Evaluation of different urinary constituent ratios in renal stone formers

Seema L. Jawalekar, Ujjwala J. Kulkarni, Vasant T. Surve and Anil Bhutey

ABSTRACT

Urine specimens were collected from 100 normal individuals and 100 stone patients and analysed spectrophotometrically for common stone promoters like oxalate, calcium, uric acid and phosphate and stone inhibitors like citrate and magnesium and creatinine. After overnight urine concentration, an oral water load was given to induce a diuresis. Hypocitraturia and hyperoxaluria were the common abnormalities found in the stone formers. Stone formers had significantly higher urinary oxalate, calcium and uric acid than normal individuals. Citrate / calcium and magnesium / calcium ratio were significantly low in stone formers and seems to be a risk factor for stone formation. The urinary calcium / creatinine ratio was found to be high when the creatinine concentration was low, but usually normal when the creatinine concentration was high. The results suggest that if the urinary calcium / creatinine ratio of random urine specimens is used as a screening procedure to detect hypercalciuria.

Key Words: Urolithiasis, Citrate, oxalate, creatinine, calcium and uric acid.

INTRODUCTION

Several researchers such as Nordin, Wills, SO Natalie and Heaton [1-4] have used the different ratios as an index of susceptibility of urine to form kidney stones in patients. To estimate the rate of excretion of urinary constituents, a 24-hour sample of urine is required and this is not always easy to collect accurately. Therefore different ratios of constituents have been calculated so as to get any specific ratio as an index in stone formers.
Nordin (1959) [2] proposed the use of the ratio of the calcium to creatinine concentration in random urine specimen as a convenient index of urinary calcium excretion. In this ratio creatinine serves as a reference standard by virtue of its relatively constant excretion rate throughout the 24 hours.

Hypercalciuria has been implicated in the frequency – dysuria syndrome, enuresis, abdominal pain, hematuria and urolithiasis. Hypercalciuria is defined as urinary calcium excretion of > 4 mg/kg/day. Traditionally, a urine calcium/creatinine of > 0.21 has been regarded as abnormal and suggestive of hypercalciuria. However, recent studies have shown that urine calcium/creatinine varies with age and geographic area (1). The variation in urine calcium/creatinine values is believed to be vary in climate and exposure to sunlight, mineral composition of drinking water, nutritional habits, age, genetics and race. In addition to this creatinine excretion is an index of endogenous protein metabolism and hence its excretion is constant therefore calcium/creatinine ratio may provide accurate index as well as the ratio of kidney stone promoters to inhibitors in urine may provide definite index for urolithiasis.

MATERIALS AND METHODS

The study included 100 patients with stone disease (76 males and 24 females) mean age 34 years, age ranges from 16-60 yrs. Stone formers were selected among those attending the local clinics at A.C.P.M. Medical College, Dhule. 100 healthy persons of Dhule district (75 males and 25 females) mean age 36 years, age ranges from 15-58 yrs who served as controls, with no recent report of ill health of any kind and had no past history of urolithiasis, including that in the family, and 24 hours urine samples and blood samples were collected from both patients and controls.

The diagnosis of urolithiasis was based on plain abdominal X-ray, ultrasonography or intravenous pyelography. Patient who had history of bowel disease, renal tubular acidosis and urinary tract anomalies were excluded from the study. There were no dietary restrictions.

A Concentration/dilution test was designed to provide urine specimens with a relatively wide range of common metabolites excreted in urine preferentially stone promoters and inhibitors concentration for each individual subject. In order to exclude the effect of diet or circadian variation all tests were performed between 6.00 AM and 11 AM with the subject fasting from 6 PM on the evening preceding the study no food or fluids were taken until the completion of the test, other than the water load taken during the test period, the patient emptied his bladder at 6 AM (this specimen being discarded), fasting was continued until 9 AM and the urinary ratios was estimated on the total urine passed at that time. Using this technique it can be assumed that the influence of recently ingested calcium and magnesium on the excretion is minimal [4] If this assumption is correct this ratio should be constant under the same condition.

Analysis of urine specimen was done which included excretion of ionic components such as oxalate, calcium, Magnesium, Uric acid, Citrate, Phosphate, creatinine. Oxalate was determined by potassium permanganate method [5]. Calcium by Trinder’s method [6], inorganic phosphate by Fiske and subbaraw method [7] uric acid by Caraway’s method [8], Creatinine [9], magnesium by Neil and Neely method [10] can be determined by standard procedures and in addition urinary citrate is quantitatively estimated by using standard methods [11]. The RA-50 Chemistry analyser was used to carry out all analysis.
Value of each constituent was compared between controls and stone formers. The value of each urinary constituent was expressed as Mean ± SD and the statistical analysis of the data was performed by students t–test.

RESULTS

In Tables 1 and 2 we have summarized the results in terms of common promoters like Calcium, Oxalate, Uric acid, Phosphates and common inhibitors like Citrate and Magnesium and Creatinine were estimated and their ratios after urine collection, and compared between stone formers and normal individuals. The urinary oxalate, calcium and uric acid concentration were persistently higher in stone formers when compared with normal individual (P < 0.00, P < 0.0001, and P < 0.01 respectively). Significantly increased oxalate / Creatinine (P < 0.05) and Calcium / Creatinine (P < 0.05) ratios were observed in stone formers when compared with normal individuals. Stone formers excreted significantly higher levels of uric acid (P < 0.01) but no difference was found in phosphate excretion. Urinary citrate and magnesium levels were low in stone formers as compared to normal individuals. Citrate / creatinine levels and magnesium / creatinine levels were also low (P < 0.0001, P < 0.01 respectively).

Hypocitraturia was the most common abnormality found in stone formers. Which is followed by hyperoxaluria. There was also statistically significant difference found in hypercalciuria, hyperuricosuria and hypomagnesuria.

The ratios of varies metabolites in stone formers versus controls (Table 2) was showed significant changes. Stone formers, where compared with normal individuals had lower magnesium / calcium (P < 0.001) and citrate / Calcium (P = 0.001) ratios found.

Table: 1 showing Laboratory findings of Urinary Constituents

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Controls</th>
<th>Stone formers</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxalate (mmol/24 hrs)</td>
<td>0.29 ± 0.07</td>
<td>0.45 ± 0.19</td>
<td>0.0000****</td>
</tr>
<tr>
<td>Citrate (mmol/24 hrs)</td>
<td>1.94 ± 0.29</td>
<td>1.00 ± 0.35</td>
<td>0.0000****</td>
</tr>
<tr>
<td>Calcium (mmol/24 hrs)</td>
<td>4.00 ± 0.96</td>
<td>11.59 ± 8.00</td>
<td>0.0001***</td>
</tr>
<tr>
<td>Uric acid (mmol/24 hrs)</td>
<td>2.58 ± 0.64</td>
<td>3.47 ± 1.31</td>
<td>0.01*</td>
</tr>
<tr>
<td>Phosphate (mmol/24 hrs)</td>
<td>31.80 ± 6.06</td>
<td>32.21 ± 8.79</td>
<td>0.813</td>
</tr>
<tr>
<td>Creatinine (mmol/24 hrs)</td>
<td>13.20 ± 2.17</td>
<td>14.62 ± 3.08</td>
<td>0.20</td>
</tr>
<tr>
<td>Magnesium (mmol/24 hrs)</td>
<td>3.82 ± 1.72</td>
<td>2.38 ± 1.23</td>
<td>0.01**</td>
</tr>
</tbody>
</table>

NOTE:- Values expressed Mean ± SD, P value <0.05= significant.
* = significant, ** and***, ****=highly significant.

Table: 2 showing Ratios of Urinary Constituents in (mmol / 24 hours)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Controls</th>
<th>Stone formers</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxalate /Creatinine</td>
<td>0.03 ± 0.02</td>
<td>0.06 ± 0.03</td>
<td>0.05*</td>
</tr>
<tr>
<td>Calcium /Creatinine</td>
<td>0.30 ± 0.44</td>
<td>0.79 ± 0.38</td>
<td>0.05*</td>
</tr>
<tr>
<td>Citrate /Creatinine</td>
<td>0.14 ± 0.13</td>
<td>0.06 ± 0.05</td>
<td>0.0001***</td>
</tr>
<tr>
<td>Uric acid /Creatinine</td>
<td>0.27 ± 0.19</td>
<td>0.23 ± 0.12</td>
<td>0.07</td>
</tr>
<tr>
<td>Phosphorus /Creatinine</td>
<td>2.40 ± 0.35</td>
<td>2.20 ± 0.35</td>
<td>0.09</td>
</tr>
<tr>
<td>Citrate /Calcium</td>
<td>0.48 ± 0.30</td>
<td>0.08 ± 0.04</td>
<td>0.001**</td>
</tr>
<tr>
<td>Magnesium /Calcium</td>
<td>0.95 ± 0.55</td>
<td>0.20 ± 0.15</td>
<td>0.001**</td>
</tr>
<tr>
<td>Calcium /Oxalate</td>
<td>0.07 ± 0.07</td>
<td>0.03 ± 0.02</td>
<td>0.02*</td>
</tr>
<tr>
<td>Magnesium /Creatinine</td>
<td>0.38 ± 0.07</td>
<td>0.26 ± 0.03</td>
<td>0.01*</td>
</tr>
</tbody>
</table>

NOTE:- Values expressed Mean ± SD, P value <0.05= significant.
* = significant, ** and***, ****=highly significant
DISCUSSION

The recurrent nature of stone disease is a well recognized clinical problem [12] and often required surgical intervention for management. Despite the introduction of recent technique like Extracorporeal Shock Wave Lithotripsy (ESWL) for the removal of stones, kidney stones remain the major source of morbidity in human [13]. It is generally believed that metabolic defects are less likely to occur in the first time stone formers than in patients with recurrent disease. Therefore we evaluated comprehensively the urinary abnormalities in patients with stone disease.

Citrate/Calcium has been considered to be an important cause for the formation of urinary calculi. In our study a citrate/calcium ratio i.e. inhibitor to promoter ratio is significantly low in the stone formers when compared with normal individuals.

It seems, as the calcium level of the urine increases and corresponding citrate level decreases the urinary stone formation sets in. It is apparent from the data of stone formers that most of the patients present with low urinary citrate levels and relatively increased calcium levels on the other hand. This results in a loss of balance between citrate and calcium levels. Citrate’s capacity to sequestrate calcium ions is lost. It concluded that despite a person suffering from hyperoxaluria, the stone formation may not set in as long as he is normocitraturiac [14].

Magnesium/calcium ratio is significantly low in stone formers when compared with normal individuals. The ratio is low in the kidney stone patients indicating in adequate magnesium intake. The recommended dietary allowance (RDA) for calcium is 800 mg / day, where as for magnesium it is 400 to 450 mg /day. Only about one third of magnesium is absorbed from dietary sources. Therefore, a daily magnesium intake of 1200 mg /day has been recommended by some researchers. The traditional ratio of approximately two parts calcium to one part magnesium needs to be upgraded to increase magnesium intake in view of the overwhelming beneficial role of magnesium as it is a well documented inhibitor of urinary calcium oxalate supersaturation and, thus, the nucleation of calcium oxalate crystals.

The absorption and metabolism of calcium and magnesium is one of mutual dependence and therefore, the balance between these two minerals is especially important. If calcium consumption is high, magnesium intake needs to be high also [15].

Oxalate/Creatinine ratio as an indicator for hyperoxaluria. In our study an oxalate/creatinine ratio is significantly higher in the stone formers when compared with normal individuals. As the oxalate level of the urine increases and the creatinine levels is in normal limits, because excretion is independent of diet. It is apparent from the data of stone formers that most of the patients present with high urinary oxalate levels.

Hyperoxaluria is a significant risk factor for calcium oxalate urolithiasis because increased urinary oxalate promotes calcium oxalate crystallization and stone formation.[16] Dietary hyperoxaluria results from excessive intake of nutrients high in oxalate content and increased intestinal absorption. Diet low in calcium lead to increased intestinal oxalate absorption and subsequent hyperoxaluria, as less calcium is available to bind oxalate and to form poorly absorbable calcium oxalate complexes in the gut. Indeed, even a minor increase of the urinary concentration of oxalate exerts a substantial lithogenic effect.
Urinary citrate and the citrate / creatinine ratios were significantly reduced. Our data indicate that the kidney appears to be involved in the pathogenesis of hypocitraturia in kidney stone patients and that a substantial proportion of these patients show a reduced urinary excretion of citrate. The evaluation of the citrate / creatinine ratio may replace the measurement of the substance on the basis of a 24 hours urine collection.

It is considered a major, correctable cause of calcium oxalate nephrolithiasis. Citrate chelates calcium in the urine, helping to prevent precipitation of calcium salts. When citrate excretion is reduced, less calcium is chelated and nephrolithiasis formation is promoted [17]. It has been shown that urinary oxalate excretion inversely correlates with the dietary intake of calcium [18]. Urinary oxalate is more important than urinary calcium for stone formation because slight increases in oxalate concentration rapidly increase urinary calcium oxalate saturation [19]. The result of our study is in accordance with those in the literature. Our study of ratio of inhibitor to promoters is an addition definite finding in urolithiasis. Accordingly, increased urinary calcium excretion (As water of Dhule is hard water containing highest calcium) significantly decreased urinary oxalate excretion (P = 0.05). Since the greatest crystal mass is produced when calcium and oxalate are present in urine at a 1: 1 ratio, any increase in urinary oxalate excretion has a greater effect on crystal formation than an increase in calcium. [20] We found a positive relationship between the oxalate to calcium ratio. These results are in accordance with those in the recent literature emphasizing that a high calcium intake may have a protective effect against stone disease or at least does not increase stone formation.[21]

Magnesium / Creatinine ratio as an indicator for insufficient magnesium intake. Intestinal malabsorption (including low dietary magnesium) or renal losses cause hypomagnesaemia. The interplay between magnesium and calcium is complex and crucially influences calcium homeostasis. Hypomagnesaemia is a relatively common and often overlooked cause of ion disturbances, such as hypocalcaemia and hypokalaemia. Although its causes are diverse, if chronic, it can induce plastic changes in the parathyroid hormone (PTH) and calcium regulatory axis.[22] Primary hyperthyroidism, which resulted in hypocalcaemia, hypocalcaemia distal tubular damage and magnesium wasting that ultimately, presented as hypomagnesaemia.

CONCLUSION

Our results show that low urinary ratios of citrate / Calcium and Magnesium /Calcium can be used as an index of susceptibility to stone formation where as high calcium / creatinine ratio of random urine specimens is used as a “screening” procedure to detect hypercalciuria. Dietary restrictions/ increase water intake and enhance stone inhibitors like citrate are used as a preventory measures.

REFERENCES