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REVIEW

Current Dietary and Medical Prevention of Renal Calcium Oxalate Stones

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Abstract: Kidney stones refer to abnormal crystal formation that occurs in the kidney. Among a variety of components of kidney stones, calcium oxalate (CaOx) is the most common type. Despite many efforts to investigate the pathogenesis of CaOx stones, the pathogenesis remains an issue of debate. With high occurrence and recurrence, individuals with stone formation are prone to frequently consult a doctor and to be hospitalized, and the treatment of kidney stones poses a heavy burden on the patients. Concerns should be focused not only on treatment but also on prevention. Herein, we reviewed the studies on prevention methods of CaOx stones through diet, lifestyle, and medication extending until the current time frame. As hyperoxaluria is the most common metabolic disorder among CaOx stone formations, we also included several studies on the treatment and prevention of hyperoxaluria. Our objective was to outline the effective methods to prevent renal CaOx stone formation.

Keywords: prevention, kidney stone, nephrolithiasis, calcium oxalate, diet, medication, risk

Introduction

Kidney stones, or nephrolithiasis, are a common condition in urologic surgery. The majority of kidney stones consist of calcium oxalate (CaOx), with other types being phosphate struvite (which refers to magnesium ammonium phosphate stones that are usually generated by an infection with bacteria that has an enzyme called urease), uric acid, and cystine.[1,2] Stone formation does not merely involve supersaturation and deposition of crystals in urine but also involves complex interactions between crystals and cells. Despite the fact that the pathogenesis of nephrolithiasis has yet to be elaborated, several biological processes have been found to play a part in nephrolithiasis, including phagocytosis, oxidative stress, inflammation, and apoptotic cell death.[3] In addition, urine chemical properties are also associated with stone formation, such as urine volume, urine pH, urine calcium, urine magnesium, urine oxalate, and urine uric acid.[1]

Nephrolithiasis poses massive financial burdens on patients and societies because of its high prevalence and high recurrence. It has been reported that nephrolithiasis had an annual recurrence of approximately 10–23%, a 5 to 10-year recurrence of approximately 50%, and a 20-year recurrence of up to 75%.[4,5] Approximately half of pediatric patients suffer recurrence within 3 years after recovery.[6] Therefore, patients are prone to frequent visits to the hospital. The care for nephrolithiasis elicited costs to the health system of the United States of America of 5 billion dollars in 2005, and the expenditure will increase by 1.24 billion dollars annually by 2030.[7,8] The cost is increasing with the booming population and the increasing incidence of obesity, metabolic syndrome, and diabetes mellitus.[9]

The prevention of the recurrence of kidney stones has been a highly contentious issue and a considerable challenge for urologists. Unfortunately, due to the fact that our knowledge of the pathogenesis of nephrolithiasis is limited, experiments in laboratories have not yielded any specific and efficacious medications for the prevention of nephrolithiasis. To address this problem, scholars have endeavored to intervene in stone formation with the use of existing drugs and therapies, and certain therapies have been shown to be conducive to the clinical prevention of kidney stones. In this article, we reviewed the clinical studies of the past several years regarding dietary and medical prevention of CaOx stones. Our objectives are to identify gaps and limitations in the current understanding of kidney stone prevention, assess

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the effectiveness of different preventive strategies for kidney stones, and distill the strategies into practical recommendations for clinicians, patients, and the public.

The Effect of Dietary Factors

Water and Liquid Intake

Supersaturation and crystallization of salts in the urine play vital roles in stone formation. Whether supersaturation and crystallization occur mainly depends on urine volume, which influences the concentration of ions and the flow rate in nephrons. Increasing urine volume by increasing fluid intake can reduce the inclination of supersaturation and crystallization, thus curbing stone formation. Several studies have demonstrated an inverse association between fluid intake and stone formation.[10–15] Currently, liquid that is available for drinking cannot be limited to water. Total fluid intake is the sum of tea, coffee, water, and alcohol intake.[16] A cohort study using data from the UK Biobank noted that after adjusting for multiple lifestyle and socioeconomic factors, increased overall fluid intake was associated with a lower risk of kidney stones. Therefore, the guidelines of the European Association of Urology on urolithiasis (2022) recommend that stone formers should increase fluid intake to achieve a volume of diuresis of 2.0–2.5L per day.

Water quality varies from district to district, which is once suspected to play a potential role in kidney stone formation. However, this fact is not what we initially believed it to represent. Mitra et al conducted a study to evaluate whether the quality of drinking water has any effect on disease prevalence.[17] They gathered information regarding the prevalence of kidney stones and drinking water resources; additionally, they collected drinking water from the investigated water resources. They analyzed water samples for pH, alkalinity, hardness, total dissolved solutes, electrical conductivity, and salinity. However, they found that none of the examined parameters differed significantly between the case and control areas.

Beverages

Beverages are able to not only increase liquid intake but to also provide nutrients and specific flavors. Common beverages include juice, soda, coffee, tea, milk, energy drinks, and alcoholic beverages such as beer, wine, and spirits. Some beverages have been identified as affecting the risk of kidney stones. In a large prospective analysis on the association between the intake of several types of beverages and the incidence of kidney stones in three large cohort studies, sugar-sweetened soda was demonstrated to increase the risks of stone formation, whereas the consumption of coffee, tea, beer, grape wine, and orange juice could reduce the risk of nephrolithiasis.[18] Another cohort study demonstrated that higher consumption of tea [Hazard Ratio (HR) per 200mL/d = 0.95, 95% confidence interval (CI): 0.92–0.99], coffee (HR per 200mL/d = 0.92, 95% CI: 0.88–0.95), and alcohol (HR per 200mL/d = 0.85, 95% CI: 0.82–0.88) was individually significantly associated with a lower risk of incident kidney stones.[16] However, no detailed recommended volume of the beverages was provided by the authors. Regarding tea, Siener and Hesse investigated the effect of black tea consumption and the risk of kidney stones, and they found that the intake of black tea led to increased excretion of citrate, which was identified as being protective from kidney stones.[19]

Soft drinks (or sodas) are nonalcoholic, carbonated beverages. They are widely popular throughout the world for their pleasant flavor. Some soft drinks contain base and citrate. Citrate was identified as being able to effectively curb renal stone formation, and base can enhance the urine excretion of citrate.[20] Nevertheless, the consumption of soft drinks does not demonstrate a favorable effect on stone formers. Shuster et al found that abstaining from soda drink consumption could significantly reduce the recurrence of kidney stones.[21] In a prospective study, Sumorok et al found that a type of orange soda known as Diet Sunkist Orange soda failed to change the components of 24h urine in healthy volunteers.[22] However, the sample volume was relatively small, and the volume of the orange soda that was prescribed was insufficient. The volunteers found it difficult to adhere to the prescribed volume, and the larger volume may have been even more difficult to manage. The volunteers may also eat food that can interfere with the urine properties without recording and informing the researchers.[22]

The consumption of Coke is another trend among young people. Rodgers et al reported that the consumption of cola, which contains sugar and caffeine, increased the levels of urinary stone risk parameters, such as increased oxalate

excretion, decreased urine pH, and increased relative supersaturation factors.[23] Furthermore, Weiss et al reported that the consumption of this type of cola led to a reduction in magnesium and citrate excretion, as well as an increase in oxalate excretion.[24]

There is an increasing awareness of the importance of controlling blood sugar, thus leading more people to choose diet drinks because they have a lower sugar content. In a prospective study, Passman et al investigated the effect of Le Bleu® water, caffeine-free Diet Coke®, and Fresca® (citrate-containing) on kidney stone risk factors.[25] The findings demonstrated no significance in the risk parameters. A reason for this result could be that the citrate contents of the beverages were obviously lower than those of lemon, lime, grapefruit, or orange juice.[25] Previous studies have indicated that the intake of sugar- and caffeine-free cola reduced the risk of stone formation when compared to cola containing sugar and caffeine, which increased the risk of stone formation.[25,26] Another prospective blinded crossover study demonstrated that diet lemonade significantly decreased the supersaturation of urine CaOx, thus suggesting that lemonade can reduce the risk of recurrence of CaOx stones.[27]

To summarize, an adequate fluid intake of water and different beverages (except for soft drinks) and an achievement of urine volume of 2.0–2.5L are indispensable in guarding against recurrent CaOx nephrolithiasis. However, due to the lack of high-quality randomized controlled trials (RCTs) for comparing the indicated beverages, it remains unclear as to which beverages have stronger impacts on reducing the recurrence of CaOx stones.

Vegetarian Diets

A vegetarian diet focuses on plants and abstaining from eating fish, meat, and poultry. It includes a variety of healthy plant-based foods, such as whole fruits and vegetables, legumes and nuts, and whole grains. It has been demonstrated that vegetarian diets can lower the risks of cardiovascular disease, obesity, diabetes, osteoporosis, and some cancers.[28]

In studies of the association between vegetarian diets and kidney stones, the results are debatable.[29,30] Recently, Littlejohns et al found that vegetable intake was not associated with incident kidney stones (HR per 100g/d = 0.94, 95% CI: 0.87–1.03), whereas fruit intake (HR per 100g/d = 0.88, 95% CI: 0.83–0.93) and fiber intake (HR per 10g/d = 0.82, 95% CI: 0.77–0.87) were significantly associated with a lower risk of kidney stones.[16] A cohort study by Turney et al indicated a reverse association between fresh fruit consumption and risk of kidney stones (HR for the highest versus lowest third of consumption=0.70, 95% CI: 0.53–0.93; p trend = 0.03), whereas there was no association between consumption of vegetables and risk.[31] Sorensen et al found that women with a history of kidney stones had lower mean intake of fiber, fruit, and vegetables. In contrast, women without a history of kidney stones with the highest dietary fiber, vegetable, and fruit intake were 22%, 15%, and 22% less likely to report of kidney stone events, respectively.[32] These studies showed that a vegetarian diet is helpful in reducing the risk of nephrolithiasis, which is predominantly due to fruits. Particularly, fruits abundant in citric acid, such as lemons, oranges, and grapefruits, can be beneficial in reducing the risk of nephrolithiasis.[33] Citric acid helps in preventing the formation of kidney stones by binding to calcium in the urine, thus reducing the formation of CaOx crystals that can lead to stones.

Animal Proteins

Animal proteins are composed of complete proteins, thus providing us with all of the necessary amino acids. However, patients with CaOx stones should avoid excessive consumption of animal protein because excessive consumption could lead to an increase in serum uric acid, a decrease in urine pH, and an increase in urine oxalate, thus enhancing the recurrence of CaOx stones.[34,35]

In a retrospective study on females using a validated food frequency questionnaire, Meschi et al found that compared with the controls, the stone formers consumed significantly more sausages, ham, and meat.[36] Notably, after dividing the ages, the differences were augmented in participants under 30-year-old who had increased consumption of sausages, ham and meat and had less consumption of fruit and vegetables. A cohort study found that the consumption of meat was associated with the risk of kidney stone formation.[31] The HR estimates for high meat eaters (100g/day), moderate meat eaters (50–99g/day), low meat eaters (50g/day), fish eaters, and vegetarians were 0.80 (95% CI: 0.57–1.11), 0.52 (95% CI: 0.35–0.80), 0.73 (95% CI: 0.48–1.11), and 0.69 (95% CI: 0.48–0.98), respectively.[31] Furthermore, both red meat and poultry were found to have a significant association with the risk of kidney stones (HR for the highest versus lowest third

of intake: 1.53, 95% CI: 1.04–2.26 for red meat [p trend = 0.02] and 1.35, 95% CI: 0.95–1.93 for poultry [p trend = 0.04]). However, processed meat was not associated with the risk of kidney stones. Another cohort study indicated similar trends, although these did not reach statistical significance.[16]

Regarding the relative intake of animal protein, a prospective investigation found that compared to those with a high intake of meat (>100g/day), the HR estimates for moderate meat eaters (50–99g/day), low meat eaters (<50g/day), fish eaters, and vegetarians were 0.80 (95% CI: 0.57–1.11), 0.52 (95% CI: 0.35–0.8), 0.73 (95% CI: 0.48–1.11), and 0.69 (95% CI: 0.48–0.98), respectively (30). Xiang et al conducted a large study to investigate protein consumption and the risk of kidney stones based on data acquired from men and women in Shanghai, China. The findings indicated that compared with those in the lowest quintiles, subjects in the highest quintiles of animal protein intake had an increased risk of kidney stones.[37] Additionally, high animal-to-plant protein ratios were found to be positively associated with stone risk. However, the association was not observed in plant proteins.[37]

The intake of animal protein is related to urine calcium and urine urea. Rotily et al found that with adequate fluid intake, the participants with a low animal protein diet (<10% of total energy) showed a significant decrease in urea; additionally, when the decrease was more than 50mmol/day, a significant decrease in urine calcium was observed. Of note, the correlation between the output of calcium and that of urea was significant among patients with hypercalciuria.[38] However, there was no significant decrease in urine urea among patients with a high-fiber diet (>25g per day). This study suggested no evidence of scaffolding of the increase in consumption; however, there is evidence supporting the idea that idiopathic calcium stone formers could expect to benefit from a low animal protein diet.[38]

In general, the latest studies on the association between animal proteins and kidney stones are consistent with the prior findings that consuming animal proteins can increase the risk of stones.

Mediterranean Dietary Pattern

The Mediterranean dietary pattern is based on the traditional cuisines of Greece, Italy, and other countries that border the Mediterranean Sea.[39] It includes plant-based foods, such as whole grains, vegetables, legumes, fruits, nuts, seeds, herbs, and spices, which are the foundation of the diet. Olive oil is the main source of added fat. Fish, seafood, dairy, and poultry are included in moderation. Furthermore, red meat and sweets are eaten only occasionally.

Leone et al conducted a cohort study on the relationship between preference for the Mediterranean dietary style and the incidence of nephrolithiasis.[40] The baseline preference for the Mediterranean dietary style was obtained through a valid 136-item food frequency questionnaire. The subjects were identified as those with nephrolithiasis when they were reported by a physician. It was found that the risk of renal stones was lower in those with a Mediterranean dietary style (HR: 0.93 [95% CI: 0.79–1.09] with relatively lower consumption and HR: 0.64 [95% CI: 0.48–0.87] with relatively higher consumption). The Mediterranean dietary pattern was demonstrated to reduce the risk of kidney stones.

Fructose

Fructose is a type of simple sugar that naturally occurs in fruits and vegetables. Currently, it is frequently added to beverages and processed food to improve flavor. Dietary total fructose intake is identical to the intake of free fructose and to half the intake of sucrose.[41] Taylor and Curhan found that both free and total intake of fructose were associated with an increased risk of kidney stones.[41,42] The mechanism for kidney stone risk associated with fructose intake may be the conversion of fructose into glycolate, which is a precursor of oxalate.[43]

Calcium and Magnesium

Calcium is a mineral that composes bones and teeth and has vital functions such as the contraction of muscles, heart rhythms, nervous function, and blood clotting. Most kidney stones are composed of calcium salt. Hypercalciuria is a common metabolic disorder causing nephrolithiasis. Thus, a reduction in calcium intake seems useful for the prevention of stone formation. However, this fact is not entirely supported or clear.

The consumption of calcium should be restricted, and supplemental calcium is not recommended for the prevention of kidney stones. It has been found that a higher intake of dietary calcium was strongly associated with a reduced risk for kidney stones, even when the intake of supplemental calcium was associated with an increase in risk for kidney stones.[44]

Von Unruh et al found that with increasing calcium intake, oxalate absorption decreased.[45] However, a low-calcium diet can increase the risk of stone formation because the reduction in calcium ingestion causes less combination of calcium with oxalate in the gastrointestinal tract.[29] As a consequence, more oxalate is absorbed, thus increasing urine oxalate. Over the range of calcium intake from 200 to 1200mg Ca/d, the mean oxalate absorption is linear; however, when considering the whole tested range tested (ie, 200 to 1800mg Ca/d), the oxalate absorption was nonlinear.[45] Nevertheless, this study did not include an investigation of the impact on stone formation.

It is recommended that calcium supplementation be administered only in the instance of enteric hyperoxaluria. Patients with enteric hyperoxaluria can suffer from fat malabsorption, which may cause increased binding of dietary calcium by free fatty acids, thus reducing the calcium available to precipitate diet oxalate.[46] Notably, under circumstances where adults have to use supplemental calcium (such as for the prevention of postmenopausal osteoporosis), individuals should ensure adequate hydration.[47]

For stone formers with chronic kidney disease, calcium supplementation should be performed cautiously. As a daily source of calcium, milk should be limited and replaced by other food. Borin et al compared concentrations of ingredients that are key to kidney stones and chronic kidney disease in indices of milk alternatives and found relatively favorable ones. They demonstrated that oat, macadamia, rice, and soy milk compare favorably in terms of kidney stone risk factors with dairy milk, whereas almond and cashew milk have more potential stone risk factors. Coconut milk may be a favorable dairy substitute for patients with chronic kidney disease based on low potassium, sodium, and oxalate levels.[48]

Magnesium is an agonist of calcium. The two cations compete in the modulation of muscular contraction and in the regulation of several enzymatic reactions involved in energy metabolism, signal transduction, and brain activity.[49] A cross-sectional study by Wu et al demonstrated that individuals with serum magnesium levels that were lower than average (but still within the normal range) had a greater possibility of developing kidney stones in a dose-dependent manner.[50] The findings indicated that magnesium is a protective factor against stone formation. Therefore, daily supplementation with magnesium is a possible method to prevent kidney stone diseases.

Consumption of Sodium

Sodium is present in tremendous amounts in organisms. It plays pivotal roles in the maintenance of normal blood pressure, the support of the functions of muscles and nerves, and the regulation of body fluid balance. In the kidney, sodium-calcium exchangers are responsible for calcium regulation. Via the actions of the exchangers, high levels of urine sodium could lead to secondary hypercalciuria, thus facilitating stone formation. Nevertheless, the complicated interaction between the intake of sodium, especially sodium chloride, and other dietary factors has not yet been clarified.[51]

Dietary Oxalate

CaOx is the most common type among a variety of kidney stones. In CaOx stone formers, hyperoxaluria is a common metabolic disorder and an important risk of stone formation. Excreted oxalate originates from liver metabolism and the intestine. Liver metabolites are converted from vitamin C, purine, amino acids, and carbohydrates, whereas most intestinal-origin oxalate is from foods that are high in oxalate, such as leafy greens and legumes.[52] The impact of the intestinal origins of oxalate has been identified, and the limitation of excessive consumption of food with high oxalate is necessary; however, an oxalate-free diet or an exact calculation of oxalate in foods is impractical and difficult to perform.[46]

Lifestyles

The risk of kidney stone formation is also linked to lifestyle (Figure 1). Lifestyles that lead to overweight and obese conditions could increase the risk of kidney stones. In a study conducted by Siener et al, 527 CaOx stone formers, including 363 men and 164 women, were involved and examined.[53] The participants received no specific dietary instruction, and their 24h urine samples were collected. The analysis demonstrated a significant positive correlation between body mass index (BMI) and uric acid, sodium, ammonium, and phosphate, as well as a negative correlation between BMI and urine pH, in both sexes. Additionally, BMI was associated with urine oxalate only among women and with urine calcium only among

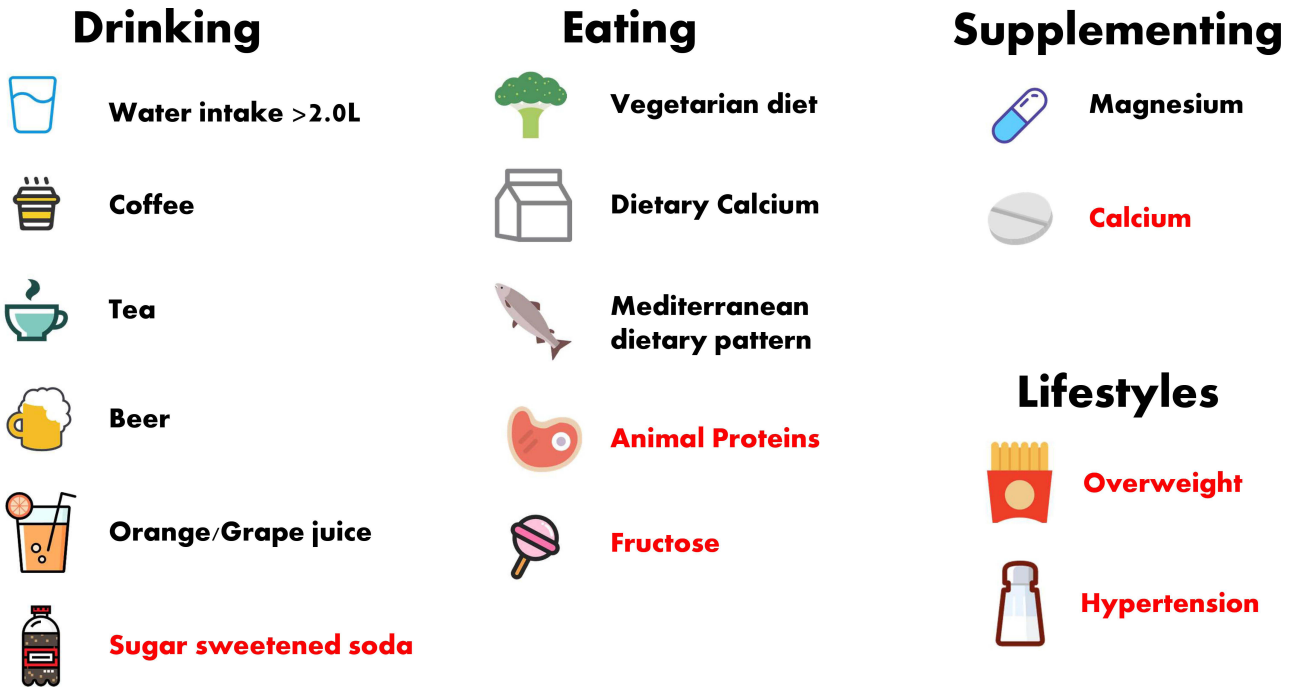

Figure 1 The dietary and lifestyle factors that influence renal stone formation. The black ones represent the ones that were reported associated with lower risk of stone formation, while the red ones represent the ones that reported associated with higher risk of stone formation.

men. Moreover, no association was found between BMI and any inhibitors of CaOx stone formation. It was demonstrated that the risk of CaOx stone formation was increased with BMI among both sexes and was higher in men.[53]

The lifestyle leading to hypertension may also influence the risk of kidney stones. A positive association between nephrolithiasis and hypertension was found in two large cohort studies conducted by Madore et al. The age-adjusted odds ratio (OR) for hypertension for men with a history of nephrolithiasis compared with those without was 1.31 (95% CI: 1.30–1.32), and for women, the OR was 1.49 (95% CI: 1.34–1.67).[54,55] Among the men who reported of both a history of nephrolithiasis and a diagnosis of hypertension, 79.5% found that the occurrence of nephrolithiasis was before or concomitant with the diagnosis of hypertension.

Medicines

In addition to dietary intervention, the prevention of stone formation with drugs is another issue that clinical practitioners are concerned with. Below are medications under discussion to prevent stone formation (Figure 2).

Alkaline Citrate

Alkaline citrate has been identified as an inhibitor of kidney stones for a long period of time. Alkaline citrate is a chemical with an anion of citrate and cation(s) of sodium, potassium, and magnesium. Alkaline citrate has been identified to effectively reduce the recurrence of kidney stones by multiple studies.[56–60]

When patients are under treatment with potassium citrate, urine pH and urine calcium phosphate should be monitored because higher pH after the administration of potassium citrate possibly contributes to the formation of calcium phosphate stones.[61] Furthermore, citrus-based beverages such as lemon juice and orange juice may increase urine citrate; however, the majority of citrate exists as citrate acid rather than alkaline citrate. Without a cation such as sodium, potassium, or magnesium, beverages will be less helpful in preventing kidney stones as alkaline citrate is able to do.[62]

Sodium Bicarbonate

Sodium bicarbonate, which is also known as baking soda, has been identified as being able to inhibit stone formation through the alkalization of urine. Pinheiro et al found that after the administration of capsules of sodium bicarbonate at

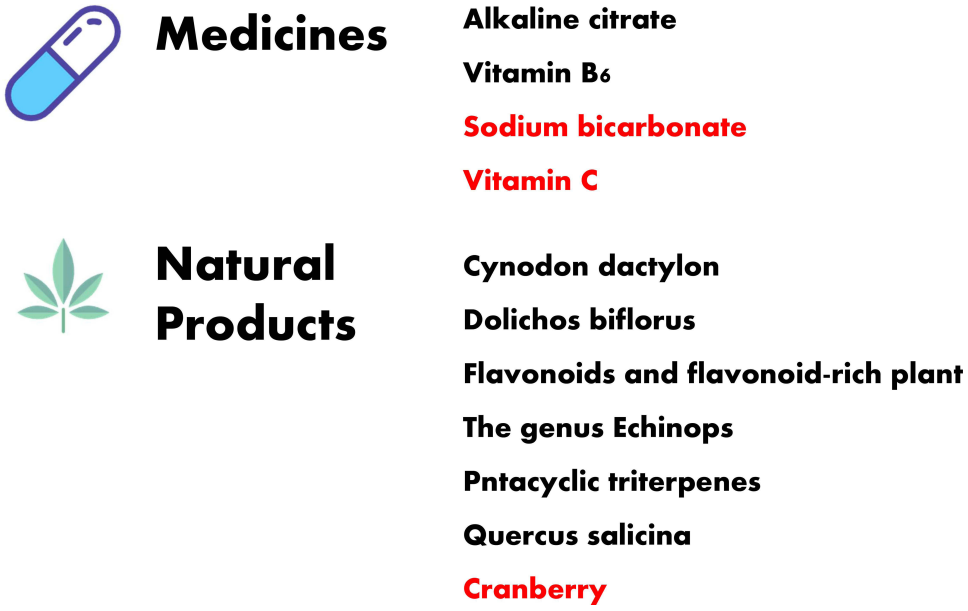

Figure 2 The medicines and natural products that influence renal stone formation. The black ones represent the ones that were reported associated with lower risk of stone formation, while the red ones represent the ones that reported associated with higher risk of stone formation.

60mEq per day for three days, there was a significant increase in urine CaOx and urine phosphate.[63] It is worth noting that such alkaline agents may increase the risk of precipitation of sodium urate and monohydrogen phosphate.[63,64]

Vitamin C

Vitamin C (or ascorbic acid) is a vital nutrient for the formation of blood vessels, cartilage, and bones, as well as for the protection of cells against free radicals. Due to the fact that the human body cannot produce vitamin C, we have to obtain it from the diet. The conversion of vitamin C to oxalate is well established, and the consumption of vitamin C has been reported to increase the excretion of urine oxalate in average people and in individuals with kidney stones, as well as to increase the risk of kidney stones in males.[65,66]

Ferraro et al conducted a prospective cohort study to investigate the relationship between total, dietary, and supplemental vitamin C intake and the risk of incident kidney stones. They observed that after multivariable adjustments, total vitamin C intake was not significantly associated with the risk of kidney stones among women but was significant among men. Supplemental vitamin C intake was not significantly associated with the risk of kidney stones among women but was significant among men (HR: 1.19 [95% CI: 1.01–1.40] for ≥1000mg/d; p trend = 0.001). Of note, dietary vitamin C intake was not associated with stones among men or women, although few participants had dietary intakes >700mg/d.[67] Therefore, EAU guidelines state that it is advisable to suggest that stone formers should avoid excessive intake of vitamin C.

Vitamin B6

Vitamin B6 is a nutrient that is abundant in poultry, fish, potatoes, chickpeas, bananas, and fortified cereals. It is also a cofactor for alanine glyoxylate aminotransferase (AGT), which catalyzes glyoxylic acid into oxalate. A deficiency of vitamin B6 may result in the conversion of glyoxylic acid into oxalate. Pyridoxine, which is a form of vitamin B6, has been demonstrated to reduce hyperoxaluria.[68–70] Regarding the effect of vitamin B6 on kidney stones, Curhan et al found that a high intake of vitamin B6 was inversely associated with the risk of stone formation.[71] However, the optimal dosage of supplemental vitamin B6 has not been confirmed. It was recommended by some scholars that when using supplemental pyridoxine, a dose of 50mg daily should initially be started, after which the dose can be titrated up to 200mg (or until a therapeutic response in urinary oxalate is observed).[72]

Vitamin E

Vitamin E is a fat-soluble nutrient that is essential to skin, sight, and reproduction. The dietary sources of vitamin E include canola oil, olive oil, margarine, almonds, and peanuts. Its antioxidative properties have been postulated to play a role in the prevention of stone formation. Recent studies have reported some anti-nephrolithiasis and renoprotective effects of vitamin E. Srinivasan et al found that among patients with renal tuberculosis, with the daily administration of vitamin E at 200 mg for 60 days, urine oxalate and urine calcium were significantly decreased, as well as biomarkers pertaining to kidney injury, such as D-lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and γ-glutamyltransferase (γ-GT).[73] Nevertheless, it was mentioned that plasma vitamin E was found to be significantly lower in patients with renal tuberculosis, and vitamin E supplementation returned the levels to normal. The decreased parameters may be attributed to restored serum vitamin E. In addition, the study did not investigate the effect of consumption of vitamin E on average people.

Vitamin E may influence stone formation in indirect ways. Kamalanathan et al found that among patients with hypertension or hyperoxaluria, the administration of vitamin E was able to decrease the interaction between Tamm-Horsfall protein (THP) and CaOx monohydrate crystals to transform the promoting effect to an inhibiting effect for both the nucleation and aggregation phases, as well as to restore the biochemical properties of THP.[74] THP is a form of inhibitor of CaOx stone formation (1). To date, no direct correlation between the consumption of vitamin E and the risk of stone formation has been investigated. There have been no guidelines recommending vitamin E as a prevention of stone formation.

Diuretics

Urine volume is an indispensable factor that influences stone formation. The elevation of urine volume through the use of diuretics can help to inhibit supersaturation and crystallization.

Thiazide diuretics are a group of diuretic medications for the treatment of hypertension and edema via the inhibition of the reabsorption of Na^+ and Cl^- in the distal ascending limb of the loop of Henle and proximal convoluted tubule and the decrease in the kidney's ability to retain water. Among thiazides, hydrochlorothiazide is the most commonly used diuretic in clinical practice. Multiple studies have reported that the administration of hydrochlorothiazide was associated with lower risks of kidney stones.[75–79] However, a recent double-blind trial by Dhayat et al demonstrated that the recurrence of kidney stones showed no significant difference (neither radiological recurrence nor symptomatic recurrence) among subjects treated with hydrochlorothiazide once daily at different doses or placebo once daily.[80] The participants were randomly assigned to receive hydrochlorothiazide at different doses (12.5mg, 25mg, or 50mg) once daily or a placebo once daily. The research included 416 individuals, and they underwent a median period of 2.9 years of observation. The occurrence of the primary endpoint event (symptomatic or radiologic recurrence of kidney stones) was compared among the placebo group and the groups receiving different doses of hydrochlorothiazide. The results showed that the rates of primary end-point events were similar across all of the groups: 59% in the placebo group, 59% in the 12.5mg hydrochlorothiazide group, 56% in the 25mg hydrochlorothiazide group, and 49% in the 50mg hydrochlorothiazide group. There were no significant differences observed between the dose of hydrochlorothiazide and the occurrence of kidney stone events (p=0.66).[80]

Another diuretic was demonstrated to be able to cause a difference. In a pilot study, Alonso et al found that long-term treatment with 1.5mg/day of indapamide resulted in significantly reduced urinary calcium, whereas serum urate was increased.[81]

Allopurinol and Febuxostat

Up to 10% of calcium stone formers have high levels of urine uric acid as an isolated abnormality; however, it has been found in combination with other metabolic abnormalities in up to 40% of calcium stone formers.[82] The pathogenesis in which hyperuricosuria induces CaOx stones has not been clarified, whereas drugs for hyperuricosuria have been utilized for the prevention of calcium stone formation.

Allopurinol and febuxostat are common medications that are used to treat hyperuricosuria and gout. It has been identified to be effective in preventing stone formation, reducing stone events, and prolonging the time before

recurrence.[83–85] A pilot study compared the effect of febuxostat versus allopurinol on calcium stone formation.[86] The effects of febuxostat and allopurinol were demonstrated to play similar roles in patients with idiopathic calcium nephrolithiasis and high excretion of urine uric acid. Moreover, an RCT made a similar comparison and found that febuxostat decreased urine uric acid more significantly than allopurinol in stone formers with high urine uric acid excretion.[87]

Empagliflozin

Empagliflozin is a novel drug for diabetes mellitus. It works by blocking the sodium-glucose cotransporters in the proximal tubular epithelium. Recently, a retrospective study enrolling 15,081 patients with type 2 diabetes demonstrated that treatment with empagliflozin reduced the risk of urolithiasis in patients with type 2 diabetes by approximately 40%, thus suggesting that empagliflozin could prevent stone formation.[88] Nevertheless, the conclusion of the study requires further verification via prospective studies or RCTs. Additionally, the enrolled population included those with type 2 diabetes instead of a population representing the general population with urolithiasis or nephrolithiasis. Several disorders that are found in those with diabetes, such as glycosuria, being overweight, and obesity, could contribute to stone formation, and stone formation can possibly be inhibited through the alleviation of the primary disorders.

Natural Products

Cranberry is a shrub and was historically used as a deterrent to infection in the bladder and kidney. A small study showed that cranberry supplementation was followed by an increased excretion of oxalate. Additionally, the majority of commercially available cranberry tablets are fortified with vitamin C.[89] A previous study by Redmond et al investigated the impacts of cranberry supplements with and without vitamin C on the risk of kidney stones. Their findings indicated that supplementing cranberry with vitamin C was associated with significantly higher urinary oxalate excretion and Tiselius index (which is proposed by Professor Hans-Göran Tiselius and used for evaluating the risk of CaOx crystallization), whereas supplementing cranberry without vitamin C was associated with a significantly higher Tiselius index.[89] Therefore, stone formers should avoid cranberry supplementation.

Some natural products can exert their preventative effects by increasing the excretion of kidney stones. Black seed is one of the traditional Persian medicines that are utilized for the treatment of urinary stones and is reported to act as a diuretic and a medicine for urinary retention.[90] It was shown that black seed had preventative and therapeutic effects on renal stones and renal damage.[90–92] A randomized controlled trial by Movaghati showed that 44.4% of patients who received black seed treatment completely excreted their stones, whereas 15.3% of patients in the placebo group achieved the same outcome.[90] Moreover, they observed a more significant reduction in renal stone size after treatment in the black seed group than in the placebo group.[90] In another randomized double-blind controlled trial, Cynodon dactylon (Poaceae family) and Dolichos biflorus (Fabaceae family) extracts were identified to be able to decrease the size of the kidney stone and to increase kidney stone excretion.[93]

In addition to the abovementioned products, natural products (such as flavonoids and flavonoid-rich plant extracts, extracts of the genus Echinops, pentacyclic triterpenes, and Quercus salicina) were reported to be effective in preventing kidney stones.

Medication for Hyperoxaluria

Hyperoxaluria is an important metabolic disorder contributing to CaOx stones in the kidney. Alleviation of hyperoxaluria could make a difference in the prevention of oxalate stone formation.

Oxalobacter Formigenes Supplements

Oxalobacter formigenes is an anaerobic bacterium that is able to degrade oxalate in the intestinal lumen. It plays an essential role in enhancing oxalate homeostasis and in preventing hyperoxaluria in humans. Supplemental *O. formigenes* are a promising choice for the prevention of nephrolithiasis.

Bernd et al conducted an RCT to evaluate the therapeutic effect of *Oxalobacter formigenes* OC5 on primary hyperoxaluria.[94] In this study, those with primary hyperoxaluria had high tolerance and no adverse reactions under the

oral administration of OC5. After 8 weeks of treatment, the patients' urine oxalate excretion and serum oxalate concentration were not significantly different between the groups. Afterwards, Bernd et al evaluated the therapeutic effect of *O. formigenes* OC3 on hyperoxaluria.[95] The oral administration of *O. formigenes* OC3 caused no significant reduction in urine oxalate. However, Ankush et al found that with 1-month treatment, the proportion of hyperoxaluria in those under treatment with magnesium potassium citrate decreased from 77.5% to 37.5%, whereas that of those treated with *O. formigenes* decreased from 82.5% to 15%.[96] *O. formigenes* showed the effect of decreasing the incidence of hyperoxaluria (Figure 3).

Oxadrop is another type of *Oxalobacter formigenes* supplement. John et al found that the 24-hour mean urine oxalate of patients treated with placebo decreased from 73.9mg to 72.7mg, whereas that of patients treated with Oxadrop had no significant decrease from 59.1mg to 55.4mg. This was not consistent with the therapeutic effect of Oxadrop on hyperoxaluria shown in previous studies.[97]

ALLN-117

ALLN-117 is an oral oxalate-specific enzyme that degenerates oxalate in the gastrointestinal tract. A double-blind RCT in Phase 1 investigated the therapeutic effect of ALLN177 on hyperoxaluria.[98] The patients were induced and maintained with hyperoxaluria through a high oxalate, low calcium diet. It was found that compared to the patients receiving a placebo, the administration of ALLN117 significantly reduced urine oxalate excretion, which is not associated with treatment period allocation or any significant difference in urine calcium, citrate, magnesium, uric acid, pH, and urine volume. This enzyme shows promise and is worth an in-depth investigation of its impact on stone formation.

Stiripentol

Stiripentol is an anticonvulsant medication that is used to treat Dravet syndrome (which is a serious genetic brain disorder) through the inhibition of the isozyme of neuron lactose dehydrogenase 5 (LDH5). LDH5 is a vital enzyme in the synthesis of oxalate in the liver. When this enzyme is inhibited, endogenetic oxalate can be reduced; thus, stone formers may benefit from the effect. Dudal et al conducted a thorough investigation on the effect of stiripentol on urine oxalate excretion and oxalate nephrolithiasis. They found that in comparison with the controls, children with Dravet syndrome who needed stiripentol treatment had significantly lower urine oxalate excretion. In addition, they reported that a 17-year-old girl with severe type 1 hyperoxaluria had a reduction in urine oxalate excretion by 75% after treatment with stiripentol for several weeks. However, the introduction of Stiripentol to average individuals may be very difficult due to its multiple adverse effects, including loss of appetite, weight loss, insomnia, drowsiness, ataxia, hypotonia, and dystonia.[99]

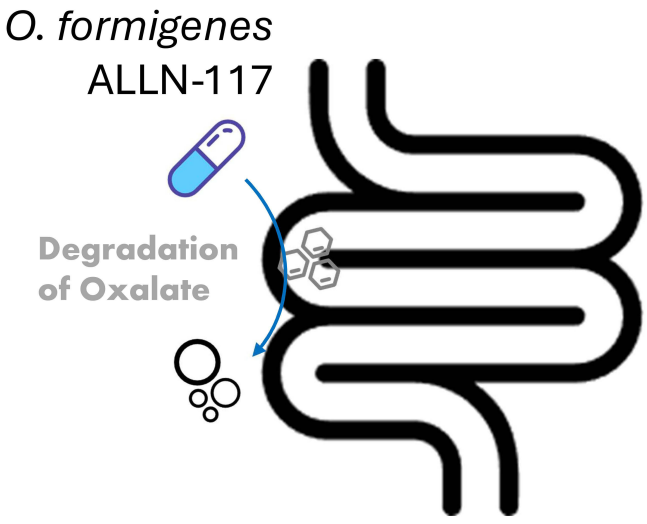

Figure 3 Medicines that play a role in reducing absorption of oxalate in the intestine. *O. formigenes: Oxalobacter formigenes*.

Table 1 Factors Associated with Risk of Renal Stone Events

Factor	Authors	Year	Association with Risk of Renal Stone Events
Fluid intake	Bao Y, et al	2012[10]	Negative
	Cheungpasitporn W, et al	2016[11]	Negative
	Sarica K, et al	2006[12]	Negative
	Curhan GC, et al	2004[14]	Negative
	Taylor EN, et al	2004[15]	Negative
Tea, coffee and alcohol	Littlejohns TJ, et al	2020[16]	Negative
Black tea	Siener R, et al	2021[19]	Negative
Sugar- and caffeine-free cola	Passman CM, et al	2009[25]	Negative
Fruit, vegetable and fiber intake	Littlejohns TJ, et al	2020[16]	Negative
	Turney BW, et al	2014[31]	None
	Sorensen MD, et al	2014[32]	Negative
Sausage, ham, meat	Meschi T, et al	2012[36]	Positive
Animal proteins	Turney BW, et al	2014[31]	Positive
	X S, et al	2019[37]	Positive
Processed meat	Turney BW, et al	2014[31]	None
A low animal protein diet	Rotily M, et al	2000[38]	Negative
Mediterranean dietary pattern	Leone A, et al	2017[40]	Negative
Fructose	Asselman M, et al	2008[41]	Positive
	Taylor EN, et al	2008[42]	Positive
A low calcium diet	Dussol B, et al	2008[29]	Positive
Serum magnesium	Wu J, et al	2020[50]	Negative
Lifestyle leading to overweight; high Body Mass Index	Siener R, et al	2004[53]	Positive
Alkaline Citrate	Soygür T, et al	2002[59]	Negative
	Lojanapiwat B, et al	2011[60]	Negative
Sodium bicarbonate	Pinheiro VB, et al	2013[63]	Positive
	Moe OW, et al	2011[64]	Positive
Vitamin C	Baxmann AC, et al	2003[66]	Positive
	Ferraro PM, et al	2016[67]	Positive
Hydrochlorothiazide	Dhayat NA, et al	2023[80]	None
Allopurinol and febuxostat	Nouvenne A, et al	2013[86]	Negative
Empagliflozin	Balasubramanian P, et al	2022[88]	Negative

Conclusion

We summarized the current prevention of CaOx stones in terms of diet, lifestyle, and medication (Table 1). Dietary and lifestyle interventions are the most fundamental and critical options for prevention; however, debates still exist. Medication interventions are commonly employed in patients with relative metabolic abnormalities. At present, the exploitation of medications for the prevention of renal CaOx stones mainly involves the targeting of modifications of oxalate crystallization, oxidative stress, and inflammation. However, thus far, the methods of prevention have been extremely limited. There are only two methods that have been identified as being clinically effective and utilized to prevent renal CaOx stones: increasing water intake to 2.0L per day and the administration of alkaline citrate. In addition, this evidence mainly originated from the early literature. Novel RCTs with larger sample sizes and more advanced trial designs are needed to in the future to further identify the protective effects.

Compliance with Ethical Standards

This article does not contain any studies with human participants or animals performed by any of the authors.

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Disclosure

The authors declare that they have no competing interests in this work.

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