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The association of cardiovascular disease and metabolic syndrome with nephrolithiasis

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Abstract

Purpose of review—This review describes the relationship between nephrolithiasis, vascular disease and metabolic syndrome.

Recent findings—There is increasing evidence that kidney stone formation is associated with a number of systemic problems including cardiovascular disease, metabolic syndrome and its components. Some of these associations are bidirectional. The reasons for these associations are not totally clear, but potential factors include metabolic responses associated with these disorders that promote a stone forming milieu in urine, environmental factors such as diet, oxidative stress and inflammation and molecular changes impacting the transport of certain analytes in urine.

Summary—Urologists need to be cognizant of these associations as they may be able to contribute to an early diagnosis of a significant medical problem, or provide counseling to patients to prevent their occurrence.

Keywords

hypertension; metabolic syndrome; nephrolithiasis; obesity; vascular disease

INTRODUCTION

There is strong evidence that kidney stone formation is associated with a number of systemic diseases. This includes cardiovascular disease, metabolic syndrome and its components. A number of these associations are bidirectional; those with stones being prone to the disease and those with the systemic disease at risk for stone formation. Herein, we review the associations between kidney stone formation, vascular disease, metabolic syndrome and its components.

CARDIOVASCULAR DISEASE

Atherosclerosis is a progressive process that generally starts years before its consequences become clinically apparent. A recent study demonstrated that young adults who form kidney stones have a higher prevalence of subclinical atherosclerosis [1■]. The Coronary

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Conflicts of interest

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Artery Risk Development in Young Adults (CARDIA) study is a US population-based observational study of 5115 adults who were between the ages of 18 and 30 years at the time of enrollment in 1985–1986. Cardiovascular risk factors including carotid intima-media wall thickness measured by B-mode ultrasound were assessed at enrollment and at 2, 5, 7, 10, 15 and 20 years later. Increases in the thickness of the intima and media of the carotid artery have been shown to be directly associated with an increased risk of myocardial infarction and stroke [2]. At the 20-year interval, 3.9% of patients reported having a symptomatic kidney stone. After controlling for other atherosclerotic risk factors, the development of a symptomatic kidney stone was associated with an increased risk of having carotid artery atherosclerosis [odds ratio (OR) 1.6].

Individuals with kidney stones have been demonstrated to be at increased risk for coronary artery disease in contemporary studies. Rule *et al.* [3■■] performed a study of inhabitants of Olmstead County in Minnesota. There were 4564 patients who were known renal or ureteral stone formers upon study enrollment who had not previously sustained a myocardial infarction. This cohort was compared with 14144 matched, nonstone forming controls. After adjusting for age and sex, the hazards ratio for sustaining a myocardial infarction was 1.31 for the stone formers. This increased to 1.35 after adjustment for a number of comorbidities (hypertension, diabetes, obesity, chronic kidney disease, gout, dyslipidemia and tobacco use). The mean follow-up in this study was 9 years. Domingos and Serra [4■] recently performed an analysis of information obtained from the Portuguese National Health Survey via questionnaires sent to 23349 individuals at least 15 years of age. The prevalence of kidney stones was 7.3%. After adjusting for age and BMI, the OR for myocardial infarction amongst stone formers was 1.3. A small case–control study in Japan demonstrated that stone formers were at higher risk for having coronary artery disease [5]. Hamano *et al.* reported that the clinical diagnosis of coronary artery disease amongst 181 stone formers was 3.9% ascompared with zero in 187 controls. Ina multivariate logistic regression analysis, they found that stone formers had a higher prevalence of a number of coronary artery disease risk factors including the following: tobacco use, OR 4.29; hypertension, OR 3.57; hypercholesterolemia, OR 2.74.

Earlier studies regarding the associations of kidney stone formation and coronary artery disease had divergent results. Elmfeldt *et al.* [6] reported that among 299 male survivors of myocardial infarction in Göteborg, Sweden, from 1968 to 1970, the prevalence of having a kidney stone was significantly higher than the general population. However, similar studies from Oslo, Norway [7] and Uppsala, Sweden [8] conducted during a similar period did not demonstrate this relationship.

Stroke may be an outcome of cardiovascular disease. There is limited information regarding associations of stroke and kidney stone formation. Li *et al.* [9] reported that a significantly higher percentage of normotensive patients sustaining a stroke had kidney stones as compared with those who did not have such an event on the basis of an aged adjusted analysis. However, a multivariate analysis demonstrated that this association was not significant.

Overall, the aforementioned studies provide evidence of an association between kidney stone formation and cardiovascular disease. This needs to be corroborated with larger cohort studies.

METABOLIC SYNDROME

Metabolic syndrome (metabolic syndrome X, cardio metabolic syndrome, syndrome X, insulin resistance syndrome, Reaven's syndrome, the deadly quartet and coronary artery disease, hypertension, atherosclerosis, obesity, stroke) is a combination of systemic factors that increase the risk of cardiovascular disease and type II diabetes. Approximately 25% of adults in the USA are afflicted with this disorder [10]. The factors include central obesity (increased waste circumference or BMI), insulin resistance (use of medication for hyperglycemia, increased fasting blood glucose and abnormal glucose tolerance test), hypertension (use of medication for elevated blood pressure, increased systolic or diastolic blood pressure), increased blood triglycerides and reduced high-density lipoprotein cholesterol. A number of organizations have used different combinations of criteria for defining metabolic syndrome [International Diabetes Federation, World Health Organization, European Group for the Study of Insulin Resistance, US National Cholesterol Education Program (NCEP), American Heart Association]. The majority of the definitions are on the basis of an individual having three or more of the aforementioned five factors.

The association between metabolic syndrome and kidney stone formation in the USA was demonstrated by an analysis of data from the National Health and Nutrition Examination Survey III (NHANES III) [11■■]. This survey generates information obtained from interviews, physical examinations and laboratory studies done on participants from 1988 to 1994. An analysis of 18825 participants 20 years and older demonstrated a significant positive correlation between the number of metabolic syndrome traits and stone prevalence. The prevalence of self-reported kidney stones with zero traits was 3 and 7.5% for three traits and 9.8% for five traits. The prevalence of stones in those defined, as having the syndrome was 8.8 versus 4.3% for those without it. After adjusting for age, sex, race/ethnicity, economic status and use of a thiazide diuretic and allopurinol, the OR for an individual with metabolic syndrome having a self-reported kidney stone was 1.52, which was substantially higher in those with four or five traits (1.93–2.42). The trait with the greatest frequency independent of the number of other traits present was hypertension, which was present in 28.2% of those with one, 45.6% with two, 71.1% with three, 87.6% with four and 100% with five traits.

The association between metabolic syndrome and kidney stones confirmed with imaging studies has also been established. Rendina *et al.* [12] assessed 2132 patients hospitalized in an institution in southern Italy with screening renal ultrasonograpy. The prevalence of stones in patients having metabolic syndrome was 10.3%. A logistic regression analysis demonstrated that the OR for having an ultrasound-detected stone with metabolic syndrome was 2.01. An analysis of this for separate traits of metabolic syndrome and presence of kidney stones demonstrated a significant OR 2.8, for central obesity based on waist circumference and 4.9 for hypertension. A recent study from Seoul, Korea of 34895 patients undergoing health screening in which either abdominal computed tomography or

ultrasonograpy was done demonstrated that 2.4% had kidney stones [13]. The OR for having a detectable stone with metabolic syndrome was 1.25.

Many of the metabolic syndrome traits have been demonstrated to be independent risk factors for kidney stone formation. Hence, a discussion of these associations is warranted.

OBESITY AND INCREASED WAIST CIRCUMFERENCE

The associations between obesity and kidney stone formation have been demonstrated in studies of three large epidemiologic cohorts (Nurses' Health Studies I and II, and the Health Professional Follow-up Study) comprising approximately 250000 patients. Curhan *et al.* [14] reported that the age-adjusted prevalence OR for kidney stones was 1.76 for Nurses' Health Study I (older female nurses) and 1.76 for women with a BMI of at least 32 kg/m^2 as compared with those with a BMI from 21 to 22.9 kg/m^2. A similar relationship was reported for the Health Professionals Follow-up Study cohort (male health professionals) wherein the OR was 1.38. A multivariate analysis for incident stone risk (events occurring during follow-up) demonstrated an OR of 1.89 for women and 1.19 for men. In a subsequent study of these cohorts, Taylor *et al.* [15] and associates reported that the relative risk (RR) for men with a BMI of at least 30kg/m^2 for developing an incident stone was 1.33 as compared with those with a BMI of 21–22.9 kg/m^2. The RR for this relationship in older female nurses was 1.9–2.09 for younger women (Nurses' Health Study II). Significant positive correlations between waist circumference and the RR of incident stones were demonstrated for all three cohorts. Using the NCEP definitions of central obesity based on waist circumference (≥36 in. for women and ≥40 in. for men), they noted that the RR for incident kidney stones for Nurses' Health Study I was 1.49 for 37–40 in. and 1.71 for more than 40 in., whereas it was 1.71–1.94 for Nurses' Health Study II, respectively. For the male cohort, it was 1.42 for 40–43 in. and 1.48 for more than 43 in.

DIABETES MELLITUS

There is a bidirectional risk association between diabetes mellitus and kidney stone formation. This was demonstrated in an analysis of the aforementioned three large epidemiologic cohorts. The multivariate RR for prevalent stones in patients with diabetes mellitus was 1.38 for Nurses' Health Study I, 1.67 for Nurses' Health Study II and 1.31 for the Health Professionals Follow-up Study [16]. The prospective multivariate RR for those with diabetes mellitus developing an incident kidney stone was 1.29 for Nurses' Health Study I, 1.6 for Nurses' Health Study II, but only 0.81 for the male cohort. Patients in all three cohorts with a history of kidney stones were demonstrated to be at risk for developing incident diabetes mellitus. The RR for this occurrence was 1.33–1.48 for Nurses' Health Studies I and II, and 1.49 for the Health Professionals Follow-up Study.

The risk of a stone former developing diabetes mellitus is partially supported by two recent investigations. Ando *et al.* [17] from Japan demonstrated that in women with a self-reported history of kidney stones, insulin resistance as determined by a homeostasis model (fasting serum glucose × fasting serum insulin) was more prevalent in stone formers. There was also a significant positive trend for age-adjusted OR observed across tertiles of serum insulin and

insulin resistance. SBP and DBP, BMI and waist circumference were significantly higher in female stone formers as well. These trends were not seen in the male participants of this study. Chung *et al.* [18] from Taiwan performed a case–control study in which 23 569 adults who were diagnosed with kidney stones from 2001 to 2003 were compared with 70 707 matched controls. Both cohorts were followed for 5 years. The hazards ratio for a stone former developing diabetes mellitus after controlling for multiple variables including income, geographic location, urbanization level, hypertension, hyperlipidemia and obesity was 1.32.

HYPERTENSION

The first evidence of the association of hypertension and kidney stone formation was generated over 50 years ago. Tibblin [19] performed a retrospective study of 895 middle-aged Swedish men in 1967. He noted that the prevalence of kidney stones in normotensive patients was 1.1%, whereas it was 13.3% for hypertensive patients. Data from a cross-sectional population-based study of 5376 residents of Gubbio, a town in central Italy, demonstrated that the prevalence of self-reported kidney stones was significantly higher amongst patients with hypertension; 5.22 versus 3.36% [20]. Other studies from Italy have demonstrated this relationship. Cappuccio *et al.* [21] performed a study of 688 male workers at the Olivetti factory in Naples, Italy. Five hundred and nine of the 688 were normotensive, 118 had untreated and 61 treated hypertension. The OR for a hypertensive patient having had a kidney stone was 2.11. A subsequent study of this cohort demonstrated that after 8 years of longitudinal follow-up 10.3% of patients developed an incident kidney stone; 16.7% of hypertensive men versus 8.5% of normotensive male patients [22]. The RR of a hypertensive male developing a kidney stone was 1.96 and was unaffected by excluding those with treated hypertension and adjustments for age, height and body weight. In addition, during this time interval, patients in this cohort with a history of nephrolithiasis were at increased risk of developing hypertension; age-adjusted OR of 1.96. Another group of Italian investigators demonstrated an association between hypertension and the development of kidney stones. Borghi *et al.* [23] from Parma, Italy, followed 132 patients with essential hypertension and 135 normotensive adults (both men and women, all nonstone formers) for 5 years. The hypertensive patients had a significantly higher rate of developing an incident kidney stone during this period; OR 5.5. Epidemiologic studies in the USA have also assessed the association of kidney stones and hypertension. An analysis of Nurses' Health Study I demonstrated that the age-adjusted RR for the development of incident hypertension was 1.24 among those with a history of stone, whereas there was no increased risk of incident kidney stone in those with baseline hypertension [24]. Similar findings were reported from an analysis of the Health Professionals Follow-up Study. Men with a history of kidney stones were at increased risk of developing hypertension; OR 1.29, and the incident stone risk was not higher in those with hypertension. In an analysis of NHANES III, the OR of female stone formers developing hypertension was 1.69 and this appeared to be increased in stone forming women with higher BMI [25]. These trends were not demonstrated in the male cohort. A case–control study of 27410 women participating in the Women's Health Initiative Study demonstrated that the prevalence of hypertension was

significantly higher in those with kidney stones as compared with nonstone formers; 41.5 versus 34.4% [26].

REASONS FOR ASSOCIATIONS

The reasons for the associations between stone formation and these various systemic processes cannot be pinpointed, but may include similar metabolic responses and dietary habits and common pathophysiologic mechanisms. A discussion of metabolic reasons will be initially conducted.

Increased urinary calcium excretion is a risk factor for stone formation [27]. Both an association, as well as a lack of one between hypertension and increased calcium excretion has been reported. Borghi *et al.* [23] found that in nonstone forming adult men and women calcium excretion was higher in those with hypertension as compared with the normotensive cohort. In addition, the supersaturation of calcium oxalate was higher in the hypertensive group. Mente *et al.* [28] found that amongst patients with kidney stones and hypercalciuria the multivariate OR for an association with hypertension was 2.9. Taylor *et al.* [29] performed a cross-sectional study of Nurses' Health Studies I and II and the Health Professionals Follow-up Study in which patients collected 24h urine specimens. In patients with or without stones, calcium excretion was not related to hypertension. However, they did report that low urinary citrate excretion, a known risk factor for kidney stone formation, was associated with prevalent hypertension in all three of these cohorts [27]. Losito *et al.* [30] found no difference in calcium excretion amongst stone formers with or without hypertension. They also noted that hypertensive stone formers had reduced citrate excretion, urine pH and increased titratable acid excretion as compared with normotensive stone formers.

Metabolic syndrome and associated components are associated with changes in the urinary environment that favor kidney stone formation. Obese individuals have lower urine pH, which places them at risk for developing uric acid stones [31]. The low urine pH is thought to be due to decreased production of ammonium in the proximal tubule of the nephron resulting in increased titratable acid and reduced urine pH. This metabolism is insulin sensitive. Abate *et al.* [32] demonstrated that uric acid stone formers were severely insulin resistant. Maalouf and coworkers [33,34] have reported that urine pH and ammonium significantly decrease with an increasing number of metabolic syndrome components. Animal experiments and cell culture models suggest that these responses may be due to lipid accumulation within the kidney [35]. Cupisti *et al.* [36] found that insulin resistance is also associated with low urine citrate excretion. Urine oxalate directly correlates with BMI and has also been reported to be higher in those with diabetes mellitus [37–39].

Some of these associations may be influenced by diet. A low calcium diet has been demonstrated to be a risk factor for the development of kidney stones [40–42]. Low dietary calcium intake has also been reported to be associated with the development of hypertension [43,44]. The reasons for this association are unclear but may be due to vitamin D responses. A low calcium diet stimulates an increase in circulating levels of $1,25(OH)_2D_3$ resulting in an influx of calcium into smooth muscle cell and raised vascular tone, whereas increased

calcium consumption does the opposite [45]. Decreased consumption of dairy products (surrogate of calcium intake) was demonstrated to increase the risk of metabolic syndrome in overweight males and females participating in the CARDIA study [46]. Increased fructose consumption has been associated with a risk of developing incident kidney stones [47]. Increased consumption of sweetened beverages, many high in fructose content, has been reported to be associated with a higher risk of coronary artery disease in women [48].

Reduced kidney function may be an influencing factor on the linkage of kidney stone formation and cardiovascular disease. Kidney stone formers are at risk for developing chronic kidney disease. Rule *et al.* [49] reported that an analysis of almost 18000 inhabitants of Olmsted County, Minnesota demonstrated that kidney stone formers were at increased risk for developing chronic kidney disease. Gillen *et al.* [50] reported that an analysis of NHANES III demonstrated that RR of a kidney stone former with a BMI of more than 27 kg/m^2 for developing chronic kidney disease was 1.87. Chronic kidney disease is a known risk factor for the development of cardiovascular morbidity [51].

Differences in renal calcium handling may be an underlying reason for some of these associations. It has been demonstrated that renal stone formers have altered renal handling of calcium in the proximal and distal nephron resulting in increased calcium excretion [52,53]. The molecular mechanisms have not yet been defined. It is possible that the mechanisms for increased calcium excretion in kidney stone formers and hypertensive individuals are similar and if so, this would provide a causative link for both disorders. Some of the potential mechanisms may include altered transcellular calcium transport through epithelial calcium channel transient receptor potential cation channel, subfamily V, cytosolic diffusion of calcium bound to calbindin-D28K, basolateral extrusion of calcium through the Na/Ca exchanger and plasma membrane Ca-ATPase [54].

Cardiovascular disease is linked to chronic inflammation. Inflammation and oxidative stress have also been proposed to play a role in kidney stone formation. A recent study demonstrated that a number of markers of chronic inflammation were elevated in stone formers including proinflammatory cytokines, acute inflammation markers, adhesion molecules, urinary microalbumin, myeloperoxidase, 8-hydroxydeoxyguanosine, 3-nitrotyrosine and monocyte chemoattractant protein [55]. Holoch and Tracy [56] reported that kidney stone formers in NHANES III had lower levels of serum antioxidant levels including α-carotene, β-carotene and β-cryptoxanthin. Perhaps, the aforementioned milieu of inflammation and oxidative stress may be behind the linkage of these two disorders.

CONCLUSION

This review clearly demonstrates that there are definite associations between kidney stone formation, metabolic syndrome and its components and cardiovascular disease. However, it is important to recognize that association does not equate with causation. A search for common mechanisms especially at the molecular level appears warranted. When treating stone formers, urologists need to be aware of these associations, as they may be able to make the diagnosis of a significant comorbidity that could impact the patient’s life span

and quality of life. Patients should also be informed of these associations and encouraged to make lifestyle modifications to improve their general health and limit cardiovascular risk.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 165).

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KYE POINTS

- There is an association between kidney stone formation and cardiovascular disease.
- The number of components of metabolic syndrome is directly correlated with the risk of developing a kidney stone.
- There is a bidirectional association between hypertension and kidney stone formation.
- There is a bidirectional association between diabetes mellitus and kidney stone formation.
- The mechanisms behind these associations have not been clearly defined.