Symposium

The evolving epidemiology of stone disease

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ABSTRACT

The epidemiology of kidney stones is evolving – not only is the prevalence increasing, but also the gender gap has narrowed. What drives these changes? Diet, obesity or environmental factors? This article will review the possible explanations for a shift in the epidemiology, with the hope of gaining a better understanding of the extent to which modifiable risk factors play a role on stone formation and what measures may be undertaken for disease prevention in view of these changing trends.

Key words: Diet, epidemiology, nephrolithiasis

INTRODUCTION

The incidence of urinary tract stone disease is increasing. According to the National Health and Nutrition Examination Survey, as of 2012, 10.6% of men and 7.1% of women in the United States are affected by renal stone disease, compared to just 6.3% of men and 4.1% of women that were affected in 1994.[1] Further, within the affected population the gender gap has narrowed substantially and the incidence of stone disease in pediatric urology patients continues to be on the rise. Multiple studies have proposed an explanation for the evolving epidemiology of renal stone disease. The purpose of this article is to explore the existing literature in an effort to identify the potential effects that changes in diet, life-style and obesity have had on the increasing incidence of nephrolithiasis. This in turn may provide a better understanding of the extent to which modifiable risk factors play a role on stone formation and what measures may be undertaken for disease prevention in view of these changing trends.

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STONE DISEASE AND GENDER – IS IT CHANGING?

One of the more striking new trends appears to be the increased incidence of stone formation in women. The increase in incidence of women affected by urinary tract stone disease has outpaced that of men. Although nephrolithiasis continues to be more common in men, the incidence rate ratio of men to women with urinary tract stones has narrowed from 3.4 to 1.3.[2] The new data is based on resource utilization studies that have examined national databases, hospital admissions and outpatient care. Similar results have been reported by studying patient self-reporting of stone events.

One hypothesis for the disproportionate increase in stone disease in women is related to obesity. In 1998, a study based on two large cohorts: The Nurses' Health Study (n = 89,376 women) and the Health Professionals Follow-up Study (HPFS) (n = 51,529 men) Curhan *et al.* found that the prevalence and incidence of calcium oxalate stone disease was directly associated with body mass index (BMI).[3] Further, the magnitude of association was significantly stronger for females that it was for males. The age-adjusted prevalence odds ratio for stone disease in women with a BMI of >32 kg/m^2 compared to those with a BMI of 21-22.9 kg/m^2 was 1.76 while in men, the ratio was 1.38. Similarly, the incidence odds ratio based on BMI for women was 1.89 compared to 1.19 for men.

These findings were confirmed by Nowfar *et al.* using the Nationwide Inpatient Sample database, which contains information on approximately 20% of hospital stays in the United States. They reported that a significant positive correlation exists between obesity and nephrolithiasis for both genders; however, obese females were more likely to

develop stones than obese males. They hypothesize that this may explain the decrease from 1998 to 2003 in the male-to-female ratio for stone risk from 1.6:1 to 1.2:1.[4] One contradictory study from Germany concluded that obese men are more prone to stone formation than obese women.[5]

A follow-up prospective study by Taylor *et al.* examined the effect of obesity and weight gain on the incidence of nephrolithiasis in subjects based on gender and age over a 46 year old span.[6] The study evaluated 3 cohorts: HPFS (n = 45,988 men), the Nurses' Health Study I (n = 93,758 women, age range at baseline 34-59), and the Nurses' Health Study II (n = 101,877 women, age range at baseline 27-44). They reported that the relative risk for development of nephrolithiasis in men whose weight was >220 lbs compared to those <150 lbs was 1.44. In contrast, the relative risk associated with these differences in body weight was 1.89 for older women and 1.92 for younger women. Further, in men whose weight gain since age 21 was over 35 lbs the relative risk of stones was 1.39 compared to men whose weight remained constant. In women, who gained weight since the age of 18, the relative risk was 1.70. Based on these results the authors concluded that both obesity and weight gain conferred an increased risk of nephrolithiasis, having a greater impact on women than men.

STONE DISEASE AND GENDER – IS IT DIET?

If the greatest association between body mass and nephrolithiasis exists in younger women, can diet explain the evolving epidemiology in this population? In a prospective study, using a cohort of young women (Nurses' Health Study II), Curhan *et al.* sought to examine a relationship between dietary factors and the risk of incident kidney stones.[7] They reported that higher intake of dietary calcium decreased the risk of urinary stone disease in young women, while supplemental calcium did not. Additionally, dietary phytate, which is found in bran and seeds, decreases the risk of stone formation.

A study by Taylor *et al.* also looked into possible association between fatty acid intake and incidence of nephrolithiasis.[8] No associated risk was established. Increased arachidonic and linoleic acid consumption did not pre-dispose to the formation of kidney stones. Increased intake of n-3 fatty acids was not found to be protective. Another study by Taylor and Curhan did not support a widely held assumption that increased dietary oxalate consumption, in foods such as spinach, posed a risk for increased incidence of urinary stone disease.[9] Although the relative risk for stone formation was 1.34 for older women who consumed >8 servings of spinach per month compared <1 serving, the authors concluded that dietary oxalate was not a major risk factor in development of nephrolithiasis. Vitamin C supplementation, which may be metabolized to oxalate, was not associated with an increased risk of stone formation in women in a prospective study by Curhan *et al.*[10] In contrast, the use of combined calcium and vitamin D supplements in post-menopausal women, was found to increase the incidence of nephrolithiasis compared to the placebo group over the course of 7 years.[11]

Increased intake of caffeinated, high-sugar content beverages has long been assumed to contribute to the rise in the prevalence of urinary stone disease. Surprisingly, a study by Curhan *et al.* showed that consumption of 8-oz of caffeinated coffee and tea decreased the risk of stone formation in women by 10% and 8%, respectively.[12] The same amount of wine decreased the risk by 59% while grape fruit juice increased the risk by 44%.

STONE DISEASE AND OBESITY: WHAT IS THE LINK?

The interplay of obesity and other components of the metabolic syndrome have been linked to stone formation through varied postulated pathophysiologies including increased urinary oxalate excretion, increased uric acid production and defects in ammoniogenesis. Hypertension as well other metabolic changes, associated with obesity may lead to the formation of stones. In a study conducted at the University of Naples by Cappuccio *et al.*, found a clinical association between hypertension and nephrolithiasis.[13] Specifically, the prevalence of urolithiasis in treated hypertensives was found to be in 32.8% of the subjects, compared to 13.4% in the normotensive subjects. In a later prospective 8-year study, the incidence of kidney stone disease was found to be greater in hypertensive men with no evidence of stone disease at baseline.[14] Over the course of 8 years, 16.7% of men developed renal calculi, compared to 8.5% of normotensive male subjects. This suggests that hypertension is a predictor for urinary stone disease, rather than a consequence of renal damage following the development of renal calculi.

Obesity has also been linked to reduction in urinary pH and associated nephrolithiasis. Najeeb *et al.* examined the effects of obesity on urinary pH and urinary stone composition[15] and reported an inverse correlation between patients' BMI and urinary pH. Patients with higher BMI's were found to have lower urinary pH and higher occurrence rates of urate, calcium oxalate and calcium phosphate stones.

A prior study by Chou *et al.* found no correlation between obesity and prevalence of calcium phosphate stones.[16] However, the percentage of uric and calcium oxalate stones was also found to be higher in obese than non-obese patients. In Chou's study, the prevalence of calcium oxalate stones in obese patients was found to be 34.9%, compared to 23.1% in patients with normal weight. Similarly, the prevalence of uric acid stones was 7.7% for the obese group and 2.8% for the normal weight group. Interestingly, a study by Daudon *et al.*, which looked at 27,980 calculi, collected between

the years 1976 and 2001, analyzing their composition via infrared spectroscopy, found that females tend to have a preponderance for calcium phosphate and struvite stones, presumably due to increased susceptibility to urinary infections.[17] The same study also found that the prevalence of uric acid stones tends to increase with age for both sexes. These studies suggest that if obesity and aging are linked to the evolving epidemiology of stone disease, one would anticipate a change in the frequency of stone compositions in female stone formers.

In a German study by Siener, *et al.*, the authors also found a positive inverse relationship between BMI and urinary pH in both genders.[5] In obese individuals there was an increase in urinary excretion of uric acid, sodium, ammonium, and phosphate. Once again several differences between the sexes were noted. An association between obesity and an increase in urinary oxalate excretion was noted only in females, but not in the male participants of the study. Conversely, an increase in urinary calcium excretion was associated with obesity in men but was not noted in women. According to the authors, as BMI increased, there was no increase in excretion of inhibitors of stone formation, such as magnesium and citrate.

STONE DISEASE AND PEDIATRICS

Another alarming trend is the increasing incidence of nephrolithiasis in the pediatric population.[18] Interestingly, girls are more susceptible to nephrolithiasis than boys. In the study by Novak *et al.*, based on inpatient admission for pediatric urolithiasis in 2003, the Healthcare Cost and Utilization Project Kids' inpatient database showed a female predominance in this age group, with a slightly higher predominance in boys within the first decade only.[19] According to the study by Sas *et al.*, the greatest rate increase in incidence of pediatric renal stone disease between 1996 and 2007 was seen in Caucasians adolescent girls.[20] Based on the data, the authors cite an increase in pediatric nephrolithiasis cases from 7.9/100,000 patients in 1996 to 18.5/100,000 patients in 2007, with female to male ratio of 1.4:1. The study was an estimate based on an analysis of a statewide database of South Carolina emergency room visits.

In 2012, a 25-year population based study by Dwyer *et al.* was published.[21] It examined 207 children under the age of 18 with computerized tomographic imaging confirming stone disease in Olmsted County, Minnesota. 41% of the children in the study were determined to be incident stone formers. They reported a 4% increase per year in the incidence rate during the period of 25 years. The numbers were in large part due to the rise in incidence in the 12-17 year old age group. The incidence rate within this age group was found to increase 6% each year. Nationwide studies are not yet available. However, such dramatic regional increases in incidence is nevertheless concerning.

Most of the pediatric renal stone disease is of idiopathic etiology, with only 9-24% having a type of identifiable underlying cause such a metabolic, neurological or congenital urinary system structural abnormality. Multiple factors, which predispose children and adolescents to form renal calculi have been proposed.

Pediatric stone composition and urinary metabolic stone risk parameters are distinct from those of adults. Although renal stone formation has a linear association with the age of the patient, pediatric patients tend to form a greater percentage of calcium-based stone than adults. Conversely, there are fewer cases of uric acid stones than in the adult population. The reason for this discrepancy has been associated with a higher urinary pH within a pediatric population seen in adults.[22] It should be noted that the risk of pediatric struvite stones has decreased; perhaps related to advancements in diagnosis and management of urinary tract infections as well as management of anatomical and neurological conditions associated with urinary infections.

With the rise of childhood obesity, large BMI has long been assumed to contribute to the pediatric stone disease epidemic. However, a recent study by Kieran *et al.* questions the existence of the link in children.[23] The authors stratified 62 boys and 50 girls with urolithiasis according to their BMI's into lower percentile body weight patients, those with normal weight, and upper percentile body weight patients. Patients with lower percentile body weight were found to have an earlier presentation of the disease while the highest percentage of stone patients was found to belong to the normal weight category. 49.1% of patients belonged to the normal weight category, compared to 41.1% in the heavier children. Further, obesity did not increase the risk for the development of larger size calculi or the need for more surgical procedure in comparison to other weight categories.

Kim *et al.* compared 110 of pediatric cases with urolithiasis to 396 matched controls in a case-control study and reported no association between high BMI and urolithiasis.[24] However, the authors noted that the black race and medicaid payer status were associated with a lower risk of stone disease.

Indeed, lack of concrete evidence linking obesity and renal stone disease in pediatric patients has led some to postulate that perhaps changes in diet rather than BMI serves as a culprit for urolithiasis in children. Shi *et al.* reported that renal uric acid and oxalate were found to vary with body fat and free glucocorticoids. Urinary calcium was associated with dietary intake of sodium and protein, but not BMI in healthy children.[25] According to a 2010 published report by US Institute of Medicine, the average dietary intake of sodium for kids aged 6-11 has increased from 200 mg in the 1970s to 3000 mg in the 2000s.[26]

Other co-morbidities associated with obesity have been closely associated with stone disease. Matlaga *et al.* observed a

strong correlation between nephrolithiasis and hypertension as well as diabetes in children less than 6 years of age.[27] In a follow-up study by Schaeffer *et al.* 14,245 children with upper tract calculi were evaluated using the kids' inpatient databases.[28] Hypertension was found to be a significant risk factor for nephrolithiasis in children 10 years of age and younger while diabetes mellitus was found to be a risk factor for children younger than 5 years. This study confirmed that obesity was not associated with a higher risk for stones.

In 2012, Kokorowski *et al.* published a conflicting report on association of urolithiasis with systemic conditions and obesity among pediatric patients.[29] In their analysis of 9,843 cases of urolithiasis and 39,047 controls, stone formers were found to have a higher prevalence of obesity and hypertension, compared to controls. Additionally, type 1 diabetes mellitus was seen less in patients with nephrolithiasis, compared to controls.

In an effort to determine the urine risk factors that pre-dispose pediatric patients to urinary stone formation Bergsland *et al.* identified hypercalciuria as the principal difference between stone-forming children and their non-stone forming relatives and normal counterparts.[30] Surprisingly, other urinary characteristics, associated with adult stone formers, namely low urinary volume, hyperoxaluria, hypocitraturia, and low urinary pH were not found to play a major risk factor in stone formation in children.

It appears the forces driving changes in the epidemiology of stone disease in children may be different than those in adults. In both adults and children, the increased use of cross-sectional imaging may be playing a role. According to an article by Stratton *et al.*, between 1996 and 1999 the use of CT scans as a diagnostic modality for children 15 years of age and younger increased 96%.[31]

CONCLUSION

As the world's population evolves, so does the epidemiology of stone disease. Obesity epidemics, aging demographics, dietary indiscretions, global warming; all likely play a role in stone disease. Unfortunately, all of these parameters point to a rise in risk – the stone-age is upon us.

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