Is Hypocitraturia Associated with Phosphaturia - A Potential Cause of Calcium Urolithiasis in First-Time Stone Formers

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Abstract

The serum and 24 hour urinary excretion levels of various lithogenic and inhibitory substances were assessed in 24 male patients with calcium stone and no previous history of urolithiasis and in 19 age-matched controls. Two groups did not differ significantly (P<0.01) except in the excretions of sodium, citric acid (being higher in nomials) and inorganic phosphate (being higher in patients). Fifty percent patients had hyperphosphaiuria, 29.2% hypocitraturia, 20.8% hyperoxaluria and 16.7% hypercalciuria. The present data suggests that hypocitraturia in association with phosphaturia might be one of the main risk factors responsible for calcium urolithiasis in this area (JPMA 44:179, 1994).

Introduction

Urolithiasis is a complex of several diseases and stones for the sake of simplicity and diagnosis of underlying cause, have been classified into four types, namely: calcium, infective, uric acid/unite and cystine stones. The problem, however, appears to be more complex in case of calcium stones - the most frequent type in Pakistani adults and the Western world. A vital prerequisite for appropriate therapy and prognosis of calcium urolithiasis is correct identification of the primary cause of disease which in turn requires accurate assessment of lithogenic and inhibitory substances present in blood and their excretions in urine. The present study was undertaken to investigate the pre-urinary and urinary risk factors predisposing calcium stone disease in male population, with no previous history of urolithiasis.

Patients and Methods

Twenty-four male patients with calcium stones but no previous history of urolithiasis (first-time stone formers), admitted in the surgical units of Liaquat Medical College Hospital, Jamshoro and 19 age matched healthy men comprising students and lower ministerial staff of the University of Sindh participated in the study. The calcium urolithiasis was confirmed by infrared analysis of the surgically recovered stones. A 24 hour urine collection was made by each subject in polythene containers with no preservative. All subjects were free to have a diet of their own choice and were advised to ensure complete collection. After determining the volume, pH (Good digital pH meter 2002) and uric acid content, concentrated HCl (1 ml/100 ml urine) was added to prevent calcium salt precipitation and the samples were refrigerated until analysed (usually for ten days) for creatinine, inorganic phosphate, oxalate, citrate, sodium, potassium, calcium and magnesium levels. On completion of the 24 hour urine collection, fasting blood samples were taken by Vacupuncture technique applying minimum stasis and the serum was analysed for the above mentioned constituents in addition to alkaline phosphatase. All determinations (in serum and urine) were carried out using the established procedures. Sodium and potassium were determined by flame photometry (Gallenkamp flame analyser FH-500), while calcium and magnesium by atomic absorption spectrophotometry (Hitachi double beam atomic absorption
spectrophotometer). For the analysis of creatinine, uric acid, inorganic phosphate, oxalate, citrate and alkaline phosphatase levels, Hitachi double beam UV-Visible spectrophotometer 220 was used. The chemicals and reagents used in this study were of analytical reagent grade supplied by E. Merek, W. Germany and the water used was doubly distilled deionised. Statistical evaluation was carried out by Student’s paired t-test.

Results

Twenty-four patients with calcium stones and 19 controls were included in this study. The mean age of the patients was 31 years (range 13-56 years) and of controls 35.5 years (range 13-55 years). No significant difference was observed in values of various parameters measured in serum, between the two groups. However, hyperphosphatemia (serum phosphate concentration greater than 4.5 mg/dl) was noted in 83.3% patients and 42.1% controls (Table I).

<table>
<thead>
<tr>
<th>Biochemical variables</th>
<th>Normal subjects (n=19)</th>
<th>Urolithiatic patients (n=24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.14±0.08</td>
<td>1.05±0.07</td>
<td>NS</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>7.29±0.37</td>
<td>6.35±0.41</td>
<td>NS</td>
</tr>
<tr>
<td>Alkaline phosphatase (mU/ml)</td>
<td>36.34±6.61</td>
<td>29.79±3.25</td>
<td>NS</td>
</tr>
<tr>
<td>Inorganic phosphate (mg/dl)</td>
<td>4.95±0.22</td>
<td>5.45±0.16</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>10.12±0.19</td>
<td>9.66±0.25</td>
<td>NS</td>
</tr>
<tr>
<td>Magnesium (mg/dl)</td>
<td>2.29±0.08</td>
<td>2.10±0.07</td>
<td>NS</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>151.31±3.30</td>
<td>141.14±4.61</td>
<td>NS</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.04±0.13</td>
<td>3.79±0.21</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant

Urinary excretion of inorganic phosphate was significantly higher (P<0.01) and citrate and sodium lower in stone formers when compared with controls (Table II).
The excretions of remaining parameters seemed to be comparable between the groups. However, it was interesting to note that 89.5% of normals and 70.8% of patients had had their urinary pH values less than 6.0. Similarly, urinary potassium excretion was less than 30.0 mmol/24 hr in 78.9% of the normals and 62.5% in patients. Twenty-nine percent of stone formers had hypocitraturia (defined as urinary citric acid excretion less than 135 mg/day), 50% hyperphosphaturia (phosphate excretion greater than 857 mg/day), 20.8% hyperoxaluria (oxalic acid excretion greater than 38 mg/day) and 16.7% hypercalciuria (calcium excretion greater than 270 mg/day) when compared with normal ranges (mean±SD). When urine concentrations are expressed in relation to 1 g of urinary creatinine (Table III).
the comparative excretion pattern of the parameters remains unchanged between the two groups, except that there is moderate increase in the level of significance for citrate and sodium, but no change for phosphate. This difference might be due to the creatinine excretion, being slightly higher in the patient group.

Discussion

Of the factors important to calcium stone formation that we investigated in this study, only inorganic phosphate, citrate and sodium differed significantly between patients and normals in 24 hour urine collections. This suggests that higher excretions of inorganic phosphate and lower of sodium and the citrate, a potent inhibitor of calcium salt crystallisation, by our patients could be the main risk factors responsible for the precipitation of calcium salts and hence calcium stones. Observation of urinary phosphate excretion in two groups in this series confirm the finding of Rahman and Rahman for adults from Karachi. Fellostrom et al reported that despite similar intake of phosphate, male stone formers excreted significantly more phosphate and sodium than did the normals, suggesting a possible link of phosphaturia with increased sodium excretion, but we failed to see such an association in our patients. Our results are, however, more in line with those of Rudman et al. A comparison of urinary phosphate excretions by patients to that of normals finds no correlation with the dietary intake of phosphates. However, a renal leak of phosphate and its conservation through increased intestinal absorption might be the primary cause of phosphaturia and hyperphosphatemia in our patients. Moreover, the low bioavailability of calcium to precipitate oxalates and phosphates in the gut may also have contributed to phosphaturia. This is suggested because most of our patients mainly consumed cereals and vegetables rich in phytates and oxalates. Many but not all investigators found hypocitraturia as a common predisposing factor for calcium urolithiasis in adult men. We confirmed this finding in our patients. Although hypercalciuria was found in 16.7% of the patients, the presence of hyperparathyroidism, hypervitaminosis D and milk-alkali syndrome as a cause of calcium urolithiasis
in our patients. Moreover, our previous finding that pure calcium phosphate stones are very rare in Hyderabad region, also argues against the involvement of parathymid hormone in the pathogenesis of calcium stones in this area. The finding that majority of the subjects of both the groups had lower levels of potassium in urine, seems to be responsible for acidic urinary pH. This is because potassium depletion induces intracellular acidosis with highly acidic urine despite the high bicarbonate content of the plasma. Hyperuricosuria has been implicated as a causative factor in calcium oxalate urolithiasis and at least two studies have reported a raised urate excretion in male calcium stone formers. In contrast, we found comparatively low uric acid excretion in our patients, suggesting that urate is not an important determinant of calcium urolithiasis. Indeed, the relatively decreased urinary uric acid excretion in patients reflects low purine content of the patient diet. In addition to factors already discussed, urinary volume is considered an important determinant of the degree of urinary saturation with calcium salts. A low urinary volume, whether caused by low fluid intake or increased fluid loss by other routes undoubtedly increases the concentration of all the stone forming salts and hence the risk of crystalalluria and stones formation. However, in the present study our failure to demonstrate lower urinary volumes in patients might be a result of their compliance with medical advice to drink more water. Therefore, it is doubtful that the measurement of urinary volume alone could be of major diagnostic value in the assessment of stone patients. In conclusion, the data discussed above suggest that hypocitraturia in association with phosphaturia might be the main risk factor responsible for the pathogenesis of calcium stones in first-time stone formers and needs more detailed investigations to suggest prophylactic measures which could discourage the likelihood of any recurrence.

References
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