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See related article, “Macrophage Phenotype Controls Long-Term AKI Outcomes—Kidney Regeneration versus Atrophy,” on pages 292–304.

New Insights Regarding the Interrelationship of Obesity, Diet, Physical Activity, and Kidney Stones

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J Am Soc Nephrol 25: 211–212, 2014.
doi: 10.1681/ASN.2013111189

Published online ahead of print. Publication date available at www.jasn.org.

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Obesity (body mass index [BMI] >30 kg/m²) is widely regarded as an epidemic in the United States, now affecting >20% of the population.¹ Kidney stone disease is also common, with a United States lifetime prevalence of 12% in men and 7% in women, with stones responsible for at least \$2 billion annually in health care costs.² Furthermore, nephrolithiasis appears to be increasingly common among both adults³ and children.⁴ Being obese (higher BMI) and experiencing weight gain have each been associated with stone risk among men and women.⁵ Hence, it is only natural to try and link the two trends, namely to infer that the nephrolithiasis epidemic is a direct result of the obesity epidemic.

Although progress is being made, the precise pathogenic steps in human kidney stone formation remain elusive. The biologic control of crystal nucleation, growth, retention, and even dissolution are likely to play important roles. How do Randall's plaques arise? What is the relative importance of collecting duct plugs and Randall's plaques in different types of stone formers? How does a stone grow upon a Randall's plaque (or plug)? These are all topics of critically needed and ongoing research. In the end, however, urinary supersaturation is an undeniable prerequisite for stone formation, and all current diet and drug therapies have the sole goal of reducing urinary supersaturation for the type of stone that the patient is making. Indeed, the urine of kidney stone formers tends to be more supersaturated than that of nonstone formers, and the type of supersaturation matches the stone type.⁶ Among those with stones, higher urinary supersaturation is caused by a combination of lower urine volume (less fluid intake), increased daily excretion of lithogenic substances, such as calcium, oxalate, and uric acid, and/or decreased excretion of natural urinary inhibitors, such as citrate. Multiple factors are often present at once (e.g., low urine volume and high urine calcium).

Nephrolithiasis has long been associated with affluence⁷ and dietary factors associated with it.⁸ Very specific diet factors were recently identified that appear to translate to higher stone risk, such as increased animal protein intake, lower potassium intake, lower fluid intake, and, somewhat surprisingly, lower calcium intake.⁹ Even higher consumption of fructose has been tied to kidney stone risk.¹⁰ All of these dietary factors are presumed to act by changing the urinary composition. In support of this idea, it has been reported that urinary supersaturation¹¹ and the risk of stones¹² are lower among individuals with food intakes closer to the Dietary Approaches to Stop Hypertension (DASH) diet, one that is high in fruits and vegetables, moderate in low-fat dairy products, and low in animal protein represents.¹² Given these observations, it becomes extremely tempting to conclude that common dietary habits explain both obesity and kidney stones, because obese individuals are presumed more likely to eat more food and, perhaps, a less healthy mix (e.g., fewer fruits and vegetables and more red meat, or a less “DASH-like” diet). Consistent with the hypothesis that diet is the key link between obesity and stones, increased urine oxalate, uric acid, sodium, and phosphate have been documented among men and women

with a higher BMI.¹³ However, in this cohort, it turned out that urine volume also rose in tandem with BMI, offsetting the increase in solutes, such that overall calcium oxalate supersaturation did not increase.¹³ Notably, in this same study, urine pH was lower among those individuals with a greater BMI.¹³ This finding is consistent with emerging evidence that obesity and insulin resistance are associated with decreased ammoniogenesis, a lower urine pH, and increased risk for uric acid stones.¹⁴ Thus, the path from obesity to urine composition to stone might be more nuanced than initially expected.

In this issue of *JASN*, Sorensen *et al.* provide another interesting observation from the Women's Health Initiative Observations Study that is relevant to our discussion.¹⁵ They observed in this prospective cohort of 84,225 postmenopausal women followed since 1993 that those with a greater BMI had a higher risk of stones, replicating findings from previous cohorts. In addition, they found that higher caloric intake and lower physical activity scores translated into more kidney stones. However, this association was *not* all about obesity because all three features (BMI, caloric intake, physical activity) were *independent* risk factors. Thus, something about being relatively sedentary increased the risk of one of these postmenopausal women forming a kidney stone. Importantly, the intensity of the activity was not important, because only mild to moderate weekly activity was enough to be protective against stones. As the authors point out, moderate exercise reduces the risk of many things that are associated with stones, such as hypertension and diabetes (discussed above). Exercise can also have a favorable effect on bone health, and nephrolithiasis has also long been associated with osteoporosis.

It is important to remember that this study only included postmenopausal women, and, thus, will need to be replicated in other populations. It is also possible that women who exercise regularly have other healthy lifestyle habits that decrease stone risk (dietary and otherwise). Nevertheless, conservative (nonpharmacologic) counseling for patients with stones often centers almost exclusively on diet, stressing increased fluid intake, normal dietary calcium, lower sodium, moderate protein, and reduced dietary oxalate. The results of Sorensen *et al.* suggest that a recommendation for moderate physical activity might reasonably be added to the mix.

ACKNOWLEDGMENTS

This work was supported by the Mayo Clinic O'Brien Urology Research Center (U54DK100227) funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), as well as by the Rare Kidney Stone Consortium (U54KD083908), a member of the National Institutes of Health Rare Diseases Clinical Research Network funded by the NIDDK, the National Center for Advancing Translational Sciences, and the Mayo Foundation.

DISCLOSURES

None.

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See related article, "Activity, Energy Intake, Obesity, and the Risk of Incident Kidney Stones in Postmenopausal Women," on pages 362–369.

Kidney Infection with HIV-1 Following Kidney Transplantation

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J Am Soc Nephrol 25: 212–215, 2014.
doi: 10.1681/ASN.2013101112

Published online ahead of print. Publication date available at www.jasn.org.

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