

The many facets of stone disease: a practical outlook on 24-hour urine and genetic testing



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Introduction

The prevalence of kidney stone disease has increased over the past several decades, with approximately 1 in 11 people experiencing a stone event in their lifetime.¹ Further, stone formers have a 30% to 45% chance of experiencing another stone event in 5 to 10 years, with 11% to 14% experiencing more than 3 recurrences.² Within pediatric urology, 19% of children with an incident stone will experience another episode within roughly 3 years, and nearly 50% of those under the age of 10 with an identifiable metabolic abnormality will have a recurrence.³

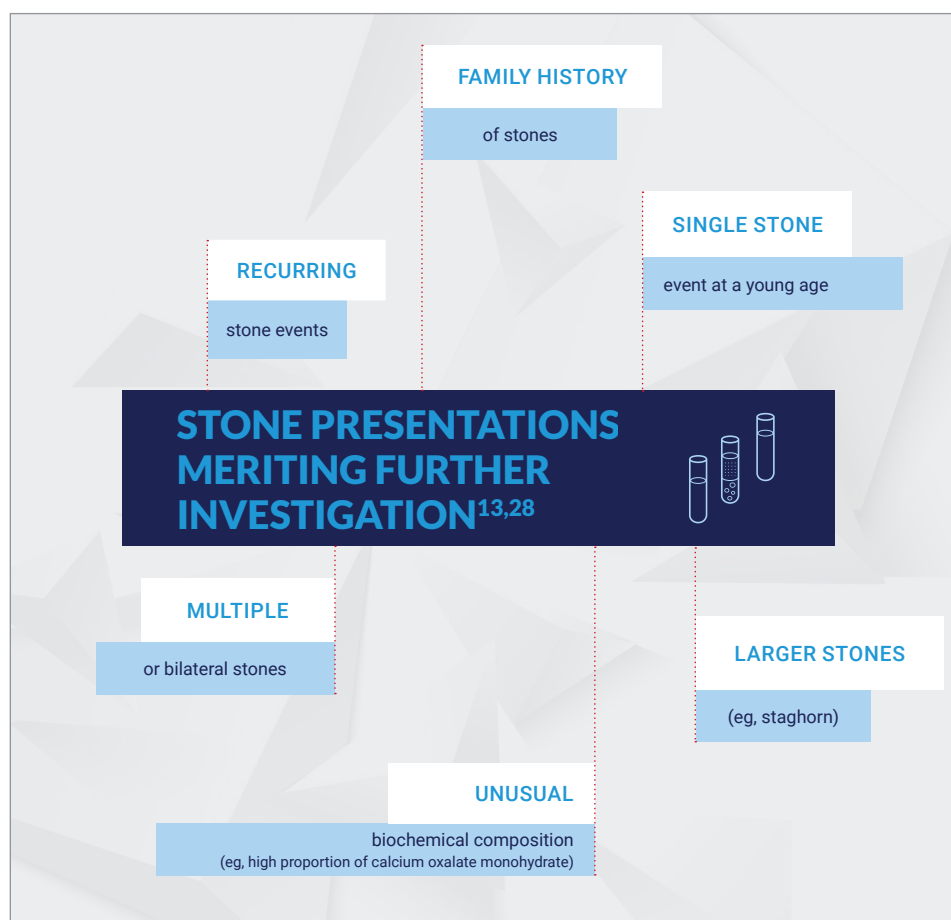
As with other chronic diseases, the causes of recurrent stone diseases may be multifactorial and associated with comorbidities such as obesity, hypertension, and diabetes or may be due to monogenic diseases such as cystinuria and primary hyperoxaluria (PH).^{4,5}

The steady rise of these comorbid risk factors indicates there will be even more stone formers needing management in the future.^{1,6} All the while, monogenic causes of stone disease account for 11% of adult patients and 29% of patients that presented with stone disease before the age of 25.^{5,7} The early identification of these conditions and a multispecialty approach to their management may lead to prevention of chronic kidney disease (CKD) and other nonurological manifestations.^{4,8-10}

The question thus arises: Are we doing enough for our stone formers in regard to workup and prevention?

Metabolic workup: the 24-hour urine test

Evidence suggests that urologists may not be doing enough to understand, diagnose, and manage stone formers.^{1,11} Recent literature highlights the underutilization of 24-hour urine testing, an immensely useful test that can aid in both medical and dietary management.^{12,13} Both the American Urological Association (AUA) Guidelines and the European Association of Urology (EAU) Guidelines recommend



24-hour urine collections in high-risk stone formers.^{13,14}

Milose et al illustrated this underutilization of 24-hour urine collections, with only 7% to 8% of patients performing collections within 6 months of diagnosis.¹² Ellison et al demonstrated that only 12% of pediatric stone formers had a 24-hour urine collection within 6 months of a stone event.¹⁵

This underutilization by urologists is in contrast to the desires of our stone formers; greater than 90% desire workup even after a single stone event.¹⁶ Testing for interested first-time stone formers is also included as a recommendation within the AUA Guidelines.¹³ Compounding the inadequate ordering of 24-hour urine collections is the fact that stone formers may not be compliant with testing or may perform inaccurate urine collection.^{12,17,18}

At my institution, we were able to increase compliance from 47% to 65% by a dedicated nurse placing all requests to the vendor on behalf of our patients.¹⁹

Although compliance with collection is important, so is the collection of accurate samples to help with determining the dietary and medical management needs of the patient. In a retrospective chart review at my institution, 51% of collections across 241 individuals were deemed inaccurate, underscoring the importance of educating our patients on the importance of proper urine collection.¹⁸

When it comes to interpreting results, there may be additional challenges.²⁰ For instance, to ensure a comprehensive evaluation, laboratory reports should factor in concentration, pH, and reference values, rather than characterize results solely as “high” vs “low” or “normal” vs “abnor-

mal.” Further, since “normal” values are not necessarily optimal values, it is important to consider levels across multiple 24-hour urine components in assessing their relative contribution to the risk of stone formation.²¹⁻²² Clear and concise reports facilitate proper interpretation and aid in determining next steps, as it can be far more difficult to analyze results when multiple reports from different laboratories have to be combined (eg, 24-hour totals vs relative concentrations).²⁰ At my institution, having all 24-hour urine testing performed within the same lab has proved optimal, allowing us to maintain consistency in interpreting findings and directing medical and dietary management.

Genetic testing: the case of primary hyperoxaluria

In addition to performing metabolic workup of our stone formers, certain cohorts of stone formers may also benefit from genetic testing.⁵ One example arises when 24-hour urine results indicate hyperoxaluria; this can be a result of primary hyperoxaluria, enteric hyperoxaluria, or secondary causes (dietary indiscretion or idiopathic).²³ The AUA Guidelines state that primary hyperoxaluria should be suspected when urinary oxalate levels exceed 75 mg/day, and genetic testing should be considered.¹³

Primary hyperoxaluria (PH) encompasses a group of rare genetic diseases that lead to overproduction of oxalate in the liver, and thus increased urinary oxalate excretion.²⁴ PH type 1 (PH1) is the most common and severe type, accounting for ~80% of patients in international registries.²⁵

Kidney stones are the most common symptom of PH1, a direct result of oxalate overproduction and subsequent calcium oxalate crystal formation.^{26,27} Stones associated with PH1 often contain high proportions of the monohydrate form of calcium oxalate.²⁸ PH1 patients fall within the category of high-risk stone formers, often presenting with recurrent or “unusual” stones as adults, or having a stone at a young age.^{25,28}

The impact of continuous calcium oxalate overproduction in PH1 goes beyond kidney stone formation. In kidney tissue, it results in nephrocalcinosis, inflammation, and progressive kidney function decline. Over time as kidney function declines, deposition and accumulation of crystals in tissue (systemic oxalosis) can lead to problems across multiple organs.²⁷

Disease progression occurs at different rates across patients, and decline in kidney function can occur suddenly even in previously stable patients.^{29,30} Available data suggest most patients eventually progress to kidney failure, incurring the need for hemodialysis or liver/kidney transplant (~50% of patients reach end-stage kidney disease [ESKD] by age 35, ~90% of patients by age 60).²⁹

Early identification, which can be facilitated by

genetic testing, could help prevent or delay the devastating effects of oxalate deposition.^{27,31,32} Sadly, in up to 70% of adult PH1 cases, severe renal insufficiency is already present at diagnosis.³²⁻³⁴

With the human genome being mapped more than 2 decades ago and the advancement of next-generation genomic sequencing, genetic testing has become more available, quicker, and cheaper.^{35,36} With the ease and cost of testing, many have integrated it into their clinics and workup for stone formers.^{37,38}

In the cohort of CKD in which genetic testing has been more routinely used, the evidence of its benefit is clear. Groopman et al studied a cohort of patients with CKD and found that genetic diagnosis changed clinical management, allowed for recognition of extrarenal and associated features and thus appropriate referrals, and informed therapies.³⁹ In other clinical conditions, genetic testing has been shown to reduce time to diagnosis and healthcare costs.⁴⁰⁻⁴⁴ In the case of PH1, medical management has demonstrated improved outcomes.⁴⁵

My experience

There is a disconnect between clinical practice and guideline-based practice. On a quick review, my institution (including urologists and nephrologists) has had 5316 24-hour urine collections from 2001 to 2020 (unpublished observations). Of these, 4.6% (243 collections across 138 individuals) showed oxalate >75 mg/day, and 38.3% of those (93 collections across 56 individuals) showed oxalate levels >100 mg/day. Many of these patients may have had bowel dysfunction as the underlying etiology, but the sheer number of individuals suggests genetic testing is underutilized. This is likely due in part to the difficulty in the past with coordinating and performing genetic testing. However, we are in a new era and as urologists, we now have the tools to integrate genetic testing into our practice.

Currently, I reserve genetic testing for those with pediatric onset of stone disease, significant recurrences, nephrocalcinosis, strong family history, associated CKD, or bilateral large stone burdens. Within a cohort of 41 patients genetically tested at my institution, 17% (7/41) had a monogenic cause for kidney stones (unpublished data). One individual that stands out was diagnosed at age 30 with familial hypomagnesemia, hypercalciuria, and nephrocalcinosis syndrome. The diagnosis led me to identify ophthalmological issues and also to be aware of the risk of CKD; involvement of a multidisciplinary approach will hopefully prevent or slow the clinical manifestations of the condition.

Conclusion

Historically, urologists may have viewed kidney stones as an episodic event instead of as a chronic

disease.^{1,46} As mentioned above, in addition to being associated with obesity, diabetes, and hypertension, recurrent stones can arise as a result of monogenic disorders.^{4,5} Links to atherosclerosis, myocardial infarction, and metabolic syndrome have also been described.⁴⁷⁻⁴⁹ This suggests that a more holistic approach to management of our stone formers may actually lead to other, far-reaching health benefits.¹

Twenty-four-hour urine testing allows for the identification of risk factors and can inform preventive therapy.^{14,19} My institution has also demonstrated the potential benefit of blood work in the evaluation of stone formers; screening for primary hyperparathyroidism in a tertiary referral center was cost-effective.⁵⁰ With a metabolic workup, the urologist can implement appropriate medical and dietary management, which can diminish stone recurrence, lessen the economic burden, and improve quality of life.^{12,14,21,51,52}

Often as urologists, we may feel that tools to treat our stone formers are limited: historically, few medications have proven beneficial and are utilized in the management of stone disease (eg, thiazides, alkalization therapy).¹⁴ To increase our knowledge, create more treatment options, and better care for our stone formers, I propose we start by utilizing the tools we currently have: metabolic workup and genetic testing. By performing these tests, we can hopefully advance our understanding and treatment of stone formers.

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