Antibiotics and Kidney Stones: Perturbation of the Gut-Kidney Axis

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The cumulative incidence of kidney stone disease in the United States has doubled over 15 years, and its prevalence is now equivalent to that of diabetes.[1,2] This dramatic and unexplained increase in incidence has

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disproportionately affected children and young women.[1,3] Nephrolithiasis is a disorder of mineral metabolism that is associated with increased risk for chronic kidney disease,[4,5] fracture,[6] and hypertension.[5,7] Individuals with nephrolithiasis also have a high risk for recurrent painful kidney stone events,[8,9] some of which require surgery and are associated with increased risk for kidney failure and death.[10]

Due the rapid shift in the epidemiology of nephrolithiasis, investigators have focused on identifying novel determinants of kidney stone disease, including antibiotics and their impact on the intestinal and urinary microbiome composition. In 2011 in the United States, 262 million courses of antibiotics were prescribed, with the highest rates of prescription for children younger than 10 years and women.[11] Thirty percent of patients are prescribed at least 1 antibiotic annually.[12] In this issue of *AJKD*, Ferraro et al[13] reported that prior antibiotic exposure is associated with incident symptomatic kidney stones among women in the well-characterized Nurses' Health Study (NHS) I and II cohorts. Strengths of the study include prospectively collected antibiotic exposures and, for a subset of participants, availability of 24-hour urine chemistry test results.

The results of this study are consistent with 2 recent case-control studies from Tasian et al[14] and Zampini et al,[15] which found that oral antibiotic use was associated with increased odds of kidney stones among children and adults. Zampini et al[15] found that adults with an active episode of nephrolithiasis were significantly more likely to have taken oral antibiotics in the last year, but not the last 30 days, compared with individuals with no history of the disease. In the Zampini study, both oral antibiotic use and incidence of nephrolithiasis were more associated with the urinary tract microbiome than the gut microbiome. Using incidence density sampling, Tasian et al[14] examined 25,981 patients with nephrolithiasis that were matched to 259,797 controls on age, sex, and practice at the date of diagnosis. The adjusted odds ratios for nephrolithiasis were 2.33 for sulfas, 1.88 for cephalosporins, 1.67 for fluoroquinolones, 1.70 for nitrofurantoin, and 1.27 for broad-spectrum penicillins. The magnitude of the risk was greatest for exposure 3 to 6 months before the date of diagnosis, with all but broad-spectrum penicillins remaining statistically significant 3 to 5 years from exposure. The risk was also greatest for those exposed at younger ages, which is consistent with reports that antibiotic exposures at younger ages lead to more dramatic changes in host macronutrient metabolism than those later in life.[16] These findings are also consistent with studies that have reported persistent reduction in the abundance of gut bacteria for months after antibiotic exposure, and that antibiotic use leads to a persistent reduction in oxalate metabolism by gut bacteria, which has important implications for calcium oxalate stone formation.[17,18]

The current study is consistent with the growing evidence that dysbiosis is associated with nephrolithiasis and that antibiotic exposure is an important factor on this causal pathway. Compared with nonusers, women who used antibiotics for at least 2 months between the ages of 40 and 49 years and 50 and 59 years in NHS I and between 40 and 49 years in NHS II had a pooled adjusted relative risk for self-reported incident kidney stones of 1.48 (95% confidence interval [CI], 1.12-1.96). Among younger women aged 20 to 29 years, relative risk was 1.36 (95% CI, 1.00-1.84). Importantly, ~80% of the subset of stones confirmed by medical record review were composed of calcium oxalate.

In addition, Ferraro et al, for the first time, were able to examine the association between antibiotic exposure and urine chemistries. While limited by having only a subset of 24-hour collections that were obtained after antibiotic exposure, the finding that antibiotic exposure of at least 2 months was associated with lower urine pH and urine citrate level indicates that there is likely a complex interplay between the intestinal and urinary tracts in nephrolithiasis. This gut-kidney axis is the pathway between the gut microbiome, intestinal metabolites, and urine chemistry results in human health and disease (Fig 1). Together, the Ferraro et al, Tasian et al, and Zampini et al studies indicate that exposure to oral antibiotics is a novel risk factor for nephrolithiasis, and that it may be as important as diet. Of note, this may be a preventable risk for the 30% of patients who receive inappropriate outpatient antibiotic prescriptions[19] or may be modifiable through targeted preventive measures in the setting of appropriate prescriptions.

Many groups have shown that the gut microbiome of kidney stone formers is less diverse than controls.[20] A recent Italian study also demonstrated that bacterial genes involved in oxalate degradation were less abundant in the stool of adults with calcium kidney stones. This study found that the oxalate-degrading genes were represented in several bacterial species for which the

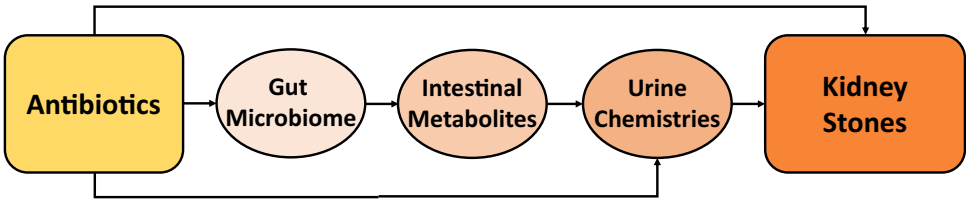

Figure 1. Proposed causal pathway of the gut-kidney axis.

combined abundance correlated inversely with urine oxalate excretion.[21]

However, it has been increasingly recognized that metabolic functions of one bacterial species affect the growth of others, which is especially true for highly symbiotic environments such as the gut.[22] A recent study by Miller et al[18] reported that a multispecies bacterial network maintains oxalate homeostasis. In particular, healthy oxalate homeostasis is likely attributed to collaborative efforts between several bacterial species, including *Ruminococcus* and *Oscillospira*. In support of bacterial symbiosis, bacterial taxa that differed between patient and control intestinal microbiota included *Desulvovibrio* and *Methanobrevibacter*, which are known to engage in sulfate reduction, methanogenesis, and acetogenesis. The dependence of members of these taxa on *Oxalobacter formigenes* is likely due to the dependency of these bacterial metabolic pathways on formate, which is the major byproduct of oxalate metabolism. It is possible that antibiotics disrupt these types of symbiotic partnerships critical for overall oxalate homeostasis within the microbiome and result in increased risk for stone formation, as reported by Ferrarro et al.

These results are consistent with prior reports that there is a sustained but not permanent reduction in the relative abundance of gut bacteria for months following antibiotic exposure.[17] The findings of Ferraro et al and others support the hypothesis that antibiotics may be contributing to the increasing prevalence, narrowing sex gap, and earlier age of onset of nephrolithiasis. In addition, investigation of the gut-kidney axis has the potential to reveal new therapeutic targets for kidney stone disease. Existing medications to decrease kidney stone recurrence include thiazide diuretics for hypercalciuria and potassium citrate for hypocitraturia. However, despite the increasing prevalence, associated morbidity, and high recurrence rate, very few drugs to prevent kidney stones have been developed, tested, and introduced in the last 30 years. Identifying the specific perturbations of the gut and urinary microbiome and the downstream effects in the urine caused by antibiotic exposure may reveal therapeutic pathways that occur upstream from urine chemistries. Most likely any treatments would have to replace more than a single organism or restore its function because early trials of oral administration of *O formigenes* and *Lactobacillus* did not lower urine oxalate levels.[23,24]

For this reason, research focusing on microbiota and kidney stone disease requires examination of the composition of the entire gut microbiome and its metabolic products rather than focusing on individual bacterial species. Given the complexity of the intestinal microbiome, a single species by itself is highly unlikely to cause incident (or recurrent) kidney stone disease. Rather, the increased risk for nephrolithiasis more likely involves overall dysfunction caused by the cumulative ripple effect of the loss of bacterial networks. A critical remaining knowledge gap is how antibiotics and other exposures such as diet affect the gut microbiome and the balance of oxalate and other intestinal and urinary metabolites in kidney stone disease. Additional areas for future research include identifying subgroups at greatest risk for kidney stones after antibiotic exposure and examining how specific classes of antibiotics perturb the gut microbiome and have downstream effects on urine metabolome and urine chemistries.

Understanding the gut-kidney axis will introduce a new paradigm for kidney stone prevention. Further studies that elucidate the specific perturbations of the gut-kidney axis in kidney stone disease will provide key insights about the rapidly changing epidemiology of nephrolithiasis and, importantly, identify targets for novel therapeutics for primary and secondary stone prevention. This current study generated new knowledge that hopefully will lead to further studies that elucidate key components of the gut-kidney axis in kidney stone disease. To achieve this goal, we need funding agencies and other important stakeholders, including the pharmaceutical industry, to invest in research that leads to new treatments for a disease that currently affects nearly 10% of the population in the United States and will likely affect many more in the future.

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