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Epidemiology of Stone Disease

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Abstract

Epidemiology has improved our understanding and management of stone. These types of studies have quantified changes in patterns and burden of disease, while identification of risk factors has changed clinical practice and provided insight into pathophysiologic processes related to stone formation. Because nephrolithiasis is a complex disease, an understanding of the epidemiology, particularly the interactions among different factors, may help lead to approaches that reduce the risk of stone formation.

Epidemiology is defined as the study of the distribution and determinants of disease. Epidemiology can help with the understanding and management of stone disease in several ways. First, epidemiologic studies can quantify changes in patterns and the burden of disease. Second, identification of risk factors in large epidemiologic studies may provide insight into pathophysiologic processes related to stone formation. Third, these types of studies allow examination of the interaction between factors, such as different dietary factors or gene-environment interactions. Because nephrolithiasis is a complex disease, an understanding of the epidemiology, particularly the interactions among different factors, may help lead to approaches that reduce the risk of stone formation.

Prevalence

Stone disease is common with the lifetime risk of stone formation in the US exceeding 12% in men and 6% in women[1,2]. However, the prevalence of nephrolithiasis, defined as a history of stone disease, varies by age, sex and race. The prevalence appears to have increased in the last quarter of the 20th century for men and women, black and whites[2] (See Figures 1 and 2). While this increase may be real, another possibility is that it was due to increased detection of asymptomatic stones due to the increasing use and sensitivity of imaging studies. Prevalence of stone disease has also increased in other parts of the world including Japan[3] and Germany [4].

Stone disease prevalence within the US varies by racial background[2,5]. A history of stone disease is most common among older white males (~10%), and lowest in younger black females (~1%). The prevalence in Asians and Hispanics falls somewhere in between.

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Prevalence of stone disease also varies by geographic location within the US. A study of over 1 million individuals found a north-south and west-east gradient such that the highest prevalence of stone disease occurred in the Southeastern US[6].

Incidence

Several population-based studies have demonstrated that incidence rates, defined as the onset of an individual's first kidney stone, vary by age, sex and race. As with prevalence, the incidence rates are highest in white males. For men, the incidence begins to rise after age 20, peaks between 40 and 60 years at ~3/1000/yr and then begins to decline[1,7,8]. For women, incidence rates seem to be higher in the late 20's (2.5/1000/yr) and then decreasing to 1/1000/yr by age 50. This rate then appears to remain relatively constant for the next several decades [1,8–10].

Although earlier studies suggested that incidence rates were rising in the US, a recent study from Rochester, Minnesota suggests that this trend may be changing. Using the same methodology as a study done 30 years earlier that showed increasing incidence rates in men and women between 1950 and 1974, the recent study found that the incidence rates since 1990 may be falling in men and have reached a plateau in women[11].

Recurrence rates

Early reports suggested that if left untreated the likelihood of forming another stone after the initial episode was 30 to 40 per cent at 5 years [1]. These figures from observational studies are similar to the recurrence rates in the control arms of recently published randomized trials [12,13]. Encouragingly, the treatment arms of many of the randomized trials have shown dramatic reductions in recurrence rates by 50% or more[12–15]. These reductions by medication or dietary interventions emphasize that recurrent stone disease is preventable.

Risk factors

Our understanding of the risk factors for stone formation has increased substantially over the past several decades. Risk factors are generally divided into non-dietary, dietary and urinary.

Non-dietary

Family history—The risk of becoming a stone former is more than 2.5 times greater in individuals with a family history of stone disease[16]. This higher risk is likely due to a combination of genetic predisposition as well as similar environmental exposures (e.g. diet). A polygenic inheritance has been proposed to account for the tendency to calcium oxalate stone formation in families[17]. While a number of genetic factors have been clearly associated with rare forms of nephrolithiasis, information is still limited on genes that contribute to risk of the common forms of stone disease.

Systemic disorders—Although nephrolithiasis has traditionally been considered a renal disorder, there is overwhelming evidence that it is in fact a systemic disorder. Primary hyperparathyroidism, renal tubular acidosis and Crohn's disease are well-described conditions that increase the risk of formation of calcium containing stones. Primary hyperparathyroidism may be found in 5% of stone formers[18].

More recently, a number of other common conditions have been convincingly linked to nephrolithiasis. Increasing body size as assessed by weight, body mass index or waistline is associated with an increasing risk of stone formation independent of other risk factors including diet[19]. The magnitude of the increase in risk from BMI is higher in women than in men. For

example, the risk of stone formation for individuals with a BMI ≥ 30 kg/m² compared to those with a BMI 21–23 was 30% higher among men but nearly two-fold higher among women. Weight gain also increases the risk of stone formation. A 35 pound weight gain since early adulthood increased risk of stone formation by 40% in men and 80% in women. The mechanism(s) for the increased risk associated with larger body size is unknown at present.

A history of gout increases the likelihood of forming kidney stones, both uric acid and calcium oxalate. In a national health survey, individuals with gout were 50% more likely to have a history of stones[20]. When examined prospectively, a history of gout was associated with a doubling of the risk of forming a stone, independent of diet, weight and medications[21]. Although the mechanism for this relation is unknown, possibilities include insulin resistance and acid-base defects.

More recently, diabetes mellitus was found to raise the risk of stone formation, independent of diet and body size[22]. Cross-sectionally, individuals with a history of type II DM were more than 30% more likely also to have a history of nephrolithiasis. Prospectively, a history of type II DM increased the risk of stone formation by 30–50% in women but not in men.

Environmental factors—Individuals working in a hot environment appear to be at higher risk for stone formation[23]. In many situations, lack of access to water or bathroom facilities may lead to lower fluid intake and thus, because of lower urine volume, a higher risk of stone formation.

Dietary Factors

The composition of the urine is influenced by dietary intake and several dietary factors have been proposed to modify the risk of nephrolithiasis. Nutrients that have been implicated include calcium, animal protein[24], oxalate[25], sodium[26], sucrose[27], magnesium[28], and potassium[29]. Because patients who develop stones often change their diet, studies that retrospectively assessed diet may be hampered by recall bias. Other studies have examined the relation between diet and changes in the lithogenic composition of the urine, often using calculated relative supersaturation. However, the composition of the urine does not completely predict risk and not all the components that modify risk are included in the calculation of supersaturation (e.g. urine phytate). Thus, prospective studies are best suited for examining the associations between dietary factors and risk of actual stone formation.

Calcium—The first prospective study of dietary factors and the risk of incident stone disease was performed in a cohort of more than 50,000 male health professionals aged 40 to 75 years at baseline[7]. Although dietary calcium had been strongly suspected of raising the risk of stone disease, men with a higher intake of dietary calcium actually had a *lower* risk of incident nephrolithiasis independent of other risk factors. This inverse association has been confirmed in two other prospective studies in women[9,10] and in an updated analysis in men[30]. Although the mechanism of this effect is unknown, low calcium intake is known to increase oxalate absorption and urinary excretion[31], and individuals with lower calcium intake have lower 24 hour urine oxalate excretion. While the reduction in risk due to higher dietary calcium intake may be due to reducing urine oxalate, it is also possible that there is some other protective factor in dairy products (the major source of dietary calcium in the US). A subsequent study showed that low dietary calcium intake may increase the risk of stone formation, even among individuals with a family history of stones[16].

The above mentioned observational data were subsequently confirmed in a randomized trial by Borghi and colleagues that compared a low calcium diet (400 mg/d) to a diet containing 1200 mg of calcium along with low sodium and low animal protein intake in men with hypercalciuria and calcium oxalate stones[12]. The rate of recurrence was reduced by 50% in

the higher calcium intake group. While some authorities still question whether a high calcium diet reduces the risk of stone formation, there is overwhelming evidence that calcium restriction is not beneficial and may in fact be harmful, both for stone formation and bone loss.

Despite similar bioavailability, the impact of supplemental calcium appears to be different from dietary calcium. In an observational study of older women, calcium supplement users were 20% more likely to form a stone than women who did not take supplements, after adjusting for dietary factors[9]. In younger women and men, there was no association between calcium supplement use and risk of stone formation[7,10]. The discrepancy between the risks from dietary calcium and calcium supplements may be due to the timing of calcium intake. In these studies, calcium supplements were often taken in between meals, which would diminish binding of dietary oxalate. The recently published Women's Health Initiative randomized trial also demonstrated a 17% increased risk of stones with calcium supplementation[32]. However, these results should be interpreted cautiously as the participants were instructed to take their supplements with meals, and the supplements contained both calcium and vitamin D.

Oxalate—The role of dietary oxalate in the pathogenesis of calcium oxalate nephrolithiasis is unclear[33]. The proportion of urinary oxalate derived from dietary oxalate is controversial; estimates range from 10 to 50%[33]. In addition to the GI absorption of dietary oxalate, urinary oxalate is also derived from the endogenous metabolism of glycine, glycolate, hydroxyproline, and vitamin C. Due to variable and often low bioavailability, much of the oxalate in food may not be readily absorbed. The dietary contribution of urinary oxalate may be higher in stone formers. Up to one-third of patients with calcium oxalate nephrolithiasis may have increased absorption of dietary oxalate, and in some cases a deficiency of oxalate degradation by the bacterium *Oxalobacter formigenes* in the gut could be the culprit[33]. The impact of dietary oxalate on risk of stone formation has not yet been studied prospectively because of the lack of sufficient and reliable information on the oxalate content of many foods. However, recent reports using modern approaches to measure the oxalate content of food [34,35] have opened the possibility of these studies being completed in the near future.

Other nutrients—Several other nutrients have been studied and implicated in the development of stone formation, but several of the associations with risk vary by age, sex or body mass index (BMI). High animal protein intake leads to increased calcium and uric acid excretion as well as decreased urinary citrate [36], all of which increase the risk of stone formation. An increased risk of stone formation was observed for higher animal protein intake only among men with BMI < 25 kg/m². [30] A higher intake of sodium[26] or sucrose[27] increases calcium excretion independent of calcium intake, whereas potassium supplementation decreases calcium excretion[29] and many potassium-rich foods increase urinary citrate due to their alkali content. Prospective studies demonstrated sucrose was associated with an increased risk in women[9,10] and higher dietary potassium intake decreased risk in men and older women[7,9,30]. Recently, phytate was also found to reduce substantially the likelihood of stone formation in younger women[10].

Magnesium complexes with oxalate, thereby potentially reducing oxalate absorption in the gastrointestinal tract and decreasing calcium oxalate supersaturation in the urine. A few randomized trials have examined the effect of magnesium supplementation on stone recurrence. However, magnesium was given in combination with other compounds (e.g., thiazide diuretic or potassium citrate) and the dropout rates were high. Currently, it is uncertain whether magnesium supplementation has an independent beneficial effect. In prospective observational studies, higher dietary magnesium was associated with a 30% lower risk of stone formation in men[30], but not in women[9,10].

Vitamin C (ascorbic acid) can be metabolized to oxalate; thus, higher vitamin C intake could increase the risk of calcium oxalate stone formation. A metabolic trial demonstrated that the consumption of 1000 mg of supplemental vitamin C twice daily increased urinary oxalate excretion by 22%[37]. An observational study in men found that those who consumed 1000 mg or more per day of vitamin C had a 40% higher risk of stone formation compared to men who consumed less than 90 mg/day (the recommended dietary allowance)[30]. This relation was observed only after accounting for dietary potassium intake. Although restricting *dietary* vitamin C does not seem appropriate (as foods high in vitamin C are also high in inhibitory factors such as potassium), a calcium oxalate stone former should be encouraged to avoid vitamin C supplements.

Vitamin B6 is a cofactor in oxalate metabolism, and vitamin B6 deficiency increases oxalate production and urine oxalate excretion. Although high doses of supplemental vitamin B6 may be beneficial role in selected patients with type 1 primary hyperoxaluria, the use of vitamin B6 in other settings remains unclear. Based on observational data, high intake of vitamin B6 may reduce the risk of kidney stone formation in women[38] but not in men[39].

Fluid Intake and Beverages—When the urine output is less than 1 L/day, risk of stone formation is markedly higher. Observational studies[7,9,10] and a randomized controlled trial [40] have demonstrated the importance of fluid intake in reducing the likelihood of stone formation.

Patients with stone disease often ask what they should and should not drink. Despite previous beliefs to the contrary, observational studies have found that coffee, tea, beer, and wine are associated with a reduced risk of stone formation[41,42]. Although citrus juices theoretically could reduce the risk of stone formation[43], orange juice consumption was not associated with stone formation and grapefruit juice intake was associated with a 40% higher risk[41,42]. Grapefruit juice is known to have a number of effects on intestinal enzymes, but the mechanism for the observed increased risk is unknown. Previous studies suggested an increased risk for soda consumption and unadjusted results from observational studies also suggested an increased risk. However, after controlling for other dietary components, consumption of soda (with or without caffeine; diet or sugared) was not associated with the risk of stone formation [41,42]. Although skim and whole milk were not associated with risk in the observational studies probably because these studies adjusted for the intake of dietary calcium, milk intake likely reduces the risk of calcium kidney stone formation.

Urinary Factors

The 24-hour urine chemistries provide important prognostic information and direct therapeutic recommendations for prevention. Traditionally, urine results have been categorized into ‘normal’ and ‘abnormal’, but recently there has been a greater appreciation of two important points. First, the urine values are continuous so the dichotomization into ‘normal’ and ‘abnormal’ is arbitrary and potentially misleading. Second, stone formation is a disorder of *concentration*, not just the absolute amount excreted. Although terms such as ‘hypercalciuria’ are often used both clinically and scientifically, the limitations of these terms should be remembered.

Hypercalciuria has been traditionally defined as urine calcium excretion ≥ 300 mg/day in men and ≥ 250 mg/day in women[44] on a 1000-mg/day calcium diet. Based on these definitions, ~20 to 40% of patients with calcium stone disease will have hypercalciuria. Although a higher cutoff value in males makes sense from a calcium balance perspective, it does not for stone formation, particularly given that 24-hour urine volumes are slightly higher in women[45].

Hyperoxaluria is defined as urinary oxalate excretion >45 mg/d. Elevated urinary oxalate excretion may be present in up to 40% of male stone formers and in up to 10% in female stone formers[45]. Although mean urinary oxalate levels may not differ between cases and controls, oxalate does appear to be an important independent risk factor for stone formation[45].

The relation between uric acid metabolism and calcium stone disease has been intriguing. Some investigators have reported that *hyperuricosuria* (defined as greater than 800 mg/day in men or 750 mg/day in women) is seen more frequently in patients who form calcium stones than normal subjects[46], but others have found no difference[45]. Although allopurinol in a double-blind trial successfully decreased recurrence rates of calcium stones in patients with hyperuricosuria[14], the role of uric acid in remains unsettled.

Hypocitraturia, typically defined as 24 hour excretion ≤ 320 mg/d, increases risk for stone formation[47] and is found in 5–11% of first time stone formers[45]. At present, there is insufficient evidence to conclude increasing urinary citrate into the high-normal range provides additional protection.

Low urine volume, for which a variety of definitions have been used, is a common and modifiable risk factor. When defined as 24 hour urine volume less than one liter per day, 12–25% of first time stone formers will have this abnormality[45]. Observational studies have demonstrated the risk of stone formation decreases with increasing total urine volume[45], and a randomized trial confirmed the value of increasing urine volume[40].

Summary

Epidemiologic studies have expanded our understanding of stone disease. It is clear that a variety of risk factors contribute to the risk of stone formation and that the importance of these risk factors varies by age and sex. The individual impact of traditional risk factors (e.g. calcium, animal protein) has been quantified and new factors (e.g. body size, phytate) have been identified. Scientifically, results from these studies have forced a reappraisal of our view of risk factors for stone disease. Importantly, the results from epidemiologic studies can be applied in the clinical setting with the goal of reducing the likelihood of stone formation.

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Adapted from reference 2.

Figure 1.
Prevalence of stone disease by sex and age

Adapted from reference 2.

Figure 2.
Prevalence of stone disease by race and age