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Understanding epidemiology and etiologic factors of urolithiasis: an overview

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ABSTRACT

Urolithiasis is a condition in which stones are formed in the urinary tract and considered to be one of the most common urological disorders, longstanding medical illnesses and common public health problems. People in many parts of the world including north eastern states of India are now suffering from the stone diseases. Urinary stone is formed usually due to deposition of calcium, phosphates and oxalates which are a major health hazards. It has been reported that urolithiasis as a multifactorial recurrent disease, distributed worldwide in urban, rural, non-industrial and industrial regions with different chemical composition of analyzed stones in context to various risk factors. Besides diet, genetic factors are also reported to contribute in pathogenesis of urolithiasis. Better understanding of the various aspects of this disease including causative agents may provide an insight of this disorder to the researcher and common people in order to contain this disease. The epidemiology and various etiologic factors of urolithiasis are highlighted in this communication.

Key words: Urolithiasis; diet; genetic factors; northeast India.

INTRODUCTION

Urolithiasis is a term originated from three Greek words, '*ouron*' for urine, '*oros*' for flow, and '*lithos*' for stone. It is the process of forming stones in the kidney, bladder and/or urethra and is a complex phenomenon yet not clearly understood. It is considered to be one of the most common urological disorders and has afflicted humans since time immemorial. It is a longstanding medical illness and still a common public health.[1] A large population of world suffers from urinary tract and kidney stones, formed due to deposition of calcium, phosphates and oxalates. In this process, the chemicals start accumulating over a nucleus, which ultimately takes the shape of a stone. These stones may be persisted for indefinite time, leading to secondary complications causing serious consequences to patient's life. It is also very painful and a proper cure is very much needed to get rid of the problem. Many parts of the world includ-

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ing India are now suffering from the stone disease which poses a major health hazard affecting 20% of the general population worldwide. In the United States alone, up to 12% of men and 6 % of women will develop urolithiasis at some point in life. In Thailand, the highest prevalence rate of 16.9 % was reported in the Northeast provinces, while in Middle Eastern countries, the lifetime prevalence of kidney stone is even higher.[2,3] As urolithiasis usually recurs with recurrence rates as high as 50 % in 10 years, it poses difficulty in management and burdensome medical costs.[4]

Urolithiasis disease exists in 'endemic' proportions in some parts of country. Areas of high incidence of urinary calculi include the British Isles, Scandinavian countries, Northern Australia, Central Europe, Northern India, Pakistan and Mediterranean countries.[5]

Renal stones, one of the most painful urologic disorders, have beset humans for centuries. Each year, worldwide people make almost 3 million visits to health care providers and more than half a million patients go to emergency room with urolithiasis. Epidemiological studies indicate many factors like age, sex, industrialization, socioeconomic status, diet and environment, influences urolithiasis. In urothiolisis, calcareous stone is the most common type of kidney stone disease and accounts for more than 80% of all stones. The primary chemical complexes are calcium oxalate (CaOx) and calcium phosphate (CaP).[6] Besides this, urinary stones contain both crystalloid and colloid components. The crystalloid components are mainly calcium oxalate, calcium phosphate, calcium carbonate, magnesium-ammonium phosphate, uric acid and cysteine. Uric acid (UA) stone represents about 4.5–23% and the other less frequent types of kidney stones are magnesium ammonium phosphate (MAP) or struvite stones, ammonium urate stones, cystine stones, xanthine and other miscellaneous stones.[3,7]

The literature has reported that urolithiasis as a multifactorial recurrent disease, distributed worldwide in urban, rural, non-industrial and industrial regions with different chemical composition of analyzed stones in context to various etiological and risk factors. It includes both intrinsic factors such as demographic (age, gender and race), anatomic and genetic aspects, and extrinsic factors such as geographic predilection, climate, lifestyle pattern as well as dietary habits. During the past few decades, the prevalence of kidney stones in both males and females has markedly increased in industrialized countries.[6] This is presumably due to changes in lifestyle and dietary habit of the peope in these regions.

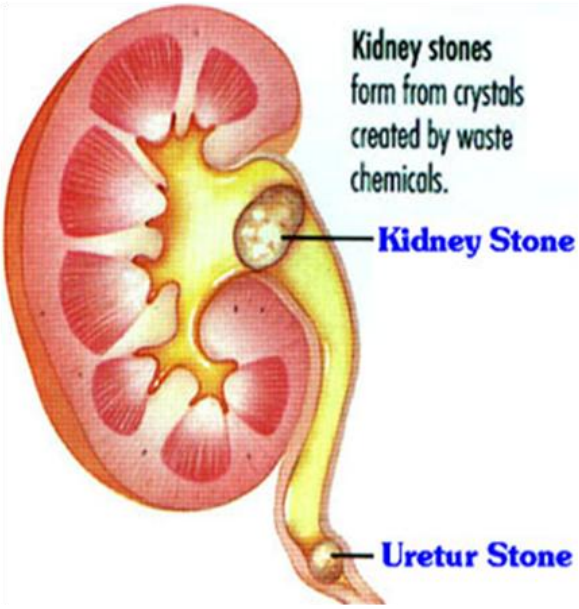

Figure 1. Stones in the kidney and ureter.

Influence of Diet on Urolithiasis

Dietary factors are also considered to play an important role in kidney stone formation, and dietary modification can reduce the risk of stone recurrence. Though only 10% to 20% of urinary oxalates come from dietary sources, dietary reduction is commonly advised for calcium oxalate stone formers. It has been suggested that since there is much less oxalate in the urine than calcium in the urine, urinary oxalate concentration is much more critical to the formation of calcium oxalate crystals than is the urinary cal-

Table 1. Major and subtypes of stones in urolithiasis according to chemical components.[7]

Major Type	Subtypes
Calcium Stone (70-80%)	Calcium oxalate monohydrate (40-60%) Calcium oxalate dehydrate (40-60%) Calcium hydrogen phosphate (brushite) (2-4%) Calcium orthophosphate (<1%)
Uric Acid Stone (5-10%)	-
Cystine Stone (1%)	-
Struvite (1%)	-
Xanthine Stone (1%)	-
Mixed Stones (50-60%)	Mixed calcium oxalate-phosphate (35-40%) Mixed uric acid-calcium oxalate (5%)

cium concentration; reducing urine oxalates may have a more powerful effect on stone formation than can reduction of urine calcium. Patients with calcium oxalate stones, particularly those with documented hyperoxaluria, should avoid foods high in oxalates.[8] Moreover, vitamin C is a precursor to endogenous production of oxalates, so some clinicians recommend avoiding mega-doses of vitamin C. The rare genetic condition of primary hyperoxaluria is only slightly impacted by dietary reduction, and causes serious medical problems besides kidney stones. The effect of excess animal protein (purine) is also most obvious for the uric acid stone former. Uric acid, a by-product of purine metabolism, is excreted in large quantities in the urine. Excess protein creates urine with high total urine uric acid, potentially high super saturation of urine uric acid, and a low pH, necessary for formation of uric acid stones. There is no inhibitor of uric acid crystal formation, so dietary measures focus on reducing uric acid and increasing urine volume.[9] In regard to this, reduction of animal protein to 12 ounces per day for adults is recommended. This is plenty to meet the dietary needs of most population in India, many of whom typically consume several more ounces of animal protein daily than is recommended. Protein from plant sources (beans, legumes, etc.) can be substituted as a dietary alternative without negative consequences however calcium oxalate stone formers reducing their animal protein should also note the oxalate content of substitute proteins. The role of excess protein in promoting calcium stone formation is less obvious, but equally important. High dietary protein is associated with increased urinary calcium. Thus, there is a link between meat consumption and both uric acid and calcium stone formation.[10] Therefore, the benefits of protein restriction for stone formers are many. It has been reported that super saturation of urinary lithogenic promoters such as calcium, oxalate, phosphate and uric acid mostly obtained from the diet are considered as the risk factors of renal stone formation. On the other hand, a decreased urinary concentration of stone inhibitors such as citrate, potassium and magnesium is also a critical risk. The urinary levels of these stone modulators are greatly influenced by diet.

Candidate Genes for Urolithiasis

Genetic factors are known to play a role in urolithiasis. Studies have tried to identify genes related to ureter calculi in an effort to clarify the cause of urolithiasis and to advance the diagnosis and treatment of urolithiasis.[11,12] It has been reported that the use of single-nucleotide polymorphisms (SNPs) associated with genetic diseases has been fruitful in identifying candidate disease genes. Recent genetic advances in urolithiasis indicate the potential of a new approach towards the gene polymorphism.[9,13-15] Moreover,

Table 2. Candidate genes and type of patients as reported by different studies.

Candidate Genes	Type of patients	References
T*aqI* and A*paI* gene polymorphism	Calcium stone patients	Nishijima *et al.*[17]
B*smI* endonuclease polymorphism	Calcium oxalate stone patients	Wen-Chi Chen *et al.*[18]
VEGF gene B*stUI* polymorphism	Calcium oxalate stone patients	Chen *et al.*[15]
F*okI* and T*aqI* VDR genes polymorphism	Calcium oxalate stone patients	Mittal *et al.*[19]

polymorphism in manganese superoxide dismutase gene (Mn-SOD) is a new approach to identify its probable association with urolithiasis through oxidative stress. MnSOD is one of the primary enzymes that directly scavenge potential harmful oxidizing species. It has been reported that A valine (Val) to alanine (Ala) substitution at amino acid 16, occurring in the mitochondrial targeting sequence of the MnSOD gene, has been associated with an increase in urolithiasis risk.[16] Moreover, number of studies has been carried out by many scientists in many parts of the world to identify the probable candidate genes responsible for urolithiasis. Some of the results as reported from the studies done by the scientists are shown in Table 2.

As numerous studies have been dedicated to interpreting the possible association between the polymorphisms of genes and urolithiasis susceptibility. However, the results were remained inconclusive. The controversial results across many of these studies could possibly be related to the small sample size from an individual study, ethnic difference or the biological genetic model applied for the analysis. Therefore, it was necessary to quantify the potential between-study heterogeneity and summarize results from all eligible studies with rigorous methods. In view of this, very recently, Yiwei Lin *et al.*[20] carried out a meta-analysis with the most updated data in order to revisit the association between VDR (vitamin-D receptor) variants (i.e., *Apa*I, *Bsm*I, *Fok*I and *Taq*I) and urolithiasis risk and reported that some VDR gene polymorphisms are associated with an increase in the probability of urolithiasis with certain populations under an indicated genetic model. Considering the predictive value, this meta-analysis study also warrants further investigation in this field to better clarify these SNP-urolithiasis associations and to reinforce their findings.

Status of Urolithiasis in Northeast India

The northeastern states of India, which border Burma (Myanmar) on one side and can be said to fall in the broad belt area of stone disease covering south-east, middle-east, north-east Asia and facing an acute problem of stone diseases. Due to lack of research facilities, the remoteness, difficult geographical situations, the prevalence of urolithiasis is are virtually unknown outside of these states. A preliminary survey from the laboratory highlighted the fact that urolithiasis is a major problem in these regions and required urgent attention.[21] It is commonly believed that almost every family has a member afflicted with this disease. The incidence of urolithiasis is very high among the natives of these regions who are different in food habits, and also socially, culturally and ethnically from the people of the mainland of India. Most of the living population in these states have different food habits like rice as staple diet, high consumption of fermented fishes, soybeans, bamboos and other types of indigenous food stuffs. Non-vegetarian foods are one of the major recipes in the daily menu of the most of the people living in this region. But study of literatures revealed that there have been non-existent of data on the studies of etiologic chemical factors of urolithiasis found in the in the different vegetables and meat foodstuffs commonly available and consumed by the natives of this region. Moreover, no publish literature have been re-

ported on marker genes polymorphism for this disease from this region of India. In fact, the following key questions are still needed to consider as far as the prevalence of urolithiasis in the northeastern states of India is concern.

1. Why the prevalence of urolithiasis is very high in the living population of north eastern states of India as compared to mainland India? And is the epidemiology of urolithiasis endemic to this region only?
2. Is the different dietary habits of the natives of this region playing any role for the high prevalence of urolithiasis?
3. Is genetic factor playing a role in the pathogenesis of urolithiasis in the natives of this region?
4. Is different climatic condition from other parts of the country play a major role for the epidemiology of urolithiasis in this region?
5. What are the remedies and preventive measures which can be look out by the scientist and health professionals to contain this disease?

Conclusion

In view of the conflicting data reported from other parts of the world on the role of diet and genetic factors in the pathogenesis of urolithiasis, further in-depth studies are still needed so that finding from such studies may be of great importance both as a guide for the clinical management and also for better understanding of physicochemical principles underlying the formation of calculi that may help to give advice and suggestions for the people and patients to carry out preventive measures in reducing the risk of prevalence and recurrence of urolithiasis and the present article have highlighted some of the aspect of this diseases.

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