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INVITED REVIEW

Empiric therapy for kidney stones

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Abstract
Careful phenotyping of patients to classify those with kidney stones has a long and important history in revealing the chemical basis for stone formation. Advances in our genetic understanding of kidney stones will lead to incredible insights regarding the pathophysiology of this common disorder. At this time, both evaluation of urine chemistry and genotyping of patients are extremely useful in the setting of a university and research-based kidney stone clinic. For much of the world, in a more clinically focused setting, these techniques are neither available nor absolutely necessary. Careful implementation of an empiric prescription based on stone composition would have an important effect to reduce stone recurrence in the world's many stone formers. Increased fluid intake, generic dietary manipulations, and prescription of potassium citrate and thiazides are all appropriate empiric therapies for people with calcium and uric acid kidney stones.

Keywords Diet · Genetics · Kidney calculi · Nephrolithiasis · Potassium citrate · Thiazides · Uric acid · Urolithiasis

Introduction

In making a case for empiric preventive therapy for recurrent kidney stones, I aspire to not be viewed as a Luddite, opposed to modern scientific investigation of the pathophysiology of stone disease. As a member of the Rare Kidney Stone Consortium (RKSC), I support our efforts to understand the genetic causes of stone disease and promote the genotyping of a wider selection of patients with kidney stones [1]. The classic twin study that my collaborators and I performed is probably the best evidence that heredity is responsible for a large proportion of stones in the general population, not accounted for by the rare, autosomal recessive or X-linked stone diseases that the RKSC studies [2].

However, we must recognize that thorough genotyping of stone disease is not yet widely available and remains relatively expensive to perform in many clinical settings throughout the world. While my colleague and friend Dr. John Sayer in this issue promote "precision medicine" as a way of diagnosing and treating kidney stones, we both recognize that we have access to genetic testing in our research settings that cannot yet be easily applied by the primary care practitioners, nephrologists, and urologists that take care of the world's stone formers. Similarly, the ability to analyze 24 h urine collections is either lacking or not practiced widely. A practical point of view regarding the management of stone disease must follow, with acknowledgements that appropriate diagnostic and therapeutic strategies vary between the primary care setting, the urology office, and the stone clinic in the university medical center. I will make a case for empiric therapy and express confidence that most kidney stones will be adequately prevented using such a strategy.

The current reality

Limited data suggest that most patients with kidney stones are not offered much advice, if any, for prevention of stones. Many patients that I and my nephrology colleagues seen have been told to "drink a lot of water", not given any advice about dietary intake, and not offered any pharmacologic therapy. It is not unusual to meet patients who were not told that restriction of dairy (calcium) intake is no longer appropriate, though in the past, this was often part of the preventive prescription. Only 8% of one group of patients judged

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to be "high risk" for recurrence had a 24 h urine collection done [3]. Only a minority of patients seen in emergency rooms with renal colic are evaluated by a urologist, and many fewer see a nephrologist.

Perhaps, intimidation of some practitioners by urine chemistry and renal physiology may contribute to the neglect of preventive strategies applied to patients with stones. The notion that interpreting a 24 h urine collection requires knowledge of arcane lore seems prevalent. There was a time when the classification of the etiology of higher urine calcium excretion required more complex, time-consuming evaluation [4]. However, the guidelines of neither the American Urological Association (AUA) nor the European Association of Urology (EAU) recommend such evaluations [5, 6].

The association of stones with reduced bone mineral density, hypertension, vascular disease, metabolic syndrome, myocardial infarction, and chronic kidney disease is not widely appreciated among non-lithologists. Kidney stones do not, fortunately, have the gravity (i.e., the mortality rates) of heart disease or cancer, yet these associated co-morbidities offer ample reasons to consider them markers of indications to address diet, weight loss, and exercise [7]. The relative ignorance of these associations comes despite many of us highlighting these relationships during medicine and nephrology grand rounds.

This rather dim reality leaves the bearers of stones in a difficult situation. They are often neglected, the way sufferers of gout are. Both disorders are intermittent, famously painful and incapacitating, but relatively infrequent, enough so that they may be conveniently forgotten in between episodes. That intermittent quality leads to some ambivalence among practitioners about whether to perform 24 h urine collections and ambivalence and lack of motivation among patients about whether dietary or pharmacologic manipulations are worthwhile. The Recurrence of Kidney Stone (ROKS) nomogram is intended to address uncertainty about whether a first-time stone former is at higher, or lesser, risk for recurrence and encourage prospective identification of those for whom such evaluation and treatment are most appropriate, but is not yet in widespread practice [8].

Lifestyle

Since overweight and weight gain are consistently associated with kidney stones, addressing weight is appropriate not only for stone prevention but to mitigate the advancement of the associated co-morbidities [9, 10]. How best to achieve weight loss is beyond the purview of this review. Educating patients that stones may be their first manifestation of their otherwise unhealthy lifestyles may lead them to an epiphany [7].

Fluid therapy

Unquestioned is the significant benefit of increasing fluid intake to achieve an increase in urine volume [5, 6, 11]. The benefit was demonstrated in one randomized trial in which kidney stone recurrences were noted in 12 of 99 patients instructed to increase fluid intake and in 27 of 100 patients who were not so advised ($p = 0.008$). The average interval for recurrences was 39 months in the first group and 25 months in the second [12]. In a meta-analysis of 15 studies deemed relevant, each 500 mL increase in water intake was associated with a significantly reduced risk of kidney stone recurrence [13].

The science which explains that a reduction in supersaturation resulting from urinary dilution can prevent stone formation can be made easily understandable to lay stone formers, and has a simple, intuitive appeal. The therapy is profoundly inexpensive. It is also perfectly safe (if prescribed appropriately), and for practical purposes, has only one adverse effect: polyuria. The increase in urinary frequency is particularly problematic in men with prostatic hypertrophy and in men and women with incontinence. It may also be difficult to achieve in those with occupational circumstances that diminish their access to fluids and to bathroom facilities, such as drivers [14]. One other adverse effect of increased fluid intake which has not been studied in stone formers is disturbance of sleep, which potentially leads to an increase in cardiovascular morbidity [15]. One informal estimate is that 80% of stone recurrences could be prevented by attention to adequate volume intake.

Genetics

Advances in the understanding of how genotype affects phenotype are awesome in their implications for the therapy of human disease. All medical fields have been deeply altered by these advances, including by the increasing availability and declining cost of appropriate testing. I hope and expect that these advances will continue to progress and that I will be a part of such progress. The concept of "precision medicine" is a most attractive one, as my colleague Dr. Sayer opines about in this issue of Urolithiasis, and we have promoted elsewhere [16]. As of this writing, however, it is not yet a practical concept, but that assertion may seem badly outdated in the coming few years.

In the general population, there is good evidence that kidney stones are heritable. Two studies have demonstrated that significant proportions of patients seen in an emergency room or in a kidney stone clinic have first degree relatives with a history of stones [17, 18]. Our twin study demonstrated that the rate of concordance for stones among monozygotic male twins was about twice that seen in dizygotic twins, leading to an estimate of heritability of 56% [2]. Our soon-to-be published data from the Washington State Twin Registry also demonstrate heritability in women but to a lesser extent. We assume that most stones in these studies are calcium-based, but lack those data.

Yet, the genetic basis for this high degree of heritability remains unexplained. With the assumption that the most common urinary abnormality among calcium stone formers is higher urine calcium excretion, candidate genes have been screened among such patients and have not been fully explanatory [19]. Examples of genes, mutations of which do not account for the relatively high prevalence of calcium stones or higher urinary calcium excretion include *TRPV5, CASR, CLCN5, ALPL*, and multiple claudins, among others [20]. Some evidence demonstrates that single nucleotide polymorphisms affecting these genes may be associated with stones in some families, but are not broadly represented in the general population [21].

Even broader screening of populations of stone formers has not demonstrated significant proportions of patients with identified mutations accounting for stone disease [22, 23]. These studies of patients in stone clinics include patients with rare autosomal recessive disorders such as cystinuria and primary hyperoxaluria, or X-linked Dent disease. Many of the patients with identified monogenic mutations were diagnosed before genetic screening was performed, based on stone composition (cystine), urinary chemistry (primary hyperoxaluria), or low serum bicarbonate and higher urine pH with renal tubular acidosis. The authors conclude that less than 10% of patients in a tertiary care stone clinic were diagnosed with a genetic cause of stones. They point out that the populations studied are highly enriched with younger patients and more severely affected patients, characteristics that increased the likelihood of finding monogenic causes of stones [22, 23].

Making these genetic diagnoses will clearly have important implications for understanding pathophysiology and prognosis [23]. In some cases, they will have important implications for treatment as well. To take one example, if more cases of primary hyperoxaluria are diagnosed as the result of genotyping stone formers, new treatments with interfering RNA or small molecules may soon be applied with dramatic effects [24] (see also this issue [25]). On the other hand, the genes that are responsible for cystinuria have long been known, and to date, no phenotype/genotype correlations have been conclusively demonstrated and no treatment taking advantage of the identification of the mutated genes has been developed [26]. Based on the progress made in cystic fibrosis, where transport potentiators and correctors led to significant improvements in pulmonary function, some mutations in cystinuria may be amenable to such therapy in the future [27].

However, as investigators making numerous genetic discoveries employing high-throughput exon sequencing analysis have said, appropriate treatment for many patients will be the application of consensus guidelines. These include "increased fluid intake, limited sodium intake, treatment with thiazide diuretics, and potassium citrate therapy that may not directly address the pathophysiology of a particular molecular diagnosis" [23]. These empiric prescriptions are discussed further below.

Twenty-four hour urine collections

We have recently reviewed both the benefits and the deficiencies of doing 24 h urine collections [28]. The AUA guidelines suggest that "Clinicians should perform additional metabolic testing in high risk or interested first-time stone formers and recurrent stone formers" [5]. Additional metabolic testing entails ordering a 24 h urine collection. An international consensus statement said "A 24-h urine test for creatinine, pH, calcium, oxalate, citrate, uric acid and qualitative cystine will detect major systemic causes of stone disease" [11]. Many kidney stone specialists, including myself, find that these collections are very useful in managing patients with stones for several reasons. First, the urine collections have a strong correlation with kidney stone composition and, therefore, appear to reflect a relevant pathophysiology [29]. Second, advising patients regarding dietary manipulations can be guided by the results of the collections, so that the dietary prescription can be limited to relevant ingestions and not made too broad and too difficult to implement [30]. Finally, the tests are useful in demonstrating whether urine chemistry has changed favorably, as the result of fluid and dietary prescriptions or as the result of pharmacologic interventions. To a degree, such changes are indicative of the patients' adherence to the prescription.

However, we acknowledge that no study has shown prospectively that managing patients based on 24 h urine collections is superior to prescribing empiric therapy without 24 h urine data. The collections may not be representative of what patients normally drink or eat. They may not represent the peaks of urinary supersaturation that occur after meals or at night. They may differ during the week when patients are working as compared to weekends when they are at home; most often patients do the collection when the latter conditions apply. They are considered inconvenient for some

and expensive for others. In addition, much of the world does not have the ability to perform and evaluate 24 h urine collections in a convenient, relatively inexpensive, repeated fashion as has been available in the United States for more than 20 years [31].

An additional issue is that the interpretation of urine collections is not settled. Terms such as hypercalciuria and hyperoxaluria imply that there are dichotomous values distinguishing normal from abnormal values, but in fact, there is an increase in risk at higher compared with lower values of these urinary analytes, even within the so-called "normal range", and no clear demarcation of a threshold value for calcium or oxalate excretion below which no risk exists [32]. Given that fact, we can ask whether identifying a patient's specific values is necessary. Whatever calcium and oxalate values are present, lowering them will reduce supersaturation and reduce risk for stone disease [5]. A similar analysis pertains to urinary citrate excretion, so that higher values are associated with lesser risk, with no clear value delineating hypocitraturia.

Finally, the benefits of thiazides and citrate supplementation to prevent stones in patients who did not have what were thought to be the requisite urinary abnormalities is well recognized. Thiazides have shown benefits in studies of calcium stone formers who were not selected based on 24 h urine calcium excretion, and citrate supplementation has shown benefits in patients who did not have lower urinary citrate excretion. Because of such studies, the AUA guidelines suggested that "Clinicians should offer thiazide diuretics and/or potassium citrate to patients with recurrent calcium stones in whom other metabolic abnormalities are absent or have been appropriately addressed and stone formation persists" [5]. In other words, if urine chemistry values appear unremarkable, a reasonable strategy, if untested in randomized trials, is to further reduce supersaturation. One could argue that this strategy also makes the 24 h urine collection superfluous: lowering supersaturation is always appropriate.

It is, therefore, reasonable to recognize that some degree of equipoise must exist about 24 h urine collections. They have unquestioned value, but the necessity of using them as the basis for all prescriptions must be questioned. Empiric therapy can also be called "unselected" therapy in that it could be applied to patients regardless of their urine profile, irrespective of urinary calcium, oxalate, or citrate excretion.

Empiric prescription for calcium stones

At this time, an empiric prescription for prevention of recurrent stones, as opposed to one based on 24 h urine collections, or based on comprehensive genotyping, is defensible. A trial comparing selected "precision" therapy (based on either the results of 24 h urine chemistry or genotyping) to empiric therapy, would certainly favor the latter. Such an empiric prescription is utilized today in many settings, throughout the world. Cost, convenience, and availability are also obvious considerations. Table 1 summarizes an empiric prescription for prevention of recurrent kidney stones.

Table 1 Empiric therapies for kidney stone prevention

Calcium stones	Prescription	Dose
1. Lifestyle	Weight loss	
2. Fluids	Water, coffee, juice, beer, wine	Total 3 L per day, mostly water
3. Diet	Borghi [33] or DASH [38]	
	Less sodium, animal protein, oxalate; more dairy	2 g Sodium 1000 mg Calcium 50–80 g Protein Less oxalate
4. Medications	Potassium citrate	15–30 meq Twice a day
	Potassium bicarbonate	25 meq Twice a day
	Chlorthalidone	25 mg Once a day
	Indapamide	2.5 mg Once a day
	Alendronate	70 mg Once a week

First, appropriate prescription of adequate fluid therapy to achieve a urine volume of greater than 2 L is an obvious manipulation. More time and attention to patient understanding and methods of encouraging adherence are needed to make this prescription more formal and powerful, but its efficacy is clear. Its efficacy to reduce urinary supersaturation and prevent most stones will be evident in patients with identified monogenic disorders and among patients with nearly any extreme of urine chemistry. It is important to note that this prescription may be ineffective or impossible to implement in younger children, in infrequent voiders, and in those with prostatic hypertrophy or incontinence.

A prescription for dietary alteration can also be recommended in a generic fashion. Two strategies have been promoted. The Borghi diet, which increases calcium intake, while restricting sodium, animal protein, and oxalate intake, remains the only diet shown to prevent stones in a randomized, controlled trial [33]. Increased calcium intake reduces absorption of dietary oxalate and should mostly come from dairy products, as vegetables with higher calcium intake tend to be also higher in oxalate content. The goal is 3–4 daily servings; milk, yogurt, cottage cheese, and calcium-fortified orange juice contain about 250–300 mg per 8 ounces, or 250 ml, serving. This prescription is not so easily achieved in lactose-intolerant patients, which often includes older people and certain ethnic groups. Lactose-free products are widely available and presumably useful in that setting. Limiting sodium intake reduces urinary calcium, but is difficult to achieve in "Western" societies. This recommendation is best achieved by limiting food to items that do not come in a can or a package and that do not

have a label to read. Restricting animal protein intake to one serving the size of a smart phone per day will limit purine excretion, citrate-reducing acid ingestion and in some, limit oxalate-yielding collagen ingestion. Restricting obvious, frequent, and voluminous oxalate intake is also worthwhile, though accompanying oxalate-containing foods with dairy products, limiting fructose intake, avoiding vitamin C, may be more useful [34, 35].

The other dietary manipulation that has not been tested in a randomized trial, but may yield improvements in urine chemistry is the Dietary Approaches to Stop Hypertension (DASH) diet [36–38]. People who follow a more DASH-like diet have higher intake of fruits, vegetables, nuts and legumes, dairy products, and whole grains with low intake of sweetened beverages and red and processed meats. DASH can also be modified by further restriction of sodium intake. The urinary effects of a DASH-like diet include higher urinary citrate excretion and higher urine volume. Applying either the Borghi diet or DASH to people can be made more palatable if the prescription focuses on the patient's detailed diet assessment to limit the extent of the required changes.

Pharmacologic therapy for kidney stones can also be prescribed empirically, without having a 24 h urine result. One wonders what proportion of stones would be prevented if every calcium stone former, not selected based on urine chemistry, was simply prescribed potassium citrate at a dose of 15–20 meq twice a day. Gastrointestinal intolerance which particularly affects older people can be reduced by administering after breakfast and dinner. Potassium bicarbonate in an effervescent 25 meq tablet can be diluted and imbibed in a larger urine volume-inducing serving, and may be better tolerated than potassium citrate by some. The risk of calcium phosphate stones is usually overstated; occasionally, a calcium oxalate stone former could become a calcium phosphate stone former, but it is likely that with the additional citrate and appropriate volume administration, fewer stones of any composition will result [39]. In addition, potassium citrate supplementation is associated with increased bone mineral density, a useful benefit, as reduced bone density affects many people with higher urine calcium excretion and calcium stones [40, 41].

The addition of thiazides to the empiric prescription without regard to urinary calcium excretion is also effective. The drugs are most effective if sodium intake restriction is also achieved. My preference is for the longer acting chlorthalidone and indapamide over the shorter acting hydrochlorothiazide. In patients with normal or lower blood pressure readings, I prefer indapamide, but caution about the possibility of symptomatic hypotension must be expressed [42]. Even lower doses may have an effect to reduce urine calcium excretion. This class of drugs prevents stones in people with and without higher urinary calcium excretion [43]. Like alkalinizing potassium salts, thiazides are associated with increased bone mineral density [44]. Their effect to lower blood pressure might be considered an adverse effect in stone formers, but I tell patients that I am extending their life expectancy as the drugs are associated with as good cardiovascular outcomes as any other treatment for hypertension if not better [45]. Hypertension is perhaps the most important, but not only, adverse cardiovascular trait associated with stone formation [46, 47]. Accompanying thiazides with some potassium citrate or amiloride helps prevent hypokalemia and hypocitraturia [48]. Adding potassium probably helps prevent the associated hyperglycemia. Hyperuricemia and gout, hyponatremia, and mildly increased serum cholesterol levels occur, but very infrequently limit therapy [42].

Finally, when thiazides are not tolerated, there are growing data demonstrating that bisphosphonates may reduce urine calcium excretion and prevent stones in people with reduced bone mineral density [49, 50]. This effect is magnified when prescribed with thiazides. Prescription of bisphosphonates for calcium stone prevention should follow measurement of bone density with dual energy X-ray absorptiometry, as no evidence suggests benefit if bone density is normal.

Empiric prescription for uric acid stones

Uric acid stones constitute a predominant stone composition among people with overweight, metabolic syndrome, and diabetes and may be part of the continuing increase in kidney stone prevalence [51]. No randomized trial for prevention of uric acid stone recurrence has been performed, probably because clinical lore makes clear that urinary alkalinization is effective [52]. The basis for the "unduly acid urine pH" seen in many patients with uric acid stones appears to be most often related to defects in ammoniagenesis in patients with overweight and metabolic syndrome [53, 54]. The role of a genetic contribution to the low urine pH in such patients has not yet been demonstrated. However, it is likely that genes encoding uric acid transporters may affect urinary uric acid excretion [55]. In addition, genes affecting urinary ammonia excretion may be implicated in clinical observations of urine pH [56]. Performance of 24 h urine collections in uric acid stone-forming patients might add some clinical information regarding the role of dietary protein and proton ingestion, but alkalinization is often effective without such data and without dietary change.

Therefore, when stone composition is shown to be uric acid, empiric treatment without further evaluation may be initiated. Treatment with potassium citrate, potassium bicarbonate, or sodium citrate is effective if urine pH can at least intermittently be brought to values greater than 6.0. Urate lowering therapy may not be effective if urine pH remains low [53]. Uric acid stones are so amenable to alkalinization

that administration as infrequently as once nightly or even every other day is sufficient [57].

Conclusion

Careful phenotyping of patients to classify those with kidney stones has a long and important history in revealing the chemical basis for stone formation. Advances in our genetic understanding of kidney stones will lead to incredible insights regarding the pathophysiology of this common disorder. At this time, both evaluation of urine chemistry and genotyping of patients are extremely useful in the setting of a university and research-based kidney stone clinic. For much of the world, in a more clinically focused setting, these techniques are neither available nor absolutely necessary. Careful implementation of an empiric prescription based on stone composition would have an important effect to reduce stone recurrence in the world's many stone formers.

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Compliance with ethical standards

Conflict of interest Goldfarb: consultant: Alnylam, Retrophin; funding from NIDDK, NCATS.

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