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STONES

Utilizing bacterial factors for kidney stone prevention

> *O. formigenes* bioactive factors retain their biological activity and can effectively reduce urinary oxalate excretion in mice

Colonization of the intestine with *Oxalobacter formigenes* is associated with a reduced risk of calcium oxalate kidney stones. Now, researcher Hatim Hassan and colleagues show that bioactive factors derived from these probiotic bacteria stimulate oxalate secretion in the distal colon, leading to a reduction in urinary oxalate excretion.

O. formigenes is an anaerobic bacterium that exclusively metabolizes oxalate in the intestinal tract and has been shown to induce colonic oxalate secretion in rodents. "Maintaining *O. formigenes* colonization in the absence of high exogenous oxalate levels is problematic, underscoring the need to identify *O. formigenes*-derived bioactive factors that exert effects similar to the live bacteria, and might have significant potential for clinical application," says Hassan. He explains that using probiotic-derived factors rather than probiotic bacteria as novel therapeutic agents also avoids difficulties in determining intestinal bacterial bioavailability as well as biosafety concerns regarding the administration of live bacteria.

To investigate whether bioactive factors produced by *O. formigenes* regulate intestinal oxalate transport, Hassan and colleagues treated human intestinal Caco2-BBE (C2) cells with conditioned media from the cultured bacteria. They found that this media induced a >2.4-fold increase in oxalate uptake by the C2 cells, whereas treatment with conditioned media from *Lactobacillus acidophilus* — which also degrades oxalate in the lumen of the intestine — had no effect. The *O. formigenes* conditioned media also stimulated oxalate uptake by the T84 human colonic cell line, demonstrating that this effect was not cell-line specific.

Heat or protease treatment of *O. formigenes* conditioned media completely abolished its stimulatory effect on oxalate uptake by C2 cells, suggesting that the bioactive factors are proteins or peptides. Using selective ultrafiltration of the conditioned media, the researchers determined that these factors have molecular masses of 10–30 kDa. Further investigations indicated that the *O. formigenes*-derived bioactive factors stimulate intestinal oxalate transport through a mechanism involving activation of protein kinase A and enhancement of SLC26A6 transporter activity.

Finally, the researchers showed that rectal administration of *O. formigenes* conditioned media stimulated distal colonic oxalate secretion and significantly reduced urinary oxalate excretion (by >32%) in a mouse model of primary hyperoxaluria. "The fact that the *O. formigenes* bioactive factors retain their biological activity and can effectively reduce urinary oxalate excretion in mice indicates their potential as novel therapeutic agents for the prevention and/or treatment of hyperoxaluria, hyperoxalemia, and related calcium oxalate kidney stones," says Hassan. "Our findings provide a compelling rationale for the aggressive pursuit of characterization of these factors, which is currently underway."

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