Risk of Chronic Kidney Diseases in Kidney Stone Formers: Current Concepts in Management

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Kidney Stones: A Preface

Kidney stone disease is the most common disease of the urinary tract, with a history dating back to 4000 B.C.[1] These stones can develop anywhere in the urinary tract – kidney, ureter or urinary bladder – with symptoms ranging from none to severe pain.[2] In recent times, kidney stone disease has become a major economic and health burden worldwide, with increasing prevalence and recurrence rates globally.[1,3] It affects about 12% of the world population at some point in their life, with a predilection towards males and age group of 20-49 years. In India, about 12% of the population is expected to have urinary stones, out of which 50% might result in loss of kidney functions.[1]

Mechanism of Kidney Stone Formation

The pathophysiology of kidney stone formation is not understood completely.[1] It is hypothesized that consumption of oxalate rich foods or genetic factors result in development of hyperoxaluria, hypercalciuria, hypocitraturia, hyperuricosuria, or microorganisms produce magnesium ammonium phosphate. This results in supersaturation of salts such as calcium oxalate or uric acid or calcium phosphate or magnesium ammonium phosphate. In the supersaturated urine, these free atoms, ions or molecules begin forming microscopic clusters, a process known as crystal nucleation and this is followed by crystal growth. The crystals then aggregate together and induce the formation of reactive oxygen species (ROS). Renal injury induced by ROS leads to retention of crystals and finally formation of kidney stones (Figure 1).[1,4]

Risk of Chronic Kidney Disease in Stone Formers

There exists an increased risk of chronic kidney disease (CKD) and end-stage renal failure in patients having kidney stones.[5] Also, among the stone formers, those with rare hereditary diseases (cystinuria, primary hyperoxaluria, Dent disease, and 2,8 dihydroxyadenine stones), recurrent urinary tract infections, struvite stones, hypertension, and diabetes are suggested to be at the highest risk for CKD.[6] In a population based research study done by Rule *et al*, during a mean follow up of 8.6 years, stone formers (n=4774) were found to be at an increased risk for a clinical diagnosis of CKD as compared to controls (n=12975); 6.9% versus 3.1%. Moreover, after exclusion of patients with prevalent CKD, there were higher chances of stone formers to receive a subsequent diagnosis of clinical CKD compared with control subjects.[7]

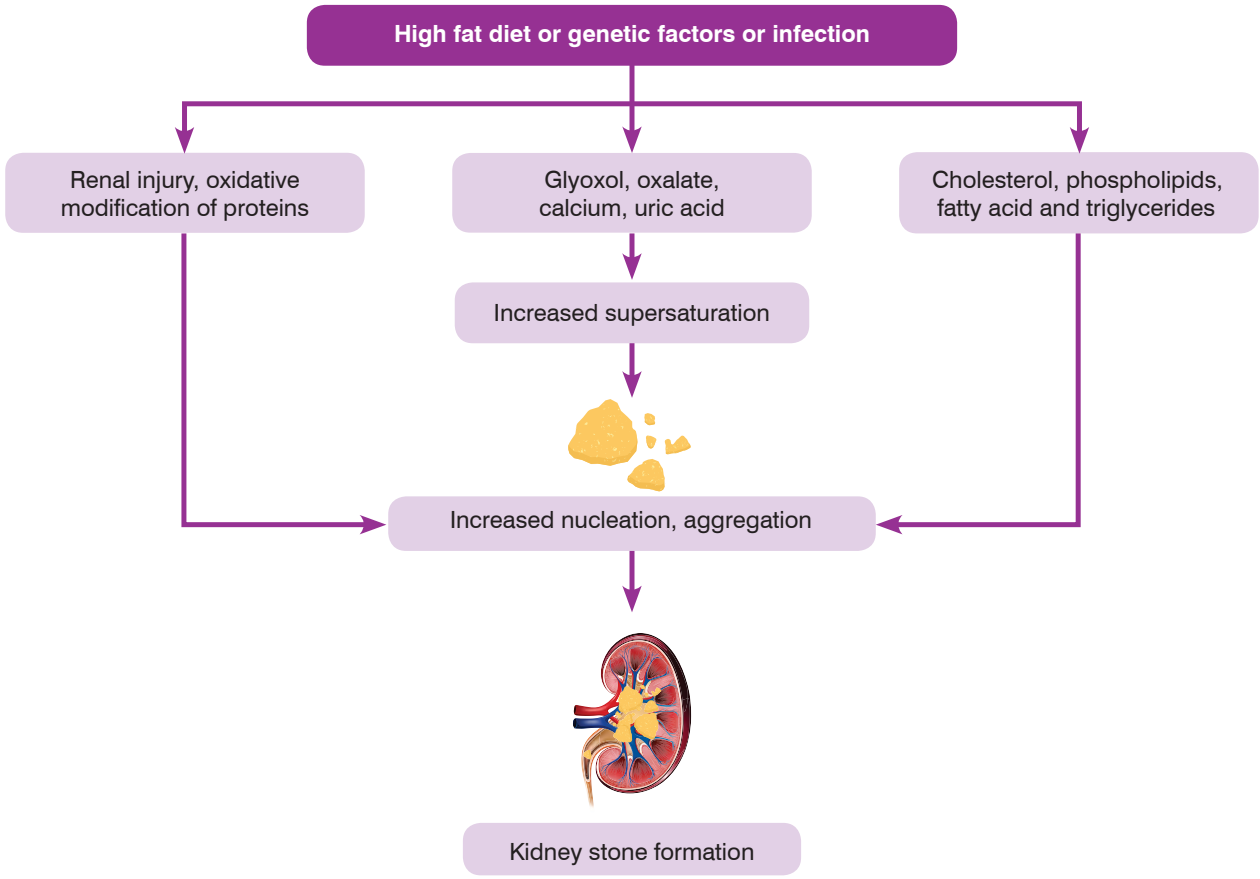
A complete understanding of the pathophysiologic relation between kidney stones and CKD has not been achieved yet, but various possible pathways have been suggested. These pathways associate repeated episodes of obstruction, injury due to toxicity of ammonium ions, rare hereditary disorders, extracorporeal shock wave lithotripsy, etc. with development of CKD in stone formers (Figure 2).[8] In addition, various stone-specific risk factors for kidney stone-associated CKD have been identified:[9]

a. Metabolic – Hypertension, diabetes, obesity, micro-albuminuria
b. Anatomic - Ileal conduit, neurogenic bladder, solitary kidney, hydronephrosis
c. Stone-specific – Struvite, uric acid, symptomatic
d. Infectious - Struvite stones, recurrent urinary tract infections
e. Others - Female sex

Current Concepts in the Management of Kidney Stones to Reduce CKD Risk

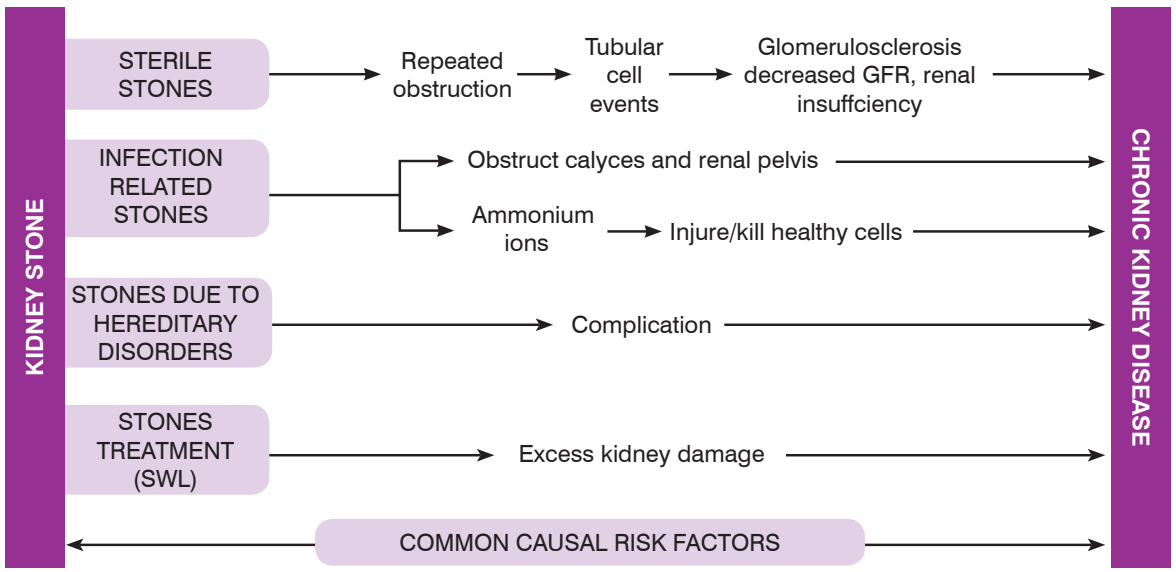
The role of kidney stones and its various associated risk factors in increasing the risk for CKD implicate the need for more aggressive screening for subclinical CKD in patients with kidney stones. It is also suggested that aggressive medical treatment for prevention of recurrent kidney stones

Figure 1: Mechanism of kidney stone formation



Adapted from: Devarajan A. Cross-talk between renal lithogenesis and atherosclerosis: an unveiled link between kidney stone formation and cardiovascular diseases. *Clinical Science* 2018,132(6):615-626.

Figure 2: Possible pathways for CKD in kidney stone formers



Abbreviations: GFR, glomerular filtration rate; SWL, shock wave lithotripsy; CKD, chronic kidney disease.

Adapted from: Shang W, Li L, Ren Y, Ge Q, Ku M, *et al*. History of kidney stones and risk of chronic kidney disease: a meta-analysis. *PeerJ.* 2017;5:e2907.

might play an important role in decreasing the CKD risk in these patients.[7]

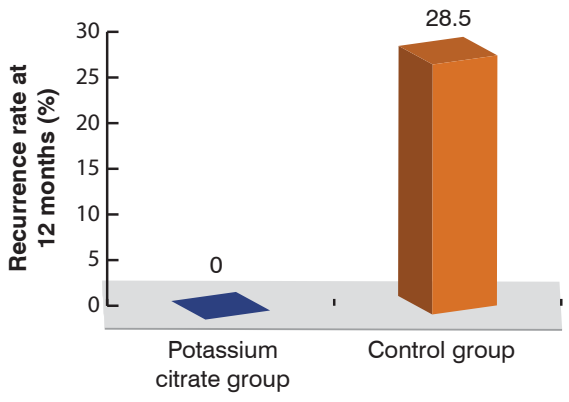
The first step in prevention of kidney stones recurrence is identification of the associated risk factors. The main risk factors for stone formation are low urine output, high urinary concentrations of calcium, oxalate, phosphate, and uric acid compounded by a lower excretion of magnesium and citrate. A complete metabolic workup is highly recommended in patients with recurrent disease, along with a dietary regimen low in salt and protein, rich in calcium and magnesium and coupled with adequate fluid intake.[10]

Potassium Citrate to Prevent Stone Formation and Recurrence

It is well known that citrate is an inhibitor of stone formation, and achieves this by a variety of mechanisms. It complexes with calcium in the renal tubule, increasing its solubility and reducing the concentration of free calcium in the urine. Formation of this calcium-citrate complex restricts supersaturation with calcium and prevents nucleation of both calcium oxalate and calcium phosphate. Moreover, crystal agglomeration and growth is also inhibited by citrate as it has the ability to bind to the crystal's surface and prevent adhesion of calcium oxalate to renal epithelial cells.[10]

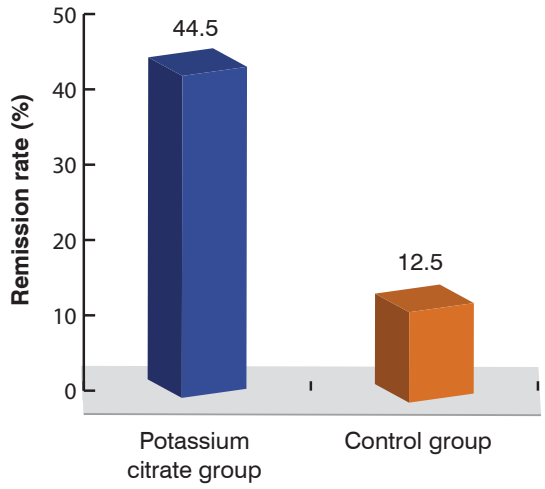
As mentioned above, low urinary citrate is a major risk factor for stone formation. A urinary citrate excretion of <320 mg/day is known as hypocitraturia. It is found in about 20%–25% of patients with recurrent calcium stones.[11] Hypocitraturia may be treated with dietary modifications and use of citrate preparations. Potassium citrate therapy has been shown to cause a significant increase in urinary citrate, pH, and potassium, thereby leading to significantly less stone formation.[10] In addition, potassium citrate is also effective in preventing stone recurrences after shockwave lithotripsy (SWL). In a study conducted by Soygur *et al*, patients (n=110) who underwent SWL due to lower caliceal stones and who had residual stone 4 weeks later, were randomized to receive potassium citrate or serve as controls. It was found that the stone recurrence rate at 12 months was zero in the group receiving potassium citrate, in comparison to the control group with a stone recurrence rate of 28.5% (Figure 3). Also, the remission rate in the residual fragment group was found to be significantly higher (Figure 4).[12]

Figure 3: Stone recurrence rate at 12 months in the group receiving potassium citrate versus the control group after shockwave lithotripsy



Adapted from: Soygür T, Akbay A, Küpeli S. Effect of potassium citrate therapy on stone recurrence and residual fragments after shockwave lithotripsy in lower caliceal calcium oxalate urolithiasis: A randomized controlled trial. *J Endourol.* 2002;16(3):149-52.

Figure 4: Remission rate in the residual fragment group receiving potassium citrate versus the control group after shockwave lithotripsy



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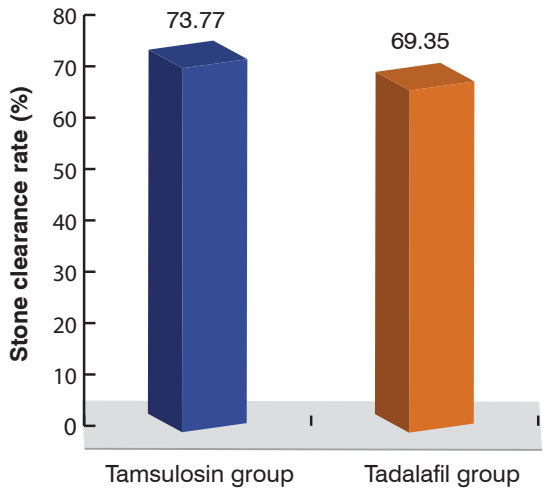
Role of Medical Expulsive Therapy and Tamsulosin

Medical expulsive therapy (MET) has been proposed as an effective conservative approach for the initial management of small distal ureteral stones. Amongst the various agents being used for MET, role of alpha blockers has been well-elaborated.[13] The European (EAU) as well as American Urological Associations (AUA) support the use of alpha blockers as a possible treatment option in select patients, that is, in patients who are medically stable with symptom control and with ureteral stones less than 10 mm.[14]

Alpha-1 receptor is the most common in all segments of the ureter, Tamsulosin is a selective alpha-1a adrenergic antagonist.[15,16] Tamsulosin is the most researched molecule

Figure 5: Stone clearance rate with tamsulosin versus tadalafil in patients with distal ureteric stones



Adapted from: Goyal SK, Singh V, Pandey H, Chhabra MK, Aggarwal SP, *et al*. Comparative efficacy of tamsulosin versus tadalafil as medical expulsive therapy for distal ureteric stones. *Urol Ann* 2018;10:82-6.

in MET amongst alpha blockers.[13] A plethora of studies provide evidence of its efficacy in improving kidney stone passage. A prospective study done by Goyal *et al*, the relative efficacy of tamsulosin and tadalafil as medical expulsive therapy for distal ureteric stones was compared. Patients (n=123) with distal ureteric stones of size 6-10 mm were randomized to receive tamsulosin or tadalafil once daily for a maximum of 4 weeks. Primary end point was expulsion of stone. It was found that tamsulosin was more effective for stone clearance than tadalafil (Figure 5).[17]

Conclusion

Kidney stones disease is the most common condition of the urinary tract. Although a complete understanding has not been achieved, there exists an increased risk of chronic kidney disease and end-stage renal failure in patients having kidney stones. Currently, medical therapy with potassium citrate and tamsulosin for medical expulsive therapy are amongst the commonly used therapeutic approaches to manage and prevent recurrence of stones and thereby reducing the risk of chronic kidney disease.

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