Chapter

Stone Prevention: Dietary Factors, Current Evidence, and Metabolic Workup

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Abstract

Urolithiasis is a highly recurrent disease. The incidence of urolithiasis is on the rise. Although stone prevention is highly desirable, there is significant controversy and lack of quality evidence to suggest a standard approach to prevention. In the current chapter, we have looked at the contemporary evidence, lack of long-term compliance, and various dietary and pharmacological treatment options for prevention of recurrent stone disease.

Keywords: prevention, metaphylaxis, translational research, dietary factors, urolithiasis

1. Introduction

Urolithiasis is an endemic condition in certain parts of the world, particularly where weather is dry and hot. However, current data suggest that it is now increasingly identified in high income countries and its prevalence is independent of the weather conditions. Genetic and dietary influences are two important predispositions. Urolithiasis is now considered as a systemic disorder. The exact etiology is still elusive, however, there is a complex and intricate interplay of genetic and dietary factory. The epigenetics play provides an important link between environment and genetics. Urolithiasis is not only highly prevalent but has a very high recurrence risk. This chapter looks at the various preventive strategies, the contemporary evidence in support and influence of diet on urolithiasis prevention.

2. Why stone prevention is important?

An episode of ureteric colic or urosepsis secondary to urinary stones is an alarming experience for a patient. In many cases, stones may require medical or invasive endourological procedures to remove them with its attendant cost and morbidity. The estimated cost of urolithiasis management is likely to be ~$4.1 billion by 2030 in United States alone [1]. Additionally, recurrent kidney stones can lead to long-term

complications and continue to be a significant cause of end stage renal disease in the developing world [2].

3. Patients with high risk of stone recurrence

The risk of recurrence after the first stone episode may be as high as 90% in 5 years. However, this risk is quite variable and depends upon several patient and stone-related factors. A subset of patients is identifiable for which the risk of recurrence is much higher [3]. These patients should be specifically directed for metabolic workup and implementation of stone prevention strategies.

3.1 Patient factors

Age at first stone episode, number of previous episodes, time since last stone episode, family history, male gender, and body mass index are important predictors of stone recurrence.

3.2 Some other factors

Uric acid, struvite, and brushite stones are more likely to recur as compared to calcium oxalate stones [4]. Singh and colleagues [5] noted that symptomatic recurrence at 10 years was approximately 50% for brushite, struvite, and uric acid but approximately 30% for calcium oxalate and hydroxyapatite stones ($P < .001$). Patients with cystine stones can have an episode of stone requiring intervention almost every year or even more frequently [6]. Moreover, patients with a greater number and size of stones at first presentation and those with bilateral stones are more likely to experience recurrence of the disorder.

3.3 Specific medical conditions

Rarely during basic workup is a specific medical condition identifiable which increases the risk of stone recurrence such as gout, renal tubular acidosis, obesity, diabetes, cystinuria, recurrent UTI, or hyperparathyroidism [7, 8].

Dietary and social habits such as dehydration, a high intake of sodium, and animal protein all increase the risk of stone recurrence [9].

4. Difficulties in developing stone prevention strategies

Multiple factors have traditionally shifted the focus of research away from stone prevention. Firstly, the safety and efficacy of endoscopic stone removal have increased exponentially over the last few decades. This has shifted the focus to early diagnosis and intervention for stones, whereas workup to determine a specific cause of stones does not always provide useful answers. The mainstay of workup namely 24-hour urinalysis for identifying metabolic factors is cumbersome and usually not a true representative of patient's day-to-day life [10]. Lastly, even if a specific metabolic abnormality is identified, it may not be amenable to a specific treatment [11].

Preventing stone recurrence involves identifying the underlying causes of the stones and implementing strategies to address those causes. Developing stone prevention strategies is challenging due to several factors, including the following:

4.1 Complexity of stone formation

Kidney stone formation is a complex process that involves several factors, including genetics, diet, and environmental factors. The simple pathogenesis of solutes increasing the supersaturation of urine with respect to one of the stone constituents does not completely account for all these factors, whereas prevention strategies have mostly focused on either increasing the quantity of the solvent (i.e., water) or reducing that of the solutes (e.g., calcium, sodium, and oxalate) [12].

4.2 Limited understanding of dietary factors

Diet plays an important role in the development of kidney stones, but there is still limited understanding and lack of evidence for the role of specific dietary factors other than water intake and their contribution to stone formation.

4.3 Patient adherence

Stone prevention strategies often require significant lifestyle changes, such as increased fluid intake and dietary modifications. However, patient adherence to these changes can be challenging, which can limit the effectiveness of prevention strategies.

4.4 Limited access to health care

Stone prevention strategies may require access to specialized healthcare services, such as urology and nephrology. However, limited access to these services in some areas can make it difficult for patients to receive appropriate care and follow-up [13].

4.5 Cost

Developing effective stone prevention strategies may require significant investment in research, education, and healthcare services. The cost of these efforts can be a barrier to the development and implementation of effective prevention strategies.

5. Empiric therapy

The fact that stones are the outcome of multiple genetic, dietary, and environmental causes along with difficulties in identifying specific factors and targeting them for stone prevention has shifted focus toward a more generic empiric therapy [14]. This can be applied to all patients presenting with renal stones without subjecting them to the cost and burden of a detailed workup. However, it cannot be overemphasized that some of the patients who are at greater risk of recurrence, as mentioned above, or have a stone type other than calcium and uric acid stones, should be identified for targeted therapy.

5.1 Fluid intake

A Cochrane review published in 2019 evaluated the effectiveness of increasing water intake as a prevention strategy for kidney stones. The review analyzed three randomized controlled trials with a total of 255 participants that compared increased water intake to standard fluid intake. The review found that increasing water intake reduced the risk of kidney stone formation by 50%. The effect was most significant for individuals with a history of calcium oxalate stones. This provides strong evidence to support the importance of adequate water intake as a key prevention strategy for all kidney stones specially calcium oxalate stones.

Recent studies have also suggested that the timing and distribution of water intake throughout the day, known as circadian water intake, may also play a role in the prevention of urolithiasis [15]. Drinking water at regular intervals throughout the day can help to maintain adequate hydration levels and reduce the risk of stone formation by keeping the concentration of stone-forming substances like calcium and oxalate below their formation product [16].

5.2 Weight loss

Reducing weight can play a significant role in preventing renal stones, especially if the stones are caused by metabolic syndrome. Obesity is associated with insulin resistance, which can lead to increased urinary excretion of oxalate and calcium [17]. Moreover, insulin resistance can lead to metabolic acidosis, which lowers urinary pH, thereby promoting uric acid stone formation [18]. Losing weight can improve insulin sensitivity, thereby reducing the urinary excretion of oxalate and the risk of kidney stone formation [19].

5.3 Generic dietary manipulations

These include limiting sodium and animal protein intake besides maintaining a diet rich in fruits and fibers. A high intake of sodium can increase calcium excretion in the urine, thereby promoting stone formation. Limiting sodium intake to less than 2300 milligrams per day as per American Heart Association Guidelines, i.e., not more than 3–5 g of salt has been found to lower the risk of renal stones as well [20].

Several studies have linked a high intake of animal protein to an increased risk of kidney stones [21–23]. However, it is important to note that not all animal proteins are equally problematic when it comes to kidney stone risk. Fish and dairy products, for example, have been shown to have a protective effect against kidney stones (references required). This may be due to the high magnesium and citrate content of these foods, which can help prevent the formation of kidney stones. A systematic review of 14 prospective cohort studies studying the effect of total protein and protein sources showed that each 5% increase in total protein intake was associated with a 10% increase in kidney stone risk [22].

A balanced diet that includes plenty of fruits and vegetables can help reduce the risk of kidney stones. This may be partially due to a reduction in animal proteins and salts in such a diet. However, diets high in citrus fruits and low-fat dairy products have been shown specifically to prevent stone formation [24].

5.4 Empiric medications

These include prescription for potassium citrate, allopurinol, and thiazides without specifically analyzing a 24-hour urine. A comparison of empiric medications based upon clinical assessment alone with targeted therapy based upon 24-hour urine analysis showed that targeted therapy is not better than empiric therapy in reducing the risk of stone recurrence [25]. However, a similar comparison for high-risk groups including children indicated that targeted therapy is more likely to reduce stone recurrence in high-risk groups [26]. Therefore, a stratified approach of using empiric therapy for low-risk groups and targeted therapy for those with high risk of recurrence is appropriate.

6. Targeted therapy

Several advances in the field of precision medicine have improved our ability to identify and target specific risk factors for kidney stone formation. For example, genetic testing can identify inherited mutations that increase the risk of certain types of stones, while spot metabolic testing can measure urine and blood levels of key substances involved in stone formation avoiding the cumbersome 24-hour urine collection.

Using this information, clinicians can address the specific factors contributing to a patient's stone formation. This may include lifestyle modifications, dietary changes, and medications such as thiazide diuretics, citrates, and allopurinol.

6.1 Thiazide diuretics

Generally, a low dose of a thiazide diuretic, such as hydrochlorothiazide 12.5–25 mg/day is best suited for patients with documented hypercalciuria. By inhibiting the Na^+/Cl^- co-transporter, thiazide diuretics reduce sodium reabsorption in the distal convoluted tubule, thereby increasing calcium reabsorption. A meta-analysis of 8 RCTs (what does this mean?) involving 571 patients showed that thiazide diuretics almost halved the risk of stone recurrence but at the expense of side effects leading to poor patient compliance [27]. This is one of the main reasons that thiazide diuretics are less commonly used for this indication.

6.2 Citrate

Citrate is commonly used for the prevention of kidney stones, particularly those composed of calcium oxalate or calcium phosphate. Citrate can be given in the form of potassium citrate or potassium citrate. Citrate acts by binding to calcium in the urine, which reduces the amount of calcium available to form stones. Citrate also raises the pH of the urine, which makes it less favorable for stone formation. Studies have shown that citrate therapy is effective in reducing the risk of recurrent kidney stones. A Cochrane review of seven trials involving 477 patients showed that citrate therapy reduced the risk of recurrent stones by 75%. Citrate therapy was also associated with a reduction in stone burden and fewer surgical interventions [28].

6.3 Xanthine oxidase inhibitors

By inhibiting xanthine oxidase, allopurinol increases the levels of hypoxanthine and xanthine, which are more soluble than uric acid and are more readily excreted in the urine. While allopurinol is an effective medication for the prevention of uric acid stones, there are practical problems that limit its long-term use including adherence and cost. In one study, patients who were non-adherent to medication, were more likely to require surgical treatment for stone recurrence [29]. Febuxostat in another xanthine oxidase inhibitor is more effective in reducing uric acid levels both in blood and urine. However, this does not necessarily translate into a greater clinical effectiveness in preventing renal stones [30].

7. From lab to the clinic in stone research

Translation research in urolithiasis is essentially a process of covering an observation made in the laboratory, clinic, or community into an intervention that provides meaningful and applicable results. In the area of urolithiasis, it has impacted two major domains of management, i.e., firstly, the active management which is treatment of the stone itself and, secondly, the prevention of recurrence which is a major issue. Indeed, there has been significant progress in the first domain which is active management. Open stone surgery has been completely replaced by endourology even in the developing world [31]. Even the most complex kidney stones can be treated by minimally invasive surgery.

Kidney stone disease is a systemic disorder. The overall prevalence in the general population is increasing. In the USA, datum indicates that 1 in 11 persons have a kidney stone. This is almost equivalent to the prevalence of diabetes. Besides the high incidence of *de novo* stones, there is a high recurrence rate which together not only have a cost implication but also a significant impact on the overall health of patients. Stone prevention is therefore important, and measures are likely to not only decrease the recurrence but may have beneficial effect on other heath related matters. Shadman and Bastani [32] noted that urolithiasis is associated with chronic kidney disease, hematologic cancers, various endocrine disorders and metabolic syndrome, type 2 DM, autoimmune diseases, inflammatory bowel diseases, bone loss and fractures, hypertension, and coronary heart diseases and most recently ischemic strokes.

The first step in stone prevention is to identify the cause in an individual patient. Ferraro et al. [33] shared interesting datum concerning the practice patterns in various European and non-European centers. In this survey, the authors noted that a basic blood workup is performed in most patients and nutritional advice and stone composition analysis are carried out in a significant proportion. However, the 24-hour urinary parameters are not assessed in every patient. About half of the patients have only 7 out of 16 parameters assessed. So, the question is that when should it be done and in whom? In the review by Coninck, Keller and Traxer [34], they advised that medical and lifestyle history, physical examination, basic urine and blood workup, radiological examination, and stone analysis should be performed in all patients. Detailed 24-hour urine analysis is indicated in patients who are at high risk of recurrent stone disease. In a review written by us about five years ago, we also advocated the use of a tailored metabolic workup for urolithiasis which should be performed on selective individuals [35].

Currently we lack quality evidence regarding stone prevention strategies. In a meta-analysis from the Cochrane database, it is noted that there no RCT (what does this mean?) on the role of increased water intake for the primary prevention of urinary stones. However, for secondary stone prevention, increasing urinary output to achieve a two-liter volume is suggested. The "PUSH trial" [36] is an interesting proposal published in the American Journal of Kidney Diseases for the prevention of urinary stone with hydration. One of the fundamental problems with advice related to lifestyle is the lack of compliance. The proposed trial is set to study in a randomized trial of a multicomponent behavioral intervention program to increase and maintain a high fluid intake. Participants are randomly assigned (1:1 ratio) to the intervention or control arm. The proposed sample size is 1642 subjects.

In pediatric urolithiasis, there is very little controversy about the role of metabolic analysis to identify the cause of the stone and treating the patient to prevent long-term morbidity and stone recurrence. Compliance and tolerating medications are a greater issue. In a recent Cochrane database systematic review authors noted that oral potassium citrate supplementation may reduce recurrent calcium stone formation in children following lithotripsy. However, the majority of children poorly tolerate potassium citrate [37].

Besides the indication for metabolic workup, the main controversy is the extent of the workup. It is important to assess minerals forming stones like calcium, oxalate, uric acid, phosphate, etc. One also needs to assess what prevents stones such as citrate and stone promoters such as sodium, since hypernatriuria leads to hypercalciuria. Extremes of urinary pH may result in the either uric acid or magnesium ammonium phosphate and calcium phosphate stones. Potassium and creatinine estimations are indicators of adequacy of the specimen and compliance with treatment. Urine microscopy indicates the presence of bacteria. Red cells and white cells indicate that there is a likelihood of not only mechanical irritation secondary to stone but also urine tract infection. The presence of crystals, like those typical of cystine, is indicative of cystinuria. The coffin-lid crystals of magnesium ammonium phosphate and the double tetrahedrons of calcium oxalate dihydrate are also indicative of these respective types of stones. Kidney stone disease is associated with so many other conditions; for example, recurrent calcium oxalate urolithiasis is associated with osteoporosis, and it is not old-age osteoporosis as it is seen in male patients aged 35 years and female patients aged only 38 years. Dexascan can identify patients who have osteoporosis versus osteopenia and normal density [38]. Stone analysis to identify the mineral contents and composition is of utmost importance.

Interpretation of the findings is the next logical step. Following analysis, stones are broadly classified into calcium-containing or non-calcium containing. In the case of calcium-containing stones, you need to measure urinary calcium excretion. For normocalciuric patients, however, one needs to look for other risk factors such as hyperuricosuria, hyperoxaluria, and hypocitraturia. For hypercalciuric patients, serum calcium and PTH levels should be performed, and the patients treated appropriately. Non-calcium stones such as uric acid, cystine or infection-related stones should be treated accordingly [39].

In an interesting study, the authors noted that the consumption of carbonated drinks (which are high in phosphoric acid) in the presence of *Proteus mirabil*is infection can cause struvite stones [40]. Residual stone becomes the nidus for stone formation. In this study by Sorensen et al. [41], the authors concluded that removal of secondary small stones at the time of primary stone removal significantly decreases the chances of relapse without increasing surgery-related complications.

Most of the patients have calcium oxalate stones, without any metabolic disorder.

8. Stone prevention; dietary components

Before embarking on to a topic as vast as the role of diet in kidney stone prevention, it is imperative to first revisit briefly some of the well-known basics about stone formation itself. Kidney stones are aggregates composed of varying amounts of crystalloid substances. While theories explaining stone formation remain incomplete at best, there is an undeniable underlying role of supersaturation of urine in stone formation. Supersaturation of urine, in turn, is dependent on three major determinants, namely solute content, solvent volume, and the pH of urine, and consequently, any factor that were to alter any of these determinants would have an eventual effect on stone formation to some degree [42]. It is also useful to be familiar with certain concepts. The first of these is solubility product, at which point the solvent has reached its limit of solute content, and a further increase in ionic content beyond this point can potentially result in crystal nucleation [43]. The reason why this usually does not occur is the basis of the second concept, namely the presence of certain urinary constituents referred to as "inhibitors", which, as their name implies, oppose the formation of stones. As with the ionic concentration, alteration of the concentration of inhibitors would likewise have an eventual effect on stone formation. While in theory ions can still aggregate at their solubility product, the likelihood of doing so increases many-fold once they attain higher concentrations, a phenomenon referred to as the formation product [44] of the salt or acid concerned. It is postulated that concentrations beyond this point are unstable and can spontaneously initiate the process of crystal formation that may lead to stones. Lastly, it is important to be aware of different ions present in urine. To recall, the most important ions for causing stones include calcium, oxalate, phosphate, uric acid, and sodium [45], while the protective ions (inhibitors) mainly include citrate, magnesium, and sulphate. Rogers et al. [46] noted that increasing urinary sulfate could theoretically reduce calcium oxalate and calcium phosphate stone risk. The detailed role of each in stone formation is beyond the scope of this chapter. With this information, let us now proceed to the role of diet in stone formation.

Dietary factors can be approached in a variety of ways. The author's preference is to divide dietary items into food items and beverage items and the resultant impact of each on stone formation. It is pertinent to remember that renal stones have been increasingly linked to obesity and arterial hypertension, and hence, diet that predisposes to these latter conditions can reasonably be associated to have an indirect relationship with stone formation.

The paucity of randomized trials on diet entails that most information on the subject is derived from cohort studies.

8.1 Beverages

The effect of an increased fluid intake is beneficial with respect to stone formation, mainly because of increased dilution of the ionic solutes, decreased supersaturation, and the resultant prevention of crystal nucleation. This inverse relationship has been demonstrated in several studies [47, 48]. However, as pointed out before, fluids that cause changes in urinary pH or ion-rich fluids can have varying effects. Most experts agree that the 24-hour fluid intake for stone prevention should be approximately 2.5 to 3 liters and that this intake be circadian rather than bolus-like at varied intervals [49]. Simultaneously, the target urine volume should be approximately 2 to 2.5 liters (higher for certain pathological conditions) [50]. While

the effects of beverage-induced reduced incidence of stone formation are attributable mainly to increased solubility of ions in urine, certain beverages including alcohol, coffee, and tea have an additional mechanism of stone prevention through promotion of diuresis with or without natriuresis. The only exception is soda, which has inconsistently been shown to increase the risk of stone formation, likely owing to its effect on the increased excretion of calcium, oxalate, and uric acid. The effect of fruit juices is mainly determined by the presence of citrate or bicarbonate and can work both ways [51] . Citric juices including lemon, orange, and grapefruit provide a high load of citrate and in theory can be a good alternate to pharmacotherapy [52]. However, fruit juices are also a source of sugar and oxalate, and hence, consumption should be limited to one glass per day, diluted in water.

8.2 Diet

One way to look at dietary factors is to employ a balanced-diet approach and avoiding excess of any food groups. However, it is helpful to elucidate the contribution of different food items to urinary ions, especially in situations where an individual is prone to forming a certain type of stone owing to an underlying abnormality.

Meat intake is significantly associated with risk of stone formation (reference!). This relationship has been consistently observed in observational studies and is attributed to higher levels of calcium, uric acid and possibly oxalate in urine, lower levels of citrate, and a lower urinary pH favoring the formation of both calcium and uric acid stones. There have been attempts to differentiate between red meat, processed meat, and poultry, and while the quality of the evidence remains low, a significant association was demonstrable with red meat while mixed results were found with poultry and fish, varying from null to a significant association. The consensus is to limit animal protein intake to 1 gram per kilogram per day [53] .

Fruits have a protective effect against stone formation owing to their citrate and potassium content. Dietary citrate is absorbed in the gastrointestinal tract and metabolized to bicarbonate, which may then increase urine pH and citrate excretion [54]. A similar effect on urine has been noted with potassium supplements [55].

Vegetables have been shown to exert the same effect as fruits, which seems to be linked to both the mechanisms linked above, or simply because a diet that is rich in vegetables is more likely to be lower in meat content. The main concern, however, is the presence of oxalate in certain vegetables such as spinach, beetroot, soya beans, and okra, all of which have the potential to cause mild hyperoxaluria with resultant stone formation. A reasonable advice is to restrict the aforementioned vegetables, however they can other leafy vegetables like cabbage, green peas, and turnip that have a lower oxalate content [56, 57].

While they are not food items in their own accord, the roles of calcium and sodium have also been well studied. Calcium complexes with oxalate in the gut to prevent its reabsorption and resultant excretion in urine. Thus, calcium intake must not be reduced, especially in people known to have hyperoxaluria, and should adhere to the recommended daily allowance of 1000–1200 mg/day [58]. Higher intake can potentially result in hypercalciuria. Sodium has been shown to be a promoter of hypercalciuria with a simultaneous decrease in citrate. While the intake of sodium should not exceed 3–5 grams per day, a reasonable rule of thumb is to avoid adding salt to food at the table [28].

While it is useful to know what the effect of a certain nutrient is, it might be difficult to individualize these nutrients in each meal. Hence, a wiser approach would be to target dietary patterns. One such program is the dietary approaches to stop

hypertension (DASH) diet. A diet rich in fruits and vegetables, and low in saturated fat, is advised. It has been shown to have a beneficial effect on the urinary composition with higher levels of inhibitors and lower levels of supersaturates [59].

As pointed out earlier in the text, dietary prevention of stone disease is a vast topic, and all aspects concerning interactions at the ionic level are beyond the scope of this chapter. However, the data can be summarized quite conveniently for the sake of better patient understanding and compliance. Circadian fluid intake with neutral pH beverages to maintain a urine output volume of 2–2.5 liters is the cornerstone of preventive measures. Patients should be encouraged to maintain a balanced diet comprising a high intake of fruits, vegetables and fiber, a moderate intake of animal protein, and a low intake of salt, while avoiding excess of any particular food group.

While the role of dietary factors in the prevention of stones is vital, it is crucial to remember that stone disease has also been linked to higher calorie intake, higher body mass index, and cardiovascular disease. Therefore, dietary recommendations should be made into consideration of an overall healthier lifestyle including exercise. Furthermore, the majority of the conclusions are drawn from large cohort studies, and stronger randomized trials will likely be needed to confirm what is already known.

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