

Kidney Stones as a Systemic Disease

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Dr. Gary Curhan is an Associate Professor of Medicine at Harvard Medical School and an Associate Professor of Epidemiology at the Harvard School of Public Health. He is a leading researcher in the field of kidney disease, as well as a number of other chronic diseases, including interstitial cystitis and high blood pressure. The following represents highlights of a scientific presentation by Dr. Curhan at the September 2007 meeting of the NIDDK National Advisory Council. Dr. Curhan shared with the Council his view of kidney stone disease as an organ-specific manifestation of a more generalized systemic disorder, rather than simply a disease of the kidneys.

Kidney stone disease is a common and painful health problem in the U.S. It is also a growing problem: the number of people in the U.S. with kidney stones has increased significantly over the past 30 years. White Americans are more prone to develop kidney stones than African Americans, and men are more likely to develop stones than women. For unknown reasons, some individuals are prone to repeatedly developing stones. Each year, people make almost three million visits to health care providers and more than half a million people go to emergency rooms for kidney stone problems.¹

The first symptom of a kidney stone typically appears when the stone moves from the kidney into the ureter, causing irritation or blockage and resulting in extreme pain. Most kidney stones can pass harmlessly—though not painlessly—through the urinary system. In such cases, medication to alleviate the pain may be the only medical intervention needed. Stones that cause lasting symptoms or other complications may be treated by various techniques, most of which do not involve

major surgery. In severe cases, however, surgery may be required to remove the stone.

In addition to being extremely painful, kidney stones also are costly to treat. According to the 2007 edition of *Urologic Diseases in America*, kidney stones are the second-costliest urologic disease, accounting for over \$2 billion spent on medical care,² with another \$4 million to \$14 million spent on prescription drugs.³ These numbers do not include costs not associated with direct medical expenditures, such as time lost from work.

Composition of Kidney Stones

Kidney stones can consist of a number of different components. The most common type of stone, accounting for two-thirds of all stones, is a combination of calcium and oxalate. Less common types of stones include stones caused by urinary tract infections, and stones made of uric acid or the amino acid cystine. “Nephrolithiasis” is the medical term used to describe stones occurring in the kidney, while stones in the urinary tract are formally designated as “urolithiasis.” For the sake of simplicity, “kidney stone” is often used to designate stones regardless of their location in the kidney or urinary tract.

Urine is a liquid with various substances dissolved in it, and there is a finite amount of material that can be dissolved in a given quantity of water. If this limit is exceeded, material will fall out of solution and crystallize. Once this process starts, the nascent crystals attract other dissolved elements in the water, and the crystal grows in size. Although the precise steps that lead to kidney stone formation are not known, one way to think about crystal formation is as a problem of too much material trying to remain dissolved in too little water.

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Risk factors for kidney stones encompass gastrointestinal, skeletal, and metabolic factors, as well as obesity. At first glance, the connection of most of these factors to the kidney may not be obvious. However, closer examination reveals clues that implicate kidney stone disease as an organ-specific manifestation of more general systemic disturbances.

Risk Factors: Gastrointestinal

Because the most common type of kidney stone, the calcium oxalate stone, consists of two components found in a normal diet, it might stand to reason that increasing consumption of these factors would increase the risk of stone formation. Indeed, patients prone to developing stones are often counseled to limit their dietary intake of calcium and oxalate. However, studies reveal that increased dietary intake of calcium does not increase the risk of stone formation and may in fact reduce the risk. Increased dietary intake of oxalate has, at best, a modest impact on stone risk. Surprisingly, however, increased dietary intake of fructose correlates with a dramatic increase in risk of developing a kidney stone. Fructose is one of the two sugar molecules that comprise ordinary table sugar and is a major component of high fructose corn syrup, which is used in a large number of food products. It seems that, in some individuals, fructose can be metabolized into oxalate. This observation underscores the complexity in using diet modification in people prone to developing kidney stones, because traditional advice to limit intake of oxalate-containing foods may not be sufficient to reduce risk of stone development (for more details regarding the assessment of dietary oxalate and its role in stone formation, see the accompanying research advance, “Dietary Oxalate Is Not a Major Contributor to Kidney Stone Formation”).

Risk Factors: Bone

In addition to providing structural support and protecting internal organs, the skeleton represents a large repository for calcium. The skeleton is an active site of tissue breakdown and regeneration throughout

life. In diseases such as osteoporosis, more calcium is lost from bone than is deposited, resulting in a net negative calcium balance. Researchers have known for years that patients with elevated calcium levels in their urine are likely to have lower bone mineral density, emphasizing that there are metabolic sources for urinary calcium, as well as dietary sources.

Of course, skeletal remodeling is not the only source of circulating calcium, as this mineral is an important component of the diet. Does increased calcium in the diet increase one’s risk of developing kidney stones? Quite the opposite: several large epidemiologic studies and one randomized trial suggest that high dietary calcium intake is associated with a decreased risk of kidney stones, and that people with the lowest dietary calcium intake had an increased risk of kidney stones. The reason for this is unclear, but it is possible that higher levels of dietary calcium bind to oxalate in the digestive tract and prevent it from being absorbed and eventually moving to the kidneys where it might form stones.

Risk Factors: Obesity

It has been known for years that increasing body weight puts individuals at risk for high blood pressure, diabetes, and a host of other health problems. Recent research has also uncovered a role for obesity in the formation of kidney stones. Studies have shown that the risk of stone formation can be almost twice as great in women who weigh more than 220 pounds compared to those who weigh less than 150 pounds; overweight men are also at higher risk. The increase in relative risk is also seen if one looks at body mass index, which takes both height and weight into account. The reason for this correlation is unclear, but it is the subject of ongoing research.

As rates of obesity in the U.S. continue to rise, more people are turning to bariatric surgery as a way to address the problem. In this surgery, doctors alter the digestive tract in order to restrict food intake and, in some cases, interrupt the digestive process. When

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researchers examined urine oxalate levels in patients who had undergone this procedure, they found levels were two to three times higher than normal, and elevation in oxalate seems to result in a higher risk of stone formation. This finding underscores the complex metabolic pathways that regulate oxalate absorption and excretion and how changes to the digestive tract may have unexpected results on overall metabolism.

Risk Factors: Endocrine and Metabolic Pathways

Diabetes significantly increases an individual's risk of kidney disease, blindness, amputation, and cardiovascular disease. Scientists have recently shown that diabetes also increases the risk of developing kidney stones between 20 and 50 percent, and that this increase is especially apparent in younger women. There is also evidence that people with diabetes have a lower than normal urine pH—meaning that their urine is more acidic. This change in urine composition, sometimes accompanied by a decrease in urine volume, may also contribute to stone formation in these individuals. This observation further emphasizes that kidney stones may arise as much from generalized metabolic derangement as from kidney-specific factors.

Risk Factors: Genetics

As is the case with many diseases, it is likely that kidney stones arise from both environmental and genetic causes. Much of what is known about stone formation concerns dietary and metabolic factors, but it is likely that genetics plays an important role in determining an individual's likelihood of developing

kidney stones. Currently, a number of potential candidate genes have been identified, including the calcium sensing receptor, the vitamin D receptor, and the oxalate transporter protein in the intestine. Large genome-wide association scans that might identify other candidates have only recently begun, but hold great promise for the future (for more information about genome-wide association scans, see the chapter on Cross-Cutting Science.)

Conclusion

Kidney stone disease should be thought of as a systemic disorder and not just a disease of the kidneys. In the past several years, significant progress has been made in understanding the causes of the disease, but much work remains to be done. Moving forward, new paradigms regarding the underlying causes of the disease will shape the research agenda, especially regarding the origins of stones and the risk factors that contribute to their formation. Future large studies of genetics and gene-environment interactions will further our understanding of this complex disorder.

¹ *Kidney Stones in Adults*, National Kidney and Urologic Diseases Information Clearinghouse, National Institute of Diabetes and Digestive and Kidney Diseases. <http://kidney.niddk.nih.gov/kudiseases/pubs/stonesadults/index.htm>

² Litwin MS and Saigal CS: *Introduction in Urologic Diseases in America* (pp. 1-7). NIDDK, NIH Publication Number 07-5512, 2007.

³ Pearle MS, Calhoun E, and Curhan GC: *Urolithiasis in Urologic Diseases in America* (pp. 281-319). NIDDK, NIH Publication Number 07-5512, 2007.