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Updates in the Metabolic Management of Calcium Stones

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Abstract

Purpose of Review Urinary risk factors, such as hypercalciuria, hypocitraturia, and hyperoxaluria, either in combination or alone, are associated with calcium stones. Dietary habits as well as underlying medical conditions can influence urinary risk factors. Evaluation of the conglomerate of patients' stone risks provides evidence for individualized medical management, an effective and patient-supported approach to prevention.

Recent Findings Many patients with stones desire prevention to avoid repeated surgical interventions. Yet, recent practice pattern assessments and health care utilization data show that many patients are rarely referred for metabolic evaluation or management. Innovations in metabolic management over the past decade have improved its effectiveness in reducing risk and preventing calcium stones. Although no new pharmacologic agents for calcium stone prevention have recently become available, there is relatively new thinking about some diet-based approaches.

Summary This review will synthesize current evidence to support individualized metabolic management of calcium stones.

Keywords Metabolic management · Medical management · Prevention · Diet · Urolithiasis · Nephrolithiasis

Introduction

Urolithiasis is a centuries old problem. It affects people of all socioeconomic, racial, ethnic, and geographic backgrounds. Though upper vs. lower urinary tract stones are more prevalent today, and though women now appear to be afflicted in numbers similar to men [1•], the pain and symptoms associated with acute stone events have not significantly changed over time. Stone removal has been available since ancient times. Unfortunately, death was a frequent outcome due to excessive bleeding, shock, or infection [2]. Well into the twentieth century, nephrectomy as a result of renal damage from recurrent stones and even death was common [3••]. In contrast, today's procedures are minimally invasive, effective, and associated with very low morbidity, yet they are surprisingly similar in concept to ancient stone removal practices which relied on dissolution, fragmentation, or removal in toto. Stone prevention, on the other hand, appears to be a relatively recent phenomenon. Perhaps this is because the recurrent nature of urolithiasis, which motivates prevention, was masked in earlier times by frequent deaths due to obstruction or impaired renal function, infection, or an attempted surgical procedure.

The term "kidney stone disease" when applied to all urinary calculi can be misleading as different types of stones are more appropriately seen as symptoms or expressions of separate underlying disorders driven by specific pathological processes and/or environmental influences. Supersaturation and the laws of thermodynamics set the stage for the formation of all stones. But stones of different composition have different causes and risk factors. Calcium stones may be calcium

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oxalate or phosphate; there are different species of each and also different metabolic contributors. Stones can also be comprised of uric acid, magnesium ammonium phosphate (struvite) cystine, or other less common minerals or compounds. This review focuses on calcium stones.

Calcium Urolithiasis Calcium oxalate (monohydrate and dihydrate) and calcium phosphate (hydrogen phosphate and carbonate apatite or hydroxylapatite) calculi are the most common. Calcium oxalate stones are more common than calcium phosphate. While idiopathic calcium stones are the subject of this review, certain systemic diseases and other conditions that cause or predispose to calcium stones should be noted. A partial list of conditions contributing to hypercalciuria includes primary hyperparathyroidism, sarcoidosis, some autoimmune diseases (e.g., Sjögrens), resorptive hypercalciuria, renal hypercalciuria, renal tubular ectasia (medullary sponge kidney), and, in some cases, distal renal tubular acidosis. Malabsorption, such as from irritable and inflammatory bowel, bariatric surgery, and short bowel, is associated with hyperoxaluria. Some genetic monogenic diseases are associated with hypercalciuria, hyperoxaluria, or both; these include X-linked recessive hypercalciuric diseases and primary hyperoxaluria. Medical conditions associated with hypocitraturia, which increases calcium stone risk by blunting the inhibition of spontaneous nucleation, growth, and agglomeration of calcium crystals, include gout, renal tubular acidosis, bariatric surgery, and short bowel. Some medications increase the risk for calcium stones; these include carbonic anhydrase inhibitors, which can cause hypocitraturia and higher urine pH leading to calcium phosphate stones; calcitriol and loop diuretics, which can cause hypercalcuiria; and antibiotics that eliminate or reduce oxalate degrading bacteria in the digestive tract, leading to hyperoxaluria [4, 5].

Idiopathic calcium stone formation, presumably the combination and interaction of both internal and external factors but without one identifiable cause, comprises the majority of cases in the USA. Factors promoting formation include those related to renal anatomy and function, gastrointestinal physiology and function, medical history and health status, genetic influences, medication use, dietary habits, and environmental conditions and exposures. Multiple metabolic aberrations, including higher urinary excretion of calcium and oxalate and lower urinary excretion of citrate and magnesium—either alone or in combination—are associated with calcium stones.

What Is Metabolic Management? Metabolic (or medical) management of kidney stones is the use of pharmacologic and/or nutrition therapy to prevent recurrence. Prevention of calcium stones with metabolic management is recommended by multiple professional organizations and consortia [6••, 7••, 8•, 9]. The first step in management is evaluation. Information critical for evaluation includes, as available, stone composition, renal metabolism (excretion) of urinary stone promoters and inhibitors, and underlying and contributing factors, the latter of which is obtained from comprehensive medical histories and assessments of habitual dietary and lifestyle habits. Recently, attention on the gut microbiome as a contributor to kidney stones, particularly calcium oxalate, has increased [10•, 11•, 12•, 13, 14]. Subsequent steps in management include the diagnosis(es) of risk and implementation of corrective therapy (Fig. 1).

Metabolic Management: Historical Perspectives

As cited earlier, stone recurrence was probably not widely appreciated historically due to the likelihood that a single stone was often a person's one and only stone because of nephrectomy and/or death. Some of the first-known nephrectomies, many of which were fatal, were for kidney stones [15]. Moreover, an appreciation for systemic and/or urinary risk factors for stones was lacking. Accordingly, historic evidence for metabolic management and stone prevention is sparse. Hippocrates apparently recognized that high fluid intake increased urine volume and was thus favorable in preventing urinary tract diseases, including stones [16]. Around 600 BC, the Indian surgeon Sushruta theorized that consumption of "unwholesome foods" contributed to bladder stones [17]. In the ninth century, an Iranian physician known as Rhazes recommended avoiding "heavy food" to prevent stones; these apparently included cheese, milk derivatives, hard-boiled eggs, and unleavened bread [18]. The consumption of "rich meals" and wine as contributors to urolithiasis was theorized by Hildegard from Bingen, a twelfth century abbess and physician [19]. Beginning in the sixteenth century, increasing energy intake, specifically from corn and starchy foods, was reportedly implicated in stone formation [20].

Differences in stone composition were definitively identified in the nineteenth century [21]. Circadian variations in renal function were described later [22]. In the twentieth century, urinary excretory parameters contributing to calcium stones were identified [23], and 24-h urine collections began to be used to identify risk factors. At first, calcium and phosphorus were the only parameters measured. Later, other urinary parameters related to calcium stone formation were identified. But their use in assessing risk and in medical management was not widely adopted. In the first half of the twentieth century, dietary recommendations to prevent calcium stones were not well codified and focused largely on hypercalciuria, which was thought to be related to dietary calcium. Thus, dietary calcium was advised to be restricted. Toward the middle of the century, associations between kidney stones and dietary protein [24], oxalate [25], sodium chloride [26], and carbohydrates [27] were made, leading to various albeit not

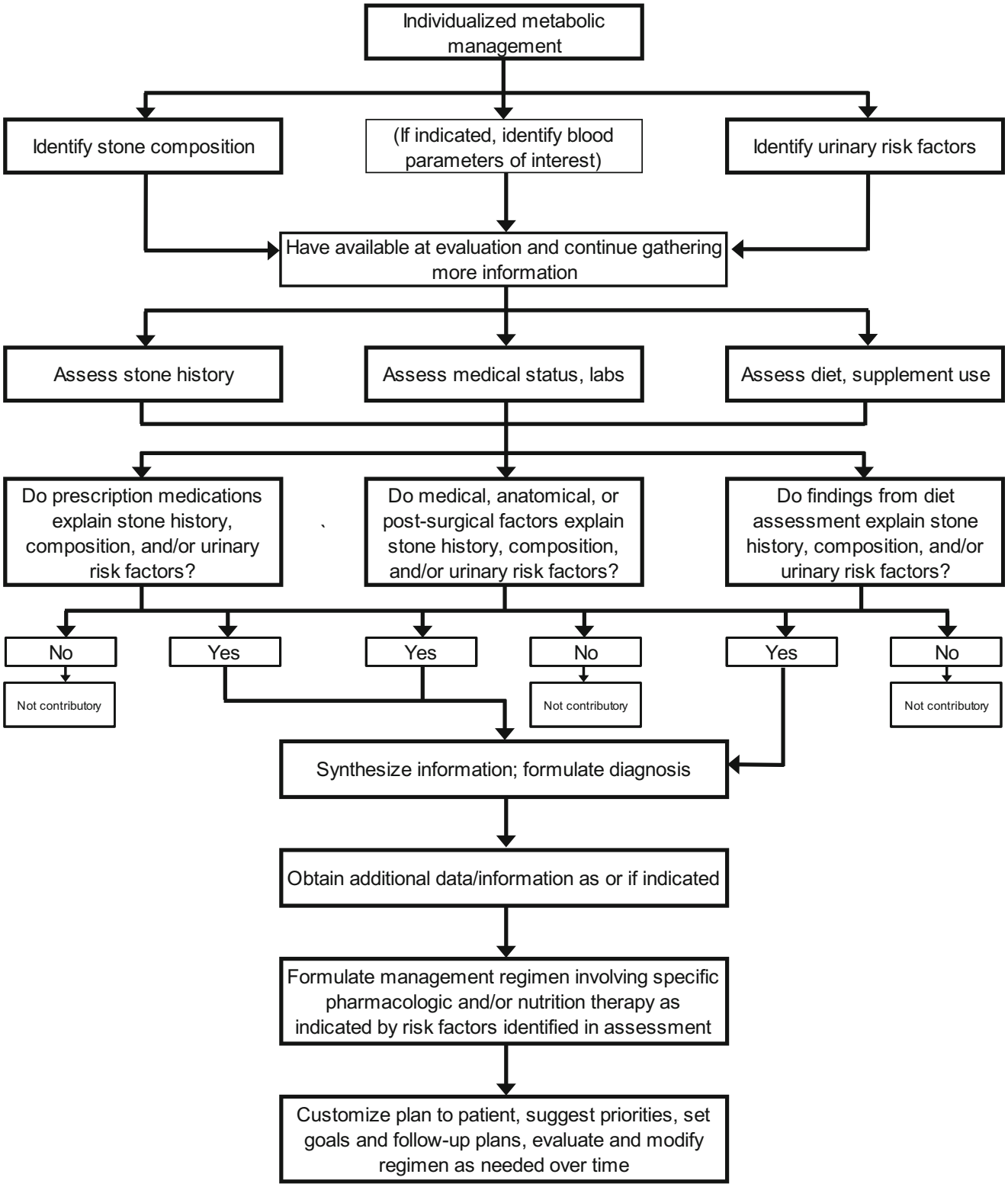

Fig. 1 Metabolic management of calcium stones. The process begins with assessment of stone composition, urinary/blood risk factors, stone history, medical status, diet history, and supplement use. This is followed by interpretation of the results and formulation of a diagnosis(es). Management concludes with the implementation of a plan to address the risk factors that were diagnosed during evaluation as contributory to calcium stones and a schedule for follow-up evaluation

well-substantiated dietary recommendations. Thiazides came into use for hypercalciuria in the 1950s [28]. The use of alkali citrate as a citraturic agent came into practice in the 1980s [29].

Metabolic Management: Current Perspectives

Today, minimally invasive stone removal surgeries have resulted in patients living longer with recurrent stones. Yet, most patients report a desire to avoid repeated surgery [30]. This is not surprising as stones are highly recurrent and contribute to deteriorations in patients' health-related quality of life [31]. Repeated procedures, especially including urinary stent placement, contribute significantly to the physical and financial burden of stones. Emotional consequences are numerous. Most importantly, stone surgery is not a cure for urolithiasis, especially in cases of high metabolic activity. Currently, however, it appears that only a small fraction of all eligible patients are offered medical management. Data show that patients reporting to emergency care units for stone-related symptoms are largely not referred for metabolic evaluation nor medical management [32]. Unfortunately, many of these patients are recurrent stone formers as well as one-time stone formers at high risk for recurrence. Additionally, data show that many urologists, those on the front lines of stone management, do not offer metabolic evaluation or medical management [33••], even after repeated procedures. Efforts to promote medical management among urologists and other providers are sorely needed.

Who Benefits from Metabolic Management? The answer to this question varies. There are many who would say all patients, regardless of whether they have formed one or 100 stones, should be offered medical management. Others advocate a more selective approach. While there is debate about whether one-time stone formers should undergo metabolic evaluation, there is expert agreement that children, no matter the number of stone events, and all recurrent stone formers should be offered evaluation. Some also add that patients with a solitary kidney and those who form brushite stones should be evaluated after a single stone event.

Metabolic Management Begins with Assessment Because calcium stones are multifactorial, the presumptive cause(s) of an individual's stone(s) is identified only with metabolic evaluation. Evaluation of stone risk is the first step in metabolic management (Fig. 1). Failure to synthesize all available information and to identify putative causes for a patient's stone formation renders the selection of an appropriate therapeutic regimen guesswork. As a comparison, consider the medical management of anemia, which, like urolithiasis, is a multifactorial condition. Although there are different types of anemia, all have a common expression (low hemoglobin). Treatment thus relies on identifying the cause. Anemia caused by iron deficiency is treated with iron supplementation. On the other hand, anemia caused by vitamin B12 deficiency will not respond to iron supplementation and requires a completely different therapeutic approach. This example underscores the point that, because of its multifactorial nature, the cause(s) or suspected cause(s) of a patient's calcium stone formation should be identified so that the appropriate treatment regimen can be put into place.

Currently, the assessment of an individual's metabolic risk factors for calcium stones is possible. Guidelines from multiple urology and nephrology organizations and consortia endorse using 24-h urine collections [6••, 7••, 8•, 9]. Spot urine collections are not useful in assessing calcium stone risk as circadian variations in renal excretion are noted. While some efforts are underway to optimize the use of spot urine samples for assessing urinary oxalate excretion [34], and though it may be imperfect, the 24-h urine collection remains the standard of care. There is strong support for the assessment of multiple urinary parameters; guesswork about the individual urinary parameters to assess is widely discouraged [35]. Commercial laboratories have thus developed risk "profiles" that provide results for a suite of the most common stone-related urinary parameters, including both promoters and inhibitors. Many recommend that a patient initiating medical management should provide two 24-h urine collections [36], but there is also support for one initial collection [37]. Other recommendations for the 24-h urine collection include that the day of collection be as typical as possible, i.e., reflecting the dietary and other habits a patient experiences most frequently in a given time period as these affect renal excretory parameters. This is important for interpretation of results as, for example, people frequently eat and drink differently on nonwork days compared to work days and/or during and around holidays vs. other times of the year.

An assessment of each patient's diet, noting whether any dietary changes were made prior to collecting the initial 24-h urine specimen, and its relationship to observed urinary risk factors, is a critical part of assessment. We believe strongly in the importance of dietary assessment and encourage that it be done by a nutrition expert. A detailed description of how to obtain accurate and comprehensive diet information and about assessment tools and strategies is beyond the scope of this review; other literature may be helpful [38]. As indicated by results of 24-h urine collections and other assessments (e.g., diet and medical history, environmental exposures, and/or stone composition) additional evaluative data may include circulatory factors related to calcium stones. If hyperparathyroidism is suspected, for example, such measures would include ionized calcium, 25-hydroxy-vitamin D, intact parathyroid hormone, and phosphate. If renal tubular acidosis or some other acid-base balance disturbance is suspected, potassium, chloride, and bicarbonate should be measured.

While efforts are underway or have been recently undertaken to identify the role of the gut microbiome in calcium stone risk [10•, 11•, 12•, 13, 14], this remains an area of discovery. The early stage of this field is underscored by multiple mixed accounts not only of a gut microbial "stone profile" (assuming there is a single such phenomenon for all patients who form calcium stones) but also of the effectiveness of therapies to manipulate gut microbiota [39–42]. Thus, while a promising future addition to metabolic assessment, gut microbial profiles are not yet ready for clinical use.

Metabolic Management without Individual Assessment Without knowledge of an individual's risk factors and the magnitude of any urinary and dietary aberrations, medical management can be applied only in a generalized manner. In the case of prescription medications, it is not possible without a 24-h urine assessment to confirm whether a patient's calcium stone risk is due, for example, to hypercalciuria or hypocitraturia. Prescribing a thiazide diuretic for a person with hypocitraturia and not hypercalciuria could have unfavorable side effects not to mention no effect on calcium stone risk. Even if the correct medication is identified, the dosage prescribed may be either insufficient or excessive as dosing regimens are driven by the magnitude of the urinary aberration. Thus, metabolic assessment before applying pharmacologic therapy is warranted if unnecessary prescriptions are to be avoided.

In the same fashion, management of diet-related risk factors for calcium stones is challenging without dietary assessment. In the event that diet is not a contributor to a patient's calcium stones, any number of recommended dietary changes would be tantamount to prescribing the wrong medication. Diet is not responsible for all calcium stones nor is it always a contributor. Diet assessment can help to rule nutritional factors in or out. We believe that nutrition recommendations should be driven by and tied to observed urinary and other risk factors. Just as the prescription of a medication for a nonexistent metabolic risk factor is unwarranted, so is the prescription of a dietary change for a nonexistent dietary risk factor. The ability of unnecessary and ineffective nutrition therapy to do harm is under-recognized. For example, a patient whose protein intake is already suboptimal should not be advised to lower his/her protein intake, which is often included on lists of dietary recommendations for calcium stone prevention. Low protein intake can result in protein calorie malnutrition, a medical condition with serious health consequences, and other conditions (e.g., sarcopenia, osteoporosis). Moreover, the course of this patient's stone disease would not be altered with a reduced protein intake as excessive protein was obviously not the cause of his/her stones. Consider in another example the patient whose dietary salt intake is not high but who is told that reducing intake, also a common feature of general lists for "stone prevention diets," will prevent calcium stones. Considering the efforts that must be taken to significantly lower one's salt intake, especially if it is already well controlled, no amount of salt reduction will lower urinary calcium excretion caused by some other factor. A mismatch between patients' expectations and outcomes could be harmful to their faith in prevention and/or to their ability to cope with and manage their health [43]. Finally, as with pharmacologic therapy, the number of dietary recommendations provided should be as few as are needed to produce favorable results. Not only are dietary changes difficult to make, they can be difficult for patients to remember [44].

Interpreting Urinary Parameters The treatment of an observed risk factor is driven by its presumed etiology. After assessment, the correct interpretation of the results is important if therapy is to be successful. The interpretation of a patient's 24-h urine collection should begin with creatinine excretion, a parameter predicted largely by the nonezymatic conversion of muscle-derived creatine to creatinine, which occurs at a constant rate (approximately 1 mL/min). Thus, the daily excretion of creatinine in a steady-state condition is approximately 1440 mL give or take variations in muscle mass, body habitus, and an estimated 4–8% variation in diet and physical activity [45]. Infection, fever, and trauma also affect urine creatinine concentration [46]. It is not uncommon for patients to collect > 24 h of urine (e.g., they did not begin the 24-h period with an empty bladder or they emptied their bladder prior to beginning timed collection but were unaware of residual/nonvoided urine). Nor is it uncommon for patients to collect < 24 h of urine. Cutoffs typically used to estimate whether a patient's collection is accurate for 24 h are based on body weight: 15–25 mg creatinine/kg body weight for adults (some advise using 15–20 mg/kg/day for women and 18–24 mg/kg/day for men). Caution in interpreting a collection as too high or low is warranted in situations of extreme muscle loss or wasting and in patients with extremely high muscle mass. The best way to know whether the collection is accurate for 24 h is to average urinary creatinine excretion from multiple collections and review with the patient the method for completing the collection. Historically, urinary parameters related to calcium stone risk have been categorized as "favorable" or "unfavorable." For stone promoters, "favorable" means lower excretion; for inhibitors, "favorable" means higher. The cutoffs for each parameter differ somewhat by laboratory, organizational guidelines, and providers' beliefs about normal and abnormal values. But this dichotomous interpretation of urinary risk factors has recently been questioned [47•]. Clinical interpretation by experts of urinary stone risk factors is increasingly trending toward a continuous perspective. Suggestions for interpreting urinary parameters using traditional dichotomous cutoffs and as continuous variables are shown (Table 1).

Table 1 Urinary risk factors for calcium stones. The top portion of the table shows suggested risk cutoffs for urinary parameters that directly promote or inhibit calcium stones and recommendations for interpreting them. The bottom portion provides the same for urinary parameters that contribute to risk or which otherwise provide useful data for assessment and diagnosis

Urinary stone risk parameters	Suggested risk cutoffs	Other recommended cutoffs	Interpretation of risks
Urine volume	• > 2.0 • > 2.5 L	Some set goal output higher, e.g., > 3 L/day, especially for those with aggressive stone history and higher stone risk factors	Lower output reflects low fluid intake and/or high extra-renal losses and increases urine supersaturation and risk for all calcium stones
Calcium	• > 250 mg/day • > 200 mg/day (F); > 250 mg/day (M)	Some advocate > 4 mg/kg/day as alternative to cutoffs; others have shown higher risk at ≥ 150 mg/day[a]	Higher excretion reflects underlying disease and/or dietary factor(s) and raises risk for all calcium stones
Oxalate	• > 45 mg/day • > 40 mg/day	Data show higher risk beginning at 30 mg/day[a]	Higher excretion reflects primary or secondary hyperoxaluria, malabsorption, and/or high dietary oxalate bioavailability and raises risk for CaOx stones
Citrate	• < 320 mg/day • < 550 mg/day (F); < 450 mg/day (M)	Some support aiming for > 600 mg/day	Lower excretion reflects acidosis from disease, medication, and/or high dietary acid load and raises risk for all calcium stones
Magnesium	• < 70 mg/day • < 80 mg/day (Nielsen)	Some advocate < 90 mg/day as this would reflect intake of ≥ 310 mg/day[b], assuming ~ 30% dietary absorption	Lower excretion reflects deficiency or insufficiency from low intake and/or malabsorption and raises risk for CaOx stones
pH	• < 5.7 or > 6.3 • < 5.8 or > 6.2		Overly acidic urine reflects acidosis; alkaline urine reflects infection or effect of alkali therapy and raises risk for CaPhos stones
Phosphorus	• > 1100 mg/day • > 1200 mg/day		Higher excretion reflects excessive bone resorption, disordered calcium-vitamin D-PTH axis, and/or higher dietary intake and raises risk for CaPhos stones
Contributors to risk	Risk cutoffs	Other recommended cutoffs	Interpretation of risks
Potassium	• < 40 mEq/day	Data support aiming for > 50 mEq/day[c]	Lower excretion reflects acidosis from metabolic or dietary factors and/or malabsorption
Sulfate	• > 80 mEq/day	May deserve lesser focus than other risk factors if urine pH is not overly acidic and/or if not accompanied by hypercalciuria	Urinary excretion reflects intake not only of foods with sulfur-containing amino acids (meats, eggs, grains, legumes, dairy) but also nonleguminous vegetables (e.g., crucifers, alliums); if from mostly animal sources, may be linked with overly acidic urine
Sodium	• > 200 mEq/day • > 150 mEq/day	Some advocate aiming for < 100 mg/day;[d] may deserve lesser focus than other risk factors if not accompanied by hypercalciuria	Higher excretion reflects intake from diet and lower extra-renal losses, contributing to expansion of extracellular volume and hypercalciuria
Ammonium	• > 40 mEq/day • > 60 mEq/day	Urinary ammonium excretion fluctuates greatly with dietary acid load	Higher excretion reflects infection and/or higher dietary acid load, especially if accompanied by lower urine pH, raising risk for hypercalciuria; lower excretion may suggest distal renal tubular acidosis

[a] Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. Kidney Int 2001;59:2290–98

[b] The Food and Nutrition Board of the Institute of Medicine has set the recommended dietary allowance for magnesium at 310–320 mg for adult women and 400–420 mg/day for adult men

[c] Turck D, Bresson J-L, Burlingame B, Dean T, Fairweather-Tait S, Heinonen M, et al. Dietary reference values for potassium. ESFA Journal 2016. https://doi.org/10.2903/j.efsa.2016.4592

[d] The 2015–2020 Dietary Guidelines for Americans recommends sodium intake < 2300 mg/day, which is higher than the recommendation (1500 mg/day) set by the Food and Nutrition Board of the Institute of Medicine

Interpreting Blood Parameters When interpreting blood tests, it is helpful to engage a specialist familiar with calcium stones as conventional laboratory norms are sometimes irrelevant for assessing calcium stone risk. The collaboration of a nephrologist or endocrinologist is strongly recommended. Briefly, if hypercalciuria is suspicious for parathyroid hormone involvement, then serum calcium and parathyroid hormone would be elevated; hypophosphatemia may or may not

be present. Hyperparathyroid activity due to low vitamin D status would be corroborated by low 25-hydroxy-vitamin D. If vitamin D status in the setting of high parathyroid hormone is normal, then referral to endocrinology for direct testing of gland activity would be in order. For confirming renal tubular acidosis, low serum bicarbonate and/or low potassium would be expected.

Interpreting Dietary Parameters The importance of accurate dietary assessment was previously stressed. The interpretation of the results of dietary assessment is best done by a nutrition expert familiar with dietary risk factors for calcium stones. Nutrition expertise is particularly required if quantification of individual nutrients is desired; nutrition experts, such as registered dietitians, have broad knowledge of food values for various macro- and micronutrients. Because dietary assessment is a subjective measure and because the ability or willingness to be accurate and truthful varies widely between patients, registered dietitians have developed strategies to optimize the accuracy of dietary information [48]. These include obtaining information about portion sizes and frequency of intake as well as providing a nonjudgmental patient-provider interaction that promotes truthful reporting. The information derived from nutrition assessment should be interpreted individually based on the above. Dietary risk factors and their suggested interpretation and importance are summarized (Table 2).

Managing Calcium Stone Risk with Medication No new pharmacologic agents for reducing calcium stone risk have become available in the recent decade. The same thiazide and thiazide-like medications that were historically used are still used today. Thiazides for hypercalciuria not related to diet or not responsive to nutritional intervention include chlorthalidone (12.5 or 25 mg once/day), hydrochlorothiazide (25–50 mg once/day or 12.5 mg twice/day), hydrochlorothiazide with amiloride (50 and 5 mg, respectively, once/day), and indapamide (1.25 mg once/day). Similarly, no new prescription alkalinizing or citraturic drugs are available. For hypocitraturia not responsive nor due to dietary influences, prescriptive alkalinizing agents include potassium citrate (available in 10, 15, or 20 mEq tablets), potassium citrate plus citric acid (packet of crystals provides 30 mEq alkali), potassium bicarbonate (dissolving tablet provides 25 mEq alkali), sodium citrate plus citric acid (oral solution, 15 cm^3 provides 15 mEq alkali), and sodium bicarbonate (650 mg tablet provides 7.7 mEq alkali). These are usually short-acting and thus prescribed in divided doses. As the cost of some alkalinizing agents has recently become excessive, patients and providers alike are reaching for cheaper alternatives. Baking soda (sodium bicarbonate) is inexpensive and available in grocery stores; one half teaspoon provides 26 mEq alkali. Also available without a prescription is potassium. Over-the-counter potassium tablets are inexpensive but are available only in 99 mg tablets and thus provide a mere 2.5 mEq alkali each. At this dosage, 12 tablets would be required to deliver 30 mEq of alkali. Examples of over-the-counter potassium-based alkali formulations include potassium citrate, potassium gluconate, potassium bicarbonate, calcium magnesium potassium, and potassium chloride and iodide. Note that some of these contain micronutrients that might not be advised, such as calcium in the setting of an already adequate calcium intake. Note also that potassium chloride, while effective in treating hypokalemia, does not alkalinize urine nor increase citrate [49]. New pharmacologic agents that increase urinary citrate without increasing urine pH would be useful as higher urine pH increases risk for calcium phosphate stones.

Managing Calcium Stone Risk with Diet Nutrition therapy for stones is both appropriate and effective [50] and includes the use of foods and beverages as well as over-the-counter nutrition supplements, which are regulated as foods in the USA [51]. Nutrition interventions can be designed to address low urine volume and, if diet-related, hypercalciuria, hyperoxaluria, hypocitraturia, and hypomagnesiuria. It is important to distinguish whether these risk factors are diet-related, else dietary modifications are not useful and may waste time during which pharmacologic intervention could be implemented. Table 2 provides recommendations for dietary risk factors revealed in assessment. It is now widely accepted that a low calcium diet should not be recommended for patients who form calcium stones, even those with hypercalciuria, though references suggesting this still abound on the Internet and in other sources. Aside from a shift in thought about low calcium diets, there is new information that a low oxalate diet may not be effective in reducing urinary oxalate excretion, at least not for all with hyperoxaluria, and that it may actually raise urine calcium oxalate supersaturation by reducing urinary citrate and magnesium excretion [52]. Other studies suggest high oxalate exposure in the gut may actually be beneficial as it increases the relative abundance of bacterial taxa involved in acetogenesis, methanogenesis, and sulfate reduction [53], all of which, in appropriate concentrations, play a beneficial role [54–56]. Thus, other means by which to reduce urinary oxalate excretion should be tried. Finally, there is new interest in the alkali potential of diet-derived organic anions other than citrate (e.g., malate, tartrate, succinate), as evidenced by recent studies examining the alkali potential of various juices, sodas, and fruits [57–60]. As results of these and other studies are confirmed, strategies related to nutrition therapy for calcium stones may be improved.

Table 2 Dietary risk factors for calcium stones. The mechanisms for how each dietary factor increase calcium stone risk are shown as are recommendations for interpreting and prioritizing the importance each

Dietary risk for calcium stones	Mechanism for risk	Suggested interpretation of dietary risk factors and recommendations
Suboptimal fluid intake	Concentrated urine, high supersaturation	May need to compensate for extra-renal losses; address any barriers to intake (e.g., occupational, unnecessary limitation of certain beverages, conscious restriction due to incontinence, etc.)
Excessive salt (sodium chloride) intake	Expansion of extracellular volume and higher urinary calcium excretion	Address and prioritize if hypercalciuria is present and thought to be diet-related; focus on highest-salt foods and those consumed most frequently (consider higher priority if thiazide is in use or will be prescribed)
Higher dietary acid load	Imbalanced intake of alkaline/neutral vs. acidogenic foods[a] leading to acidosis, renal citrate reabsorption, bone resorption	Interpret in context of serving size and frequency of intake of grains, meats, eggs, and cheeses vs. fruits/vegetables; shift balance of consumption in setting of hypocitraturia and/or hypercalciuria
Excessive calcium and/or vitamin D supplementation	Higher calcium absorption from gastrointestinal (GI) tract	Determine intake from foods and beverages and then recommend either to discontinue supplement completely or supplement only with amount needed to meet intake goals (e.g., per Dietary Reference Intakes)
Suboptimal calcium/magnesium intake; consumption not timed with meals	Higher oxalate absorption (both); lower urinary oxalate solubility (magnesium); lower urinary citrate excretion due to enhanced renal citrate reabsorption (magnesium)[b]	Prioritize and address especially in setting of hyperoxaluria and/or hypomagnesiuria (low magnesium may require supplement); increase calcium from foods and beverages first then add supplement if needed
Intake of oxalate-rich foods not sufficiently opposed by calcium/magnesium	Higher oxalate absorption from GI tract	To be addressed in setting of hyperoxaluria. Oxalate-rich foods provide bicarbonate precursors, fiber and prebiotics, magnesium, and phytate—optimize GI binding first, limit highest-oxalate foods if needed
Use of supplemental ascorbic acid; over-the-counter herbal supplements or concentrated plant extracts	Ascorbic acid is metabolized to oxalate; some plant extracts and tablets deliver oxalate load[c,d]	If urinary oxalate excretion high, and if other factors (e.g., calcium intake) are addressed, suggest trial of elimination; monitor effect in next urine collection
Low intake of dietary prebiotic material	Dysbiosis may reduce oxalate degrading bacteria in GI tract and promote higher oxalate absorption	If other factors, such as antibiotic exposure and chronic diarrhea, are ruled out or addressed, optimize prebiotic intake with a variety of high-fiber foods; data to drive prebiotic supplementation are currently lacking
High intake of carbohydrates	Increased calcium absorption from GI tract; increased plasma insulin and reduced renal calcium reabsorption[e]	Important in setting of hypercalciuria, obesity (an independent risk factor for stones); focus first on sweetened beverages and juices, candy, baked goods, refined cereals and grains, and snack foods
High intake of caffeine	Decreased renal calcium reabsorption via blocking cyclic adenosine monophosphate[f]	Assess frequency and portion size of high-caffeine beverages; suggest limits in setting of hypercalciuria that cannot be adequately explained by other factors
High intake of alcohol	Increased osteoclast activity and bone resorption[g]	Assess frequency and portion size of alcoholic beverages; suggest limits in setting of hypercalciuria that cannot be adequately explained by other factors

[a] Foods with a net acid load include all grains, cereals, meats (mammals, fowl, fish, seafood), eggs, and cheeses. Foods with a net neutral value for acid load include milk and yogurt. A few fruits and vegetables have a slight acid load (much less in magnitude than the aforementioned foods with high acid load), but on the whole, all fruits and vegetables confer a net alkaline load

[b] Rudman D, Dedonis JL, Fountain MT, Chandler JB, Gerron GG, Fleming GA, Kutner MH. Hypocitraturia in patients with gastrointestinal malabsorption. N Engl J Med 1980;303:657–61

[c] Siener R, López-Mesas M, Valiente M, Blanco F. Determination of oxalate content in herbal remedies and dietary supplements based on plant extracts. J Med Food 2016;19:205–10. https://doi.org/10.1089/jmf.2015.0068

[d] Tang M, Larson-Meyer DE, Liebman M. Effect of cinnamon and turmeric on urinary oxalate excretion, plasma lipids, and plasma glucose in healthy subjects. Am J Clin Nutr 2008;87:1262–67

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Conclusion

Metabolic management of calcium stones is effective and desired by patients. Efforts to increase referrals for medical management by those on the front lines of kidney stone care—emergency and acute care providers as well as urologists—are needed. Calcium stones, especially if idiopathic in nature, are multifactorial in etiology and thus require a multifactorial treatment approach. Metabolic evaluation, the first step in medical management, should be as detailed as possible; interpretation of the results should include, as needed, multidisciplinary input. As metabolic evaluation reveals specific risk factors, whether urinary or dietary, management should be tailored to these and not applied in a "cookie cutter" or generalized approach. A new frontier for evaluation of stone risk, though still in its infancy, is the assessment of gut and urinary tract microbial profiles. We look forward to the next generation of treatment algorithms for calcium stones.

Compliance with Ethical Standards

Conflict of Interest Kristina L. Penniston reports personal fees from Retrophin.

Stephen Y. Nakada declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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