Urinary Stone Disease: Advancing Knowledge, Patient Care, and Population Health

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Abstract

Expanding epidemiologic and physiologic data suggest that urinary stone disease is best conceptualized as a chronic metabolic condition punctuated by symptomatic, preventable stone events. These acute events herald substantial future chronic morbidity, including decreased bone mineral density, cardiovascular disease, and CKD. Urinary stone disease imposes a large and growing public health burden. In the United States, 1 in 11 individuals will experience a urinary stone in their lifetime. Given this high incidence and prevalence, urinary stone disease is one of the most expensive urologic conditions, with health care charges exceeding $10 billion annually. Patient care focuses on management of symptomatic stones rather than prevention; after three decades of innovation, procedural interventions are almost exclusively minimally invasive or noninvasive, and mortality is rare. Despite these advances, the prevalence of stone disease has nearly doubled over the past 15 years, likely secondary to dietary and health trends. The NIDDK recently convened a symposium to assess knowledge and treatment gaps to inform future urinary stone disease research. Reducing the public health burden of urinary stone disease will require key advances in understanding environmental, genetic, and other individual disease determinants; improving secondary prevention; and optimal population health strategies in an increasingly cost–conscious care environment.

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Introduction

The excruciating experience of urinary stone passage impels patients to seek care and providers to intervene. For these reasons, treatment for urinary stone disease (USD) historically dealt with removing the offending stone, with dramatic improvements in efficacy of interventional treatments. Emerging evidence suggests that the next advances in USD will arise from a broader disease model focused on prevention. In this narrative, we review the changing epidemiology of urinary stones; risk factors and the exposome; treatments and preventive measures; and finally, population health aspects of USD. Advances in these four areas suggest the need for a new chronic disease model.

Epidemiology

USD poses a growing public health burden in the United States. USD can be conceptualized as a chronic pathophysiologic process, creating mineral deposits, most commonly calcium oxalate and calcium phosphate, in the kidneys. The prevalence of USD is similar to diabetes, affecting 1 in 11 people in their lifetime (1). Over the past 15 years, the prevalence of USD has nearly doubled (1), and it is growing even more rapidly among historically lower–risk groups, such as children, women, and blacks (2). Among women, the prevalence of USD has increased by 75% since 1994; among blacks, it has increased >120% (1). The frequency of USD in children seems to be increasing to between 4% and 6% yearly, particularly among adolescents (2). Among children >10 years old, USD is more common among girls, whereas USD is more common among adult men (3). The causes of increasing USD prevalence require additional elucidation (Table 1); contributing factors likely include changes in body habitus, fluid status, dietary habits, and the environment (4). It is likely that computed tomography (CT) incidentally detects asymptomatic stones; the extent to which this phenomenon contributes to increasing prevalence of USD warrants investigation.

USD is associated with other common conditions, such as atherosclerosis, hypertension, CKD, and low bone mineral density (BMD). USD is associated with increased risk of fracture, likely mediated by low BMD, which is most pronounced among women (5–7). Among women in their fourth decade of life, USD was associated with a 55% excess risk of fracture.

Examination of the Nurses' Health Study and the Health Professionals Follow-Up Study showed that women with USD had a slight but statistically significant higher risk for myocardial infarction or coronary artery revascularization after adjusting for key confounders (8). Increased rates of low BMD and increased carotid artery wall thickness have also been identified in preliminary studies of children and adults with USD (9–12). USD is also associated with CKD, diabetes mellitus, and hypertension (13, 14). Although it is uncertain whether these associations are causal or caused by shared risk factors, a symptomatic stone event heralds future morbidity.

Table 1. Key priorities for research in urinary stone disease

Topic	Key Research Priorities
Epidemiology	Causes of the increasing prevalence of USD in children; identifying modifiable risk factors for stone recurrence; determinants of the risk difference between men and women; causal mechanism underlying the association with metabolic syndrome; associations between USD and extrarenal disease (*e.g.*, coronary heart and bone disease); updated estimates of stone recurrence rate
Microbiota	Influence of urinary microbiota; gastrointestinal microbiota, oxalate metabolism, and stone risk
Exposome	Temperature, climate, and USD risk; sunlight exposure and USD risk; mineral composition of water and USD risk; diet (including beverages) and USD risk; occupation
Prevention	Dietary interventions—secondary prevention (high-quality trials); water intake—primary and secondary prevention (high-quality trials); age–appropriate behavioral/social interventions to increase adherence; role of 24-h urine chemistry analysis in predicting recurrence risk after starting pharmacologic therapy
Care delivery	Ureteral stent discomfort—mechanism and amelioration; patient-reported outcomes/patient-reported experience; optimal evaluation of a patient with acute stones (imaging and laboratory analysis); care coordination/multidisciplinary approach; cost drivers for USD burden of care

USD, urinary stone disease.

The economic burden of USD is substantial. Although precise data on United States costs remain lacking, total charges are estimated to exceed $10 billion annually (15); inpatient care and ambulatory procedures seem to be the largest contributors. Repeat or unplanned care is common and a key health policy focus. One in six patients undergoing a stone removal procedure will experience unplanned follow-up care (16). Repeat emergency department (ED) visits occur after 11% of initial evaluations (17). Associated indirect costs are substantial given the pain, temporary disability, and work loss in a primarily working age population (18).

Determinants

Genetics

A subset of USD, such as primary hyperoxaluria and cystinuria, results from monogenic conditions; ≥30 genes exist in which mutations result in monogenic forms of USD and/or related conditions, such as nephrocalcinosis (19,20). USD unrelated to these mutations also seems to have a marked genetic component. For instance, a heritability calculation on monozygotic twins showed that 56% of USD risk is caused by genetic contributions (21). Additionally, 79% of children with USD have a first or second degree family history (22). The genes that contribute to idiopathic USD and their causal interactions with environmental stressors require elucidation.

Sex

Historically, USD was three times more common among men (23). Recent investigations suggest a decreasing disease excess in men (1,2,24). Obesity may confer greater USD risk in women than in men (25). Stone composition may also vary by age and sex. Women have fewer calcium oxalate monohydrate stones and more struvite and calcium phosphate stones (23,26). Uric acid stones are more likely in men and the elderly (26). Additional research on USD risk also is needed to explore hormonal effects, such as estrogen and progestin influences on urine chemistry, particularly given increasing USD frequency among adolescent girls and adult women (1,2,24).

Microbiota

Although urease-producing bacteria that cause struvite USD are pathogens and not microbiota constituents, they exemplify microorganisms' influence on local crystal formation. Whether particular bacteria are associated with calcium oxalate USD is less understood. Urinary tract infection (UTI) and USD often occur in the same patients: 34% of children with USD had associated UTIs, and only 1.3% had underlying structural anomalies of the urinary tract (27). Furthermore, bacteria have been cultured from between 19% and 32% of calcium oxalate stones (28). Additional investigation is required to determine the extent to which this calcium oxalate USD-UTI link is causal or merely coincidental.

A number of conditions, including obesity, childhood-onset asthma, and cardiovascular disease, are associated with changes in the intestinal microbiota (29,30). Recent studies suggest a link between USD and the intestinal microbiota. For example, intestinal colonization with *Oxalobacter formigenes*, which degrades oxalate, is associated with lower urine oxalate levels and fewer recurrent stones (31,32), although a protective effect of exogenous *Oxalobacter* remains unproven (32). Advances in DNA-based sequencing may identify other bacterial communities, which will further clarify the association between stone formation and urinary or intestinal dysbiosis (Table 1).

Exposome

The exposome is the accumulation of environmental exposures during an individual's lifetime and includes exposures such as climate, pollution, infection, occupation, stress, and diet. An individual's genetic makeup is the filter through which the exposome becomes an important determinant of USD risk.

Environmental Exposures

The association between high ambient temperatures and USD is supported by higher frequency among populations exposed to hot environments (33). Additionally, investigations have shown an association between hot and cold days and an increased risk of kidney stones (34). Presumably, the effect of temperature on stone risk is mediated by dehydration from insensible water loss. The differential effect of temperature on USD risk between adults and children remains unknown (Table 1). An alternative hypothesis is that sun exposure contributes to stone formation when ultraviolet light causes increased production of vitamin D, increasing intestinal absorption of dietary calcium and potentially, causing more renal calcium excretion. Recent data suggest an association between higher levels of 1,25-dihydroxyvitamin D and stone risk (35). However, the resulting vitamin D levels are not very high, and data have not consistently shown any effect on urinary calcium content (36). Because cities feature urban heat islands (locales where temperature elevations are magnified versus more rural settings), urbanization may expose more people to warmer ambient temperatures and contribute to the increasing worldwide prevalence of USD (37).

Occupation is likely to be an important variable associated with USD, although the data regarding its influence are sparse (Table 1). Some occupations are associated with exposures to higher ambient temperatures, such as factory work. Some workers (*e.g.*, cabdrivers) have infrequent fluid intake, because access to bathroom facilities is inadequate, leading to low-volume-associated stones (38).

Strontium, cadmium, and zinc are trace elements and have been associated with USD in laboratory and epidemiologic studies (39,40). Additionally, calcium oxalate stones have been found to contain zinc and strontium (39). Although urbanization is an increasingly important source of zinc in the environment (41), the role of environmental exposures to zinc in USD has never been studied. Cadmium, which inhibits urinary secretion of citrate, is another potential USD–associated environmental exposure (42). Occupational exposures to cadmium increase stone incidence in those who work with batteries (43).

Diet

Water intake offers an inexpensive intervention that corrects dehydration and decreases USD recurrence (44–47), but knowledge of the effect of the mineral composition of water on stone risk is limited. Water hardness and alkalinity, determined by calcium and magnesium concentrations, have been both positively and negatively associated with USD. Studies that examined the relationship between calcium and magnesium contents in the water supply had methodologic limitations and produced conflicting results (Table 1) (48).

The association between calcium consumed from food sources is better understood. Low dietary calcium is associated with an increased USD risk, and moderate dietary calcium intake is associated with a decreased risk (46). Diets containing normal calcium, low protein, and low sodium levels reduce recurrence risk (49). This seemingly paradoxical relationship is likely caused by intestinal binding of oxalate by calcium, thereby decreasing absorption. Magnesium is a potent inhibitor of kidney stone formation, but the role of dietary magnesium on stone risk is uncertain. Fructose consumption, which increases urinary excretion of calcium, oxalate, and uric acid, may increase risk of USD among adults (50). A number of studies indicates that ascorbate (vitamin C) is associated with stones and attributed to its metabolism to oxalate (51). Vitamin D supplementation, conversely, has not been associated with stones (52), perhaps because its conversion to 1,25-dihydroxyvitamin D is limited by activity of 1-α-hydroxylase. An association between high dietary zinc intake and an increased odds of USD has been observed (40).

The recent increase in pediatric USD incidence suggests that changes in diet and behavior are partly responsible for rapid shifting epidemiology. The higher prevalence of USD among young girls and adult men also raise questions as to differences in risk factors between pediatric and adult patients; up to 75% of adolescents have inadequate water intake (53). Calcium intake is also decreasing (54), with almost 90% of adolescent girls not eating the recommended amount (55). Because 25% of United States adolescents consume at least 15% of calories from fructose (56), studies are needed to determine the association between fructose and USD in children. Despite the potential for similar risk factors for idiopathic USD among children and adults, there also seems to be some differences. Obesity, which has been associated with an increased risk of USD among adults, has not been shown to be associated with an increased risk among children (57).

Treatment and Prevention Strategies

Initial Evaluation

Patients with symptomatic stones frequently require urgent or emergent care for severe pain, with >1 million ED visits annually (58). Initial evaluation often includes laboratory testing to assess kidney function as well as diagnostic imaging. The most common imaging modality in the ED setting is noncontrast CT (59), which is the preferred modality for adults with suspected USD because of its cross–sectional anatomic detail and excellent sensitivity and specificity (60). Although ultrasound is less sensitive and specific than CT (61), it accurately identifies clinically significant stones and is the recommended first–line imaging modality for children (62). Because many individuals with USD will undergo multiple imaging procedures, radiation exposure is concerning. For this reason, a recent randomized trial examined clinical outcomes when renal ultrasound was used as the initial imaging modality for patients with suspected USD who were stable and without clinical evidence of sepsis (63). Initial renal ultrasound reduced average radiation dose by nearly 50% without any increase in adverse events or alternative high–risk diagnoses versus CT. Many of those who underwent initial ultrasonography had subsequent CT (41% in the point of care ultrasonography arm); however, mean total costs were still lower for those randomized to ultrasonography. This study highlights a key research question: what is the most appropriate initial imaging modality? Incorporating clinical decision rules, such as the sex, timing, origin, nausea, erythrocytes (STONE) score, to predict the probability of symptomatic ureteral stones may further reduce unnecessary imaging and radiation by using CT in higher-risk patients, while reserving ultrasound or forgoing imaging for low-risk patients (64).

For patients who may require surgical intervention, the size and location of the stone are important prognostic and operative planning parameters, and thus, subsequent CT imaging may still be required. Ultrasound is operator dependent and requires specialized training for both radiology technicians and physicians. The generalizability of this study's findings to hospitals without the resources of large tertiary referral institutions is uncertain. In addition to the cost of patient care associated with ultrasound and CT, the costs of training providers to use ultrasound and assuring their competency must be considered. Techniques to improve ultrasonography, including manipulating stones (65), as well as assessments of reduced dose radiographic approaches (66) are also key research opportunities in USD.

Medical Expulsive Therapy

Current guidelines endorse the use of α-blockers to facilitate passage of ureteral stones $<$10 mm in diameter in appropriately selected patients (60). A meta-analysis of 32 randomized trials (5864 participants) suggested that use of α-blockers increased stone passage by 48% compared with placebo and decreased time to stone passage (67). Observational studies also support medical expulsive therapy (MET) for children (68). In most studies, however, methodologic quality was limited. A recent randomized trial challenges the clinical effect of MET: subjects with a stone $<$10 mm were randomized to placebo, tamsulosin, or nifedipine to facilitate stone passage, with a primary outcome of additional intervention on the basis of self-report (69). In this trial, there were no differences between placebo and either α-blocker or calcium channel blocker; however, the study may have been underpowered to detect a difference among patients with distal ureteral stones. A National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) –supported randomized trial is recruiting patients to evaluate the effect of MET, with the primary end point of stone passage at 28 days.

Surgical Intervention

Patients unable to pass stones or those who develop AKI, sepsis, or pain refractory to analgesics require procedural intervention. Shock wave lithotripsy (SWL) and ureteroscopy are the most commonly used procedures for stones. SWL can be performed as an entirely noninvasive procedure using high–energy shock waves to fragment the stone; the patient subsequently passes fragments spontaneously, although about two in five patients have a stent placed at the time of the SWL (70). Ureteroscopy is an endoscopic procedure that can access stones throughout the ureter or kidney; typically, a laser is used to fragment stones. Together, these constitute about 95% of procedural interventions for stones in the United States (71). Randomized trials suggest that these two techniques are of similar efficacy, and therefore, guidelines endorse both as first-line options. However, SWL has been associated with an increased risk of hypertension (72), and emerging comparative effectiveness studies favor ureteroscopy (73), which is increasing in use (70,71,74). When patients undergo procedural interventions, a temporary ureteral stent is often placed to prevent ureteral obstruction and other adverse sequelae: in claims-based analyses, approximately 82% after ureteroscopy and 42% after SWL (75). However, meta-analyses suggest that, after uncomplicated procedures, ureteral stents do not reduce readmission, fever, infection, or late complications; however, ureteral stents clearly increase pain and lower urinary tract symptoms (76). Ameliorating stent discomfort and developing patient-reported outcomes generally for these procedures remain critical opportunities to advance clinical care for patients with USD.

Prevention

Individuals who experience a symptomatic stone are likely to have a recurrence: rates are estimated at $\leq$50% within 5 years, although they are lower in recent clinical trials; population–based recurrence rates remain an important area for investigation, because the recurrence rate has important implications for cost–effective prevention strategies (Table 1) (77). Secondary prevention strategies include increased fluid intake, dietary modifications, and pharmacologic therapies (78,79). Given the high rate of recurrence, the American Urological Association (AUA), the European Association of Urology (EAU), and the American College of Physicians (ACP) have each published preventive recommendations (80–83).

Increased fluid intake is associated with reduced USD in a limited number of studies. In one randomized trial, stone recurrence after 5 years was 12% among patients randomized to high water intake resulting in $\geq$2 L urine output per day (baseline of approximately 1 L) compared with 27% of those not randomized to increased fluid intake (44). Furthermore, after SWL, patients randomized to increased fluid intake had a lower recurrence rate after 2–3 years compared with those with no treatment (84). A recent meta-analysis concluded that a significantly reduced risk of incident stones was shown among individuals with high fluid consumption (85). Fluid composition may also be important in prevention of USD recurrence. For example, intake of sugary beverages is associated with increased risk, whereas intake of alcoholic beverages, tea, coffee, and orange juice is associated with lower risk (86). We note, however, that increasing fluid intake may be difficult for those in whom an absence of thirst cannot be overcome and those with occupational impediments to fluid and bathroom access.

Dietary prevention was addressed in a recent review, which noted that few randomized trials existed and that most had substantial methodologic flaws (87). The AUA and the EAU recommendations include normal dietary calcium intake along with limited sodium and animal protein for patients with calcium stones (49). This was tested in a randomized trial versus a low-calcium diet, and the trial was limited to a small group of Italian men, all of whom had hypercalciuria; applicability to other populations is unclear. The participants achieved the prescribed urine sodium excretion of 50 mEq/d, which presumably prevented an increase in urine calcium excretion, despite the increased dietary calcium. This goal may be unachievable in societies dominated by high–sodium processed food. In addition, a relatively high prevalence of lactose intolerance among some populations and older people may impede feasibility of greater dietary calcium prescriptions. The diet trial prescribed a limitation in animal protein intake, which has been shown to favorably alter urinary chemistry

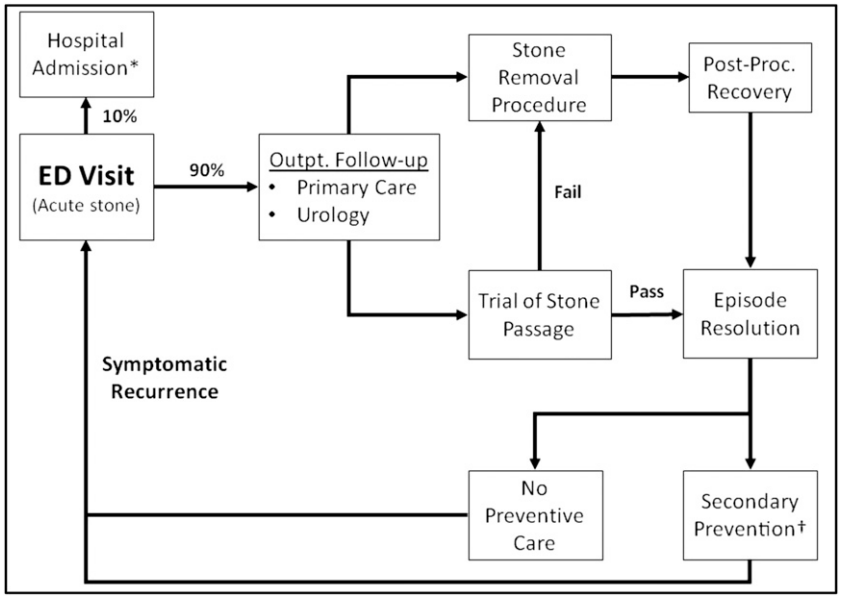

Figure 1. | **Schematic for an episode of care for a patient with a symptomatic stone**. *A similar pathway is likely after hospital discharge; †includes dietary/lifestyle changes and/or pharmacotherapy. ED, emergency department; Outpt., outpatient; Post-Proc., postprocedure.

(88); more vegetarian diets are associated with greater urine volume and citrate excretion and despite modest increases in urine oxalate excretion, less urinary supersaturation of calcium oxalate and uric acid. However, a small randomized, controlled trial of restricted protein intake, with imperfect patient adherence, did not show a benefit (89).

Other AUA and EAU dietary recommendations are on the basis of expert opinion, whereas the ACP concluded that dietary modifications outside of increased fluid intake did not have sufficient evidence to warrant a recommendation (80–83). Nonetheless, dietary modifications and USD risk are areas of expanding research. For instance, the Dietary Approaches to Stop Hypertension diet (90), which is high in unrefined grains and vegetables and low in dietary fat and sodium, is associated with decreased USD risk, although this association has not been validated in a randomized, controlled trial (91).

USD pharmacotherapy recommendations are on the basis of stone composition and metabolic evaluation. Pharmacologic therapy is generally recommended for patients with high risk of recurrent stones (80,81). Thiazide or thiazide-like diuretics, citrate, and allopurinol reduce USD compared with placebo or control in patients with hypercalciuria, hypocitraturia, or hyperuricosuria, respectively (92–95). Guidelines for pharmacologic USD management differ. For instance, the EAU and the AUA guidelines but not the ACP guidelines differentiate pharmacologic recommendations on the basis of stone composition and metabolic evaluation (80–83). Existence of disparate guidelines emphasizes the need for better evidence from robust clinical trials focused on comparison of pharmacologic preventive measures versus each other and versus dietary modifications. Relevant outcomes, such as symptomatic versus asymptomatic stones, need consensus. The utility of 24-hour urine collections to guide therapy is often assumed, although data remain lacking (Table 1). Furthermore, health care provider awareness and application of USD management guidelines (96) along with patient adherence to long–term USD management are suboptimal (97). In addition to randomized, controlled trials of treatments, strategies to increase adherence to guidelines will be important for USD prevention.

Population Health and USD

Multidisciplinary Participation in the Episode of Care

Individuals experiencing the pain of an obstructive stone receive care from multiple specialties during an episode of care (defined as symptom onset to stone passage or procedural removal). Many aspects of care utilization remain poorly understood. Among those presenting to the ED, approximately 90% are treated and released (Figure 1). The nature and location of follow-up care after ED discharge remain poorly defined, although about 10% will experience an ED revisit (17). The utilization of primary care by patients with USD remains poorly understood along with inpatient care. Approaches to care coordination between generalist and specialist physicians are lacking and may represent an opportunity to achieve better outcomes at lower costs. Across the episode of care (Figure 1), a number of key unanswered questions exists, the answers to which will likely inform development of more efficient care delivery models.

Population Health Management—Primary and Secondary Prevention

Given the high prevalence and substantial burden of USD, the role of population health management warrants investigation. For example, are primary or secondary prevention efforts effective or cost-effective across populations? Perhaps first degree relatives of stone formers merit intervention as a higher-risk group. A first iteration of a recurrence risk prediction nomogram (Recurrence of Kidney

Stone) is available (98). It could be useful to identify patients most worthy of prevention strategies. With substantial evidence of associations between USD and the metabolic syndrome, should population health campaigns be narrowly focused on stones or more generally, note prevention of USD as a potential benefit of general health interventions along with reduced hypertension, diabetes, and cardiovascular disease? What are the key patient–reported outcomes and patient–reported experiences that should drive health policy and care delivery for patients with USD? These questions and other aspects of population health management become increasingly important when conceptualizing USD as a preventable chronic metabolic condition with intermittent, acutely symptomatic stone events.

Conclusion

USD is more than just a symptomatic stone: the body of evidence today suggests not only a chronic metabolic condition punctuated by severely symptomatic acute events but also, a condition that heralds substantial future chronic morbidity and demands preventive efforts. The burden of treating patients with USD falls across many specialties in addition to urology, including emergency medicine, nephrology, radiology, and primary care. The substantial clinical and research opportunities noted above will require a multi-institutional and transdisciplinary approach, which has prompted the NIDDK to support the formation of a Urinary Stone Disease Research Network (99). Through a collaborative approach, physicians, researchers, and patients will improve care and ameliorate the public health burden of excruciating acute stone events and more importantly, their inciting chronic metabolic derangements and morbidities.

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