

KIDNEY STONE DISEASE: ETIOLOGY AND EVALUATION

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ABSTRACT : The purpose of the present review is to provide an update about the most common risk factors or medical conditions associated with renal stone formation as the incidence of kidney stone disease is increasing in tropical developing countries. The potent risk factors identified include the “classic” risk factors in the urine (low urine volume, hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitrauria, and hypomanesuria) and epidemiological factors include climate, race, ethnicity, age, sex and body weight. We have found that sedentary lifestyle habits, an unhealthy dietary plan, and overweight problems may be important promoters. We suggest that there is a need for further studies to be carried out in larger sample sizes with emphasis on above risk factors for rational, efficient and specific management.

Keywords: Kidney stones; Nephrolithiasis; Hypercalciuria; Hyperuricosauria; Hypocitrauria

Kidney stone disease is a multi-factorial disorder resulting from the combined influence of epidemiological, biochemical and genetic risk factors. Kidney stones are of four types. The overall probability of forming stones differ in various parts of the world and is estimated as 1-5% in Asia, 5-9% in Europe, 13% in North America (Robertson 1993) and the recurrence rate of renal stones about 75% in 20 years span (Sutherland et al 1985). It occurs both in men and women but the risk is generally high in men and is becoming more common in young women (Selvem 2002).

Epidemiological risk factors

Geography

Kidney stone incidence varies in different parts of the world, high incidence areas are Scandinavian countries, Mediterranean countries, British Isles, northern Australia, central Europe, portions of the Malayan Peninsula, China, Pakistan and northern India where as the incidence of kidney stone formation is lower in areas like Central and South America, some parts of Africa. In Asia stone-forming belt has been reported to stretch across Sudan, Saudi Arabia, the United Arab Emirates, the Islamic Republic of Iran, Pakistan, India, Myanmar, Thailand, Indonesia and Philippines (Hussain et al 1995). The effect of geography on the incidence of stone formation may be direct, through its effect on temperature, high temperatures increase perspiration, which may result in concentrated urine, which in turn promotes increased urinary crystallization.

Age and Sex

The disease affected all age groups from less than 1 year old to more than 70, with a male to female ratio of 2:1. The incidence of formation first kidney stone between the ages of thirty and seventy vary between approximately 100 – 300 per 100,000 per year in men and 50-100 per 100,000 in women i.e.6%–9% in males and 3%–4% in females (Johnson et al 1979, Hiatt et al 1982, Soucie et al 1994, Curhan et al 1997, Madore et al 1998, Sowers et al 1998, Downey and Tolley 2002, Stamatelou et al;2003). Baker et al (1993) reported that the peak age for the development of calcium oxalate stones was between 50–60 years. However the increased incidence of recurrence in patients in the older age may be attributed to the influence of ageing and diet. The relation between diet and kidney stones may be different in older adults. The intestinal absorption of many nutrients that influence stone formation, such as calcium, may be reduced in the elderly (Saltzman et al 1998, Abrams 2001). In men, the incidence of kidney stones declines markedly after 60 years of age (Hiatt et al 1982, Curhan et al 1993, Souice et al 1994), suggesting that the pathophysiology of nephrolithiasis is different in the elderly. Older stone formers excreted less urinary calcium than their younger counterparts (Goldfarb et al 1998) and may exhibit defects in urinary inhibitors of crystallization (Bergland et al 2002).

Increased incidence in males also has been attributed to increased dietary protein intake, which increases urinary excretion of phosphates and magnesium and reduces urinary citrate concentration. The lower risk of stone formation in women was attributed initially to increased urinary citrate concentrations due to the lower urinary saturation of stone forming salts (Welshman et al 1975) while later reports indicated that endogenous estrogen and estrogen treatment in postmenopausal women may decrease the risk of stone recurrence by lowering urinary calcium and calcium oxalate saturation.

Estrogen may also help to prevent the formation of calcium stones by keeping urine alkaline and raising protective citrate levels (Heller et al 2002.) Experiments in animals demonstrated that testosterone promoted crystal growth by suppressing osteopontin expression in the kidney and increasing urinary oxalate excretion while estrogen possibly inhibited stone formation by increasing osteopontin expression in the kidney and decreasing urinary oxalate excretion (Yagisawa et al 2001, Parmar 2004).

Nutritional aspects

An unbalanced diet or particular sensitivity to various foods in stone formers can lead to urinary alterations such as hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitrauria and excessive acid urinary pH. Over the course of time, these conditions contribute to the formation or recurrence of kidney stones, due to the effect they exert on the lithogenous salt profile. The fundamental aspects of the nutritional approach to the treatment of idiopathic nephrolithiasis are body weight, diet and water intake.

a) Diet

Some reports have described that vegetarians are at lower risk for stone formation in contrast to non-vegetarians (Robertson et al 1982). The role of animal protein and potassium intake in the etiology of calcium stone formation is paradoxical. Some studies have shown a positive association between animal protein intake and stones (Curhan et al 2004), whereas others have not (Curhan et al 1997, Curhan et al 2004). The consumption of a diet rich in animal protein (from meat, dairy, poultry, or fish), sodium (Muldowney et al 1982, Silver et al 1983, Sabto et al 1984) and refined sugars increases urinary calcium and uric acid concentrations and lowers urinary citrate concentration. Kidney stones formers have been reported to process sugar abnormally (Rao et al 1982) by increasing urinary oxalate (Li et al 1986) and urinary calcium as well (Lemann et al 1969). Dietary potassium restriction increases and potassium supplementation may decrease urinary calcium excretion (Lemann et al 1991). Calcium intake, particularly through milk and dairy products, may be associated with hypercalciuria and stone formation. However, inverse relationships between dietary calcium and stone formation have been demonstrated, in that groups of men and women with the highest calcium intake have been shown to have nearly one half the rate of stones as groups with the lowest intake (Curhan et al 1993, 1997). Dietary calcium binds in the intestinal lumen with dietary oxalate, forming an insoluble, non-absorbable complex. The reduction in urinary oxalate levels that occurs with increased intake of dietary calcium is proportionally more important than the increased urinary calcium levels. Like oxalate, some dietary calcium may also be less bioavailable. (Curhan et al 1993 & 1997, Siener et al 2003, Curhan et al 1997 & 2004).

Animal protein induces stone formation, reports indicated operation of different mechanisms. Protein ingestion generates renal acid load that gives rise to metabolic acidosis where by the urinary excretion of citrate is reduced and the excretion of calcium increased by bone resorption. There is also an inhibition of calcium reabsorption in the distal tubules caused by the acidosis. Further excessive intake of animal protein, increases the glomerular filtration rate and this hyperfiltration contributes to an increased urinary excretion of oxalate, calcium and urate (Trincheri et al 1991).

b) Water intake

Supersaturation of the urinary environment with stone -forming constituents is a prerequisite for calculus formation and increased fluid consumption results in excretion of higher volume of urine, which is less supersaturated with stone -forming constituents. Patients with kidney stones are advised to increase their fluid intake especially water intake to decrease the risk of stone recurrence since the area of Hippocrates (Adams 1929). Some evidences (Curhan et al 1998, Borghi 1996) support this recommendation, where as some (Ryall and Marshall 1983) do not. There is consensus that a daily intake of fluid should be at a level that results in at least 2.0 to 2.5 L of urine output (Curhan et al 1998). Increased fluid intake has been demonstrated to have a positive effect on two urinary inhibitors, citrate and Tamm-Horsfall protein. Hydration augments urinary citrate excretion, which was thought to result from an increased fluid flux in the proximal tubule to the cells of this portion of the nephron (Hess et al 1994, Simpson 1983). The ensuing intracellular alkalosis blunts citrate reabsorption, leading to increased excretion of citrate. Urinary dilution has been found to increase the inhibitory activity of Tamm-Horsfall protein in calcium oxalate crystal aggregation in the urine of stone patients (Dean et al 2000). Depending on the degree of physical activity and surrounding temperature, it is necessary to drink 2.5 to 3.0 L, evenly distributed over the day c) Body weight : in a study by Siener et al (2004), overweight condition and obesity was found in 59.2% of the men and 43.9% of the women and both these conditions were strongly associated with an elevated risk of stone formation in both genders due to increased urinary excretion of promoters but not inhibitors of calcium oxalate stone formation and further concluded that overweight and obese men are more prone to stone formation than overweight women. Similar study by Powell et al (2000) showed that obesity was associated with increased urinary concentrations of sodium, oxalate, uric acid, sulfate and phosphate in men.

Excess body weight may be associated with various functional /structural lesions of the kidney and will lead to nephrolithiasis, glomerulomegaly, diabetic nephropathy, carcinoma of the kidney (Rutkowski et al 2006).

Kidney stone and other diseases

It has been proposed that essential hypertension, cardiovascular diseases (CVD), diabetes, and other medical conditions predispose to stone disease (Strazzulo and Cappuccio, 1995, Gillen et al 2005).

Recurrence

The recurrent nature of stone disease is a well-recognized Clinical problem. Urinary metabolic abnormalities such as low urine volume, hypercalciuria, hyperoxaluria, hyperuricosuria and hypocitraturia predispose a patient to early recurrence (Rajgopal, 1985). Male gender, multiple stones (Sun, 1998), stone location (Yu1993), residual fragments (Fine 1995) and some anatomic or functional urinary tract abnormalities (Stroom, 1995) are known to be major risk factors for recurrence.

Occupation

The role of occupation in stone formation is highly debated. Kidney-related complications are on the increase because of geographic factors: residence in the "stone belt, occupation related lifestyle changes - in case of indoor occupation - sedentary habits, stress, unhealthy dietary plan in terms of healthy or over healthy food intake, irregular food habits and fluid intake (intake of juices and beverages instead of water) or the other spectrum of physical manual labour - involving working outside exposed to heat and sun, low socioeconomic status, malnutrition and reduced fluid intake. Some experts speculated that this increased risk might be due to a hormone called vasopressin, which is released during stress, which increases the concentration of urine (Harvey 2002). A report (Tanthanuch et al 2005) suggested that manual workers had a higher incidence of urolithiasis when compared to sedentary workers, where as another report by Abomelha et al (1990) did not showed a clear relation of stone formation with occupation.

Biochemical studies

Primary stone formation and recurrence of stone formation is one of the biggest challenges faced by urologists today and remain a major source of morbidity in humans (Curhan et al 1994). Despite intensive studies in the last decade many aspects of nephrolithiasis / urolithiasis, the complete pathogenesis and thus prevention, still remains to be clarified. Studies have concentrated on the metabolic defects in urine and mechanisms of supersaturation, reasons for cytotoxic damage of renal tubular cells, and interference with some natural inhibitors. It is believed that, like urinary metabolic defects, biochemical variations in blood are less likely to occur in first time stone formers than in patients with recurrent disease.

Increased excretion of oxalate and deposition of calcium oxalate crystals in the renal tubules is associated with renal epithelial injury and that products of cellular damage can act as heterogenous nucleators of both calcium oxalate and calcium phosphate crystals in animal model (Khan 1995). Oxalate can induce lipid peroxidation. Lipid peroxidation represents oxidative tissue damage by superoxide, hydroxyl radicals, and hydrogen peroxide, which results in structural alteration to membranes and the functional impairment of the cellular component. The oxalate induced peroxidative injury has been implicated in the pathogenesis of calcium oxalate stone formation (Troyer et al 1986, Thamil selvan et al 2000). An alteration in the balance between oxidants and antioxidants favoring a prooxidant state is a hallmark of chronic renal failure and various kidney diseases, cancer, hypertension, atherosclerosis and diabetes. Supersaturation, crystal nucleation and crystal adherence to the surface of renal epithelial cells are considered as initiating events in the genesis of calcium oxalate monohydrate stones (Finlayson 1978, Mandel 1994). There is strong evidence that tubular dysfunction or damage is involved in calcium oxalate monohydrate stones binding and subsequent pathology (Ravichandran and Selvam, 1994, Selvam 1991, Grases et al 1998).

Oxidative stress is a common source of cell injury and results from increased production of reactive oxygen (nitrogen) intermediates RO (N)Is. The generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in hyperoxaluric condition has been proved experimentally. This may result in the formation of the cytotoxic metabolite peroxynitrite, which is also capable of causing lipid peroxidation and protein modification. The presence of nitrotyrosine in proteins - nitrosative stress mediated modified Tamm-Horsfall glycoprotein) was detected in calcium oxalate stone former (Pragasam et al 2006). These species initiate diverse cellular effects ranging from upregulation of key transcription factors, through gene induction, to cell proliferation or necrotic/apoptotic cell death (Hensley et al 2000). Oxidative stress may be caused by increased concentrations of free oxalate ions or by insoluble calcium oxalate interacting directly with other inflammatory events. It has also been shown that hydrogen peroxide and superoxide anion can promote the activation of cytosolic phospholipase A2 with consequent release of arachidonic acid, it follows that this could be the arachidonic acid metabolism catalyzed by cytosolic PLA2 may be the mechanism by which oxalate elicits renal epithelial cell injury. The finding that oxalate can trigger a known lipid signaling pathway may provide new insight into the initial events in the pathogenesis of nephrolithiasis (Kohjimoto et al 1999). Free radical production has been reported to be increased accompanied by reduction in superoxide dismutase, glutathione synthetase and glutathione peroxidase activities in kidney stone disease. The reduction in superoxide dismutase activity has been attributed to the opening of the mitochondrial PT pore, disruption of the osmotic equilibrium of the matrix and rupture of the outer membrane which leads on to leakage of mitochondrial superoxide dismutase in to the cytoplasm. Glutathione synthetase and glutathione peroxidase activity are reduced in intracellular magnesium deficiency. A mitochondrial dysfunction can lead on to inhibition of membrane Na⁺- K⁺ -ATPase and accentuation of the abnormalities in calcium, sodium and potassium.

Molecular Aspects

Stone disease is a multifactorial disease; the cause of calcium oxalate stones is heterogeneous and might involve both genetic and environmental factors. Although extensive genetic studies were carried out, no chromosomal mapping has been conducted in patients with stones and idiopathic hypercalciuria (IH) (Goodman 1997, Danpure 2000). The only conclusive evidence through genetic studies (Coe 1992) is that urolithiasis is a polygenic defect and partly penetrative.

Although it is currently not possible to identify the gene responsible for stone disease, with the accumulation of mapped genes, the likelihood that these regions will contain a candidate gene is promising (Kwok and Gu 1999). The candidate genes might provide further analysis for tissue expression or clinical presentations in a variety of groups.

Conclusion

Bearing in mind the observations of the present study, knowing that most of the biochemical abnormalities if treated can considerably lower the recurrence rate of stone disease, and urinary and blood evaluation can pick up multi-system pathology, one can conclude that, for rational, efficient and specific urolithiasis management further studies in larger sample size is needed to confirm the observations in blood.

Modern lifestyle changes, sedentary habits, lack of easiness, an unhealthy dietary plan, and overweight problems of the affluent societies-emerge to be the important promoters of the "stone-boom" in the new millennium both in developed and underdeveloped countries. Major risk factors that contribute to stone formation and its recurrence include "classic" risk factors in the urine (low urine volume, hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitrauria, and hypomanesuria), epidemiological factors - climate, race, ethnicity, age, sex, body weight. Several studies from West indicated that in the industrial countries, kidney stones are a common problem (Morton et al 2002), affecting 1 person in 1,000 annually, and the incidence is increasing in tropical developing countries too (Robertson 2003). Factors such as age, sex, ethnic and geographic distribution determines prevalence. The peak age of onset is in the third decade, and prevalence increases with age until 70. The Afro-Asian stone-forming belt stretches from Sudan, the Arab Republic of Egypt, Saudi Arabia, the United Arab Emirates, the Islamic Republic of Iran, Pakistan, India, Myanmar, Thailand, and Indonesia to Philippines. The prevalence of calculi ranges from 4 to 20 percent (Hussain et al 1996). Other reports suggested that kidney stone disease is uncommon before the age of twenty years. Thus men are at greatest risk of developing kidney stones with incidence and prevalence rates between 2–4 times that of women (Johnson et al 1979, Hiatt et al 1982). Curhan et al (1999) demonstrated that men have higher oxalate concentrations than in women.

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