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Urinary Stone Disease: Progress, Status, and Needs

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Urinary Stone Disease (USD) (also known as urolithiasis, nephrolithiasis, kidney stones, and nephrocalcinosis) is a generic term that indicates the presence of stones and calcification within the urinary tract. Although the majority of stones initially form in the kidneys, the exact mechanisms of stone formation in humans remain unknown. Stones can form anywhere in the proximal urinary tract in the presence of congenital urogenital abnormalities, urinary obstruction, or infection. While the majority of people with USD have only one episode, 35 % experience 2 or more recurrences (Urological Diseases in America, UDA, unpublished data).

USD is as old as the history of mankind. Large bladder stones have been found in Egyptian mummies. USD is mentioned in the Hippocratic Oath: “I will not use the knife, not even on sufferers from stone, but will withdraw in favor of such men as are engaged in this work.” Many remedies and surgical treatments have been described throughout medical history. However, until the 20th century, open surgery remained the treatment of choice for stones that did not pass spontaneously.

The treatment of USD has advanced over the last 30 years. Endourology allowed bladder stones to be treated endoscopically without the need for a skin incision. Technical advances have improved surgical USD treatment strategies. Improved optic lens systems and fiberoptic light sources have enabled better visualization. Increased instrument flexibility and miniaturization along with effective energy sources for stone disintegration led to the development of percutaneous nephrolithotomy and ureteroscopic lithotripsy. Extracorporeal shock wave lithotripsy (SWL) was developed for stone fragmentation without invasive instrumentation of the body. Innovative methods such as ultrasonic stone repositioning, new energy sources, and acoustic lenses are currently being tested.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) believes that we should conduct more research in addition to what is being supported in order to advance this field.

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Epidemiology and Economics

Obesity and type 2 diabetes are both associated with USD^{1, 2}. In parallel to the epidemic increase of obesity and diabetes, the prevalence of USD is also increasing. USD is an important healthcare problem affecting both adults and children, and 1 out of 11 Americans now have or had USD. The prevalence in men has nearly doubled in the last 15 years from 6.3% in 1988-1994 to 10.6% in 2007-2010³. Although USD is predominantly found in white men, the prevalence in black, non-Hispanic and Hispanic populations and women is increasing. The exact pathophysiological mechanisms of the association between these comorbid conditions and USD are still under investigation. Diet and lifestyle factors may be underlying causes of diabetes, obesity, and USD.

An acute symptomatic episode of USD is excruciatingly painful, and frequently results in emergency department care. We recently showed that emergency department visit rates for USD have increased from 178/100,000 in 1992 to 340/100,000 in 2009⁴. Cross-sectional analysis show that about 10% of these emergency care visits are for recurrent episodes. According to the UDA project funded by the NIDDK, the annual direct medical cost of USD in the US is \$10 billion, making USD the most expensive urologic condition⁵. As increases in obesity, diabetes, and population size increase, the cost of USD is likely to increase by \$1.24 billion/year by 2030⁶. Computed tomography use for USD in the emergency department has tripled during this period and use of drugs has also increased.

Current Status

During an acute episode of USD, spontaneous passage occurs in about 68% of stones smaller than 5 mm and 47% between 5-10 mm⁷. Thus, larger stones and many smaller stones need some form of intervention. While SWL and endourologic approaches have greatly improved treatment of USD, monotherapy does not seem to be sufficient for most stones. Up to 35% of patients with ureteral stones may not be rendered stone-free and thus require multiple interventions⁷. Despite a major shift towards ureteroscopy and ureteroscopic lithotripsy, the rate of ancillary procedures, repeat encounters, and complication rates have not fallen dramatically. Clinical studies are needed to identify people with stones that are not likely to pass, and determine the optimal treatment in these cases.

Recurrence is common. Although trend data is not entirely reliable, prevention of recurrences has not improved. A recent study shows that symptomatic recurrence rates at 10 and 15 years are 31% and 39% respectively⁸. Recurrences may partly be due to provider variation in evaluation and management⁹. There is an urgent need to identify the underlying metabolic causes and to improve prevention strategies.

The limited state of knowledge is reflected in management guidelines that have been published by the American Urological Association (AUA), and European Association of Urology (EAU) using systematic reviews and data extraction^{7,10}. Only 1 of 27 and 3 of 17 recommendations were based on Level 1 evidence.

Urinary stones cause kidney damage by two distinct mechanisms: obstruction in the urinary system, and urinary tract infections. One would expect that advances in the management of USD should decrease the rate of chronic kidney disease (CKD) associated with USD. A recent study using the National Health and Nutrition Examination Survey (NHANES) demonstrated that USD is associated with increased risk of CKD and treatment with dialysis even after adjusting for comorbid conditions¹¹. Despite all the advances in the management of USD, the ultimate goal of reducing CKD caused by USD has not been achieved.

Basic Research

Many studies using a variety of methods have sought to understand the mechanisms and to prevent the recurrence of USD. USD is not a single disorder, but rather comprises several distinct disorders based upon stone composition that includes calcium oxalate (CaOx), calcium phosphate (CaP), uric acid, struvite (magnesium ammonium phosphate), cystine, and 2,8-dihydroxyadenine (2,8-DHA). The large majority of patients (80%) with idiopathic disease form either CaOx or CaP stones.

One major focus of basic research is how stones form. It has recently been appreciated that early events are driven by anatomy and stone type. CaOx stones form (nucleate) on Randall's plaques at the surface of the kidney at the tips of the renal papilla, whereas CaP stones form in solution. Interestingly, patients with shortened bowel with enteric hyperoxaluria form CaOx stones without substantial Randall's plaque¹².

Physiology also plays a key role in stone formation, as individuals who excrete high levels of oxalate and/or calcium are especially prone to stone formation. In some rare cases, this is caused by Mendelian diseases, as discussed below. However, for the majority of individuals with hyperoxaluria or hypercalciuria the cause is unknown and genetic studies have not succeeded in identifying contributing loci. A substantial fraction of the body's oxalate comes from the diet via the gastrointestinal tract. The intestine has two major oxalate transporters: DRA (Slc26a3) and PAT1 (Slc26a6). The gut microbiome can reduce the oxalate concentration substantially, as several bacterial species (including *Oxalobacter formigenes* and *Bifidobacterium*) metabolize oxalate as an energy source. However, the microbial ecology of the oxalate-metabolizing bacteria is not well understood, and human trials using probiotic mixtures have not succeeded in achieving long-term reduction in oxalate excretion, perhaps because individuals do not remain colonized for long periods of time¹³.

Genetic stone disease is much rarer than idiopathic stone formation, and includes Primary Hyperoxaluria (caused by mutations in AGT, GPRT, and HOGA1) and Dent Disease (CLCN5). Primary Hyperoxaluria mutations are more prevalent (1:70) than observed clinically, suggesting undiagnosed cases or incompletely penetrant mutations¹⁴.

Research Opportunities

There are many unanswered research questions in USD that can be best addressed by multidisciplinary approaches involving urologists, nephrologists, pediatricians, pediatric urologists, pediatric nephrologists, radiologists, nutritionists, microbiologists, clinical

trialists, translational and basic scientists, and chemical and mechanical engineers. Some of the questions can be addressed by epidemiologic research. For example, there is a need to identify the causes of increasing prevalence of USD in the US, to define the USD episode recurrence rate, evaluate the impact of metabolic assessment on USD and recurrence rate, evaluate the increasing prevalence in the pediatric population, interrogate the extra-renal manifestations, and to define the economic impact of USD.

Several critical basic science questions remain: what are the earliest events in stone formation; how do exposures from the environment, diet, and lifestyle interact with genetic, epigenetic, and physiology; what new technologies are available to characterize the microbial ecology of the intestine and determine how bacteria can be used to reduce hyperoxaluria and USD; how do we better leverage model systems to understand stone formation; are the mechanisms of stone formation different in children; are there sex differences; how does USD contribute to CKD?

Outstanding clinical research questions include: a) first and second line surgical and medical therapies for USD episodes, b) identification of predictors of spontaneous stone passage, c) determining factors causing USD episode recurrence, d) developing strategies to prevent USD recurrences (secondary prevention), e) assessing the impact of medical therapy for uric acid USD, f) improving the techniques/approaches to reduce x-ray exposure of the affected individual during diagnosis, treatment, and follow-up of USD, g) reducing the urinary stent associated symptoms, h) learning the long-term outcome of small asymptomatic stones. These questions will require pilot studies to test key design criteria, then large multi-site clinical studies.

Conclusions

Unquestionably, USD is an increasingly common, consequential, costly, and chronic healthcare problem causing pain and suffering for the patient and a financial burden for the Nation. An acute episode of USD is one of the most painful conditions and usually requires emergency department evaluation. The intangible costs to the affected individual and the family, such as pain, quality of life, time-off from work or school, and professional risks are enormous.

Despite technological advances in the management of patients with USD, only minimal advance has been made in the prevention of USD or its episodes. The minimally invasive surgical and non-surgical treatment options, while attractive, usually require ancillary and secondary procedures that prolong treatment, increases suffering, and use costly healthcare resources. Some of the energy sources used for stone disintegration may also cause local stone formation and/or damage to surrounding structures. It is time to conduct basic, translational, and clinical research to improve prevention and effectiveness and reduce acute and long-term complications and consequences. NIDDK recently held a workshop on USD to seek community input that will help us develop a future funding opportunity announcement on USD¹⁵.

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