The New Epidemiology of Nephrolithiasis

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Historically nephrolithiasis was considered a disease of dehydration and abnormal urine composition. However, over the past several decades, much has been learned about the epidemiology of this disease and its relation to patient demographic characteristics and common systemic diseases. Here we review the latest epidemiologic studies in the field.

Key Words: Nephrolithiasis, Epidemiology, Pediatrics, Systemic disease, Risk factors

HISTORICAL PERSPECTIVE

Descriptions of the treatment of urolithiasis can be found in ancient Indian, Chinese, Babylonian, and Greek texts.[1] Although estimates of prevalence are not available, it was common enough that to not "cut for stone" was a central tenet of the Hippocratic oath. In the year 2015, nephrolithiasis is a common cause of morbidity, with nearly 11% of men and 7% of women in the United States reporting a lifetime stone event.[2] Here we review epidemiologic characteristics of nephrolithiasis in the modern era—much of the focus of this review is on calcium stones that account for the majority of stones in developing countries.

INCIDENCE, COST, AND GENDER

Multiple studies over the past decade have documented an increased incidence of nephrolithiasis. The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional survey of noninstitutionalized adults in the United States that has been used to estimate the prevalence of kidney stones. Comparing NHANES II (1976-1980) and NHANES III (1988-1994), it was estimated that stone prevalence had increased from 3.8% to 5.2% for a period of 20 years covered by the surveys.[2,3] A recent updated analysis of NHANES data from 2007 to 2010 reported that the prevalence had increased to 8.8% (10.6% among men compared with 7.1% among women) compared with 5.5% in NHANES III.[2] Stone disease also appears to be more common in whites than blacks, with Hispanics and Asians falling in between.[2,4] Studies using claims data from the Healthcare Cost and Utilization Project found that the costs associated with kidney stones have also increased from 1994 to 2000. Although inpatient stays for urolithiasis decreased from 1994 to 2000 by 15%, there were substantially more outpatient physician visits for the evaluation of stone disease between those 2 years. This resulted in a total cost of $2.07 billion in 2000 from $1.37 billion in 1994. This 50% increase occurred despite the shift from an inpatient to an outpatient setting for stone treatment, with the total proportion of total expenditure on outpatient treatment increasing from 43% to 53%.[5] Retrospective claims-based data have also been used to evaluate the incidence of nephrolithiasis in the United States: in 2000, it was estimated that more than 1% of working-age adults were treated for an episode of nephrolithiasis. On average, per person work loss was 19 h/y, and the incremental costs of nephrolithiasis (conditional on receiving treatment) were nearly $3500 per person per year.[6]

The population of Rochester Minnesota has provided some of the best long-term data on stone prevalence and incidence. In a cohort followed from 1950 to 1974, the age-adjusted incidence of first episode of kidney stones remained stable among women (36 per 100,000) but increased significantly among men (124 per 100,000 from 79 per 100,000).[7] Interestingly, observations of this cohort from 1970 to 2000 found that the increase in incidence did not continue in men but actually decreased by 1.7% per year. This decrease was offset by an increase in prevalence among women of 1.9% per year, such that the overall incidence being relatively unchanged.[8]

Studies in other countries have also identified an increasing prevalence of nephrolithiasis. A report from Germany using a nationally representative survey found that urolithiasis prevalence had increased from 4.0% to 4.7% from 1979 to 2001. In this survey, the prevalence among those older than 65 years increased from 6.8% to 9.5%. The authors were also able to estimate the incidence of urolithiasis in the year 2000 and found that it had increased to 1.47% from 0.54% in 1979.[9] Similarly, a report from a village near Milan, Italy, in 1986 and 1998, found that stone prevalence had increased from 6.8% to 10.1% over that period.[10] The prevalence of stones increased in Japan as well. By examining patient visits with a diagnosis of upper tract stones, it was estimated that the annual incidence of first upper tract stones had increased steadily from 54.2 per 100,000 in the population in 1965 to 114.3 per 100,000 in 2005.[11,12]

When considering the relation between gender and nephrolithiasis, recent data from NHANES corroborated earlier findings that nephrolithiasis is more commonly found in men than women, with respective lifetime prevalence in the United States of 10.3% vs 6.7%. However, other data have demonstrated that stone disease may be increasing in women at a greater rate than in men. Using

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the Nationwide Inpatient Sample, Scales and colleagues[13] evaluated discharges for stone disease from the US hospitals from 1997 to 2002 and reported a reduction in the male:female ratio among treated stone patients from 1.7:1 to 1.3:1. Another study, using statewide ambulatory surgery and inpatient databases, noted that for a period of 6 years (1998-2004), 38% of discharges for stone disease occurred in women. However, the growth rate for women was greater than for men: although both groups increased in utilization of outpatient and ambulatory surgery, only women had increased inpatient utilization.[14] The Rochester Epidemiology Project also described greater increases in women compared with men from 1970 to 2000.[8]

STONE RECURRENCE RATES

Early studies reported that the recurrence of stone disease after an initial episode occurred in nearly 30% to 50% within 5 to 10 years of the initial stone event.[15,16] Of note, a majority of the imaging in these earlier studies was plain radiography and ultrasound, with few, if any, computerized tomographic (CT) scans. Using data from the Rochester Epidemiology Project, followed from 1984 to 2003, which included CT scans, the recurrence of kidney stone (ROKS) nomogram for predicting stone recurrence was developed.[17] The data used to develop the ROKS nomogram noted symptomatic recurrence after the initial stone event at the following rates and time points: 11% in 2 years, 20% in 5 years, 31% in 10 years, and 39% in 15 years. Some of the factors that increased the risk and rate of recurrence in this model included the following: family history of stones, any nonobstructing stone on imaging, and uric acid stone composition.

CLINICAL SUMMARY

- Large epidemiologic cohort studies have contributed significantly to our understanding of nephroloithiasis.
- The epidemiology of adult and pediatric nephrolithiasis is evolving in terms if incidence and risk factors.
- It is now understood that nephrolithiasis is related not only to diet and hydration, but to common systemic conditions including metabolic syndrome, cardiovascular disease, and chronic kidney disease.

URINE AND STONE COMPOSITION

Calcium stones (pure calcium oxalate, pure calcium phosphate, or mixed calcium) predominate in developed nations.[18,19] Calcium-containing stones comprise 70% to 85% of all stones, uric acid 5% to 10%, struvite 1% to 5% (more common in women than men), and rare stones (eg, cystine) 1% or less.[19] A recent analysis of more than 200,000 stone analyses for a period of 30 years from Germany reported stable rates of uric acid stones, decreasing rates of struvite stones, and increasing calcium stones in patients aged 40 to 49 years.[19] Another report, comparing stone analyses from a single laboratory in the years 1990 and 2010 noted a decrease in the proportion of uric acid stones in men (from 9.7% to 7.6%) although the proportion of uric acid stones in women remained constant. Among those with calcium stones, the proportion of hydroxyapatite per stone increased significantly in men (8.7% to 11.4%), whereas it decreased in women (19.7% to 11.7%).[20]

GEOGRAPHY AND TEMPERATURE

It has been recognized for some time that there appears to be a "stone belt" in the Southern United States. One of the earlier studies characterizing this geographical distribution used the second Cancer Prevention Study that surveyed 1,185,124 men and women regarding kidney stone history. Using the state-level data available from this survey, it was found that residents in the Southeast were nearly twice as likely to have a stone history than those in the Northwest (odds ratio were 1.79 for men and 1.84 for women). The prevalence of stones in men ranged from 5.6% in North Dakota to 14.9% in North Carolina.[21] Higher temperatures have also been associated with clinical kidney stone presentation, with daily mean temperature of 30°C associated with significantly increased episodes compared with daily mean temperature of 10°C in 4 major metropolitan areas studied (Atlanta, Chicago, Dallas, and Philadelphia).[22] Mathematical modeling has been used to examine the association between geography and stone incidence. Brikowski and others[23] used predictions based on climate modeling to show a concentration of greatest increase in nephrolithiasis over the next century to be in California, Texas, Florida, the eastern United States, and a geographic band stretching from Kansas to Kentucky—states that on the whole are affected by much warmer temperatures than the rest of the country.

DIET

Although many dietary factors have been suggested to contribute to stone disease, the best characterized contributors are dietary calcium and fluid intake. Longitudinal cohort studies have been particularly valuable. The Health Professionals Follow-up Study (HPFS) in men and the Nurses' Health Studies I and II in women involve nearly 46,000 men and 195,000 women followed prospectively for more than 4 decades. Studies evaluating these cohorts have shown the following dietary factors to be "protective" against stone recurrence in men: greater fluid intake, calcium from dairy and nondairy sources, magnesium, and potassium.[24,25] In women, foods that reduced kidney stone risk were greater fluid intake, dietary calcium, and phytate.[25] Dietary intake of fruits, fiber, and vegetables has also been shown to decrease risk of incident kidney stones in another large cohort of more than 83,000 women, the Women's Health Initiative.[26] Coffee (caffeinated or decaffeinated), tea, wine, beer, and orange juice all decrease risk of stone formation.[27]

Animal protein intake did increase risk of nephrolithiasis only in men with body mass index less than 25 kg/m^2, as did high intake of vitamin C (in men who consumed >1000 mg/d compared with men who consumed <90 mg/d) but not in women.[25,28] Sugar-sweetened noncola beverages, in addition to sugar-sweetened juices

and high fructose intake from other food sources, are associated with increased risk of stone formation.[27,29]

The following foods and supplements, hypothesized by many to affect stone risk, have not been shown to play a role in the risk of recurrent stone disease in men: sodium, sucrose vitamin B(6), vitamin D, and supplemental calcium.[28] Whether there is an increased risk of nephrolithiasis in women taking supplemental calcium is equivocal. Some studies have shown a modest increased risk of nephrolithiasis with supplemental calcium intake for women,[30] whereas others have shown no increased risk.[25]

Because the majority of stones in developed nations are composed of calcium oxalate,[19] dietary oxalate has been a topic of great concern both for patients with nephrolithiasis and the physicians who treat them. However, epidemiologic studies have not shown a strong relation between dietary oxalate intake and the risk of stone formation. In a study of 24-hour composition in more than 3300 participants, it was shown that the highest oxalate consumers excreted only 1.7 mg/d of urinary oxalate more than the lowest dietary oxalate consumers (median daily oxalate excretion was 39 mg/d in men, 27 mg/d in older women, and 26 mg/d in younger women).[31] This led the authors to conclude that the impact of dietary oxalate on urinary oxalate "appears to be small." Further studies from the HPFS and Nurses' Health Studies I and II have demonstrated that urine oxalate excretion in the highest quintile of dietary oxalate consumption compared with the lowest quintile was increased by nearly 20% in men and older women. In addition, high intake of spinach (the food with the highest oxalate content) does increase risk of stone formation in men and older women but not younger women. Of note, this risk was observed for those with the highest spinach intake (≥8 servings/mo) compared with those who consumed fewer than 1 serving.[32] The authors concluded that dietary oxalate is not implicated as a major risk factor for nephrolithiasis.

NEPHROLITHIASIS AS AN SYSTEMIC DISEASE

Epidemiologic studies have linked stone disease with 3 medical traits that are part of the metabolic syndrome—obesity, diabetes mellitus, and hypertension. Cardiovascular disease is also associated with kidney stones. When this association first became apparent in the early 2000s, a shift in thinking occurred: earlier literature focused on nephrolithiasis as an isolated, benign, painful condition.[33] More recently, with the discovery of the associations, internists, nephrologists, and urologists have turned to thinking of nephrolithiasis not as an isolated disorder of urine composition but as a risk factor for, and consequence of, the metabolic syndrome and cardiovascular disease.

OBESITY, HYPERTENSION, AND DIABETES MELLITUS

The NHANES III and the HPFS and Nurses' Health Studies I and II have been used to study the relation between nephrolithiasis and metabolic syndrome traits. West and colleagues[34] performed a cross-sectional analysis of nearly 15,000 Americans and reported that the prevalence of self-reported kidney stones increased with the number of metabolic syndrome traits, from 3% for those with 0 traits to 7.5% for those with 3 traits and to 9.8% for those with all 5 metabolic syndrome traits.[35]

Taylor and coworkers reported that the relative risk of developing a kidney stone for participants weighing more than 220 lbs compared with those weighing less than 150 lbs was 1.44 for men, 1.89 for older women, and 1.92 for younger women. In addition, weight gain of more than 35 lbs (since age 21 in men and since age 18 in women), compared with no weight change, was associated with a relative risk for nephrolithiasis of 1.39 in men, 1.70 in older women, and 1.82 in younger women. Similar results were found in both men and women comparing body mass index of 30 or greater vs 21 to 22.9 kg/m^2. Thus, the authors concluded that obesity and weight gain are independent risk factors for the development of nephrolithiasis in both genders.[35]

Diabetes mellitus and nephrolithiasis have been shown to have a reciprocal relation—that is, an antecedent diagnosis of diabetes mellitus increased the risk of future development of nephrolithiasis and an antecedent diagnosis of nephrolithiasis increased the risk of the onset of diabetes mellitus. In the HPFS and Nurses' Health Studies I and II, the risk of prevalent nephrolithiasis in patients with diabetes compared with those without was 1.31, 1.38, and 1.67, respectively. Conversely, the risk of prevalent type 2 diabetes according to kidney stone history was 1.49, 1.33, and 1.48 in men, older women, and younger women, respectively.[36,37] From a pathophysiological standpoint, patients with diabetes mellitus have been shown to have decreased urine pH, which may increase the risk of uric acid calculi,[38] and also have been shown to excrete higher amounts of urine oxalate, which may predispose them to calcium oxalate stone formation.[31,39] Using NHANES 2007 to 2010, it was demonstrated that the severity of diabetes as assessed using fasting plasma insulin, hemoglobin A1c, and fasting plasma glucose was associated with kidney stone risk.[40]

Nephrolithiasis appears to be a risk factor for the development of incident hypertension, but the converse does not appear to be true. Studies from HPFS and Nurses' Health Study demonstrated that the relative risk of development of incident hypertension in men and women with nephrolithiasis was 1.29 and 1.24, respectively but that the risk of development of incident nephrolithiasis was not different in those with and without a history of baseline hypertension.[41,42]

CARDIOVASCULAR DISEASE

A 20-year longitudinal study of 5115 men and women followed for heart and cardiovascular disease for more than 20 years (CARDIA) first demonstrated the link between cardiovascular disease and nephrolithiasis.[43] In this cohort, there was a significant association between kidney stones and carotid atherosclerosis. Those with a history of stone disease were at increased risk of carotid stenosis or of being in the upper quartile of internal carotid/bulb wall thickness.[43] A prospective examination of HPFS and Nurses' Health Studies I and II demonstrated that, in women, a history of kidney stones was associated with a modest increase in risk of coronary heart disease (defined as fatal or nonfatal myocardial infarction or

coronary revascularization). The hazard ratio was 1.18 in older women and 1.48 in younger women. The association was not significant for men after a multivariate analysis. Data from the Rochester Epidemiology Project demonstrated that during a mean of 9-year follow-up, stone formers had a 38% increased risk for myocardial infarction after multivariate adjustment for confounders.[44]

CHRONIC KIDNEY DISEASE

Several studies have demonstrated an association between nephrolithiasis and the development of CKD. A case-control study of nearly 5000 stone formers and 13,000 controls with 8.6 years of mean follow-up demonstrated that stone formers were at increased risk for a clinical diagnosis of CKD but not at increased risk for end-stage kidney disease (ESKD) or death with CKD.[45,46] A similar association between kidney stones, CKD, and ESKD were seen among a cohort from The Alberta Kidney Disease Network.[47] This same association was found in NHANES III and in a recent analysis of NHANES 2007 to 2010.[48,49] This study demonstrated that patients with self-reported nephrolithiasis also demonstrated greater prevalence of CKD and ESKD (ie, treatment with dialysis): odds ratios were 1.50 and 2.37, respectively.[49]

PEDIATRICS

A growing number of epidemiologic studies have shown that the prevalence of nephrolithiasis among children and adolescents has risen dramatically in the United States for the past 25 years.[50–52] In what is arguably the most generalizable study of the changing epidemiology of nephrolithiasis among children, Sas and others[53] reported that the incidence of nephrolithiasis among children aged 0 to 18 years presenting to emergency departments in South Carolina increased from 1996 to 2007. When stratified by age, the annual incidence of kidney stones was highest among school-aged children and adolescents. Additionally, the change in the incidence rate for a study period of 12 years was also highest among adolescents. In 1996, approximately 25 per 100,000 14- to 18-year olds presented to the emergency departments. By 2007, the incidence was 54 per 100,000, which represents a 2.5% annual increase in the number of adolescents seeking emergency care for kidney stones. In contrast, the incidence of stones for children younger than 9 years remained stable at less than 5 per 100,000.

Although the gender gap has narrowed among adults, kidney stones are still more common among men.[2,13] Among children and adolescents, however, girls have consistently been observed to have a higher frequency of stones compared with boys.[50,53,54] The reasons for this observation are unclear, in part because of the lack of robust cohort studies in which the interaction of gender and putative stone risk factors could be explored. It appears that children are similar to adults with nephrolithiasis with respect to race and stone composition. Nephrolithiasis is most common among non-Hispanic white children, followed by Hispanics and African-Americans.[50,52,53] Approximately 80% of kidney stones in children are comprised predominantly of calcium oxalate, which is similar to adults, but calcium phosphate stones are slightly more common and pure uric acid stones are less common in children.[55] Notably, the notion that stones that form during childhood are because of rare genetic causes and inborn errors of metabolism is no longer true.

Indeed, the causal mechanisms that account for the increase in nephrolithiasis among children are uncertain, although the rapid shift in the epidemiology of the disease strongly suggests an environmental cause. Obesity, diets high in sugar and salt, and low water intake are associated with an increased risk of nephrolithiasis among adults[25,28,29] and could all contribute to the risk among children. The prevalence of obesity and nephrolithiasis among children has increased in parallel.[56] Adolescents and young adults consume more fructose than any other age group,[57] and most children eat too much salt[58] and do not drink enough water.[59] However, these associations are purely ecologic. Further studies are needed to determine the contribution of dietary risk factors for nephrolithiasis among children, who may have different metabolic responses to dietary exposures than adults.[60,61]

The increase in the incidence of nephrolithiasis among children has implications for future health care spending, harms resulting from treating children like adults, and the risk of developing comorbid diseases associated with nephrolithiasis. In 2000, kidney stone disease accounted for more than $2 billion a year in health care expenditures in the United States.[5] Nephrolithiasis will likely represent a growing economic burden to the US healthcare system because of the increased prevalence of nephrolithiasis among younger patients and the recurrent nature of the disease.[15] Additionally, children with nephrolithiasis may be exposed to unnecessary harm if physicians apply adult management strategies to pediatric patients. For example, although CT is the gold-standard imaging study

Table 1. Dietary Risk Factors for Kidney Stones Examined in Epidemiologic Studies

Parameter	Risk of Stone Formation
Fluid intake	↓ Risk in men and women
Calcium (dairy and nondairy)	↓ Risk in men
Calcium (dietary)	↓ Risk in women
Magnesium	↓ Risk in men
Potassium	↓ Risk in men
Phytate	↓ Risk in women
Fruits, fiber, vegetables	↓ Risk in women
Coffee, tea, wine, beer, orange juice	↓ Risk in men and women
Sugar-sweetened beverages	↑ Risk in men and women
High fructose intake	↑ Risk in men and women
Animal protein consumption	↑ Risk in men with BMI <25 kg/m^2
Vitamin C	↑ Risk in men consuming >1000 mg/d
Spinach	↑ Risk in men and older women
Sodium	No change in risk
Sucrose	No change in risk
Vitamin B(6)	No change in risk
Vitamin D	No change in risk
Supplemental calcium	No change in risk

for adults with kidney stones, professional societies recommend using ultrasound as the initial imaging study for children with suspected nephrolithiasis and reserving CT only for children with a nondiagnostic ultrasound in whom the clinical suspicion for stones remains high.[62,63] However, use of CT as the first imaging study for children with nephrolithiasis is common and demonstrates substantial regional variability across the United States.[64] Finally, because nephrolithiasis is associated with an increased risk of ESRD,[47] coronary heart disease,[65] and bony fracture,[66] it is possible, although unproved, that patients who develop kidney stone disease during childhood will be at higher risk for these adverse health conditions given the long lifetime over which they can develop. Table 1 is a list of dietary risk factors for kidney stones examined in epidemiological studies.

CONCLUSIONS

Nephrolithiasis continues to be a common cause of morbidity. The evolving epidemiology of this disease includes changes in gender distribution, associations with systemic disease, and increasing prevalence in children. Future investigations into the physiology underlying these relations may further elucidate the mechanisms underlying nephrolithiasis.

REFERENCES

1. Eknoyan G, De Santo NG. The enlightenment kidney-nephrology in and about the eighteenth century. *Semin Dial.* 2012;25(1):74-81.
2. Scales CD Jr, Smith AC, Hanley JM, Saigal CS, Urologic Diseases in America Project. Prevalence of kidney stones in the United States. *Eur Urol.* 2012;62(1):160-165.
3. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC. Time trends in reported prevalence of kidney stones in the United States: 1976-1994. *Kidney Int.* 2003;63(5):1817-1823.
4. Curhan GC. Epidemiology of stone disease. *Urol Clin North Am.* 2007;34(3):287-293.
5. Pearle MS, Calhoun EA, Curhan GC. Urologic Diseases of America Project. Urologic diseases in America project: urolithiasis. *J Urol.* 2005;173(3):848-857.
6. Saigal CS, Joyce G, Timilsina AR, Urologic Diseases in America Project. Direct and indirect costs of nephrolithiasis in an employed population: opportunity for disease management? *Kidney Int.* 2005;68(4):1808-1814.
7. Johnson CM, Wilson DM, O'Fallon WM, Malek RS, Kurland LT. Renal stone epidemiology: a 25-year study in Rochester, Minnesota. *Kidney Int.* 1979;16(5):624-631.
8. Lieske JC, Pena de la Vega LS, Slezak JM, et al. Renal stone epidemiology in Rochester, Minnesota: an update. *Kidney Int.* 2006;69(4):760-764.
9. Hesse A, Brandle E, Wilbert D, Kohrmann KU, Alken P. Study on the prevalence and incidence of urolithiasis in Germany comparing the years 1979 vs. 2000. *Eur Urol.* 2003;44(6):709-713.
10. Trinchieri A, Coppi F, Montanari E, Del Nero A, Zanetti G, Pisani E. Increase in the prevalence of symptomatic upper urinary tract stones during the last ten years. *Eur Urol.* 2000;37(1):23-25.
11. Yasui T, Iguchi M, Suzuki S, Kohri K. Prevalence and epidemiological characteristics of urolithiasis in Japan: national trends between 1965 and 2005. *Urology.* 2008;71(2):209-213.
12. Yoshida O, Terai A, Ohkawa T, Okada Y. National trend of the incidence of urolithiasis in Japan from 1965 to 1995. *Kidney Int.* 1999;56(5):1899-1904.
13. Scales CD Jr, Curtis LH, Norris RD, et al. Changing gender prevalence of stone disease. *J Urol.* 2007;177(3):979-982.
14. Strope SA, Wolf JS Jr, Hollenbeck BK. Changes in gender distribution of urinary stone disease. *Urology.* 2010;75(3):543-546, 546.e1.
15. Ljunghall S, Danielson BG. A prospective study of renal stone recurrences. *Br J Urol.* 1984;56(2):122-124.
16. Trinchieri A, Ostini F, Nespoli R, Rovera F, Montanari E, Zanetti G. A prospective study of recurrence rate and risk factors for recurrence after a first renal stone. *J Urol.* 1999;162(1):27-30.
17. Rule AD, Lieske JC, Li X, Melton LJ 3rd, Krambeck AE, Bergstralh EJ. The ROKS nomogram for predicting a second symptomatic stone episode. *J Am Soc Nephrol.* 2014;25(12):2878-2886.
18. Daudon M, Donsimoni R, Hennequin C, et al. Sex- and age-related composition of 10 617 calculi analyzed by infrared spectroscopy. *Urol Res.* 1995;23(5):319-326.
19. Knoll T, Schubert AB, Fahlenkamp D, Leusmann DB, Wendt-Nordahl G, Schubert G. Urolithiasis through the ages: data on more than 200,000 urinary stone analyses. *J Urol.* 2011;185(4):1304-1311.
20. Moses R, Pais VM Jr, Ursiny M, Prien EL Jr, Miller N, Eisner BH. Changes in stone composition over two decades: evaluation of over 10,000 stone analyses. *Urolithiasis.* 2015;43(2):135-139.
21. Soucie JM, Thun MJ, Coates RJ, McClellan W, Austin H. Demographic and geographic variability of kidney stones in the United States. *Kidney Int.* 1994;46(3):893-899.
22. Tasian GE, Pulido JE, Gasparrini A, et al. Daily mean temperature and clinical kidney stone presentation in five U.S. metropolitan areas: a time-series analysis. *Environ Health Perspect.* 2014;122(10):1081-1087.
23. Brikowski TH, Lotan Y, Pearle MS. Climate-related increase in the prevalence of urolithiasis in the United States. *Proc Natl Acad Sci U S A.* 2008;105(28):9841-9846.
24. Taylor EN, Curhan GC. Dietary calcium from dairy and nondairy sources, and risk of symptomatic kidney stones. *J Urol.* 2013;190(4):1255-1259.
25. Curhan GC, Willett WC, Knight EL, Stampfer MJ. Dietary factors and the risk of incident kidney stones in younger women: Nurses' Health Study II. *Arch Intern Med.* 2004;164(8):885-891.
26. Sorensen MD, Hsi RS, Chi T, et al. Dietary intake of fiber, fruit and vegetables decreases the risk of incident kidney stones in women: a Women's Health Initiative report. *J Urol.* 2014;192(6):1694-1699.
27. Ferraro PM, Taylor EN, Gambaro G, Curhan GC. Soda and other beverages and the risk of kidney stones. *Clin J Am Soc Nephrol.* 2013;8(8):1389-1395.
28. Taylor EN, Stampfer MJ, Curhan GC. Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. *J Am Soc Nephrol.* 2004;15(12):3225-3232.
29. Taylor EN, Curhan GC. Fructose consumption and the risk of kidney stones. *Kidney Int.* 2008;73(2):207-212.
30. Curhan GC, Willett WC, Speizer FE, Spiegelman D, Stampfer MJ. Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. *Ann Intern Med.* 1997;126(7):497-504.
31. Taylor EN, Curhan GC. Determinants of 24-hour urinary oxalate excretion. *Clin J Am Soc Nephrol.* 2008;3(5):1453-1460.
32. Taylor EN, Curhan GC. Oxalate intake and the risk for nephrolithiasis. *J Am Soc Nephrol.* 2007;18(7):2198-2204.
33. Sakhaee K. Nephrolithiasis as a systemic disorder. *Curr Opin Nephrol Hypertens.* 2008;17(3):304-309.
34. West B, Luke A, Durazo-Arvizu RA, Cao G, Shoham D, Kramer H. Metabolic syndrome and self-reported history of kidney stones: the National Health and Nutrition Examination Survey (NHANES III) 1988-1994. *Am J Kidney Dis.* 2008;51(5):741-747.
35. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. *JAMA.* 2005;293(4):455-462.
36. Taylor EN, Stampfer MJ, Curhan GC. Diabetes mellitus and the risk of nephrolithiasis. *Kidney Int.* 2005;68(3):1230-1235.

37. Cameron MA, Maalouf NM, Adams-Huet B, Moe OW, Sakhaee K. Urine composition in type 2 diabetes: predisposition to uric acid nephrolithiasis. *J Am Soc Nephrol.* 2006;17(5):1422-1428.
38. Daudon M, Traxer O, Conort P, Lacour B, Jungers P. Type 2 diabetes increases the risk for uric acid stones. *J Am Soc Nephrol.* 2006;17(7):2026-2033.
39. Eisner BH, Porten SP, Bechis SK, Stoller ML. Diabetic kidney stone formers excrete more oxalate and have lower urine pH than nondiabetic stone formers. *J Urol.* 2010;183(6):2244-2248.
40. Weinberg AE, Patel CJ, Chertow GM, Leppert JT. Diabetic severity and risk of kidney stone disease. *Eur Urol.* 2014;65(1):242-247.
41. Madore F, Stampfer MJ, Willett WC, Speizer FE, Curhan GC. Nephrolithiasis and risk of hypertension in women. *Am J Kidney Dis.* 1998;32(5):802-807.
42. Madore F, Stampfer MJ, Rimm EB, Curhan GC. Nephrolithiasis and risk of hypertension. *Am J Hypertens.* 1998;11(1 Pt 1):46-53.
43. Reiner AP, Kahn A, Eisner BH, et al. Kidney stones and subclinical atherosclerosis in young adults: the CARDIA study. *J Urol.* 2011;185(3):920-925.
44. Rule AD, Roger VL, Melton LJ 3rd, et al. Kidney stones associate with increased risk for myocardial infarction. *J Am Soc Nephrol.* 2010;21(10):1641-1644.
45. Rule AD, Bergstralh EJ, Melton LJ 3rd, Li X, Weaver AL, Lieske JC. Kidney stones and the risk for chronic kidney disease. *Clin J Am Soc Nephrol.* 2009;4(4):804-811.
46. El-Zoghby ZM, Lieske JC, Foley RN, et al. Urolithiasis and the risk of ESRD. *Clin J Am Soc Nephrol.* 2012;7(9):1409-1415.
47. Alexander RT, Hemmelgarn BR, Wiebe N, et al. Kidney stones and kidney function loss: a cohort study. *BMJ.* 2012;345:e5287.
48. Gillen DL, Worcester EM, Coe FL. Decreased renal function among adults with a history of nephrolithiasis: a study of NHANES III. *Kidney Int.* 2005;67(2):685-690.
49. Shoag J, Halpern J, Goldfarb DS, Eisner BH. Risk of chronic and end stage kidney disease in patients with nephrolithiasis. *J Urol.* 2014;192(5):1440-1445.
50. Bush NC, Xu L, Brown BJ, et al. Hospitalizations for pediatric stone disease in United States, 2002-2007. *J Urol.* 2010;183(3):1151-1156.
51. Dwyer ME, Krambeck AE, Bergstralh EJ, Milliner DS, Lieske JC, Rule AD. Temporal trends in incidence of kidney stones among children: a 25-year population based study. *J Urol.* 2012;188(1):247-252.
52. Routh JC, Graham DA, Nelson CP. Epidemiological trends in pediatric urolithiasis at United States freestanding pediatric hospitals. *J Urol.* 2010;184(3):1100-1104.
53. Sas DJ, Hulsey TC, Shatat IF, Orak JK. Increasing incidence of kidney stones in children evaluated in the emergency department. *J Pediatr.* 2010;157(1):132-137.
54. Matlaga BR, Schaeffer AJ, Novak TE, Trock BJ. Epidemiologic insights into pediatric kidney stone disease. *Urol Res.* 2010;38(6):453-457.
55. Kirejczyk JK, Porowski T, Filonowicz R, et al. An association between kidney stone composition and urinary metabolic disturbances in children. *J Pediatr Urol.* 2014;10(1):130-135.
56. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. *JAMA.* 2012;307(5):483-490.
57. Vos MB, Kimmons JE, Gillespie C, Welsh J, Blanck HM. Dietary fructose consumption among US children and adults: the Third National Health and Nutrition Examination Survey. *Medscape J Med.* 2008;10(7):160.
58. Clark MA, Fox MK. Nutritional quality of the diets of US public school children and the role of the school meal programs. *J Am Diet Assoc.* 2009;109(2 Suppl):S44-S56.
59. Kant AK, Graubard BI. Contributors of water intake in US children and adolescents: associations with dietary and meal characteristics–National Health and Nutrition Examination Survey 2005-2006. *Am J Clin Nutr.* 2010;92(4):887-896.
60. Eisner BH, Eisenberg ML, Stoller ML. Influence of body mass index on quantitative 24-hour urine chemistry studies in children with nephrolithiasis. *J Urol.* 2009;182(3):1142-1145.
61. Kim SS, Luan X, Canning DA, Landis JR, Keren R. Association between body mass index and urolithiasis in children. *J Urol.* 2011;186(4 Suppl):1734-1739.
62. Fulgham PF, Assimos DG, Pearle MS, Preminger GM. Clinical effectiveness protocols for imaging in the management of ureteral calculous disease: AUA technology assessment. *J Urol.* 2013;189(4):1203-1213.
63. Goske MJ, Applegate KE, Boylan J, et al. The Image Gently campaign: working together to change practice. *AJR Am J Roentgenol.* 2008;190(2):273-274.
64. Tasian GE, Pulido JE, Keren R, et al. Use of and regional variation in initial CT imaging for kidney stones. *Pediatrics.* 2014;134(5):909-915.
65. Ferraro PM, Taylor EN, Eisner BH, et al. History of kidney stones and the risk of coronary heart disease. *JAMA.* 2013;310(4):408-415.
66. Denburg MR, Leonard MB, Haynes K, et al. Risk of fracture in urolithiasis: a population-based cohort study using the health improvement network. *Clin J Am Soc Nephrol.* 2014;9(12):2133-2140.