Original Article

Studies on Metabolic Evaluation of Urinary Risk Factors in Southern Punjab, Pakistan

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ABSTRACT

Objective: The aim of the present study was to assess the metabolic abnormalities such as hypercalciuria, low urine volume , hypocitraturia, hyperoxaluria and hyperuricosuria in recurrent stone formers of southern Punjab as these abnormalities vary in different populations.

Study Design. Prospective study.

Place and Duration of Study: This study was conducted at the Department of Biochemisty, Bahauddin Zakarya University Multan and Nisthar Medical College Multan from December 2010 to January 2012.

Materials and Methods: One hundred adult patients who were known idiopathic recurrent calcium oxalate renal stone formers ($RCSF_S$) were selected from the various districts of the Southern Punjab, Pakistan. Twenty four hour urine collections were made while the subjects were on their usual diet. Samples were collected in clean polyethylene containers. Volume was measured using a graduated cylinder. Hydrochloric acid N/10 HCl (1 ml/100 ml of urine) was added to stop auto-conversion of ascorbic acid to oxalate during storage. Thymol was added as a preservative.

Results: Common metabolic change found in the present work was hypercalciuria. It was found in 38 patients (38%) it was isolated in 25 cases and associated with other changes in 13 patients.

Conclusion: Most of the patients were noted to have metabolic abnormalities. Hypercalciuria, low urine volume, and hypocitraturia were common metabolic defects. Hypercalciuria was the most frequent risk factor.

Key Words: Renal calculi, risk factors, hypercalciuria, low urine volume, hyperoxaluria, hypocitraturia, hyperuricosuria, Southern Punjab, Pakistan

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INTRODUCTION

Renal calculus formation is a common medical problem. It has been estimated that its prevalence is 15% once in life. Age, gender, race and geographical location are the factors which chiefly affect this disorder. That is why its incidence rate is different in different countries[1]. In a particular population the incidence rate fluctuate between 68 to 72 per 1000 000. This variation may be due to difference of the region under study[2]. Pakistan lies in stone belt. Renal calculus disease is endemic in this country as whole and in particular Punjab[3]. McCarrison[4] was the first person to carry study of this illness in various parts of Pakistan. He reported that the incidence of this disorder was quite high in Dera Ghazi Khan, Sukkur, Hyderabad and Dera Ismail Khan. It was found that as compared to Southern Punjab (33 %) the incidence of this problem was more in Northern Punjab (67 %).

Both extrinsic and intrinsic factors are responsible for this disease in different provinces of Pakistan. Majority of Pakistanis are inhabited in villages where the environment is hot[5].

In Pakistan, very little work has been done on the studies of risk factors for renal stone formation[6].

Metabolic studies on the population of this region show that major risk factors encountered are low urinary volume (20-30%), hyperuricosuria (20-60%), hyperoxaluria (50- 60%), hypomagnesuria (20-30%) and hypocitraturia (30-40%)[7].

It is very necessary to know the risk factors responsible for renal stone formation for efficient medical treatment and prevention of recurrence of this disease [8]

Reliable stone analysis and basic metabolic evaluation are highly recommended in all patients after stone passage. Every patient should be assigned to a low- or high-risk group for stone formation. High-risk stone formers should undergo specific metabolic evaluation with 24-h urine collection.[9]

The aim of the project is to study the metabolic abnormalities such as hypercalciuria, low urine volume, hypocitraturia, hyperoxaluria and hyperuricosuria in recurrent stone formers of southern Punjab as these abnormalities vary in different populations.

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MATERIALS AND METHODS

Selection of patients

Patients' group: One hundred adult patients who were known idiopathic recurrent calcium oxalate renal stone formers ($RCSF_S$) were selected from the various districts of the Southern Punjab. Ages ranged from 18 years to 67 years. The group of patients consisted of 75 male stone-formers (mean age 45 ±9. 97years) with recurrent calcium oxalate renal calculus disease and 25 female stone formers (mean age 33.76±11.15). These patients were referred to the different clinical laboratories by the consultants for further investigations of renal calculus disease after the stone removal. Most of these patients were those who were operated for renal calculi and visiting clinical laboratories for chemical analysis of renal calculi.

A recurrent stone former patient is one who has renal stone in his urinay tract besides evidence of previous renal stone formation. In addition he has history of passing renal stone, proof of renal stone on previous KUB X-ray or history of operation for urinary tract stone.

There were no dietary restrictions per se, but the patients were advised not to take oxalate rich and calcium rich diet. Major source of drinking water was either tap water in cities or hand pump water in the rural areas.

First time stone formers and children less than 18 years were excluded from the study. Patients suffering from any other diseases were also excluded from the study.

Control Group: The control group consisted of 48 healthy subjects, age and sex matched, 32 males and 16 females (mean age of either sex 35.0±7.1 years) .They were attendants of the patients and had no history of stone formation or renal diseases. No additional diagnostic procedure was performed to confirm the absence of renal stones. All subjects gave informed consent to participate in the study.

Collection of samples: Twenty four hour urine collections were made while the subjects were on their usual diet. Samples were collected in clean polyethylene containers. Volume was measured using a graduated cylinder. Hydrochloric acid N/10 HCl (1 ml/100 ml of urine) was added to stop auto-conversion of ascorbic acid to oxalate during storage. Thymol was added as a preservative.

Metabolic diagnosis consisted of five categories: low urine volume, hypercalciuria, hyperoxaluria, hyperuricosuria, and hypocitraturia. The parameters for the group of patients and the group of controls were expressed as mean value ± standard deviation. Volume of the specimen was noted and used for the analysis of biochemical parameters.

Biochemical determination: Urinary calcium and urinary uric acid were determined using Human diagnostic kits (Germany). Urinary oxalate was determined using the trinity biotech diagnostic kit (Ireland). Citrate was determined by using a simple modified Method for urine citrate determination by Sekar et al [10]. A spectrophotometer UV/VIS (Helios, Unicam, UK) was employed to take the measurements.

Analytical work was done at Bahauddin Zakariya University Multan and Nisthatr Medical College, Multan, Pakistan.

RESULTS

In the present study, common metabolic risk factors for renal calculi formation in the idiopathic recurrent calcium oxalate stone formers of Southern Punjab, Pakistan were identified.

The percentage of patients of either gender whose urinary constituents were abnormal is shown in table 1, figure. 1

Table No.1 Overall metabolic abnormalities in patients N=100

Metabolic Abnormality	Number of Cases
Hypercalciuria	25
Hypercalciuria +low urine volume	4
Hypercalciuria+hypocitraturia	9
Low urine volume	11
Low urine volume+ hypocitraturia	20
Hyperoxaluria	10
Hyperuricosuria	3
No abnormality detected	18
Total	100

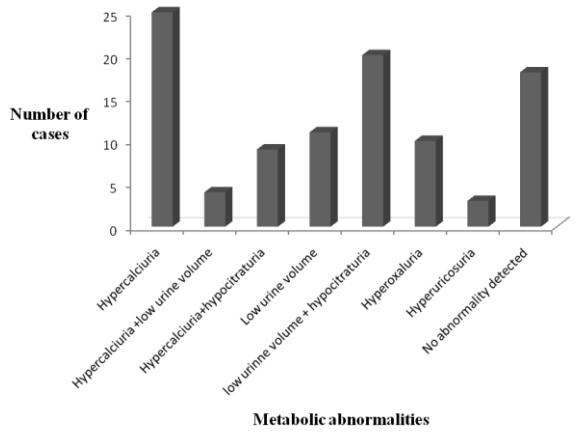

Figure No.1. overall urinary abnormalities in patients

Common metabolic change found in the present work was hypercalciuria. It was found in 38 patients (38%) it was isolated in 25 cases and associated with other changes in 13 patients.

The next most common abnormality was low urine volume noted in 35 patients. It was isolated in 11 patients and associated in remaining patients. Hypocitraturia was the abnormality next in prevalence.

Of the total one hundred patients, 29 were having hypocitraturia and this abnormality was associated. This was followed by hyperoxaluria in 10 patients and hyperuricosuria in three patients. Value of each metabolic abnormality in 24-h urine expressed as mean with standard deviation is shown in Table 2

Table No. 2: Values of metabolic abnormalities in 24- h urine

Parameters hour Urine	Normal limit	Control Mean ± SD	Abnormal Values Mean± SD	P value
Volume (ml/24h)	<1500	1754.29 ±134.4	1160 ±53.05	<0.0001*
Calcium (mg/24h)	>300	235.52 ±13.08	349.6 ±28.36	<0.0001*
Citrate (mg/24h)	<300	262.23 ±6.18	227.59 ±28.52	<0.0001*
Oxalate (mg/24h)	>40	28.58 ±4.61	55.5 ±6.5	<0.0001*
Uric acid (mg/24h)	>750	421.85 ±125.41	840 ±37.42	<0.0001*

*p value< 0.0001= highly significant

DISCUSSION

Even though risk factors for urolithiasis have been recognized but the precise reason of renal stone formation is often not known[11]. When urine is tested, the metabolic or other abnormalities are detected in renal stone formers. Low urinary volume (20-30 %), hypercalciuria (25-40%), hyperoxaluria (10-50%) hyperuricosuria (8-30%) and hypocitraturia (5-30%) are the common abnormalities[12].

In most of idiopathic calcium oxalate stone formers, hypercalciuria, low urine volume, hypocitraturia either alone or in combinations are the main abnormalities. Imbalance between promoters and inhibitors appears to be underlying cause of the abnormalities[13]. In other studies, hypercalciuria was the most common finding in the stone formers[14].

In this study the most common metabolic risk factor was hypercalciuria (38 %) which was isolated in 25 (25 %) cases and associated in 13 cases.

Thirty nine patients in India underwent metabolic evaluation and it was found that metabolic abnormalities were detected in 92.3% of the patients (n = 39) studied. Of them, almost 60% had two or more metabolic abnormalities. The most common metabolic abnormality was hypo-citraturia (82%), followed by hyper-oxaluria (56%) and hyper-calciuria (41%)[15].

A study in Argentina revealed that the abnormalities present, single and associated, in order of frequency, were idiopathic hypercalciuria, (56.88%), hyper-uricosuria (21.08%), unduly acidic urine (10.95%), hypocitraturia (10.55%), hypomagnesuria (7.9%), primary hyperparathyroidism (3.01%), hyperoxaluria (2.6%), and cystinuria (0.32%)[16].

Regarding hypercalciuria, the result of this study is in close proximity to that of Khan and Shahjahan in Pakistan[17], which showed that in the similar study carried by them, 31.7% patients, were hypercalciuric.

Higher excretion of calcium in the urine is found in studies conducted in Pakistan and other countries[18]. Similar results were encountered in western countries. It was found that hypercalciuria was the most frequent risk factor for urinary stone formation. The percentage of this abnormality was 60%. It was higher than in the present study. Hypercalciuria causes more than 50% of metabolic disorders in adults and 53 to 75% in children[19]. The most frequently found metabolic change investigated by Amaro et al[20] was hypercalciuria, present in 117 patients (74%), which was isolated in 62 cases (53%) and was associated with other changes in 55 (47%). Consequently, hypercalciuria is commonly found in the patients with renal stone disease. In studies of metabolic risk factors, hypercalciuria has been reported in up to or more than 50 percent of the patients.

In a study conducted in China, it was found that hypercalciuria, hyperoxaluria, high urine sodium levels, and hyperuricosuria were found to be the common metabolic risk factors of the calcium oxalate stone formation with hyperuricemia[21].

Hypercalciuria and recurrent calcium oxalate stone formers are related to each other. It has been known for a long time but the exact nature of this relation is not known as yet. Research is underway to know this relation.

As a result of Hypercalciuria, renal stone is formed heterogeneously consisting of many entities[22]. As a result of increase in the concentration of urinary calcium the concentration of calcium ion increases. Consequently urine becomes saturated with stone forming salts, i.e., calcium phosphate and calcium oxalate[23]. In addition, urinary inhibitors such as citrate and glycosamin complexes with calcium. This results in reduced urinary inhibitor activity. Consequently risk of renal stone formation is inceased[24].

The main cause of this defect is overproduction of 1, 25-dihydroxy-vitamin D3 [1, 25 (OH) 2 D3]. This is vitamin D in its active form. Its moves calcium ions into intestinal cells. Calcium enters the intestine via lumen of the intestine through the brush border membrane. It also controls transport of calcium from intestinal cells[25].

Vitamin D3 comes from diet. Besides, it is also synthesized in the liver from provitamin. It is synthesized when skin is exposed to ultraviolet light. Body has large store of 25 (OH) D3 and enzyme 1α-hydroxylase converts vitamin D to 1,25 (OH)2 D3[26].

In the present study, low urine volume was the next metabolic abnormalilty encountered. Out ot 100 cases it was found in 35 patients.

Dehydration and inadequate fluid intake are the causes of low urine volume. It may also be caused by malabsorptive bowel disorders which also result in excessive fluid loss.high fluid intake is the most effective means of urinary supersaturation[27]. Among the metabolic abnormalities investigated in 24 hour urine, low urine volume is the most common[28]. Low urine volume increases the supersaturaton of stone forming salts[29]. Chronic diarrhea or hard physical exercise leads to low urine volume and ultimately inceases urinary supersaturation of renal stone forming salts[28]. As a result low urine volume is an important risk factor for renal stone formation. There is evidence to prove that low urine volume is an actual lithogenic risk factor. To support this idea some workers have drawn probability index for formation of calcium oxalate. This index proves that even if non stone fomer has low urine volume e.g., if it drops below 1 litre/day this normal subjects can run high risk of developing renal stone[1].

The prevalence of renal stone tends to be higher in the areas of hot climate. This is well known fact now[30]. Insufficient fluid intake, loss of water from the skin/respiratory tract , diarrhea are the principal causes of low urine volume. These conditions lead to chronic dehydration. In such circumstances risk of stone formation increases. These condition may include high surrounding temperature, high degree of physical activity and insufficient water replacement. The most important factor is insufficient intake of fluid. This factor plays major role in high frequency of renal stone disease in the area of hot climate[31].

Urine dilution prevents stone recurrence and this is achieved by adequate fluid intake. When we take enough fluid risk of renal stone formation is decreased this process lowers the supersaturation of stone forming constituents[32].

Low urine flow rate is the cause of high prevalence of renal stone in this region. In Pakistan river Indus and its branches mainly supply water otherwise it is barren. Composition of water varies throughout the country. At some places it is very hard having more than 300 parts per million calcium but how this relationship increases risk of renal stone formation is unclear[33].

The metabolic abnormality next in abundance was hypocitraturia. Iqbal et al[34] conducted a study and found that the most common risk factor was hypocitraturia. It was present in 81.2% percent patients. Hypocitraturia was found in 57 % renal stone formers in a study conducted in Pakistan on much larger scale.

In a study conducted in Iran, the most common metabolic abnormalities were hypocitraturia (40.5%)[35]. These observations are in contrast to the present study where percentage of hypocitraturia is much less (29 %) than these studies.

Citrate forms complex with calcium and in this way process of renal stone formation is slowed down. It also results in the inhibition of nucleation and growth[36]. When there is low concentration of citrate, calcium is free to combine with oxalate and this is how hypocitraturia inceases the risk of renal stone formation In most of the cases, it is idiopathic. Distal renal tubular acidosis, chronic diarrhea, urinary tract infection and thiazide medication can also induce hypocitraturia.

High prevalence of hypocitraturia has been found in calcium oxalate renal stone patients in many studies. These studies provide convincing evidence that this abnormality is a significant pathogenic risk factor in renal stone formation disease[37].

In the present study, hyperoxaluria is not a common abnormality in the stone formers. It was found only in 10 percent of the patients in the present work. In contrast to this study, Hyperoxaluria (61.4%) was the most common abnormality detected, in a study conducted in Malaysia[38].

CONCLUSION

Most of the patients were noted to have metabolic abnormalities. Hypercalciuria, low urine volume, and hypocitraturia were common metabolic defects. Hypercalciuria was the most frequent. The findings suggest that metabolic derangements play a role in stone formation. Metabolic studies are necessary to treat the underlying cause and prevent further recurrence. More comprehensive metabolic evaluatioin in southern Punjab is required to establish the results.

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