EVALUATION OF URINARY ABNORMALITIES IN UROLITHIASIS PATIENTS: A STUDY FROM NORTH INDIA.

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ABSTRACT

Metabolic abnormalities were investigated in 44 stone patients with first time (group 1) and 56 with 2 times stone formation (group 2), and in 25 normal individuals. 24hr urine was analysed spectrophotometrically for oxalate, calcium, magnesium, citrate, uric acid, phosphate and creatinine. Hypocitraturia and hyperoxaluria were the common abnormalities in the stone formers. Stone patients had significantly higher urinary oxalate, calcium and uric acid and lower phosphate than normal individuals. Citrate/calcium and magnesium/calcium ratio were significantly high in normal individuals than stone formers. Patients in group 2 excreted significantly higher urinary calcium and lower citrate than patients in group 1. Citrate/calcium ratio was higher in group 1 than group 2. Hypocitraturia, hyperoxaluria, hypercalciuria and increased citrate/calcium and magnesium/calcium ratio seem to be an essential risk factor for stone formation. Patients with recurrent stone formation could be distinguished from patients with first time stone formation on the basis of urinary calcium and citrate.

KEYWORDS

Recurrent stone formation, metabolic abnormality, hypercalciuria, hypocitraturia, hyperoxaluria

INTRODUCTION

The recurrent nature of stone disease is a well-recognized clinical problem (1,2). Patients with more or less severe disease can have various episodes of recurrent stone formation (3,4). Male gender, multiple stones (5), stone location (6), residual fragments (7) and some anatomic or functional urinary tract abnormalities (8) are known to be major risk factors for recurrence. In addition, urinary metabolic abnormalities such as low urine volume, hypercalciuria, hyperoxaluria, hyperuricosuria and hypocitraturia also predispose the patient to early recurrence (9).

It is yet not clear whether patients with recurrent stones have specific, more severe or an additional number of urinary abnormalities compared with first time stone formers. The present study was

undertaken to evaluate urinary metabolic abnormalities in patients with stone disease in order to establish a comparison of changes in urinary constituents between patients with one episode and two or more episodes (recurrent) of stone formation.

MATERIALS AND METHODS

The study included 100 patients with stone disease (90 males and 10 females, mean age 39years, age range 18-56years) seen from 1999 to 2001 at the Urology clinic of Sanjay Gandhi Post Graduate Institute of Medical Sciences. Renal stone was diagnosed either by plain abdominal X-ray, ultrasonography or intravenous pyelography. Patients who had history of bowel disease, renal tubular acidosis and urinary tract anomalies were excluded from the study. There were no dietary restrictions per se, but the patients were advised not to take oxalate rich and calcium rich diet. Forty-four (mean age 38years, age range 18-55years) patients were with one episode of stone formation (group 1) and 56 (mean age 40, age range 22-56years) were with two or more than two episodes of stone formation (group 2). Stone analysis was verified by X ray crystallography. 24 hr urine samples were also collected from the 25 healthy staff members of our Institute (20 males and 5 females,

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mean age 35years, age range 23-40years), who served as controls and did not have any history of stone disease.

Analysis of the 24hr urine specimen was done which included urine volume and excretion of ionic components such as oxalate, calcium, magnesium, uric acid, citrate, phosphate and creatinine. Oxalate was determined by the oxalate oxidase enzymatic method with an oxalate assay kit from Sigma. Calcium, magnesium, creatinine, uric acid and phosphate were investigated using kits from Glaxo. Citrate was assayed using standard procedure (10).

Metabolic diagnosis consisted of 5 categories: hypercalciuria males: ≥ 7.5 mmol (300 mg)/24hr, females: ≥ 6.25 mmol (250mg)/24hr, hyperoxaluria 0.46mmol (40mg)/24hr, hyperuricosuria: ≥ 4.46 mmol (750 mg)/24hr, hypomagnesuria: ≤ 3 mmol/24hr and hypocitraturia: ≤ 1.56 mmol (300mg)/24hr.

The frequency of each metabolic abnormality and value of each constituent was compared between controls and stone formers and amongst the groups 1 and 2. The value of each urinary constituent was expressed as mean $\pm$ standard deviation and the statistical analysis of the data was performed by Student's unpaired t-test. The frequency of metabolic abnormality was compared by chi-square statistical analysis.

RESULTS

There was not much difference in the mean age of the patients selected for groups 1 and 2. X-ray crystallographic results revealed that all the patients enrolled in the study had calcium oxalate monohydrate (whewellite) as major component in their stones (Table 1). In Tables 2 and 3 we have summarized the results in terms of urinary volume, oxalate, calcium, magnesium, citrate, uric acid, phosphate and creatinine estimated after 24 hr urine collection and compared between stone formers and normal individuals and stone formers having one and two or more than two episodes, respectively. The 24hr urinary oxalate and calcium concentration were persistently higher in stone patients when compared with normal individuals ($p < 0.01$, $p < 0.05$ respectively). Significantly increased oxalate/creatinine ($p < 0.05$) and calcium/creatinine ($p < 0.05$) ratios were observed in stone patients when compared with normal individuals. Stone patients excreted significantly higher levels of uric acid ($p < 0.05$) and lower levels of phosphate ($p < 0.05$) than

normal individuals. Phosphate/creatinine ratio was less in stone patients than normal individuals ($p < 0.05$). Urinary citrate and magnesium levels were low in stone patients as compared to normal individuals. However, the difference in the two parameters was not statistically significant.

Patients with two or more than two episodes (group 2) of stone formation excreted significantly high levels of calcium ($p < 0.05$) and lower levels of citrate ($p < 0.01$) than patients with one episode of stone formation. Citrate/creatinine levels were also low in group 2 patients as compared to group 1 patients ($p < 0.01$). Patients in group 2 excreted more oxalate however significant difference was not found among the groups (Table 3).

Hypocitraturia was the most common abnormality found in stone formers of two groups (55% in group 1, 78% in group 2) followed by hyperoxaluria (55% in group 1, and 61% in group 2). The frequency of hypocitraturia was statistically higher in group 2 as compared to group 1 ($p < 0.05$). There was no statistically significant difference found in the frequencies of hypercalciuria (30% in group 1 and 49% in group 2), hypomagnesuria (30% in group 1 and 32% in group 2) and hyperuricosuria (8% in group 1 and 8% in group 2) among the groups (Fig. 1).

An attempt was also made to stipulate significant changes in the ratios of various metabolites in stone formers vs. controls (Table 2) and stone formers of two different groups (Table 3). Stone patients, when compared with normal individuals had lower magnesium/calcium ($p < 0.001$) and citrate/calcium ($p < 0.01$) ratio (Table 2). Citrate/calcium ratio was significantly elevated in group 1 patients when compared with group 2 patient ($p < 0.001$) (Table 3).

As the ratio of male to female in totality of stone patients was 90:10, it was difficult to subdivide on gender basis and evaluate metabolic comparison separately.

DISCUSSION

Recurrence of stone disease is one of the biggest challenges faced by the urologists today. Despite the introduction of noninvasive techniques for the removal of stones, kidney stones remain the major source of morbidity in human (11,12). This is partly because complete pathogenesis and thus prevention of urolithiasis remains to be clarified. It is generally

believed that metabolic defects are less likely to occur in the first time stone formers than in patients with recurrent disease. With this view we evaluated comprehensively the urinary abnormalities in patients with stone disease to compare the differences in urinary abnormalities in age matched patients having one and two or more than two episodes of stone.

In our study hypocitraturia was the most common abnormality. Numerous studies have shown that low urinary citrate can cause calcium urolithiasis (13). Mean urinary citrate concentration was less in patients as compared to normal individuals but it was not statistically significant. However significant difference was found when recurrent stone formers were compared with first time stone formers. Thus it can be assumed that deficient urinary citrate is an important risk factor for stone disease as well as recurrence of calcium oxalate stones in our country. Normal individuals also excreted lower levels of citrate and are therefore at a risk of stone formation. However, large population based studies are required to draw any conclusion. Potassium citrate therapy could be given to the patients with calcium oxalate stones in order to prevent the recurrence of stones.

Hyperoxaluria was the second most common abnormality in both groups of patients. The difference in the frequency of hyperoxaluria as well as in the mean urinary oxalate excretion was not statistically significant between the patients with first time and recurrent stone formation. However, mean oxalate level was statistically high in stone formers when compared with normal individuals. It has been reported that oxalate plays an important role in stone formation and has about 15-fold greater effect than urinary calcium (14). In our population oxalate seems to be one of the major contributing factors in stone formation in first time stone formers as well as in recurrent stone formers but they cannot be distinguished on the basis of urinary oxalate levels. So patients with calcium oxalate stones should be recommended to live on low oxalate diet.

A significant difference in mean calcium excretion was observed between normal individuals and stone patients and between patients with one and two or more episodes of stone formation. Increased urinary calcium levels as observed in our study plays an

important role in the recurrence of stone disease. We did not study the cause of hypercalciuria, therefore we cannot stipulate whether it was absorptive hypercalciuria, renal leak hypercalciuria or resorptive hypercalciuria as the major determinant factor of stone recurrence. Since magnitude of hypercalciuria is an interesting feature so studies should be done to examine the causes.

There was no appreciable change in either volume or pH of 24hr urine between groups 1 and 2. The increased urine volume in patients as compared to normal individuals and with increasing number of episodes could be due to the advice given to the patients to consume large volumes of water in order to avoid recurrence of stone formation. There was no change observed in urinary excretion of magnesium, uric acid and phosphate between the two groups of patients.

Citrate/Calcium and Magnesium/Calcium have been considered to be an important cause for the formation of urinary calculi (15). In our study a Citrate/Calcium and Magnesium/Calcium ratios were significantly low in the stone formers when compared with normal individuals. Also significantly low Citrate/Calcium ratio was found in recurrent stone formers than first time stone formers.

Our results show that in our population hypocitraturia along with hyperoxaluria and hypercalciuria are the major contributory factors in stone formation. Hypocitraturia coexisting with hypercalciuria in recurrent stone formers is an interesting observation that should be further investigated in a more heterogeneous population. Emphasis should be in the form of dietary restrictions/counselling to the patients to enhance stone inhibitors like citrate to prevent recurrence of stone formation.

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Table 1

Stone composition in patients with first time stone formers (FSF)
and recurrent stone formers (RSF)

Composition	FSF (1 episode) n = 44	RSF (≥ 2 episode) n = 56
Whewellite	31 (70.5 %)	33 (58.9 %)
Whewellite + weddellite	8 (18.2%)	12 (21.4%)
Whewellite + uricite	3 (6.8%)	4 (7.1%)
Whewellite + weddellite + uricite	2 (4.5 %)	7 (12.5%)

Table 2

Twenty-four hour urinary constituent and their ratios in normal individuals and stone formers

Parameters	Normal Individuals (n=25)	Stone Patients (n=100)
Volume (ml/24hr)	1650 ± 546	2852 ± 1435
Oxalate (mmol/24hr)	0.39 ± 0.12 ^a	0.63 ± 0.35 ^a
Calcium (mmol/24hr)	4.75 ± 2.84 ^b	7.30 ± 3.99 ^b
Magnesium (mmol/24hr)	3.84 ± 0.38	3.65 ± 1.22
Citrate (mmol/24hr)	1.59 ± 0.75	1.46 ± 0.94
Uric acid (mmol/24hr)	1.74 ± 0.93 ^b	2.49 ± 1.29 ^b
Phosphate (mmol/24hr)	28.33 ± 18.15 ^b	21.94 ± 10.67 ^b
Creatinine (mmol/24hr)	9.72 ± 2.22	10.54 ± 2.84
Oxalate/Creatinine (mmol/24hr)	0.04 ± 0.02 ^b	0.07 ± 0.04 ^b
Calcium/Creatinine (mmol/24hr)	0.48 ± 0.26 ^b	0.73 ± 0.43 ^b
Magnesium/Creatinine (mmol/24hr)	0.40 ± 0.09	0.38 ± 0.19
Citrate/Creatinine (mmol/24hr)	0.18 ± 0.12	0.15 ± 0.12
Uric acid/Creatinine (mmol/24hr)	0.18 ± 0.10	0.26 ± 0.20
Phosphorus/Creatinine (mmol/24hr)	3.00 ± 1.75 ^b	2.27 ± 1.30 ^b
Magnesium/Calcium (mmol/24hr)	1.16 ± 0.73 ^c	0.63 ± 0.37 ^c
Citrate/Calcium (mmol/24hr)	0.52 ± 0.41 ^a	0.28 ± 0.30 ^a

Statistical analysis performed by Student's t test

The data are expressed as Mean ± S.D.

^ap<0.01, ^bp<0.05, ^cp<0.001

Table 3

Twenty-four hour urinary constituent and their ratios in first time and recurrent stone formers

Parameters	Group 1 1 episode (n=44)	Group 2 ≥2 episode (n=56)
Volume (ml/24hr)	2583±1214	3043±1555
Oxalate (mmol/24hr)	0.58 ± 0.30	0.68 ± 0.38
Calcium (mmol/24hr)	6.43 ± 3.38 ^a	8.06 ± 4.35 ^a
Magnesium (mmol/24hr)	3.43 ± 1.18	3.84 ± 1.23
Citrate (mmol/24hr)	1.76 ± 1.10 ^b	1.20 ± 0.70 ^b
Uric acid (mmol/24hr)	2.37 ± 1.20	2.60 ± 1.37
Phosphate (mmol/24hr)	19.64 ± 8.15	23.94 ± 12.94
Creatinine (mmol/24hr)	10.15 ± 2.94	10.89 ± 2.74
Oxalate/Creatinine (mmol/24hr)	0.06 ± 0.04	0.07 ± 0.04
Calcium/Creatinine (mmol/24hr)	0.66 ± 0.34	1.80 ± 0.50
Magnesium/Creatinine (mmol/24hr)	0.37 ± 0.20	0.38 ± 0.18
Citrate/Creatinine (mmol/24hr)	0.19 ± 0.15 ^b	0.12 ± 0.08 ^b
Uric acid/Creatinine (mmol/24hr)	0.26 ± 0.18	0.26 ± 0.22
Phosphorus/Creatinine (mmol/24hr)	2.16 ± 1.20	2.36 ± 1.40
Magnesium/Calcium (mmol/24hr)	0.67 ± 0.43	0.60 ± 0.32
Citrate/Calcium (mmol/24hr)	0.39 ± 0.40 ^c	0.18 ± 0.12 ^c

Statistical analysis performed by Student's t test

The data are expressed as Mean ± S.D.

^a p<0.05, ^b p<0.01, ^c p < 0.001

Fig 1: Frequency of urinary abnormalities in normal individuals and stone patients with one episode (Group 1) and two or more episodes (Group 2) of stone formation

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