum 1,25$(OH)_2D_3$ (ng/ml) (median, range)	32 (16–134)	20.4 (8–27)
24-h urinary calcium excretion (mg/day) (median, range)	349 (160–772)	296 (152–580)
Fasting urinary Ca/Cr ratio (mean ± SD)	0.33 ± 0.16**	0.07 ± 0.03
Post load urinary Ca/Cr ratio (mean ± SD)	0.6 ± 0.41	0.53 ± 0.21
24-h urinary calcium excretion (mg/day) on metabolic diet (mean ± SD)	258.45 ± 126	156 ± 52.81
Concurrent metabolic abnormalities (*n*)		
Hyperoxaluria	7	3
Hypocitraturia	2	1
Hyperuricosuria	2	1

*P<0.038; **P<0.0001

Hyperoxaluric renal calculus disease

Hyperoxaluria was present in 54% of subjects [Table 4]. Six subjects had high urinary oxalate excretion (>100 mg/day), but none of them had deranged renal or hepatic functions or clinical bowel pathology.

Hypocitraturic renal calculus disease

Hypocitraturia was present in 77% of 18 subjects tested. Distal RTA was diagnosed in four subjects, two with complete RTA and the other two with incomplete RTA. These subjects had bilateral stones, high alkaline phosphatase, and a low urinary citrate [Table 5]. There was no significant difference in the age of onset of RCD between those with and without RTA.

Hyperuricosuric renal calculus disease

Nine (18%) patients were diagnosed to have hyperuricosuric RCD. One patient had gouty diathesis with high serum uric acid and a radiolucent renal stone.

Low urine volume renal calculus disease

Three patients had a low urine output (1.17 ± 0.37l vs. 3.61 ± 1.33l; P<0.0001).

There was no correlation between the number of metabolic abnormalities and the number of episodes of renal stones. The results of two separate urinary collections had a correlation of 0.7 which was statistically significant (P<0.04). There was no statistically significant difference in the excretion of calcium, citrate, oxalate, or uric acid in vegetarians versus non-vegetarians.

Discussion

The results of the study, based on detailed protocol-

Table 4: Characteristics of hyperoxaluric renal calculus disease

Characteristic		Normal
Number of patients	27	
Age of presentation (years)	40.7 ± 9.8	
Sex (M/F)	20/7	
Corrected serum calcium (mg/dl)	9.48 ± 0.81	
Urinary		
Oxalate (mg/day)		<44
Median (range)	58.5 (45–239.4)	
Calcium (mg/day)	260.5 ± 143	
Total volume in ml	3677 ± 1337	
Concurrent abnormalities (*n*)		
Hypercalciuria	15	
Hypocitraturia	3	
Hyperuricosuria	5	

*All values in mean ± SD unless mentioned

Table 5: Characteristics of subjects with renal tubular acidosis

Pt.	Age/ sex	Family history	Stone site	Arterial pH/HCO_3	After NH_4Cl load	Serum alkaline phosphatase (IU/l)	Urinary citrate excretion (mg/day)	Associated conditions
1	20/M	+	B/L	7.3/8*	Not required	323	100	Short stature, genu varum, osteotomy in childhood
2	35/M	-	B/L	7.3/6*	Not required	1092	110	Severe PMW, MSK
3	43/M	-	B/L	7.4/24	7.3/19*	286	100	-
4	23/F	-	B/L	7.2/20	7.3/17*	184	262	Hyperoxaluria, PMW

*Urine pH >5.5, PMW: Proximal muscle weakness, MSK: Medullary sponge kidney

based metabolic evaluation, demonstrate that one or more metabolic abnormalities were present in 96% of patients with high-risk renal stones. The metabolic abnormalities were hypocitraturia (77%), hyperoxaluria (54%), hypercalciuria (52%), hyperuricosuria (18%), RTA (8%), PHPT (6%), and low volume (6%). This study highlights the advantage of protocol-based evaluation based on serum and urinary biochemistries, calcium loading, and urinary acidification studies.

In a significant study[4] based on 24-h urine biochemistry, recurrent stone formers had hyperoxaluria (68%), hypercalciuria (46%), hypocitraturia (76%), hyperuricosuria (6%), and hypomagnesuria (20%). This study did not involve calcium loading test and urinary acidification studies, and hence missed the important clinical conditions, e.g. primary hyperparathyroidism and renal tubular acidosis.

The study demonstrates some important differences in the prevalence of the metabolic risk factors in our patients from their western counterparts. Hypercalciuria was seen in 52% of our subjects, similar to the prevalence reported in the western population. However, prevalence of renal hypercalciuria in our patients was significantly higher (32% vs. 3% reported in western studies).[4] This subtype of hypercalciuria is the commonest type in children[13] and associated with low bone mineral density (BMD) and osteoporosis in adults.[14] Renal hypercalciuria is thought to be due to an underlying defect in the renal tubular reabsorption mechanism leading to compensatory high serum iPTH and $1,25(OH)_2D_3$ levels. A more recently reported etiology for fasting hypercalciuria is increased monocyte interleukin-1 (IL-1) activity which causes increased bone resorption and hypercalciuria and is not associated with a secondary rise of iPTH and calcitriol.[15] This could perhaps explain the absence of a significant rise in serum iPTH and calcitriol in our population. Unlike absorptive hypercalciuria, a genetic basis for renal hypercalciuria has not been described.

Subjects with hypercalciuria (absorptive or resorptive) were prescribed thiazides or indepamide. Thiazide/indepamide medications will increase the tubular reabsorption of calcium in the kidney, thereby reducing the degree of calcium in the urine. In addition, stone formers should drink enough fluid to maintain a urine output of 2l/ day. A strict low-salt diet (<3 g/day) is also advised, as elevated sodium excretion in the urine can induce or exacerbate hypercalciuria. Increased sodium excretion can also blunt the effectiveness of a thiazide-type medication used to treat hypercalciuria. Lastly, intake of a normal recommended daily allowance of calcium (1200 mg/ day) is advised. A common misconception is that a low-calcium diet is a treatment for calcium stone disease. However, such a diet can actually increase stone risk, as demonstrated in a randomized, controlled trial performed by Borghi and colleagues. Supplemental potassium may be necessary for patients receiving thiazide therapy, as these medications may promote hypokalemia, which can induce an intracellular acidosis and hypocitraturia.

Hypocitraturia too was significantly more prevalent in our patients (77% vs. 30% in western literature)[4,6] and also the proportion of patients with RTA was higher than in the western population (8% vs. 2%). Early diagnosis and treatment of these patients could have prevented the extrarenal manifestations apart from preventing stone formation. This stresses the importance of urine pH and the ammonium chloride loading test. If we see the clinical and biochemical profile of the patients with RTA, partial or complete, we find similarities in terms of bilateral renal calculi, raised alkaline phosphatase (probably due to the acidosis), and low urinary citrate. A similar high prevalence of RTA was also found in Asian Indians living abroad as compared to the western population.[8] Rest of the patients with hypocitraturia in our study were idiopathic. Oral acid load, especially diets high in animal proteins, makes the patients particularly prone to low urinary citrate stones,[16] but we observed no significant difference in urinary citrate between vegetarians and non–vegetarians, and hence could not explain the low citrate levels. The prevalence of hyperoxaluria (55%) in our study was significantly higher than in most western studies. A low calcium diet and absence of colonization

of the gut with *Oxalobacter formigenes* could be responsible for this high prevalence.[12,17] We could not classify the hyperoxaluria due to non-availability of specific enzymatic assays.

Overall, the number of metabolic abnormalities prevalent in an individual did not correlate with the number of episodes of renal calculi. Individual variations on how the metabolic abnormality is handled *in vivo* probably occur in different individuals and are perhaps genetically determined. We did not find any significant difference in the urinary excretion of citrate, oxalate, uric acid, or calcium between vegetarians and non-vegetarians. This is possibly due to the fact that meat and meat products are sparingly consumed even by the non-vegetarians. According to our inclusion criteria, we excluded patients with UTI, and hence none of our patients were diagnosed as stones due to UTI.

Stone analysis is considered as an integral part of the metabolic workup in patients with renal stones, but often patients are unable to provide the stone, especially when they have undergone newer methods of stone removal. Recent studies have shown a limited advantage of stone analysis in patients with calcareous stones.[18] A previous study from our center showed that more than 90% of the 434 stones analyzed were calcium stones.[19] As methods of stone analysis need expensive equipments and trained personnel, one can economize by performing metabolic workup of such patients. Since the study was carried out at a tertiary care center, a referral bias of more severe stone disease and hence a higher metabolic abnormality rate cannot be ruled out.

The overall natural history of stone disease is one of chronicity and the hope of a waning of disease with age for a majority of patients is unrealistic.[20] It is also apparent that stone begets stone, i.e. a stone event predisposes to further episodes.[21] Though the newer methods of stone removal like ESWL are effective, they are fraught with the dangers of renal damage and a higher incidence of stone recurrence.[22] A urine output of more than 2.5 l does not ensure against recurrence of stone formation as observed in our study, and therefore pharmacotherapy directed against the metabolic abnormality is recommended.

In conclusion, our protocol-based metabolic evaluation reveals high prevalence of metabolic abnormalities in recurrent stone formers, and hence proposes that this protocol may be applied in routine clinical practice. Studies involving larger number of patients and with more liberal inclusion criteria (single time stone formers) should be carried out in other parts of the country.

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