

NEPHROLOGY

Rounds™

Diet and the Prevention of Kidney Stones

By GARY C. CURHAN, MD, SCD

Nephrolithiasis is a frequent, painful, costly, and increasingly prevalent condition. Although substantial strides have been made in the past two decades in the urologic approach to treatment and removal of existing stones, important new information on stone prevention has also appeared. Dietary factors have long been suspected to play a role in stone formation and recent studies provide data that can be used in advising patients. While primary prevention of nephrolithiasis is not of sufficient priority, prevention of recurrent stone formation demands greater attention. This issue of *Nephrology Rounds* reviews the epidemiology of stone disease and focuses on the role of dietary factors in stone formation. Dietary recommendations tailored to the individual patient may substantially reduce the likelihood of stone recurrence.

Scope of the problem

Nephrolithiasis is a major cause of morbidity involving the urinary tract. The prevalence of nephrolithiasis is increasing as demonstrated by the changes between two consecutive National Health and Nutrition Examination Surveys (NHANES II and III; Figure 1).¹ The prevalence is increasing in men and women, whites and blacks. The total number of physician office visits for stone disease nearly doubled from 950,000 visits in 1992 to 1,825,000 in 2000.² Despite the increases in prevalence and office visits, the estimated costs have remained stable at ~\$2 billion dollars per year, likely due to the shift from inpatient to outpatient procedures.²

Over 85% of stones in men and 70% in women contain calcium,^{3,4} most commonly as calcium oxalate. Less than 10% of stones in men and 25% in women may be attributed to urinary tract infection or systemic disorders such as hyperparathyroidism. Other types of stones (eg, cystine, uric acid, and struvite) are much less common; however, these types of stone also deserve careful attention, since recurrences are common.

A kidney stone may form when the concentration of urinary constituents exceeds their solubility. Hypercalciuria, hyperoxaluria, and hyperuricosuria are all common conditions that promote calcium oxalate crystal formation. Under normal conditions, natural urinary inhibitors such as citrate help maintain the stability of the saturated solution to prevent crystal formation.

For men, the first episode of renal colic is most likely to occur between the ages of 30 and 60.^{3,5,6} The incidence rate for men who have never had a stone is approximately 3 cases/1000 men/year between the ages of 30-60 and then slowly falls with age. For women, the risk may be higher between the ages of 20 to 30 (~2/1000 women/year) and then falls to ~1/1000 women/year for the next 4 decades.^{3,6-8} Recurrences after the first stone are common and, if untreated, up to 50% of patients may experience a recurrent stone within 10 years of the initial episode. More recent evidence suggests that even simple interventions, such as increasing fluid intake, can substantially reduce the likelihood of recurrence.

The reasons for the rising prevalence of stone disease are unclear. However, epidemiologic and physiologic studies have focused attention on dietary habits and their potential role in the development of nephrolithiasis.

Diet and stones

Nutrients vs food

People eat food, but most studies have focused on nutrients. From an etiologic perspective, it is reasonable to focus on nutrients. However, foods are a complex mixture of nutrients and the content and bioavailability of the component nutrients are known to vary. In addition, there may be other factors of importance in foods that influence stone formation. This is an essential point that emphasizes the importance of studying actual stone events and not just changes in

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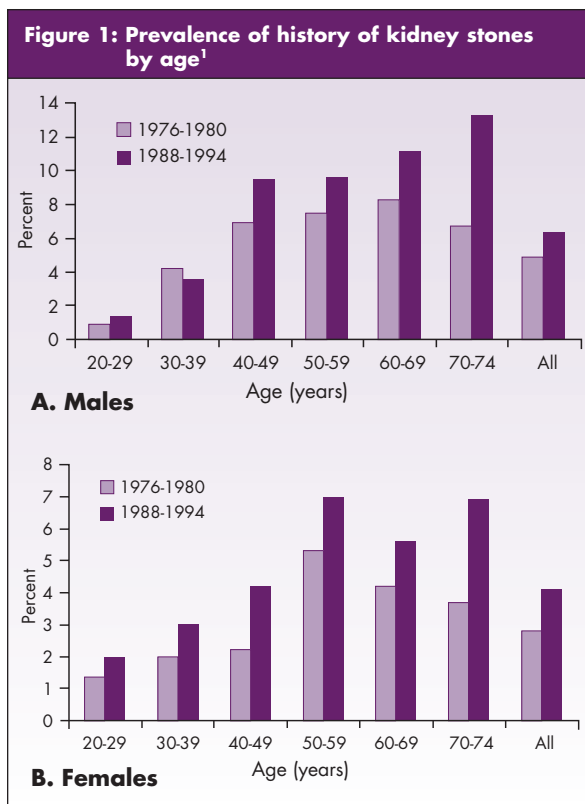
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urine composition. Many physiologic studies have examined changes in urine composition after dietary interventions and predictions about stone formation are then made based on the urinary changes. While urine composition does correlate with stone formation, it is by no means perfectly predictive. Thus, it is necessary to examine actual stone formation to be certain about the aggregate impact of dietary factors. For example, dairy products are the main source of dietary calcium, but they could also contain other factors that influence stone risk. In addition, because of common dietary patterns, it is necessary to adjust for other dietary factors to identify the independent association of an individual food or nutrient.

Stones other than calcium oxalate

For the less common types of stones (uric acid, struvite, and cystine), there is little or no information concerning the influence of dietary factors on actual stone formation (and not simply changes in urine composition).

Uric acid stones: Higher animal protein intake may influence the risk of uric acid stone formation in 2 ways. First, common foods containing animal protein are meat, chicken, and seafood. Consumption of these foods may lead to increased uric acid production due to the purine content of animal flesh. Second, animal protein contains more sulfur-containing amino acids and their metabolism leads to increased acid production with a subsequent lowering of urinary pH. Both increased uric acid excretion and lower urine pH increase the risk of uric acid crystal formation. A higher intake of fruits and vegetables, which are high in potential bases such as citrate, may raise urine pH, thereby reducing the risk of uric acid crystal formation.

Cystine stones: Higher sodium intake may increase urine cystine excretion. Because the solubility of cystine increases as pH rises, a higher consumption of fruits and vegetables may be beneficial for increasing urine pH. Although it has been suggested that cystine-containing foods should be restricted (ie, animal protein), there is little evidence that this reduces urine cystine excretion. However, reducing animal protein intake may be beneficial for raising urine pH.

Struvite stones: Because struvite stones only form in the setting of an infection in the upper urinary tract with urease-producing bacteria, it is very unlikely that dietary factors directly influence struvite stone formation.

Calcium phosphate stones: Information on dietary factors related to actual calcium phosphate stone formation is limited. However, based on known physicochemical aspects, nutrients that might influence calcium phosphate crystal formation include higher calcium intake (resulting in higher urinary calcium excretion), higher phosphate intake (resulting in higher urinary phosphate excretion), and higher intake of fruits and vegetables (resulting in a higher urinary pH, since these crystals form more readily at higher pH levels). Nevertheless, caution is advised as these “theoretical” benefits may not be realized and there are, of course, other reasons to maintain an adequate intake of calcium, fruits, and vegetables.

Calcium oxalate stones are the most common type of stone and most of our knowledge about dietary factors relates to this stone type. At this point, it should be mentioned that much of the dietary information comes from observational studies of incident stone formation. However, there are also limited, but very important data from randomized trials with recurrent stone formation as the endpoint.

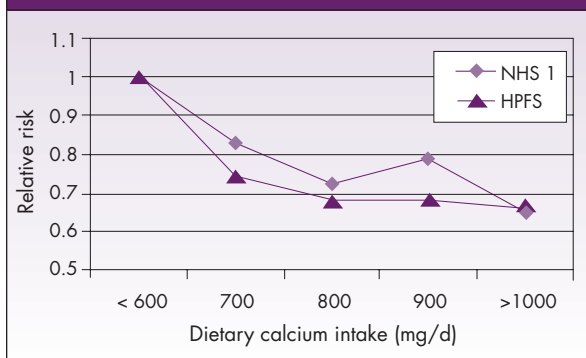
Nutrients

Dietary calcium

Historically, dietary calcium was believed to increase the risk of calcium oxalate nephrolithiasis. As a consequence, “stone formers” were advised to restrict their dietary calcium intake to prevent stone recurrence. Although dietary calcium restriction can decrease urinary calcium excretion in stone formers with and without hypercalciuria,⁹ there are no published data that demonstrate a decrease in the rate of stone formation. In fact, a low-calcium diet leads to increased dietary oxalate absorption in the gastrointestinal tract, and thereby increased urinary oxalate excretion.⁹ There are now a substantial amount of data suggesting that dietary calcium restriction may not be beneficial and, in fact, may be harmful.

Three prospective observational studies involving >200,000 individuals found that a higher dietary calcium intake was associated with a reduced risk of incident stone formation (Figure 2). The subjects were participants in ongoing longitudinal studies of diet and disease: Nurses’ Health Study I (~90,000 women),¹⁰ Nurses’ Health Study II (~90,000 younger women),⁸ and the Health Professionals Follow-up Study (~45,000).⁵ These findings for dietary calcium were independent of other dietary factors and fluid intake. For subjects in the highest quintile of dietary calcium intake, the risk of incident stone formation was >30% lower

Figure 2: Relative risk by dietary calcium intake^{5,10}



NHS = Nurses Health Study
HPFS = Health Professionals Follow-up Study

compared to subjects in the lowest quintile (Figure 2). Another observational study that included 27,000 Finnish male smokers found no association between calcium intake and risk of stone formation.¹¹ However, the median calcium intake in the “low-intake” referent group was 860 mg/day, thus the deleterious effect of a low-calcium diet may have been obscured. Nonetheless, no increase in risk was observed with higher dietary calcium intake.

A recent, randomized controlled trial in Italy studied 120 men who had recurrent calcium oxalate stones and elevated urinary calcium excretion.¹² Half of the men were randomized to the usual advice, including increased fluid intake and a dietary calcium intake of 400 mg/day (the classic low-calcium diet). The other half was randomized to low animal protein, low sodium, and a calcium intake of 1200 mg/day. At 5 years, the men in the low-calcium group were twice as likely to have experienced a recurrence compared with the men in the low animal protein, low sodium, and higher calcium group. Although this trial did not directly compare “low” vs “normal” calcium intake, there was no evidence that the low-calcium diet was beneficial.

The mechanism by which dietary calcium reduces the risk of stone formation is unknown, but may be related to the impact on dietary oxalate absorption. A higher calcium intake has been shown to reduce dietary oxalate absorption and thereby, lower urinary oxalate excretion.^{13,14} However, it is also quite possible that there is some other protective factor in dairy products, the major source of dietary calcium.

Supplemental calcium

The role of supplemental calcium is less clear than dietary calcium. There are no randomized trials of calcium supplement use with actual stone formation as the outcome. The observational data suggest that calcium supplement use may increase the risk of incident stone formation in older women by ~20%.¹⁰ Because the absolute risk of incident stone formation in an older woman is 1/1000/year, the absolute risk of stone formation in a woman who has never had a stone and takes a calcium supplement would only be 1.2/1000/year. Thus, calcium supplement use is a rare cause of incident stone formation. However, for an individual who has already had a stone, the risk of supplement use is

Table 1: Partial list of oxalate content of foods*

Food	mg of Oxalate Serving size in parentheses
Spinach, cooked	608 (1/2 cup)
Rhubarb, frozen	570 (1/2 cup)
Spinach, chopped raw	361 (1 cup)
Green beans, steamed	45 (1 cup)
Bran flakes	40 (1/2 cup)
Peanuts	27 (1 oz)
Potato, microwave	25 (1 medium)
Celery	25 (1 stalk)
Tea, brewed	18 (1 cup)
Chocolate	16 (1 oz bar)
Peanut butter	15 (1 Tbsp)
White bread	5 (1 slice)
Carrots, raw	4 (1 carrot)
Potato chips	3 (1 serving bag)
White rice, steamed	3 (1 cup)
Peaches, canned	1 (1/2 cup)
Broccoli, steamed	1 (1/2 cup)
Strawberry jelly	1 (1 Tbsp)
Apple, raw	0.7 (1 fruit)
Corn flakes	0.6 (1 cup)

*These are the values from the Channing Laboratory nutrient database. The values have been obtained from a variety of sources, including reference.¹⁵

likely to be substantially higher. It would be prudent to collect a 24-hour urine while taking the supplement and then repeating it after stopping the supplement to determine if the supplement adversely affected urine composition.

The apparent contradiction between the protective effect of dietary calcium and the detrimental effect of supplemental calcium may be due to differences in the timing of ingestion. In observational studies, the majority of supplement users did not take their supplement with meals, or only took it with breakfast when the oxalate content of the meal is likely to be low. If the calcium supplement were not taken with meals containing oxalate, a protective effect would not be expected. Rather, the observed increase in risk might be due to increased urinary calcium excretion without any change in urinary oxalate excretion.

Oxalate

Oxalate is found in small amounts in many foods and less commonly, may be present in moderate to large amounts in a limited set of foods. Unfortunately, measurements of the oxalate content of foods have varied widely due to differences among laboratories and analytic methods. A few investigators have used modern methods to measure the oxalate content of foods.¹⁵ A partial list of foods and their oxalate content is shown in Table 1. However, not all foods have been analyzed, and there can be substantial differences in the content of the same type of food depending on the growing conditions. It should be remembered that the actual oxalate content of a food might not accurately determine risk since the bioavailability of oxalate may vary substantially. Finally, the relative contribution of endogenous and exogenous oxalate sources to urinary oxalate excretion

remains a matter of debate. Clearly, calcium can influence the absorption of dietary oxalate, and other factors may be important (eg, magnesium). The lack of extensive and valid information on the oxalate content of foods has precluded the analysis of the role of dietary oxalate on the risk of stone formation in observational studies. In the Italian randomized trial (mentioned above),¹² urine oxalate fell 22% in the normal-calcium, low-protein treatment group after 1 week and remained at this level for the duration of the study. The decrease could have resulted from the higher dietary calcium intake (with increased binding of dietary oxalate in the gut).

A recent study examining the impact of diet on urinary oxalate found that high urine oxalate predominantly results from increased endogenous production.¹⁶ In addition, the findings suggest that urine oxalate excretion increases with higher fluid and vitamin C intake (see below), and decreases with increasing calcium intake. The reason for the positive correlation between oxalate excretion and fluid intake deserves further investigation because increased fluid intake is a nearly universal recommendation for stone prevention.

Animal protein

Animal protein intake may increase the risk of stone formation as a result of increased excretion of calcium and uric acid and a decreased excretion of citrate.¹⁷ Observational data suggest a slight increase in risk of incident stone formation with higher animal protein intake in men.⁵ A randomized dietary intervention trial found that those participants on a low animal protein-high fiber diet had a surprising 6-fold increase in risk of recurrence.¹⁸ However, methodological problems and an unexpectedly low recurrence rate in the control group limit the interpretation of these findings.

Potassium

A higher intake of dietary potassium may reduce the risk of stone formation by reducing urinary calcium excretion¹⁹ and, due to the higher alkali content of potassium-rich foods, by increasing urinary citrate. Two observational studies found that the risk of stone formation decreased substantially with increasing dietary potassium intake.^{5,10} There are no randomized trials of prescribed dietary potassium intake and risk of stones. The randomized trials of potassium citrate supplementation demonstrated a protective effect.^{20,21}

Sodium

A high sodium intake leads to increased urinary calcium excretion independent of calcium intake, apparently due to the inhibition of sodium and calcium reabsorption in the proximal tubule and along the loop of Henle.²² Observational studies have found an increased risk of stone formation in women with higher sodium intake,¹⁰ but not in men.⁵ The differences may be due to true differences in risk factors or an

incomplete assessment of sodium intake. The Italian randomized trial observed a reduced risk of recurrence in the group assigned to the high calcium, reduced animal protein, and reduced sodium diet.¹² Interestingly, the urinary calcium and sodium excretion decreased substantially in the high-calcium, low-sodium treatment group, suggesting that a higher sodium intake may contribute to elevated calcium excretion.

Sucrose

Although it has been known for over 30 years that sucrose and other refined carbohydrates may increase calciuria independent of calcium intake,²³ the mechanism remains unclear. In the 2 observational studies involving women,^{8,10} higher sucrose intake was independently associated with an increased risk of stone formation, but no association was found in men.⁵

Vitamins

Vitamin C (ascorbic acid) in large doses has been implicated as a risk factor for calcium oxalate stone formation. *In vivo*, ascorbate is metabolized to oxalate, which is then excreted in the urine. Several short-term feeding studies observed increased oxalate excretion and calcium oxalate supersaturation with high-dose (2 g/day) vitamin C.²⁴ A large cross-sectional study found a slightly increased risk of stone disease in men and women taking vitamin C supplements.²⁵ In prospective observational studies, no association with a risk of stone formation was observed for vitamin C intake, even among those with intakes >1500 mg/day.^{26,27} However, the relatively high intake in the referent groups may have reduced the ability to detect smaller differences. Thus, it is still possible that high-dose vitamin C increases the risk of stone formation.

Vitamin B₆ (pyridoxine) has been helpful in reducing urinary oxalate excretion in some patients with primary hyperoxaluria. However, the role of pyridoxine in reducing oxaluria in kidney stone patients with mildly elevated urinary oxalate levels is less clear. Observational studies found no decrease in the risk of stone formation in men with high pyridoxine intake, but a significant reduction in risk was observed in women consuming >40 mg/day.^{26,27} Further work clearly needs to be done to define the potential role of pyridoxine as a preventive agent.

Fatty acids

In short-term studies, fish oil supplementation (predominantly eicosapentanoic acid) decreased urinary calcium excretion in individuals with idiopathic hypercalciuria.^{28,29} High-dose fish oil supplementation for 8 weeks in 12 hypercalciuric stone formers lowered urinary calcium excretion by 36% and oxalate excretion by 51%.^{28,29} In another study, subjects with idiopathic hypercalciuria who exhibited erythrocyte ion transport abnormalities had differences in the plasma and erythrocyte membrane lipid composition com-

Table 2: Multivariate relative risks (per 240 ml) for consumption of specific beverages and risk of incident kidney stones^{33,34}

Beverage	Relative risk
Coffee	0.90
Tea	0.89
Beer	0.80
Wine	0.60
Grapefruit juice	1.40

pared with healthy controls.³⁰ The work by this group and others suggests that a subgroup of individuals with hypercalciuria may be characterized by a systemic defect in phospholipid arachidonic acid levels correctable with high-dose fish oil supplementation. There are no published observational data or randomized controlled trials that have examined actual stone formation rates rather than solely changes in urinary composition.

Fluid intake

Patients with stone disease are routinely advised to increase their urine volume, by increasing their fluid intake, in order to decrease the likelihood of recurrence. Observational studies of incident stone formation^{5,8,10} and a randomized controlled trial³¹ for recurrent stone formation convincingly demonstrated that higher fluid intake reduces the risk of stone formation. By increasing urine volume, the supersaturation of calcium oxalate falls, thereby reducing the likelihood of crystal formation.

Specific beverages

Although it is generally accepted that active stone formers should try to increase their fluid intake, limited information is available on the differential impact of individual beverages. Case-control³² and cross-sectional²⁵ studies have suggested a decreased risk for coffee and alcoholic beverages and an increased risk for carbonated beverages; the findings for tea were contradictory. Unfortunately, these studies did not control for other important potential confounders. Two prospective observational studies examined the association between the intake of 21 different beverages and the risk of incident stone formation and controlled for other potential confounders.^{33,34} Specifically, these two studies addressed whether any of the beverages had an additional impact on risk beyond simply increasing fluid intake. Consumption of caffeinated and decaffeinated coffee, tea, beer, and wine reduced the risk of symptomatic kidney stones, whereas grapefruit juice consumption increased the risk (Table 2). In contrast to previous reports, carbonated beverages were not independently associated with a risk of stone formation after adjusting for other dietary factors such as calcium, animal protein, and sodium. The protective effect of coffee and tea may be mediated through interference of caffeine with the action of antidiuretic

hormone (ADH) in the distal nephron. Alcohol may reduce the risk by inhibiting ADH secretion. The mechanism for the increased risk observed for grapefruit juice is unknown. A metabolic study examining changes in urine composition predicted that grapefruit juice should reduce the risk of stone formation by increasing urinary citrate.³⁵ This once again demonstrates that foods may have unknown effects and emphasizes the importance of studying actual stone formation rather than calculating the likelihood of crystal formation. Finally, a small, short-term study suggested that homemade lemonade is an effective approach to increase urinary citrate in individuals with hypocitraturia,³⁶ but it has yet to be shown that this translates into reduced likelihood of stone recurrence.

Conclusions

Dietary factors clearly play an important role in the etiology of many types of kidney stones. While general recommendations on dietary modification are helpful at a population level, recommendations for a patient should be tailored to that individual based on:

- Urine chemistry (eg, do not prescribe a low-oxalate diet to a patient who already has low urinary oxalate)
- Urine volume: give specific instructions about how much more they should drink beyond current intake
- Verification: recheck urine chemistries after the initial advice is given to see if the dietary changes have modified the urine composition as desired. If not, the recommendations should be modified and urine chemistries should be rechecked by 24-hour collection.

We have an obligation to inform and educate patients and physicians that kidney stones can be prevented. While primary prevention is neither practical nor relatively important, secondary prevention has been shown to be safe, effective, and money-saving.³⁷ Diet modification may be an important aspect of secondary prevention.

Dr. Gary C. Curhan is an Associate Professor of Medicine, Harvard Medical School and an Associate Physician, Renal Division, Brigham and Women's Hospital.

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