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Urinary oxalate as a potential mediator of kidney disease in diabetes mellitus and obesity

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Abstract

Purpose of review: Hyperoxaluria can cause kidney disease through multiple mechanisms, including tubular obstruction from calcium oxalate crystals, sterile inflammation, and tubular epithelial cell injury. Hyperoxaluria is also observed in individuals with diabetes mellitus and obesity, which are in turn risk factors for chronic kidney disease. Whether hyperoxaluria is a potential mediator of increased risk of chronic kidney disease in diabetes mellitus and obesity is unknown.

Recent Findings: Individuals with diabetes have increased levels of plasma glyoxal (a protein glycation product) and glyoxylate, both of which are precursors for oxalate. Increased gut absorption of oxalate in obesity may be due to obesity-associated inflammation. A recent study in individuals with chronic kidney disease found that higher 24h urinary oxalate excretion was independently associated with increased risk of kidney disease progression, especially in individuals with diabetes and obesity.

Summary: Both diabetes mellitus and obesity are associated with higher urinary oxalate excretion through distinct mechanisms. Hyperoxaluria could be a mechanism by which kidney disease develops in individuals with diabetes mellitus or obesity and could also contribute to progressive loss of renal function. Future research on pharmacologic or dietary measures to limit oxalate absorption or generation are required to test whether lowering urinary oxalate excretion is beneficial in preventing kidney disease development and progression in diabetes mellitus and obesity.

Keywords

hyperoxaluria; diabetes; metabolic syndrome; chronic kidney disease; oxalate nephropathy

Introduction

Diabetes mellitus and obesity are massive public health burdens in the United States and increasingly around the world. Both conditions lead to premature mortality and accelerated

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morbidities, including kidney disease. Diabetes is the most common cause of chronic kidney disease (CKD) and end stage renal disease in the world, and obesity is likely a contributor to CKD development and progression.[1] Both diabetes and obesity share another kidney-specific manifestation: nephrolithiasis. The most common constituent of kidney stones is calcium oxalate. Interestingly, both diabetes and obesity are independent risk factors for higher urinary oxalate excretion, which may account for the increased risk of nephrolithiasis observed in the two conditions.[2,3] Recently, evidence from animal studies and a prospective cohort study have linked oxalate to the development of chronic kidney disease.[4,5] In this review, we describe the evidence that could implicate hyperoxaluria as a novel mediator of CKD pathogenesis and progression in diabetes and obesity (Figure 1).

Overview of oxalate metabolism

Oxalate ($C_2O_4^{2-}$, a dicarboxylic acid) is a terminal metabolite in humans. Oxalate in the blood and urine is derived endogenously through metabolism and also exogenously from the diet[6–8] Endogenous synthesis occurs primarily in the liver, where the most common metabolic pathways converge on oxalate's immediate precursor, glyoxylate, which has recently been identified as a potential metabolite marker of type 2 diabetes mellitus.[9] Glyoxylate production *in vivo* occurs from the metabolism of amino acids (hydroxyproline, serine, glycine, tryptophan), glucose, fructose, ascorbic acid, and glycolate.[10–13] Another precursor of oxalate is glyoxal, which can be a product of cellular peroxidation and protein glycation; glyoxal can be directly or indirectly converted into glyoxylate, which is then metabolized into oxalate.[11,14]

Many foods contain oxalate, which is absorbed primarily in the small intestine but also in the stomach and large intestine.[15] Foods containing high amounts of oxalate include spinach, almonds, potatoes, and cocoa. Average daily oxalate intake and absorption varies across individuals due to inter-individual differences in absorption and regional differences in oxalate content of foods. A major determinant of oxalate absorption is the availability of free calcium in the gut: calcium readily and rapidly precipitates with oxalate as CaOx complexes, which are absorbed much less than free oxalate.[16] Intestinal oxalate absorption occurs passively and transcellularly, with variable amounts of absorption vs. secretion occurring along the gastrointestinal tract.[15,17,18] SLC26 anion exchangers mediate transcellular transport and are expressed on both apical and basolateral membranes of the human small intestine and colon. Evidence suggests that inflammation-induced changes in intestinal oxalate transport could account for obesity-induced hyperoxaluria due to suppression of active intestinal oxalate secretion or increased absorption, as described below.[19]

Oxalate degradation in the colon can occur through oxalate-metabolizing gut flora including Oxalobacter formigenes and other bacterial species[20,21]. Fecal excretion accounts for <10% of oxalate excretion.[18]

Circulating oxalate is freely filtered at the glomerulus, reabsorbed, and secreted by the proximal tubule.[22,23] The 24h urinary excretion of oxalate is a reflection of dietary oxalate intake, net intestinal absorption (accounting for fecal excretion and colonic degradation),

and endogenous oxalate synthesis from the liver. Hyperoxaluria therefore can occur from multiple causes. In human studies that have examined predictors of 24h urinary oxalate excretion in stone formers, clinical variables that have been linked to higher urinary oxalate excretion include age, higher BMI, diabetes, and higher fructose and oxalate intake.[2,24] In a study involving individuals with CKD, factors independently associated with higher urinary oxalate excretion included diabetes, white vs. black race, thiazide diuretic use, and lower urinary calcium excretion and lower serum calcium.[4] Hyperoxaluria is also observed in the primary hyperoxalurias, autosomal recessive disorders due to mutations in enzymes involved in oxalate metabolism, and as a secondary condition in enteric hyperoxaluria, due to increased intestinal absorption of oxalate.

Diabetes Mellitus and Urinary Oxalate Excretion

24h urine excretion of oxalate has been found to be higher in individuals with vs. without diabetes mellitus in multiple studies. Diabetes mellitus is associated with an increased risk for kidney stone formation, and calcium oxalate stones are the most common type of kidney stones.[25–27] In a study of 3,123 individuals with established CKD, diabetes mellitus was independently associated with higher urinary oxalate excretion: after adjustment for a number of variables including medications, body mass index, age, race, sex, and laboratory tests, individuals with diabetes mellitus had 11% higher 24h urinary oxalate excretion than those without diabetes.[4]

Glyoxylate, the immediate precursor of oxalate, has been identified through metabolomic profiling of human plasma to be a potential metabolite marker of diabetes mellitus.[9,28,29] A retrospective analysis of long-term blood donors found that elevated serum glyoxylate levels pre-dated the diagnosis of diabetes mellitus by up to 3 years, in analyses performed with matching for age, gender, and BMI.[9] In a mouse model of diabetes (C57BLKS/J-Lepr$^{-/-}$), glyoxylate levels were 6-fold higher in diabetic mice than control mice.[9]

Another potential precursor of oxalate is glyoxal, an alpha-oxoaldehyde which can be generated from the glycation of proteins or from lipid peroxidation from hyperglycemia in diabetes.[28,30] Glyoxal has been hypothesized to be an important source of endogenous oxalate synthesis in humans and a source of oxidative stress.[11,31]. In a small study, glyoxal was found in a HPLC-UV screen of alpha-dicarbonyl compounds to be elevated in the plasma of individuals with diabetes compared with healthy subjects, and to correlate with HBA1C, fasting glucose, and microalbuminuria.[31] Another related alpha-oxoaldehyde, methylglyoxal, was also found to be associated with incident cardiovascular disease and mortality in prospective studies of 1,003 type 2 and 159 type 1 diabetic patients.[32,33] Baseline and six-year longitudinal methylglyoxal levels were inversely correlated eGFR in 1481 screen-detected type 2 diabetic patients.[34] In a prospective three-year observational study of 150 individuals with CKD stages 3–5, higher methylgloxal levels (tertiles 2 and 3 compared with tertile 1) were associated with a >2-fold and > 6-fold increased risk for progression to ESRD, respectively.[35]

Obesity and Urinary Oxalate Excretion

Higher BMI was independently linked to higher urinary oxalate excretion in the Health Professionals Follow-Up Study, Nurses' Health Study, and Nurses' Health Study II.[3] In the Chronic Renal Insufficiency Cohort (CRIC) study, higher BMI was associated with higher urinary oxalate excretion in unadjusted analyses, but not after multivariable adjustment.[4] Obesity is known risk factor for nephrolithiasis,[36] which is most commonly due to calcium oxalate containing stones.

Two recent studies identified mechanisms of hyperoxaluria in obesity, highlighting the role of inflammation.[37,38] Amin et al. found evidence using the obese ob/ob mouse model to support reduced active intestinal oxalate secretion from local and systemic inflammation as a cause for a reduction in fecal excretion of oxalate.[38] Bashir et al. from the same laboratory also found evidence for increased paracellular absorption of oxalate all along the gastrointestinal tract.[37] They also found that proinflammatory cytokines and oxidative stress, which are elevated in obesity, significantly enhanced paracellular intestinal absorption of oxalate in vitro and ex vivo. These studies highlight an important role for increased gut absorption and decreased gut secretion – both of which are enhanced by inflammation – as a cause of obesity-associated hyperoxaluria.

Evidence on the association between urinary oxalate excretion and CKD

In 3,123 CRIC participants,[4] higher levels of urinary oxalate excretion ($\geq 40^{th}$ percentile compared with $< 40^{th}$ percentile) were found to be associated with a 32% higher risk of kidney disease progression and 37% higher risk of ESRD in multivariable-adjusted analyses. Cross-sectionally, higher urinary oxalate excretion was observed in those with lower eGFR and greater albuminuria. In prospective analyses of kidney function decline, the strongest signals were observed in those with higher BMI (45% higher risk of ESRD) and those with diabetes mellitus (44% higher risk of ESRD). A review of renal biopsy cases described the association of oxalate nephropathy as a cause of progressive CKD and ESRD.[39] The mechanisms by which oxalate can cause kidney injury have also been explored in several animal studies[5,40,41]. Sterile inflammation from the intracellular nucleotide-binding domain, leucine-rich repeat–containing receptor, pyrin domain–containing-3 (NLRP3) inflammasome activation has been reviewed as a key mechanism underlying the observation.[5,41] CKD models from oxalate feeding have also been introduced as a reproducible model of chronic kidney disease that recapitulates the clinical manifestations of CKD in humans.[5,42] Recently, Saenz et al. found that metabolic syndrome contributes to hyperoxaluria-induced renal injury in a murine model of nephrolithiasis, consistent with the observation in CRIC of a stronger signal of the oxalate association with kidney dysfunction in those with higher BMI.[43]

Potential for future therapeutics

If the association between hyperoxaluria and CKD in the setting of diabetes and/or obesity is indeed causal, then therapeutic strategies aimed at lowering urinary oxalate excretion may prove fruitful to prevent CKD or slow its progression. Reducing oxalate absorption from the

gastrointestinal tract may be accomplished by dietary modifications (e.g., avoiding high oxalate-containing foods; supplemental calcium), medications to bind oxalate in the gut (e.g., calcium or non-calcium-containing phosphorous binders[44]), or medications to enzymatically degrade in the gastrointestinal tract.[45] Reducing oxalate generation by the liver is being explored for the treatment of primary hyperoxaluria using gene-targeting technologies to inhibit enzymes involved in oxalate metabolism.[46,47] Recently, Le Dudal et al. showed promising results with stiripentol, an antiepileptic drug that inhibits lactate dehydrogenase 5 isoenzyme (the last step of hepatic oxalate production).[48] Stiripentol reduced oxalate generation *in vitro* and in rat models protected kidneys from oxalate-induced injury from ethylene glycol intoxication and chronic calcium oxalate nephropathy. The authors also found lower oxalate excretion in a small number of patients treated with stiripentol and used the drug to reduce urinary oxalate excretion in a young girl with severe type 1 hyperoxaluria.

Conclusion

Both diabetes and obesity are associated with increased absorption or generation of oxalate, which in turn may increase the risk of kidney injury. Whether targeting oxalate generation or absorption could be protective in diabetes or obesity will require additional investigation.

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Key points:

- Diabetes mellitus and obesity are both associated with higher urinary oxalate excretion and increased risk of kidney stones.
- Diabetes mellitus and obesity are also risk factors for chronic kidney disease
- Oxalate can cause kidney injury through multiple mechanisms, including obstruction and sterile inflammation
- The association of diabetes mellitus and obesity with chronic kidney disease raises the question whether oxalate may be a mediator
- Further study is required to evaluate whether targeting oxalate absorption or generation could be protective in diabetes mellitus or obesity

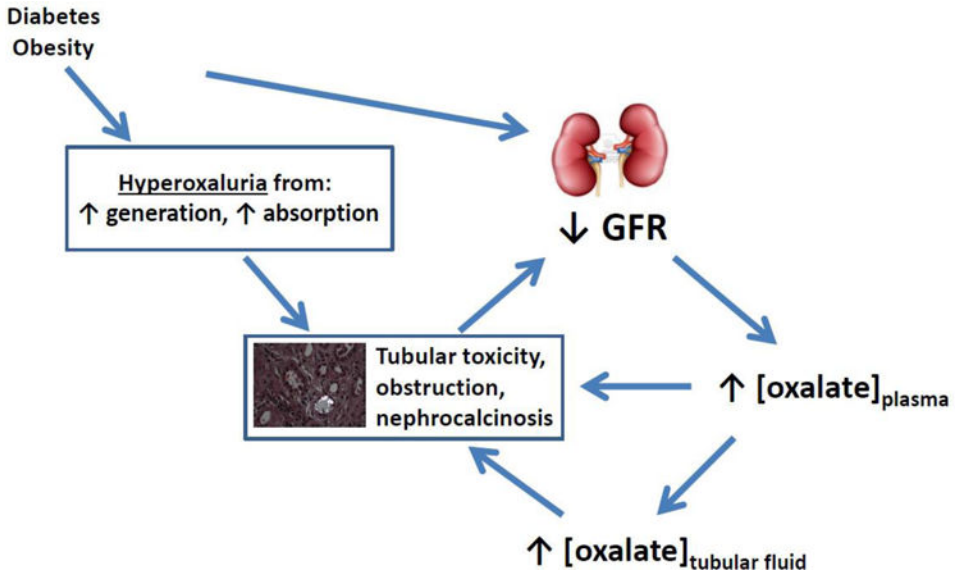

Figure 1.

A schematic depicting how higher levels of oxalate absorption or generation in diabetes or obesity could contribute to the development or progression of chronic kidney disease.