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Unraveling the mechanisms of obesity-induced hyperoxaluria

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Abstract

Kidney stones is increasingly associated with obesity. With an increasing prevalence of obesity and metabolic syndrome in the past 30 years, urinary oxalate has significantly increased. However, its underlying pathophysiologic mechanisms of hyperoxaluria have not been fully explored. This preclinical study suggests that hyperoxaluria in obesity depends on a complex network of inflammatory responses linked to metabolic outcome. The future mechanistic and clinical investigations must be targeted at elucidating the pathogenetic role of inflammation in obesity induced hyperoxaluria.

The prevalence of kidney stones has increased globally in recent decades. Nephrolithiasis has become more recognized as a systemic disorder and is known to be associated with obesity and metabolic syndrome (MS).¹ Calcium oxalate (CaOx) stones are the most prevalent type of kidney stone disease in the United States and globally and have been shown to occur in 70% to 80% of the kidney stone-forming population. Physicochemically, CaOx is sparingly soluble in aqueous solution at approximately 57 $\mu\text{mol/l}$ at a pH of 7.0. Given that normal urine volumes range from 1 to 2 liters daily with a normal urinary excretion of less than 450 $\mu\text{mol/d}$, normal urine is often supersaturated with CaOx. To elucidate the significance of urinary oxalate in CaOx stone formation, a retrospective study was conducted of urinary stone risk profiles from 667 patients with CaOx stones, using a urinary relative supersaturation of CaOx individually calculated using Equil 2 software (University of Florida, Gainesville, FL) and theoretical curve of the relationship between urinary relative supersaturation of CaOx and concentrations of urinary Ca and Ox.² In this study, urinary Ox was shown to be equally effective as urinary Ca at increasing the urinary supersaturation of CaOx. With an increasing prevalence in obesity/MS in the past 3 decades, urinary Ox has increased significantly.³ Nevertheless, the exact underlying pathophysiologic mechanisms between obesity/MS and urinary Ox excretion has not been fully elucidated (Figure 1).

The main causes of hyperoxaluria can be divided into 3 categories: (i) increased consumption from oxalate-rich foods; (ii) increased intestinal oxalate absorption; and (iii)

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DISCLOSURE

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increased hepatic oxalate synthesis as a result of an inborn error in metabolism of Ox production. Amin *et al.*⁴ carefully dissected the potential underlying mechanisms of obesity-associated hyperoxaluria in *ob/ob* (*ob*) mice. Approaching approximately 45%, the contribution of dietary oxalate to urinary oxalate excretion has been found to be much higher than it was previously defined. In the study by Amin *et al.*⁴ (2018), to exclude the contribution of the dietary indiscretion, the *ob* mice and controls were pair-fed. However, urinary oxalate remained significantly higher in *ob* mice, suggesting that hyperoxaluria was not solely due to increased oxalate consumption. To further elaborate on the role of intestinal oxalate absorption, an additional study was conducted in *ob* mice comparing them to lean control mice, following a 4-day equilibration on an oxalate-free diet. This manipulation further ameliorated hyperoxaluria in *ob* mice, but urinary oxalate remained significantly higher in *ob* mice than in control littermates. This result suggested the contribution of a potentially increased endogenous hepatic oxalate production. This possibility was tested by measuring urinary glycolate (a surrogate marker of hepatic oxalate synthesis) and was found to be similar in *ob* and control mice, which potentially excluded the possibility of hepatic oxalate over production.

The above experiments support the notion that increasing amounts of net oxalate absorbed by the intestine may play a crucial role in obesity-associated hyperoxaluria in the *ob* mice model. Supportive evidence was provided by an *in vitro* study of jejunal tissue by using an Ussing chamber, which demonstrated defective oxalate secretion in *ob* mice compared with the controls. Given that the putative anion exchange transporter *Slc26a6* (A6) is expressed in the apical portion of various segments of the small intestine and, to some extent, the large bowel, Amin *et al.*⁴ found a significantly diminished jejunal level of *SLC26A6* mRNA and protein expression in *ob* mice than with controls.⁵ It was concluded that A6 potentially plays a crucial role in defective intestinal oxalate secretion in *ob* mice. The selection of this segment of the bowel was based on the finding of jejunal wall inflammation as well as high expression of A6 in *ob* and *db* (deficient in leptin receptor) mouse jejunum and duodenum.⁵ In humans, the exact intestinal segment participating in oxalate absorption has not been well defined. Based on indirect evidence, it was proposed that, given the transit time from the stomach to the colon of approximately 5 hours, most of the oxalate absorption occurs throughout a large segment of the small bowel. The contribution of colon to oxalate absorption has been shown to occur but to a lesser extent. Moreover, the role of A6 in intestinal oxalate absorption has only been tested in 1 case with celiac disease in a subject who presented with hyperoxaluria and chronic kidney disease. In that case, the small intestinal A6 apical expression was shown to be significantly reduced compared to that of control subjects. The result suggested that reduced A6 expression was the cause of hyperoxaluria in that subject.

Obesity is established as a chronic, systemic inflammatory disorder associated with higher systemic and small intestinal levels of different inflammatory cytokines in both *ob* and *db* mice.^{6,7} The pathogenic role of systemic and/or small intestinal inflammation in CaOx nephrolithiasis was first supported by findings of high plasma and jejunal tumor necrosis factor (TNF), interferon (IFN), and interleukin-6 (IL-6) levels in *ob* mice. It was hypothesized that elevated circulating and intestinal proinflammatory cytokines in obesity inhibits A6-mediated intestinal oxalate secretion. To prove this scheme, human intestinal

epithelial colorectal adenocarcinoma (Caco2-BBE [C2]) cells were used to measure oxalate uptake, and it was shown that TNF, IFN, and IL-6 specifically significantly inhibited C-oxalate uptake by this cell line.⁴ The inhibitory action of proinflammatory cytokines on oxalate transport by C2 cells was found to be associated with reduced A6 mRNA and total protein expression. However, using this cell model does not support the contribution of oxalate secretion since it only measures unidirectional oxalate uptake.

Previous studies have shown altered gut microbiota colonization with *Oxalobacter formigenes* in obese subjects. *O. formigenes* has been demonstrated to degrade intestinal luminal oxalate as well as attach to intestinal mucosal cells and stimulate net intestinal oxalate secretion.⁸ Moreover, cross-sectional studies in human subjects have shown that patients with recurrent CaOx stones demonstrated significantly lower *O. formigenes* colonization than normal subjects matched for age and gender. However, in another study, CaOx stone formers who tested negative for *O. formigenes* were shown to have higher urinary oxalate excretion than *O. formigenes*-positive patients on a controlled diet.⁹ The increased urinary oxalate was associated with a significantly increased number of kidney stone episodes. In this study⁹ intestinal oxalate absorption using ¹³C₂-labeled oxalate in *O. formigenes*-positive patients was similar to that in *O. formigenes*-negative patients; however, plasma oxalate concentrations were significantly higher in the *O. formigenes*-negative population. This finding supports the role of diminished oxalate secretion in *O. formigenes*-negative CaOx kidney stone formers. The importance of the role of *O. formigenes* could not be examined in laboratory mice because they were usually found to be *O. formigenes*-negative.

Given that CaOx kidney stones are strongly associated with obesity and MS, it is anticipated that insights from studies in rodents may open the field to translational studies to further unravel the pathophysiologic link between obesity and urinary oxalate excretion in humans with CaOx kidney stones. The pathophysiological link between obesity and MS and uric acid nephrolithiasis has been extensively studied. However, the underlying mechanisms between obesity/MS and calcium oxalate kidney stone disease and specifically its link to inflammation has not yet been fully investigated.

Over the past several decades, no new drugs have been developed for the treatment of CaOx kidney stone formation. Preclinical findings suggest that hyperoxaluria in obesity/MS depends on the integrated network of inflammation as a metabolic response. As the pathogenetic mechanisms are being unraveled and inflammation has been identified as a key process, pharmacological agents that target this mechanism must be investigated in clinical trials. From this study, one may infer that agents that inhibit inflammatory signaling and improved insulin resistance should be tested in this population. Furthermore, it remains to be determined whether direct manipulation of intestinal microbiota with probiotics, drugs to either upregulate the intestinal secretion of oxalate by stimulating A6, provision of the enzyme products of *O. formigenes* for perpetual oxalate degradation, or secretion and provision of engineered bacteria can be a useful target in the future.

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Figure 1. Potential pathophysiologic mechanisms of obesity-induced hyperoxaluria

(i) Increased dietary ingestion of oxalate; (ii) increased net intestinal absorption of oxalate; (iii) alteration in intestinal microbiota leading to decreased intestinal bacterial metabolism of oxalate; (iv) excessive endogenous oxalate production in the liver; (v) increased circulating and intestinal proinflammatory cytokines; (vi) hyperoxaluria. IFN, interferon; IL-6, interleukin-6; TNF, tumor necrosis factor.