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URINARY METABOLIC ABNORMALITIES IN IDIOPATHIC CALCIUM OXALATE STONE FORMERS: A SINGLE CENTER STUDY

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ABSTRACT

Recurrence of stone disease is a well known clinical problem. This study was undertaken to identify the urinary metabolic abnormalities associated with idiopathic calcium-oxalate stone formation. Urinary metabolic abnormalities were determined in 53 adult idiopathic calcium oxalate stone formers based on 24hour urine collection on a free choice diet. Forty-two (79.2%) were male and 11 (20.7%) were female. Mean age was 39.5years with range from 18-77 years. Recurrent stone formers were 60.3% and 33.9% had multiple stones. Hypocitraturia was the most common abnormality found in 81.2% stone formers. Low urine volume was found in 26.4% of patients; 11.7% had hyperoxaluria followed by hypercalciuria in 11.5% and hyperuricosuria in 1.9% patients. Hypocitraturia and low urinary volume were the predominant urinary metabolic abnormalities in idiopathic calcium-oxalate stone formers.

Keywords: Hypocitraturia, calcium-oxalate stone, metabolic risk factors.

INTRODUCTION

Pakistan lies in the geographical region known as the "stone belt" stretching from Egypt and Sudan through the Middle East, India, Pakistan, Burma, Thailand, Indonesia and Philippines reporting consistently high incidence of urolithiasis (Robertson, 1984). Although the incidence and prevalence of stone disease is not known in Pakistan due to lack of centralized epidemiological data, it roughly constitutes 40-50% of urological workload in major hospitals (Hussain *et al.,*1998).

Certain minerals, such as whewellite (CaC_2O_4' H_2O), weddellite (CaC_2O_4 . $2H_2O$), struvite ($MgNH_4PO_4$' $6H_2O$) and uricite ($C_sH_4N_4O_3$; commonly called uric acid) are rare in geological environments. These minerals, along with others such as apatite, brushite ($CaHPO_4$. $2H_2O$) and whitlockite (CagMgH(PO_4h), as well as a few phases not yet found as minerals (e.g., cystine, ammonium acid urate), are frequently found in human urinary stones (calculi) which are usually in the kidney but may occur anywhere in the urinary tract (Levinson *et al*., 1985).

Calcium oxalate is the most frequently encountered stone found in 60-65% patients with stone disease (Hussain *et al*., 1995; Talati *et al*., 1997); same is true for countries like India, Bangladesh and Saudi Arabia (Jayadevan *et al*., 2000; Rashid *et al*., 1997; Abomelha *et al.*, 1990).

Recurrence for stone disease is a well-recognized clinical problem. Recurrence rate for first time stone formers has been reported to be as high as 50% (Rivers *et al.*, 2000; Seftel and Resnick, 1990; Rizvi *et al*., 2002), making it necessary to identify and correct any risk factors associated with it. Various factors like male gender, age between thirties and sixties, family history of stone disease and the urinary risk factors of hyperoxaluria, hypercalciuria, hyperuricosuria, low urine volume, hypocitraturia and lack of other inhibitors as well as anatomic and metabolic abnormalities have been identified in recurrent stone formers. In an attempt to identify such risk factors we studied the urinary metabolic abnormalities in idiopathic calcium oxalate stone formers in our setup.

MATERIALS AND METHODS

Fifty three adult patients of idiopathic calcium oxalate urolithiasis were seen at urology clinic of Shifa International Hospital Islamabad, Pakistan between May 2002 and February 2006. Forty-two (79.2%) were males and 11(20.7%) were females, with male to female ratio of 3.8:1. Mean age was 39.5 years with range from 18-77years.

All patients had calcium-oxalate as the predominant stone constituent and were either recurrent stone formers or had multiple stones or had large stone bulk with complete or partial stag horn stones. First time stone formers without these factors and children, less than 18years were excluded. Metabolic workup was performed after major stone burden had been cleared by ESWL, ureteroscopy, PCNL or open surgery.

The evaluation included serum calcium, phosphorous, alkaline-phosphatase, uric acid, creatinine and electro-lytes. Serum Parathormone was done if serum calcium

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was above normal. Urine analysis was done in all cases and urine culture when indicated. Twenty-four hour urine volume, calcium, oxalate, uric acid, citrate and creatinine were measured with patient on a free choice diet. Automated chemical chemistry analyzers measured these components.

Specimens with bacterial contamination were excluded. Idiopathic calcium oxalate stone formers were defined as not having any established cause of stone formation like hyperparathyroidism, hyperthyroidism, sarcoidosis, excessive VitD intake, overt renal tubular acidosis, medullary sponge disease, hypercalcaemia of immobilization or malignancy, history of bowel disease or surgery and structural abnormalities of urinary tract. All patients had normal serum creatinine and were not taking any medication known to cause interference in metabolic studies.

Metabolic diagnosis consisted of five categories: Hypercalciuria (>320mg/24h), Hyperoxaluria (>45mg/ 24h), Hyperuricosuria (>1000mg/24h), Hypocitraturia (<422mg/24h) and low urine volume (<1500ml/24h). The frequency of each metabolic abnormality was determined and value of each urinary constituent, both normal and abnormal was expressed as mean with standard deviation (SD). Recurrent stone formers were defined as having history of removal or spontaneous passage of two or more calcium oxalate stones.

RESULTS

Based on 24h urinary metabolic workup the overall frequency of metabolic abnormalities was 88.6 %. Hypocitraturia was the most common abnormality found in 81.2% followed by low urine volume 26.4%, hyperoxaluria 11.7%, hypercalciuria 11.5% and hyper-uricosuria in 1.9% stone formers.

Mean serum calcium level was 9.5mg/dl. Mean serum uric acid level was 6.19mg/dl. Hyperuricemia occurred in 32% patients. Thirty two (60.3%) were recurrent stone formers. Forty two (40.3%) kidneys and 31(29.8%) ureters were affected by stones. Hypocitraturia as the only abnormality occurred in 43.7% patients. Fifty four point seven percent patients had a single urinary abnormality. Multiple stones (2 or more) occurring simultaneously at different sites were found in 33.9% patients and 30.18% patients had large stone bulk. Value of each abnormal and normal urinary constituent expressed as mean with standard deviations is shown in “table 1”.

DISCUSSION

Recent technological advances and minimally invasive methods of stone removal have made even the most difficult urinary calculi accessible to treatment. Despite these achievements the problem of recurrence remains significant and considerable efforts to prevent recurrence have not been successful due to incomplete understanding of stone formation, poor patient compliance and under utilization of preventive medical therapy. This is especially important for third world countries like Pakistan where a large proportion of population lives below the poverty line and modern noninvasive methods are expensive and not freely available. Identification and correction of such factors becomes a matter of utmost importance in such circumstances.

Based on 24h urine collection the overall frequency of urinary metabolic abnormalities was 88.6%. This highlights the importance of doing metabolic workup in idiopathic stone formers and is in conformity with high frequency of abnormalities found in several studies (Rizvi *et al.*, 2002; Kumar *et al*., 2003; Pak *et al*., 1980; Hess *et al*., 1997). In our study hypocitraturia was the most common risk factor in calcium oxalate stone formers occurring in 81.2%patients. Urinary citrate is a well-recognized inhibitory factor for stone formation. It inhibits nephrolithiasis by complexing calcium in a soluble form and also by inhibiting crystal growth, nucleation and aggregation. A large number of factors affect urinary citrate level including hypokalemia, chronic diarrhea, distal renal tubular acidosis (RTA), strenuous exercise, starvation, high protein diet, acid base disturbance, increased sodium intake, pregnancy, increased urinary calcium and magnesium and drugs like acetazolamide, thiazide and ACE-inhibitors. Such a high frequency of hypocitraturia is also seen from a much larger study from Pakistan (Rizvi *et al*., 2002), where

Table 1. 24 h Urinary Constituents.

Parameters 24 hour Urine	Abnormal Values Mean $\pm$ SD	Normal Values Mean $\pm$ SD
Volume (ml/24h)	1158.5 $\pm$ 233.1	2158.7 $\pm$ 530.3
Calcium (mg/24h)	360.3 $\pm$ 36.1	145.3 $\pm$ 98.1
Oxalate (mg/24h)	65.3 $\pm$ 21.7	21.32 $\pm$ 11.3
Uric Acid (mg/24h)	*	442.4 $\pm$ 159
Citrate (mg/24h)	176.2 $\pm$ 78.3	561 $\pm$ 136

* Only 1 patient had hyperuricosuria.

Abbreviations: ESWL: Extracorporeal shockwave lithotripsy, PCNL: Percutaneous Nephrolithotomy

hypocitraturia occurred in 57% of stone formers. Data from neighboring India also reveals hypocitraturia occurring in 55-78% of stone formers (Kumar *et al*., 2003). A South African study also shows hypocitraturia to be the most important and commonest risk factor (Abdel-Goad and Bereczky, 2004). This is in contrast to western and Japanese studies where hyperoxaluria and hypercalciuria seem to be the predominant risk factors and the frequency of hypocitraturia is quite low (Hess *et al*., 1997; Yagisawa *et al.*, 1999; Orakzai *et al*., 2004; Pak, 1991; Usui *et al*., 2003; Yagisawa *et al*., 1998). Perhaps dietary and environmental factors like chronic dehydration due to hot climate, high salt intake, chronic diarrhea, malabsorbtion and low intake of citrus fruits (Rizvi *et al*., 2002) or some genetic abnormalities are the main factors responsible for predominance of hypocitraturia in this region.

Low urine volume was the second most common abnormality in our study occurring in 26.4% patients. Low urine volume is perhaps one of the most important easily preventable risk factors for calcium stone disease. Low fluid intake combined with increased loss from working in hot climate results in significantly reduced urine volume. On the other hand a large urine volume may significantly reduce urinary super saturation, thus helping to prevent stone recurrence.

The importance of hyperoxaluria and hypercalciuria has been shown in a large number of studies. We had a very low frequency of these factors. The frequency of hypercalciuria was only 11.5%. This was in conformity with studies from Pakistan (Rizvi *et al*., 2002), Japan (Yagisawa *et al*., 1999) and Saudi Arabia (Abomelha *et al*., 1990), however this was in contrast to studies from Europe (Hess *et al*., 1997; Orakzai *et al*., 2004),Turkey (Tafekli *et al*., 2003) and India (Kumar *et al*., 2003), where the frequency of hypercalciuria is high.

Hyperoxaluria occurred in only 11.7% of our patients, this however was not conforming to studies from southern Pakistan (Rizvi *et al*., 2002), India (Kumar *et al*., 2003), Japan (Yagisawa *et al*., 1999; Yagisawa *et al*., 2000) and Europe (Hess *et al.*, 1997),where hyperoxaluria appears to be the major risk factor attributable to oxalate rich diet. It is well known that oxalate plays much more important role in calcium oxalate stone formation; the effect being 15 fold greater than calcium (Borghi *et al*., 1996).Therefore these patients should be recommended a low oxalate diet.

Hyperuricosuria is a known promoter of calcium oxalate stone formation (Coe, 1978) .Although the frequency of hyperuricemia was quiet high but it was interesting to note that hyperuricosuria occurred only in 1.9%. Low frequency of hyperuricosuria is also seen in data from other studies from Pakistan (Rizvi *et al*., 2002) and neighboring India (Kumar *et al*., 2003). This in contrast to studies from affluent countries such as Saudi Arabia where frequency is as high as 60% (Abomelha *et al*., 1990), Japan (Yagisawa *et al*., 1999), Europe (Hess *et al*., 1997) and United States (Levy *et al*., 1995).This difference probably reflects difference in dietary habits between the regions.

CONCLUSION

Overall frequency of urinary metabolic abnormalities in idiopathic calcium oxalate stone formers is very high in our study. In contrast to western population where hypercalciuria and hyperoxaluria are the most common causes of stone formation, in this part of the world hypocitraturia and low urine volume appear to be the crucial factors involved in stone disease, although much bigger studies are needed to confirm these underlying factors.

Increasing the fluid intake and oral citrate supplement could be useful in preventing stones in this region.

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