

# Steppingstones in Prevention of Kidney Stone Disease in Pakistan

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### Abstract:

The prevalence and incidence of kidney stone disease (KSD) has increased in Pakistan since last 5 decades, it is not only the cause of pain, hematuria and fever but is also an important cause of chronic kidney disease, Morbidity and mortality as well if left untreated. It is recurrent disease and can be manifestation of systemic diseases, (D.M, obesity, HTN) genetic and environmental factors play a role in etiology of disease. In spite of modern methods of surgical removal available in Pakistan there is constant increase in number of patients. Economic burden of disease is quite significant, so established metaphylaxis program is essential part of management of this surgical and medical disease. Main therapies based on history, stone analysis, 24 hour urine metabolic study constitutes the basis of prevention. Increasing fluid intake dietary modification, Pharmacotherapy is the main stay of metaphylaxis. Compliance of the patient and establishment of specialized stone clinics should be managed jointly by urologist, nephrologist, dietitians, metabolic laboratory expert and Medical Social officers. Prevention is possible in many cases if these patients are managed jointly by multidisciplinary team.

**Key Words:** Prevention, kidney stone disease, Pakistan, Hydration, diet, pharmacotherapy, struvite, oxalate, primary hyperoxaluria, epidemiology, cystine.

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DOI: 10.53778/pjkd82259

Received 5 June, 2024 & Accepted 30 June, 2024

PJKD 2024;8(2):2-10

### Introduction:

Kidney stone disease (KSD) is one of the commonest disease in Pakistan and constitutes 50% of Urologic admissions in Urban and 70% in rural centers of country.<sup>1</sup> Exact prevalence in the country is not known because no population based epidemiological study has been published, rough estimate reports are 12 to 15 % but prevalence of silent kidney stones as reported by CT scan was in the range of 2.8%.<sup>2,3</sup> If we analyze the reports published by Sindh Institute of Urology and Transplantation (SIUT) Karachi, we found out that over the last 4 decades 83107 adult stone patients were treated and it is expected that in 5th decade (2015-2024) more than 10,0000 new patients will be admitted in only one institute(SIUT) in Pakistan, that shows the magnitude of the disease.<sup>4</sup> But actual national burden of disease can only be assessed when population based epidemiological study is conducted in country.

In country like Pakistan many patients with kidney stone disease present very late because of neglect by patients, delay in reference by family physicians, use of homeopathic medicines to dissolve stones, treatment by faith healers or due to poverty patients get limited access to the tertiary care centers and

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present with complications like acute and chronic kidney disease (CKD), unilateral nonfunctioning kidney, pyonephrosis, perinephric abscess.<sup>5</sup>

Traditionally disease was more common in males with M: F ratio of 4:1, data from outpatient clinics.<sup>4</sup> In patient admission and emergency episodes shows that females are commonly affected than males with change in M: F ratio from 4.5: 1.3 in (1972-1974) to 1.4:1 in year 2015. We also see more elderly patients in current practice than in past.<sup>4</sup>

The stone composition reported by Rizvi et al during (2007-2014) in 1559 kidney stone patients who underwent percutaneous nephrolithotomy (PCNL) shows 41% pure stones and 59% were mixed stones.<sup>6</sup> In pure stones 79.6% were calcium oxalate stones, uric acid in 17 %, calcium phosphate in 1.5%, Struvite Pure (0.46%) and mixed Struvite (2.8%) and less than 1% Cystine stones and Xanthine. This shows decrease in Struvite stones in Pakistan as compared to the past and we see more mixed calculi because of multifactorial etiology. With increasing trends in the prevalence, there has been a rise in acquiring new technology in the management of stone disease in Pakistan. There are about 70 extracorporeal shock wave lithotripsy (ESWL) centers in the country, 58 PCNL centers, laparoscopy for stone removal is being done in seven centers, Robotic assisted surgery for stone disease in three centers while flexible ureteroscopy in 20 centers.<sup>1</sup>

How many stone patients have been treated for 10 years in all over country and what is the cost expenditure in Pakistan is not reported but one can imagine with the predicted cost rise for treatment of KSD in USA is \$ 10 Billion by 2012 and 15 billion in 2030.<sup>7</sup>

The KSD is considered as benign disease if treated at an early stage but if left untreated, can be a cause of chronic kidney disease CKD, in Sukkhar and Larkana districts of Pakistan, KSD contributes (26%) of all ESRD patients on maintenance dialysis, another epidemiologic review from Pakistan showed KSD as a cause of CKD in 24% of dialysis patients.<sup>8</sup> This benign disease can be a cause of high morbidity and mortality and recurrence rate is as high as 50% after 5 years if no preventive strategies are undertaken.<sup>9</sup>

### **Risk Factors for Etiology:**

KSD is a multifactorial disease involving pre-urinary and urinary risk factors, physicochemical consequences, and abnormal crystaluria. There is interaction between genetic and environmental factors in the causation of KSD.

In pre-urinary risk factors age, gender, family history, ethnic background, climate, hot region, occupation of patient, body weight, diet rich in animal protein, low in calcium, high in oxalate and salt and low water intake are important.<sup>10,11</sup>

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In urinary factors promoters are low urine volume, hypercalciuria, hyperoxaluria, hyperuricosuria and low pH. Inhibitors are low citrate excretion, Tamm Horsfall protein and nephrocalcin production in the kidney tubules.

Physicochemical consequences due to environmental risk factors include: super saturation of urine with promoters, low inhibitors, crystallization, aggregation and cell damage leads to crystallization and ultimately stone formation. Genetic risk factors include: cystinuria, primary hyperoxaluria, xanthinuria and renal tubular acidosis.

### Screening and Evaluation of kidney stone Patients

KSD is a potential risk factor for CKD and other complications so it is important to diagnose the disease at early stage and identify risk factors for recurrence of disease, this includes thorough medical history, dietary history, urine analysis and culture, serum calcium, phosphate, uric acid, stone analysis and imaging studies in the form of ultrasound of both kidneys and CT scan of kidneys and urinary bladder.

In the medical history we aim to identify, primary hyperparathyroidism, renal tubular acidosis, diabetes mellitus, gout, metabolic syndrome, obesity and gastrointestinal diseases like chron's disease, ulcerative colllitis, Bariatric surgery. A history of whether it is a first time or recurrent stone formation is also important to look for causative risk factors.

Some medications are also associated with KSD, these include Topiramate, Acetazolamide, Zonisamide, ceftriaxone, Indinavir, sulphamethoxazole, excessive vitamin C, vitamin D and calcium supplement, laxatives, magnesium trisilicate.

In the dietary history it is important to note the water intake, use of salt, animal protein and calcium intake. If serum calcium is high or pure calcium phosphate stones, Parathormone is important to investigate for hyperparathyroidism. Low serum bicarbonate, low potassium and high chloride indicate renal tubular acidosis and further investigation for RTA are required, wherein patients form calcium phosphate stones and may cause early CKD. Early onset of CKD and bilateral renal calculi may indicate primary hyperoxaluria in children and adolescence. Urinary pH is important as low pH < 5.5 may indicate uric acid and pH >7 indicate infected stones. CT KUB as an initial imaging is important for decision making, for treatment, any abnormalities and nephrocalcinosis in underlying kidney stones, may indicate medullary sponge kidney (MSK), Hyperparathyroidism and RTA.

It is also important to ask about occupation of patient, such as farmers, steel workers, welders, drivers where exposure to cadmium, lead and arsenic is high for risk of developing KSD.

Dietary recall history in our KSD patients showed that 78% were taking less meat, 61% were taking less milk, 46% were taking high salt intake (more than 2.3g/day), oxalate intake was high 55%, water intake was low in 50% of patients and citrate intake in diet was low in 92.4% of patients.<sup>12</sup>

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Drinking samples from sukkur city (120 samples) shows 100% samples were contaminated with coliform bacteria and chlorine was not found in any sample, this might be a cause of recurrent diarrhea coupled with high temperature environment leading to dehydration and thus contributing to one of the factors of stone disease in Sukkur region of Pakistan, similarly assessment of water quality of Manchar lake in Dadu region of Pakistan showed high level of cadmium.<sup>10</sup> Lead and arsenic contamination in water used by local people in Pakistan is again a causative factor for KSD.<sup>11</sup>

Environmental exposures also called nephrotoxic exposome may contribute to KSD and is potential target for treatment and prevention.

### **Prevention of kidney stone disease:**

Prevention of KSD can be divided into primary prevention that includes general prophylaxis in no risk population, who have never been affected by stones and no known predisposing factors but living in geographical area at risk for KSD.

#### **Primary Prevention:**

This primary prevention includes increase water intake of about 2 to 2.5 liters a day, balance diet, reducing weight if obese and screening by Ultrasound KUB in villages where health facilities are not available to diagnose KSD at an earlier stage to prevent complications.

#### **Secondary prevention or Metaphylaxis:**

Secondary prevention is aimed at population at risk: patients already affected by stones, family history of stone disease, urinary tract anomalies, metabolic, genetic disorders or patients with recurrent urinary tract infections, younger patients, and single kidney with stone. Before start of any metaphylaxis it is important to take full history, dietary history, family history or other known systemic disease, stone analysis, and 24 hours metabolic study. It is necessary specially in high-risk patient i.e. patients with history of Bariatric surgery, GI diseases (Crohn' disease, ulcerative colitis, chronic diverticular disease, obesity/metabolic syndrome, diabetes mellitus, hyperparathyroidism, renal tubular acidosis, gout, primary Hyperoxaluria, bilateral renal calculi.

Data from SIUT stone clinic patients published BJUI journal showed Hypocitraturia (57%) and hyperoxaluria (51.8%) as the two main risk factors in Pakistani KSD population.<sup>12</sup> Hypercalciuria was seen in only 8% of patients as compared to 60% reported from western population. Similar reports in 2013 on stone analysis in children less than 2.5 years revealed bladder stones 46% and kidney stones in 23%. It was important to note that ammonium acid urate was seen in 74.3% cases. The risk factors identified were poverty, malnutrition and, dehydration, highlighting the improvement of hydration, nutrition by introducing milk and vitamins as early intervention in in KSD at risk population. We will divide the metaphylaxis into general recommendations and specific recommendation according to the cause of stone formation.

General recommendations include, increase fluid intake to over 2.5 liters/day for prevention of recurrence of stone disease. Compliance of high fluid intake can be achieved by behavioral changes and mobile health applications, reduction in animal protein intake, diet high in fruits and vegetables, reducing weight if obese and adequate physical activity are among the general recommendation for KSD patient.

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### **Increasing Fluid Intake:**

Is recommended in all stone formers because it has shown to be beneficial and cost effective, old study by Borghi L, shows that subjects who drink 3 liters of water/day for 5 years shows low recurrence than control (12 vs 27%).<sup>13</sup> Whether mineral water or mineral free water should be used for stone disease prevention? The simple answer is that all types of water can provide advantage, bicarbonate water exerts similar effect as potassium citrate by decreasing uric acid and oxalate, raising urine pH and increasing urinary citrate. Water with a high content of calcium 202 mg/L, increases urinary calcium, reduces urinary oxalate more than water with low calcium content (10mg/<), water containing calcium and magnesium reduces as many as nine stone forming factors.<sup>14</sup> Other drinks like coffee, tea, beer, red wine and orange juice reduces the occurrence of incident stone formation and sugar sweetened beverages increase the incidence of stone formation.<sup>14</sup>

### **What About Citrates in Diet?**

The beneficial effect of orange juice has been due its contents of potassium citrate. Citrate is an inhibitor of stone formation and in our population ninety % of stone formers have low citrate in diet. Renal excretion of citrate is controlled by acid base status, with status of acidosis characterized by increase renal citrate reabsorption and alkalosis causes increase in renal citrate production. Citrate is found in high quantity in lemon juice (145 mEq/L), Grape fruit juice (197.5 mEq/L). Orange juice (144 mEq/L) and in other common beverages is given in reference of Halebian etal.<sup>15</sup> Use of four ounces of lemon juice or citrate 5.9 gram citric acid daily when used in 100 calcium oxalate stone formers at 40 months follow-up, Penniston KL found lemon juice increases citrate by 203 mg/day and also increases the urine volume by 763 ml/ day although Lemonade, with K- citrate was associated with greater increase in Citrate.<sup>16</sup> Dietary source of citrate as an alternative of pharmaceutical citrate and is very much suitable in our setup because it is cheap and readily available, still requires more evidence based studies though. Barghouti et al compared three fruit juices for prevention of KSD.<sup>17</sup> His conclusion was that orange juice and grape fruit juice both increase urinary oxalate levels, may have a role in stone prevention with their citrate contents, and high content of sugar needs to be taken into account for orange juice. Lemon juice was found to have protective role by raising urinary citrates but it lacks significant effect on urine pH so may not be effective in the uric acid stone formers because protection is linked to the rise in urine pH.<sup>17</sup>

### **Dietary Management:**

Dietary advise by a qualified dietician is a proven method of reducing the risk of recurrence of KSD along with increasing fluid intake with or without pharmacotherapy, provided we know the composition of stone and underlying urinary risk factors.

If we review the published dietary pattern in Pakistan among KSD population, less animal protein and calcium intake; and high oxalate with very low citrate, high sodium in diet is prevalent. In our stone population we must make different recommendations among stone formers with malnourishment to increase the dietary protein intake and other patients to restrict to 6/8 ounces of animal protein intake. Diet recommended for recurrent calcium oxalate stones and hypercalciuria require restricted animal

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protein and salt (less than 2.3 gram/ day) and normal calcium intake 1000 to 12000 mg/day. A prospective study of dietary calcium and nutrients and risk of kidney stone disease in 505 KSD patients, Curhan et al. found that high dietary calcium intake decrease risk of symptomatic kidney stones.<sup>18</sup> Calcium supplement should be prescribed to the patient as calcium citrate, if at all other calcium supplements are taken they should be taken with meals.

### **How to treat urinary risk factors for prevention of kidney stone disease?**

**Hyperoxaluria** is seen in more than 52% of stone formers in Pakistan while 10 to 15% reported from the developed countries, warranting strategies for reducing urinary oxalate levels. We advise the patients to maintain sufficient calcium intake by taking milk yogurt and other milk products. Fish oil supplement 1 to 1.5 gram per day for 30 days can reduce urinary calcium oxalate and normalize erythrocyte oxalate exchange.<sup>19</sup> The rationale that fish oil is protective among KSD arises from widely cited claims that urolithiasis is extremely rare in Alaskan, Greenland Eskimos, whose diet is predominantly rich in fish. Pyridoxine (Vita B 6) supplementation decreases urinary oxalate in primary hyperoxaluria type 1 with benefit seen in 50% of patients at a dose of 20 mg per kg per day to the maximum of 200 mg per day. High oxalate rich foods; such as spinach, beets, nuts, chocolate, potatoes, legumes and tea should be avoided, whereas grape fruit and cranberry are rich in oxalate and should be avoided in hyperoxaluria.

Patients with enteric hyperoxaluria like short gut syndrome, bariatric surgery, chronic disease, celiac disease and use of weight loss medication orlistat need their dietary oxalate restricted along with low fat diet and use of calcium supplementation with meals to block intestinal oxalate absorption.

Bisphosphonate (by reducing urinary calcium) and sodium thiosulphate due to its antioxidant properties is recommended therapy for primary hyperoxaluria-1 (PH-1), but more studies are needed to define its role in calcium stone disease. Lumisiran is the new drug approved by FDA therapy for treatment of PH-1 which works by reducing the hepatic level of coenzyme thus depleting the substance for oxalate production.

### **Probiotics for prevention of hyperoxaluria:**

*Oxalobacter formigenes* is a gram negative bacterium that resides in intestine and uses oxalate as energy source for itself although its role in animals to reduce oxalate absorption is known but in human beings proven to decrease in urinary oxalate with potential to decrease the incidence of oxalate stones.<sup>20</sup> Use of antibiotic can interfere in colonization of the bacteria in gut and cause increase in urinary oxalate. Other probiotics like lactobacillus, Eubacteria, Enterococcus, E coli have been used to modify lithogenic substances but others have not substantiated this finding.<sup>21</sup>

### **Hypocitraturia:**

Hypocitraturia is the commonest urinary risk factor seen in 57% of kidney stone disease patients in Pakistan and 15 to 63 percent patients reported from western literature.<sup>22</sup> Citrate is important inhibitor of nucleation, agglomeration and growth of calcium oxalate and calcium phosphate stones. Increasing dietary plant-based diet increases urinary citrate excretion. Barrelo R. et al studied 57 recurrent hypocitraturic calcium stone formers and supplemented them with 30 to 60 meq K citrate daily vs placebo for 3 years.

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Patients on K citrate had high recurrence free rate compared to placebo 72% vs 20% respectively.<sup>22</sup>

This drug also shown to improve stone free after extracorporeal shock wave Lithotripsy. Reddy K et al used combination of potassium citrate and vitamin B6 for prevention of multiple and recurrent calcium oxalate and calcium phosphate stones and found reduction in recurrence of Calcium oxalate phosphate urolithiasis.<sup>24</sup> This drug can be used in patients with more than one risk factors like Hypocitraturia, hyperoxaluria and hypomagnesemia. Another study in 64 patients on the use of potassium, magnesium and citrate as prophylaxis against calcium oxalate stone were given 42 mEq of potassium 21 mEq of magnesium and 63 mg daily for 3 years. No calculus formed in 12.9% patients who received the supplementation as compared to 63.3 % of placebo. Ettinger et al. concluded from this study that it reduces risk by 85% and drug can be used without metabolic testing.<sup>25</sup>

### **Idiopathic hypercalciuria:**

Contributes 8% of Pakistani stone formers and 60% reported from west, Treatment for future recurrence consists of hydrochlorothiazide 25 mg twice a day, potassium citrate 20 to 30 meq per day.

Adequate intake of calcium 1 gram to 1.2 gram per day increase fluid intake to obtain urine output of 2 L per day.<sup>26</sup>

### **Non calcium stones and its prevention:**

**Uric acid kidney stones** constitute 17% of all pure renal calculi in Pakistan and 10% of all stones in USA.<sup>2</sup> Main risk factors include low urine pH, low urine volume, hyperuricosuria, Gout and other comorbidities such as obesity, diabetes mellitus and metabolic syndrome. Weight loss, exercise and increase fluid intake and less animal protein are the preventive strategies.<sup>25</sup>

**Infectious Stones (Struvite):** Repeated urinary tract infection with urease producing organism lead to struvite stones, more common in female with ratio of 2:1. Frequency of struvite stones has decreased in Pakistan from 15% to 1.3% in recent reports.<sup>2</sup>

Complete surgical clearance is combined with culture specific antibiotic for prolonged periods at times with acetohydroxamic acid, low doses of K citrate and hydration helps in prevention of recurrence.<sup>27</sup>

**Cystine stones:** It is a rare inherited disorder of renal and intestinal transport of 'COLA' dibasic amino acids caused by mutations in the SLC7 A7 gene and SLC7 A9 genes. In Pakistan it constitutes less than 1% of all adult kidney stones and 1.1 % in children. Urinary cystine more than 250mg/L is hallmark of this disease.<sup>2</sup> Patient should be educated to take at least 3 liters of water per day salt and animal protein should be reduced. K- Citrate should be advised to maintain the pH of 7.0 to 7.5 this is the second line therapy. Third line therapy is THIOL containing, drugs which include alpha Mercaptopropionyl (Tiopronim) and D-penicillamine have sulfhydryl group that reduces the disulfide bond of cysteine thus making it more water soluble.<sup>19</sup>

### **Endemic Bladder calculi in Children:**

Is still endemic in rural areas of our country and poor localities of cities and contributes 30% of pediatric urolithiasis cases.<sup>28</sup> Main cause is protein and vitamin deficiency in children of people who have agriculture based economies. Diet deficient in milk, dehydration are other risk factors. Increase intake of milk, increasing hydration by ORS and by adding vitamin A and B complex supplement in school along with milk can be preventive and reduces the incidence of endemic bladder calculi.<sup>28</sup>

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### **Role of Stone clinics and Conclusion:**

The success of stone prevention program depends upon follow up in specialized stone clinics which should consist of multi-disciplinary team of doctors including urologist, nephrologist, dietitian, metabolic laboratory experts, and medical social workers. Metabolic workup, and stone analysis is necessary for final prevention strategy. Patients should then be educated to increase hydration, diet modification and pharmacotherapy if needed. Nephrologist must play vital role in pharmacotherapy and its side effect.<sup>29</sup> Compliance to diet, hydration and pharmacotherapy is an essential part of success. Social media and mobile phones may play an important role in reminding to patients about hydration. Government should establish specialized stone clinics equipped with modern technology of kidney stone management, screening of new patients and advice by physicians for prevention with free medicines.

**Acknowledgments:** we are extremely thankful to Dr M Hassan khan RMO urology for typing this manuscript.

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