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Systemic implications of urinary stone disease

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Abstract: Urinary stone disease is the third most common condition affecting the urinary tract. It contributes to a great deal of morbidity for both men and women, and cost the United States (US) over 5.3 billion dollars in 2000 alone. Moreover, it is associated with systemic diseases such as hypertension, diabetes, and other components of the metabolic syndrome. Reciprocally, these systemic diseases may be contributing to the rising incidence in urinary stone disease. Previously described mechanisms of stone formation attribute stone development and growth to the urinary milieu. While this may partly influence the process, it cannot account for the associations between systemic diseases and stones observed in large community-based studies. Here we present a review of the evidence demonstrating a link between urinary stone disease and components of the metabolic syndrome. We believe a vascular etiology for the initiation of urinary stones may tie these processes together.

Keywords: Diabetes; kidney; nephrolithiasis; obesity; stone; vascular; metabolic syndrome

Introduction

Urinary stone disease has been a part of the human experience at least since the peak of the ancient Egyptian civilization (1) and continues to be responsible for a growing number of physician and hospital visits. Though exact numbers are difficult to obtain, numerous estimates suggest that up to 13% of North Americans will develop a kidney stone in their lifetime, with estimates ranging from 1-5% in Asia, and up to 20% in Saudi Arabia (2). Kidney stones have been reported in all ages, peaking between the ages of 20 and 60 and rapidly increasing in frequency from ages 40 to 59 (3). The overall prevalence of kidney stones in the United States has increased over the last thirty years. Currently, stone disease is most prevalent among non-Hispanic Caucasians (5.9%) and Mexican-Americans (2.6%) and less so among non-Hispanic African Americans (1.7%). Prevalence also is associated with region of residence, with greatest prevalence in the South (6.6%), compared to lowest in the West (3.3%) (4). Differences in state-specific prevalences are most pronounced among men in North Carolina (14.9%) and North Dakota (5.6%) and between

women in South Carolina (6.4%) and South Dakota (2.4%) (5). Furthermore, several retrospective studies have shown that those who have had one symptomatic kidney stone episode are at increased risk of recurrence, with a cumulative recurrence rate of 14% at 1 year, 35% at 5 years, and 52% at 10 years (6).

According to most global estimates men form more kidney stones than women, at a ratio close to 3:1, however, these ratios differ geographically, with a 2.5:1 sex ratio in Japan compared to 1.15:1 in Iran (3). In younger populations this trend is reversed. Among 14- to 24-year-olds in Germany, 21- to 30-year-olds in Italy, and 20- to 29-year-olds in the United States, women demonstrate higher prevalences, though the absolute differences between men and women are minimal (7). In the United states, estimates of the direct costs of treatment and indirect costs of productivity time lost to nephrolithiasis exceeded $5.3 billion in 2000 (8).

In addition to being a prevalent and costly problem, urinary stone disease is associated with several other common and morbid conditions, including the metabolic syndrome and some of its individual components -

hypertension, diabetes mellitus, and obesity. While the pathogenesis of these interactions has not been fully elucidated, there is a body of evidence indicating that these interactions exist and that they may be bidirectional.

Hypertension

Data from the United States Census Bureau and National Health and Nutrition Examination Survey (NHANES) from 2007-2008 demonstrated that 28-30%, or approximately 65 million adults, of the US population 18 years and older have hypertension (9,10). The relationship between hypertension and kidney stones has been demonstrated in multivariate regression analyses from several large cohorts. The earliest one in the 1960s included a population of 895 50-year-old men living in Goteborg, Sweden; the second one of 3,431 residents of Gubbio in central Italy, and the third one of 503 workers between ages 21-68 years at the Olivetti factory in Southern Italy (11). Cappuccio *et al.* studied Olivetti factory workers who had no evidence of kidney stone disease at baseline and saw 52 (10.3%) incident cases of symptomatic kidney stones after eight years of follow-up. They noted that the incidence of kidney stone disease was higher in hypertensive men than normotensive ones with a relative risk (RR) of 1.96 and 95% confidence interval (CI) 1.16 to 3.32 (11,12). Another study from Parma, Italy, by Borghi *et al.*, showed that 132 patients with hypertension at baseline had an increased risk of forming a kidney stone during the five years of follow-up with an odds ratio (OR) of 5.5 (CI 1.82 to 16.66) (13).

In other studies, stone formation appeared to predate the onset of hypertension. In a large prospective cohort of 51,529 men, Madore *et al.* found a positive association between nephrolithiasis and hypertension, with an OR of 1.31 (CI 1.30 to 1.32). Furthermore, they noted that among men who reported both disorders, 79.5% reported that the occurrence of nephrolithiasis was prior to or concomitant with the diagnosis of hypertension (14). Using the Nurses' Health Study, Madore *et al.* were able to explore this relationship in a cohort of 89,376 women aged 34-59 years and showed that the data was consistent with the results obtained in men. They demonstrated that patients with a history of nephrolithiasis have a RR of 1.36 (CI 1.20 to 1.43) of developing a new diagnosis of hypertension (15). Gillen *et al.* were able to reproduce this association using NHANES data of 919 persons with a baseline history of kidney stones and 19,120 without. They showed that stone forming women experienced a 69% increased odds of self-

reported hypertension (CI 1.33 to 2.17) (16).

While the aforementioned studies establish a bidirectional link between hypertension and nephrolithiasis, the underlying pathophysiology remains unclear. Numerous mechanisms have been proposed to explain why hypertensive patients form stones and why stone formers are at increased risk of developing hypertension. Some data implicate the importance of urinary composition and diet as a possible mechanism underlying this association.

In a case-control study, Strazzullo *et al.* investigated the question of why hypertension may contribute to urinary stone disease by examining calcium metabolism in patients with and without essential hypertension. The authors noted higher calcium excretion rates in the hypertensive group in the presence of similar serum total and ionized calcium levels. Furthermore, they noted that after an intravenous calcium infusion in seven hypertensive patients and controls, the hypertensive patients excreted more calcium at all serum calcium concentrations, supporting the "urinary leak" hypothesis of essential hypertension (17). The authors' data implied that the urine composition of patients with hypertension is unique, characterized by higher levels of calcium. Cappuccio *et al.* noted additional abnormalities of calcium metabolism in patients with hypertension, including evidence of increased activity of the parathyroid gland, increased urinary cyclic AMP, and increased levels of intestinal calcium absorption (18). Another group exploring the relationship of urinary calcium excretion and hypertension analyzed urine samples from 486 patients with known kidney stones and noted that patients who had elevated levels of both calcium and uric acid in the urine had an adjusted OR of 5.6 (CI 2.39 to 13.30) of having a positive family history of hypertension compared to controls (19). Taylor *et al.* compared the urine composition of individuals with and without hypertension using the Nurses' Health Studies I and II and the Health Professionals Follow-up Study to determine predictors of hypertension. Their study did not find a significant difference in urinary calcium levels, but demonstrated that low urine citrate was the only factor consistently related to hypertension (20). Borghi *et al.* demonstrated that baseline urine levels of calcium, magnesium and oxalate in hypertensive patients are different from those that are normotensive. They noted that the supersaturation of calcium oxalate (8.9 *vs.* 6.1 mg/day) and calcium phosphate (1.39 *vs.* 0.74 mg/day) in men and only calcium oxalate (7.1 *vs.* 4.8 mg/day) in women revealed the greatest predictive value for developing calcium-based urinary stones (13).

The second commonly proposed mechanism for the association between hypertension and urinary stone disease involves the impact of dietary sodium. Muldowney *et al*. showed that daily urinary calcium excretion varied with moderate changes in dietary sodium intake. A reduction of daily dietary sodium consumption from 200 to 80 mEq/day was sufficient to reclassify patients from hypercalciuric to normocalciuric, demonstrating that high sodium intake contributes to hypercalciuria, which has been shown to contribute to the formation of urinary stones (21). A meta-analysis by He *et al*. concluded that reducing sodium intake by 50 mEq/day in hypertensive patients decreased systolic blood pressure by 4.0 mmHg and diastolic blood pressure by 2.5 mmHg, however this particular study did not evaluate this impact on urinary stone disease (22). Taken together, these data reveal that reduction in dietary sodium may reduce urinary calcium excretion as well as blood pressure, providing a possible link between hypertension and urinary stone disease.

In a reciprocal fashion, there have been several studies to evaluate why some stone formers may become hypertensive. The commonly proposed mechanisms suggest that nephrolithiasis leads to renal damage, which in turn contributes to the development of hypertension. Gambaro *et al*. evaluated the renal risks of nephrolithiasis, highlighting that recurrent episodes of obstructive uropathy secondary to stones led to varying degrees of renal atrophy by inducing tubular cell changes (via the synthesis of chemoattractants and osteopontin), macrophage-mediated interstitial inflammation, and interstitial fibroblast modulation. These effects contributed to renal fibrosis, glomerulosclerosis, and damage to the renal parenchyma, ultimately resulting in a reduced glomerular filtration rate and renal failure (23). An additional mechanism of nephrolithiasis-mediated renal damage involves the direct interaction of calcium oxalate crystals and the tubular epithelium, endothelium, and fibroblasts. Knoll *et al*. demonstrated that renal epithelial cells are more vulnerable to oxalate on the basolateral side, and that calcification in the interstitium may exert toxic effects on these cells, causing marked inflammation, cell proliferation, and renal parenchyma fibrosis (24). The link between renal failure and hypertension has been well established in population cohorts. A possible mechanism was described by Weidmann *et al*. who noted that hypertensive patients with renal failure have a two-fold higher mean plasma renin level for any given sodium or blood volume state, suggesting that hypertension in end-stage kidney disease is associated with differing levels of intrarenal vasoactive mediators.

These studies demonstrate a bidirectional association between nephrolithiasis and hypertension and provide several mechanisms to explain the pathophysiology of this association.

Diabetes

As with hypertension, the relationship between nephrolithiasis and diabetes mellitus (DM) also appears to be bidirectional, as described in a number of large population studies. Taylor *et al*. conducted a cross-sectional analysis of over 200,000 patients using the Nurses' Health Studies I and II and the Health Professionals Follow-up Study to evaluate the association of diabetes mellitus and incidence of nephrolithiasis over 44 years of follow-up. They demonstrated that the RR of stone formation among those with diabetes mellitus was 1.29 (CI 1.05 to 1.58) in older women, 1.60 (CI 1.16 to 2.21) in younger women, and 0.81 (CI 0.59 to 1.09) in men. The multivariate RR of a new diagnosis of diabetes mellitus among participants with and without a history of kidney stones was 1.33 (CI 1.18 to 1.50) in older women, 1.48 (CI 1.14 to 1.91) in younger women, and 1.49 (CI 1.29 to 1.72) in men. Thus, the authors demonstrated that women with diabetes are at increased risk of developing kidney stones and that both men and women with stones are at increased risk of developing diabetes (25). Chung *et al*. demonstrated this relationship in Taiwanese patients. The authors matched 23,569 adults with a new diagnosis of urinary stone disease to 70,707 matched controls, and followed these patients for five years. They noted that the RR of developing diabetes was 1.32 (CI 1.26 to 1.39) for patients with urinary stones (26).

Daudon *et al*. demonstrated that diabetics are at especially increased risk of forming uric acid stones by analyzing 2,464 stones from 272 patients with and 2,192 patients without diabetes. The proportion of uric acid stones was 35.7% among those with diabetes and 11.3% among those without (P<0.001). Correspondingly, the proportion of diabetics was significantly higher among uric acid stone formers than calcium stone formers (27.8% *vs*. 6.9% P<0.001), with step wise regression analysis demonstrating that type II diabetes is strongly associated with increased risk of forming uric acid stones with an OR of 6.9 (CI 5.5 to 8.8) (27). Pak *et al*. used demographic and biochemical data from 59 stone forming patients with diabetes and 116 calcium oxalate stone formers without diabetes and also demonstrated that uric acid stones were more prevalent in patients with type

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II diabetes mellitus (33.9% *vs.* 6.2%), and that their urinary pH was lower than that noted in patients with calcium oxalate stones (pH=5.5 *vs.* 5.9) (28).

Several pathophysiologic mechanisms likely contribute to the observation that diabetics are at increased risk for urinary stone disease. Insulin resistance seen in diabetes mellitus has been shown to impair renal ammoniagenesis, contributing to the production of acidic urine and a perpetually low urine pH (29). Furthermore, insulin increases parallel reabsorption of sodium and uric acid in the proximal tubule, resulting in hyperuricemia. Finally, the effect of overwhelming hyperglycemia alters the tubular transport of uric acid (27). While several of the aforementioned studies elucidated possible mechanisms for increased prevalence of uric acid stones in patients with diabetes, Lemann *et al.* were able to demonstrate a mechanism that may tie hyperglycemia to the production of calcium stones. The authors demonstrated an increased rate of calcium excretion in response to sugar ingestion among stone formers compared to non-stone formers. Furthermore, they were able to show that stone formers overall excreted more calcium than non-stone formers (7.8±0.9 millimoles per day *vs.* 3.6±0.3 millimoles, P<0.001) (30). Thus, if hyperglycemia is associated with calcium excretion, diabetics may be at increased risk for calcium stone formation. Urinary calcium levels in diabetics could be examined to further explore this hypothesis.

In addition to uric acid, diabetic stone formers also differ in their excretion of oxalate. We studied urine composition of 462 stone forming patients and demonstrated that diabetic patients have a urine volume greater by 0.38 liters/day (CI 0.13 to 0.64), urine pH lower by 0.34 (CI –0.48 to –0.21), and significantly greater urine oxalate by 6.43 mg/day (CI 1.26 to 11.60) than non-diabetic patients (31).

These studies highlight a possible causal relationship between type II diabetes and nephrolithiasis and suggest several mechanisms to explain the association. Conversely, the reasons why patients with urinary stones may develop diabetes remain to be elucidated.

Obesity

The relationship between obesity and urinary stone disease has been demonstrated in several large cohorts of both men and women. Curhan *et al.* used data from the Nurses' Health Study I and the Health Professionals Follow-up Study to demonstrate that the incidence of stone disease was associated with weight and body mass index (BMI),

with a multivariate RR of 1.89 (1.51 to 2.36) for women with a BMI ≥32 kg/m^2 compared with BMI 21-23 kg/m^2, and multivariate increased relative risk of 1.19 (CI 0.83 to 1.70) for men. The data suggested that while body size is associated with stone formation, the association is stronger in women (32). Further analysis of these cohorts with the addition of the Nurses' Health Study II and longer follow-up by Taylor *et al.* demonstrated that the relative risk of incident kidney stone formation for people weighing more than 100 kg, as compared to those weighing less than 68.2 kg, was 1.44 (CI 1.11 to 1.86) in men, 1.89 (CI 1.52 to 2.36) in older women, and 1.92 (CI 1.59 to 2.31) in younger women. Using a BMI cutoff of 30, the relative risks were 1.33 (CI 1.08 to 1.63), 1.90 (CI 1.61 to 2.25), and 2.09 (CI 1.77 to 2.48), respectively. A similar association was seen between weight gain and incident stone formation among men who gained more than 15.9 kg after age 21, with a relative risk of 1.39 (CI 1.14 to 1.70) for these individuals compared to those who had less weight gain. In older and younger women with the same weight gain after age 18, a relative risk of urinary stones of 1.70 (CI 1.40 to 2.05) and 1.82 (CI 1.50 to 2.21) in the group with higher weight gain was demonstrated, respectively (33).

While these data established association, Ekeruo *et al.* analyzed urine chemistries from obese (BMI>30) urinary stone formers to elucidate a mechanism linking the two disease processes. They identified hypocitraturia (54%) and hyperuricosuria (43%) as the most common metabolic abnormalities in the urine, present at levels significantly higher than that of the non-obese stone formers (34). Taylor *et al.* looked for similar patterns in urine chemistries using stone forming and non-stone forming participants in the Nurses' Health Studies I and II and the Health Professionals Follow-up Study, and were able to demonstrate that participants with BMI in the highest quintiles excreted more oxalate (P<0.04), uric acid (P<0.001), sodium (P<0.001), and phosphate (P<0.001) than participants with lower BMIs. They also noted that urinary supersaturation of uric acid increased with BMI (P≤0.01) (35). In a similar analysis of urine chemistry among obese and non-obese stone formers, Powell *et al.* demonstrated an increased urinary concentration of sodium, uric acid, sulfate, and phosphate in obese patients of both sexes, with increased oxalate levels in obese men, and increased cystine levels in obese women (36).

The effects of insulin resistance, low urinary pH, increased levels of urinary uric acid, and insulin-mediated increases of urinary calcium and urinary oxalate all

contribute to a urinary environment conducive to stone formation. These links may provide greater clarity in the mechanisms by which risk of urinary stone formation is increased in obese patients (33).

Metabolic syndrome

While an exact working definition of the metabolic syndrome has been evolving over time, the consensus components of the syndrome are 3 or more of the following five metabolic traits: diabetes mellitus, hypertension, obesity, hypertriglyceridemia, and dyslipidemia. These factors are thought to synergistically increase the risk of cardiovascular disease (37). Greater than 25% of the US population has the metabolic syndrome and the prevalence continues to grow (38).

Several groups have described an association between the metabolic syndrome and urinary stone disease. West *et al.* used NHANES data to demonstrate that the prevalence of self-reported history of urinary stone disease increases with the number of metabolic syndrome traits, with a relative risk of 1.76 (CI 1.08-2.85) with three traits, and a relative risk of 1.93 (CI 1.04-3.56) with five traits (39). Rendina *et al.* assessed 2,132 Caucasian patients in Spinelli Hospital in southern Italy for the diagnosis of the metabolic syndrome and presence of nephrolithiasis. They noted that 50.9% of patients with ultrasound evidence of kidney stones met the criteria for the metabolic syndrome, and that the presence of urinary stones was associated with occurrence of the metabolic syndrome with an odds ratio of 2.2 (CI 1.7 to 2.9). In addition, hypertension and high waist circumference in women were individually associated with echographic evidence of nephrolithiasis with an OR of 2.7 (CI 2.0 to 3.6) and 1.9 (CI 1.5 to 2.5), respectively (40). Another cross-sectional analysis of 34,895 patients by Jeong *et al.* looked at the association between the metabolic syndrome and the presence of kidney stones by evaluating radiographic evidence of stone disease in a clinic population. The presence of the metabolic syndrome conferred an OR of 1.25 (CI 1.03 to 1.50) for patients with kidney stones. Among patients with hypertension, the OR for the presence of kidney stones was 1.47 (CI 1.25 to 1.71) compared to those without hypertension (41). These studies evaluating the association between the diagnosis of the metabolic syndrome and nephrolithiasis demonstrate that there is a cumulative and synergistic effect of each component of the syndrome in increasing risk for stones, and that stone formers, controlling for other factors, are at greater risk for

the metabolic syndrome.

Unifying discussion: Putting it all together

There is accumulating evidence that hypertension, diabetes mellitus, obesity, and the metabolic syndrome are closely associated with urinary stone disease. While these associations are clear from epidemiologic studies, no unifying elements have been identified as underlying, causal themes. We propose that the vascular renal system is intimately associated with urinary stone disease and that by addressing the renal vascular tree we may be able to develop novel therapies and prophylactic measures for the clinical management of nephrolithiasis.

The urinary milieu has been traditionally viewed as the critical and initiating factor in the formation of urinary stones and numerous urine chemistry studies have demonstrated differing levels of calcium or uric acid associated with urinary stone disease. However, this does not fully account for the evidence demonstrating the interaction of systemic disease with stones. Alexander Randall proposed one of the earliest models of stone formation by describing plaque-like regions in the renal papillae on which he believed calcium oxalate stones develop and grow (42). Evan *et al.* were able to directly observe that these plaques arise from the basement membrane of the loops of Henle, expand through the interstitium, and protrude into the epithelium of the renal papillae (43).

Our examination of Randall's plaques using radiography and immunohistochemistry noted that the calcifications are not simply subepithelial deposits as previously suggested, but extend deep into the papilla, to the basement membrane of the collecting tubules and to the vasa recta (44). This prompted us to explore an alternate etiology for stone formation, namely that the primary stone forming event occurs in the vascular bed of the renal papilla. The vascular theory of stone development suggests that the papillary vasculature is injured and repaired in an atherosclerosis-like fashion, resulting in calcification of the vessel wall and eventual erosion of the calculus into the renal papillary interstitium and eventually into the papilla (45). To support this hypothesis we analyzed urinary calculi for total and esterified cholesterol content and demonstrated that esterified cholesterol accounted for 14-16% of total cholesterol in urinary stones and the esterified-to-free cholesterol ratio appears to be related to stone composition, namely demonstrating that stones composed of 80% or greater calcium oxalate had a greater than 40% esterified-

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to-free cholesterol ratio (45). Since esterified cholesterol is associated with other examples of atherosclerosis, these cholesterol component findings suggest that the atherosclerotic plaque model may enhance understanding of urinary stone formation.

Additional interactions between the vascular system and stone formation were indirectly explored utilizing renal perfusion studies. We used scintigraphy in healthy, non-stone formers to measure renal perfusion in three typical sleep positions (supine, left decubitus, and right decubitus). We noted symmetrical renal perfusion in all volunteers in the supine position, and increased renal perfusion in the dependent kidney in the decubitus position when compared with the same kidney in the supine position (46). Given that urinary stones are largely unilateral, and the side of stone formation is the dependent sleep side in the majority of patients (47), the observation that renal perfusion is also position dependent suggests that altered renal blood flow may contribute to stone formation.

While the microscopic relationship between stone formation and the vascular system has not been demonstrated in a patient population, Rule *et al*. set out to determine this relationship by studying whether kidney stones contribute to the risk of myocardial infarction. They matched kidney stone formers with non-stone formers in Olmstead County, Minnesota and during 9 years of follow-up stone formers had a 31% increased risk for myocardial infarction, adjusting for chronic kidney disease, hypertension, diabetes, obesity, and several other factors (48). Exploring this relationship in a female cohort, we analyzed data from the Study of Osteoporotic Fractures and demonstrated that older women with nephrolithiasis have a relative risk of 1.78 (CI 1.22 to 2.62) for myocardial infarction, 1.63 (CI 1.18 to 2.25) for angina, and 2.21 (CI 1.29 to 3.79) for congestive heart failure (49). This is consistent with other studies that have demonstrated the association between nephrolithiasis and clinical cardiovascular disease.

We also analyzed 5,115 men and women between the ages of 18 and 30 years from the Coronary Artery Risk Development in Youth Adults (CARDIA) study to determine the relationship between nephrolithiasis and carotid wall thickness and carotid stenosis (assessed by B-mode ultrasound). By twenty years of follow-up, 3.9% of CARDIA participants had reported having kidney stones, and the association of kidney stones with carotid atherosclerosis was significant, with an odds ratio of 1.6 (CI 1.1 to 2.3), adjusting for other major risk factors (50).

While this study does not provide a mechanism for this interaction, it solidifies the association of nephrolithiasis and atherosclerosis.

Conclusions

Clinicians that deal with urinary stone disease frequently provide global recommendations for patients to prevent nephrolithiasis recurrence, including increasing fluid intake, reducing sodium intake, and moderating animal protein consumption. It can be perplexing to physicians and patients when these dietary recommendations are followed but the patient subsequently presents with a new urinary stone. Many physicians will direct blame to the patient for non-compliance (particularly inadequate fluid intake) rather than looking to other underlying mechanisms by which stones may develop. In reality, these dietary guidelines are the components of a heart-healthy diet. In making these recommendations, we may not only be preventing the development of urinary stones, but also in part preventing and treating obesity, hypertension, coronary artery disease, and the metabolic syndrome. Conversely, these associated metabolic diseases may be the true culprit driving the formation of urinary stones and as such warrant further study. Future research focusing on total energy consumption and physical activity may shed light on the association between urinary stone disease and diseases of the vascular tree.

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Footnote

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