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INVITED REVIEW

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# The impact of dietary oxalate on kidney stone formation

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**Abstract** The role of dietary oxalate in calcium oxalate kidney stone formation remains unclear. However, due to the risk for stone disease that is associated with a low calcium intake, dietary oxalate is believed to be an important contributing factor. In this review, we have examined the available evidence related to the ingestion of dietary oxalate, its intestinal absorption, and its handling by the kidney. The only difference identified to date between normal individuals and those who form stones is in the intestinal absorption of oxalate. Differences in dietary oxalate intake and in renal oxalate excretion are two other parameters that are likely to receive close scrutiny in the near future, because the research tools required for these investigations are now available. Such research, together with more extensive examinations of intestinal oxalate absorption, should help clarify the role of dietary oxalate in stone formation.

**Keywords** Oxalate · Dietary oxalate · Oxalate absorption · Oxalate excretion · Urolithiasis

## Introduction

The genesis of a calcium oxalate stone is a complex process due to a variety of contributing factors that are dietary and genetic in origin. While unraveling this process is daunting, an obvious starting point is understanding the factors that influence a critical component in the process, the amounts of calcium and oxalate that are excreted in urine. Because of the critical structural role of calcium in bone biology, its intestinal absorption and the renal handling of calcium have received intense scrutiny. In comparison, the passage of oxalate through the human body has been largely ignored. The fate of these ions differs sharply after ingestion. About 30% of the ingested calcium, 5–10 mmoles is absorbed, and approximately 97% of the filtered load to the kidney is reabsorbed. By contrast, only 10% of the ingested oxalate, 0.1–0.2 mmoles is absorbed, and nearly all of the filtered load is excreted. In addition, there is evidence that secretory oxalate fluxes occur.

As some of the oxalate that is ingested is excreted in urine, intuitively one would suspect that the amount of oxalate in urine that is derived from the diet has an impact on stone disease. Until recently, however, this important potential role of dietary oxalate has been ignored due to the belief that its contribution was small, at most amounting to 20% of the oxalate excreted. This initial conclusion on the contribution of dietary oxalate was due to the assumption that there is a linear relationship between the amount of oxalate ingested and the amount excreted. The amount of oxalate absorbed was determined by measuring the difference in oxalate excretion of individuals consuming metabolic diets with and without sodium oxalate supplementation [1]. We have established that this relationship is in fact curvilinear, apparently due a much higher absorption of oxalate at low intakes than at high intakes [2]. We speculate that this is due to a much higher proportion of the ingested oxalate being ionized and available for absorption at low oxalate intakes than will occur at higher intakes, when a large fraction of the oxalate will be complexed or crystallized and unavailable for absorption. We estimate that on average, half of the urinary oxalate excreted is derived from the diet, with the recognition that this figure can vary substantially depending on the relative amounts of calcium and oxalate ingested.

## The amount of oxalate ingested

Two recent studies have attempted to quantify the amount of oxalate that is ingested as part of a normal Western diet [3, 4]. They suggest that the mean intake is

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100–150 mg/day. These studies used direct analytical techniques to measure the oxalate content of foods, with the first study using ion chromatography and capillary electrophoresis [3], and the second an HPLC technique coupled with an enzymatic detection method [5]. For making broad generalizations, these studies are limited by sample size and the number of days examined. Regional and cultural differences in the amount of oxalate ingested may occur, and temporal changes may occur related to the season or food availability. Furthermore, a seemingly endless variety of foods are now available at large supermarkets, making a complete assessment difficult. Other significant issues are the variability in the oxalate content of a particular food and the effects of food preparation. If dietary oxalate intake is to be reduced, the current practice of advising the avoidance of foods thought to be oxalate-rich seems unsatisfactory because of these issues. What is required is a more complete identification of foods that, on analysis, contain moderate or high levels of oxalate in relation to the portion size normally ingested.

Due to the lack of accurate information until quite recently on the range of oxalate contents in foods, there is no data suggesting that stone formers ingest more oxalate than non-stone formers. The amount of calcium ingested, as assessed by semi-quantitative food questionnaires, has been shown to be a risk factor for stone formation [6]. It was argued that this risk is due to the modulation of the amount of oxalate available for absorption in the intestinal tract, by calcium. Thus, the question of whether the amount of oxalate ingested is also a risk factor for stone disease certainly warrants attention. The use of semi-quantitative food questionnaires to assess oxalate intake may be of only limited value when we consider that many of the oxalate-rich foods, such as spinach, beets, and chocolate, are consumed by most people on an irregular basis and that their consumption is not adequately addressed in the questionnaire. A questionnaire specifically devoted to a more accurate assessment of such irregularly eaten, oxalate-rich foods could be helpful in obtaining more meaningful data. Perhaps a potentially even larger confounding factor is the variability in the oxalate content of foods. We will argue below that spikes in oxalate loads on the kidney following the ingestion of oxalate-rich food are potentially critical factors in determining the impact of ingested oxalate on stone disease. One could speculate that the frequency of these spikes is correlated with the rate of stone growth. If this proves to be true, the timing of oxalate ingestion and its interaction with other food constituents may be influential.

## Absorption of oxalate

### Amount absorbed

Only small amounts of ingested oxalate are absorbed into the body, most estimates suggest 6–14% in normal individuals [7, 8]. Absorption appears to occur all along the intestinal tract with approximately half occurring in the small intestine and half in the large intestine [7]. This absorptive process is not well understood despite its potential clinical significance, which is discussed below. In examining absorption itself, as distinct from the bioavailability of ingested oxalate, investigators have focused on the absorption of oxalate from an oral sodium oxalate dose to characterize the process. As it has been difficult to date to directly measure absorption from the amount entering the circulation after ingestion, it has been measured from the amount excreted in urine. This measure is valid if significant amounts of the absorbed oxalate are not taken up by tissues, are not metabolized in the body, or are not secreted back into the intestine or other fluids such as sweat. In normal individuals this assumption appears to be valid, but a growing body of evidence indicates that with hyperoxalemia and renal dysfunction a significant amount of circulating oxalate may be secreted into the large intestine [9]. It does raise the question of whether, with high transient circulating oxalate concentrations following the ingestion of an oxalate-rich meal, some oxalate is secreted back into the large intestine in normal individuals. Several studies reviewed in [8], indicate that stone formers on average may absorb ~50% more oxalate than normal individuals. Krishnamurthy et al. also recently reported that hyperoxaluric stone formers absorb more oxalate from an oxalate load than normo-oxaluric stone formers [10]. The reasons for this difference and its physiological, biochemical and genetic underpinnings require further research.

### Bioavailability of ingested oxalate

Measures of the bioavailability of oxalate in food may be influenced by a number of factors. These include: (1) its localization in the food, (2) its structural form, crystalline or soluble, (3) its digestibility on ingestion, (4) gut transit time, (5) the presence of oxalate-degrading organisms, (6) and absorption properties of the intestine. Significant intra- and inter-individual variability could influence each of these parameters, making the overall process difficult to dissect. One factor in particular that has attracted attention is the relationship between the amount of soluble versus insoluble oxalate in foods and the bioavailability of the oxalate. Some investigators have suggested that the soluble oxalate content of a particular food may be a more useful measure of food oxalate content than total levels because of its purported equivalency with bioavailable oxalate. As shown in Table 1, this is clearly not the case. The bioavailability of oxalate in foods with a high soluble oxalate content was much lower than that of sodium oxalate. The amount of soluble oxalate is usually assessed as the amount of oxalate in food that is soluble after homogenization of the food in heated water. The insoluble oxalate is assumed to be primarily crystalline calcium oxalate. To our knowledge no other types of oxalate crystals have

**Table 1** Bioavailability of oxalate in foods estimated by the increase in urinary oxalate excretion 6–8 h post-food ingestion. These bioavailabilities are an underestimate due to the limited time period studied

| Food | Total oxalate (mg/100 g) | Soluble oxalate (mg/100 g) | Bioavailability (%) | References |
|---|---|---|---|---|
| Oca (tuber) | 373 | 373 | 1.44 | [41] |
| Soy products | 5.6–287 | | 2.2–5.4 | [42] |
| Spinach | 957 | 737 | 0.6–2.4 | [11, 43, 44] |
| Black tea | 4–6 | 4–6 | 1.9–4.7 | [5, 45] |
| Rhubarb | 1,235 | 380 | 4.0 | [5, 11] |
| Chocolate | 140 | | 2.6 | [44] |
| Sodium oxalate | | | 6.2–7.3 | [45, 46] |

been identified in plant-derived foods. The equivalency of soluble oxalate with the amount of free or complexed oxalate and insoluble oxalate with crystalline calcium oxalate becomes uncertain when one considers the amount of calcium in the food and its solubility. These uncertainties are identified in Table 1 with the analysis of rhubarb. One hundred grams of rhubarb contains ~10 mmoles of insoluble oxalate, but only 2 mmoles of calcium according to the United States Department of Agriculture nutrient database. Other factors besides calcium oxalate crystallization that may be affecting the distribution of oxalate in this hot water fractionation include the homogenization efficiency and the binding of free oxalate to insoluble components. A further issue is that it is generally perceived that sodium oxalate is more bioavailable than calcium oxalate, but the results of Prenen et al. suggest they are similar [11]. Clearly, more research is required to fully understand oxalate bioavailability and the factors that influence it.

### Modulation of oxalate absorption

Factors that may modulate the absorption of oxalate include the co-ingestion of calcium and magnesium, the presence of oxalate-degrading bacteria in the gut and inherent absorption characteristics. An inverse relationship between calcium intake and stone formation was reported by Curhan et al. in a large prospective of health professionals [6]. It was proposed that this effect was due to calcium binding to oxalate in the gut and limiting its uptake. Such an effect of calcium on oxalate excretion was observed in dietary studies by Hess et al. [12] and in load studies by Liebman and Chai [13]. The presence of oxalate-degrading organisms in the gut, particularly *Oxalobacter formigenes*, may lower the amount of oxalate available for absorption. Two studies have linked the absence of *Oxalobacter* colonization with increased stone formation [14, 15] and one with increased oxalate excretion in stone formers [16]. Further studies are required to verify this relationship in larger populations, to determine its association with antibiotic use, and to ascertain whether the numbers of *Oxalobacter* or other oxalate-degrading bacteria that are present have an effect. There is also evidence that the absorption of oxalate differs between normal individuals and stone formers. Hesse et al. [8] report that on average stone formers absorb 50% more oxalate than non-stone forming individuals using a $^{13}$C-oxalate absorption test. As reviewed by these authors, there are mixed reports from similar studies that have used $^{14}$C-oxalate absorption as a marker. The reason for these disparities may lie in the methodology. A large intra-individual variability in repetitive assays of normal individuals, ranging from 1.7–20%, was reported in one study using a $^{13}$C-oxalate absorption test [17]. The reasons for this variability need to be determined to either design a test with lower variability or to identify other causes for this wide range. A more complete understanding of the absorption process is also required to complement such investigations. Such studies appear to be required before extensively examining the reasons for an apparently elevated absorption in some stone forming individuals. It is possible that such differences could have a genetic basis [18]. Mount and Romero have suggested that SLC26A6 and possibly other anion exchangers in the SLC26 family play a role in small intestine oxalate transport [19]. The development of knock-out mice deficient in this protein could provide a valuable insight into their role in oxalate absorption.

## Renal oxalate excretion

Oxalate absorbed from the diet is almost all excreted from the body by the kidney. Greater than 93.5% of intravenously injected oxalate is recovered in urine [20, 21]. The fraction of plasma oxalate that is filtered is important to know in determining how the kidney handles oxalate. This fraction will depend on how much oxalate, a highly charged anion, binds to non-filterable plasma components. Estimates in the literature suggest that the large majority of it, >98%, is ultrafiltrable and thus able to be filtered through the glomerulus [22, 23]. Oxalate excretion in the kidney can occur by both glomerular filtration and secretion. It is unlikely that significant reabsorption of oxalate occurs. The negative electrochemical gradient across the apical membrane of nephron-lining epithelial cells and the potential role of oxalate as a toxin would suggest that such a process is limited and an undesirable event.

A secretory pathway for oxalate in the kidney has been observed in a number of animal species, including humans, dogs, rats and chickens [24, 25, 26, 27]. In this process, oxalate is removed directly from the blood flowing through kidneys following uptake by epithelial cells lining the nephron. Following transcellular flux, oxalate is released into the nephron lumen. Microperfusion of proximal tubules in the rat kidney suggested that the process occurred in the proximal tubule where secretory pathways for other anions and cations are present [26, 28]. Thus, the secretory pathway for oxalate in humans most likely occurs in the proximal tubule. It is also possible that the pathway is concentrated in a

particular sub-segment of the proximal tubule, but this awaits further investigation.

The transport processes and individual steps underlying the oxalate secretory pathway are not fully understood. An oxalate transporter, sat-1 (SLC26A1), has been identified in the basolateral membrane of proximal tubule cells that exchanges oxalate for either sulfate or bicarbonate [29, 30]. This exchanger will transport oxalate from the circulation into the proximal tubule cell. Several exchangers of the SLC26 family have been identified on the plasma membrane of cells that can transport oxalate, including A6, A7, A8, and A9 [31, 32, 33]. Of these, SLC26A6 is localized in the proximal tubule of the kidney and may play a role in secreting oxalate from the proximal tubule [34]. The identification of four splice variants and their resulting isoforms suggests that a complex interplay of transport processes may exist in the proximal tubule [32, 35]. The working model we are examining is that as plasma oxalate rises, sat-1 becomes active and oxalate is transported into the cell. In the absence of known specific carriers to facilitate transcellular oxalate transport, akin to the role of calbindin in calcium uptake, it is hypothesized that oxalate concentration in the cytoplasm increases and moves transcellularly by diffusion. This would create a transcellular oxalate gradient in the cell. The increase in intracellular oxalate would trigger its efflux from the cell. The magnitude of these cytoplasmic oxalate changes, their impact on the cell, and the properties of the oxalate transporters require a more extensive characterization in order to better define the process.

## Transient diet-induced renal oxalate loads

To date the existence of a transient oxalate load on the kidney following an oxalate-rich meal has largely been ignored. This stems from the difficulties in reliably measuring urinary oxalate, plasma oxalate and food oxalate, and a focus on measuring urinary excretions in 24 h periods. A further difficulty, resulting particularly from unreliable estimates of food oxalate content, has been an inability to adequately control the dietary intake of oxalate. We instigated such dietary control in experiments, which has enabled us to confirm the significance of dietary oxalate in contributing to urinary oxalate excretion and to more accurately define the renal handling of oxalate loads [2; R.P. Holmes, W.T. Ambrosius and D Assimos unpublished data]. When individuals ingested high loads (8 mmoles) of sodium oxalate, a significant secretion of oxalate accompanied the oxalate derived from glomerular filtration. The transient hyperoxaluria that occurred was equivalent to that observed chronically in individuals with primary hyperoxaluria where such conditions cause pathological changes. The recognition that the magnitude of such spikes can be large lends credence to hypotheses that oxalate itself could potentially act as a renal toxin, injuring the kidney through the promotion of oxidative stress or up-regulation of cytokine production. A schematic drawing of the secretory process and how stimulation of oxidative stress and cytokine production may occur in proximal tubule cells is shown in Fig. 1.

In this context, it is important to relate the magnitude of these loads on the kidney following an oxalate-rich meal to any evidence that they could be injurious. Three different approaches have been used to assess this possibility, each with their limitations: (1) cell culture experiments, (2) animal models, and (3) human studies. Much of the evidence on oxalate-induced oxidative stress in cultured cells and experimental animals has recently been reviewed by Sellvam [36] and Jonassen and coworkers [37]. Experiments with humans, however, have been quite limited. We have not observed any increases in markers of oxidative stress or renal cell injury in normal individuals following sodium oxalate loads of up to 8 mmoles (R.P. Holmes, W.T. Ambrosius and D Assimos unpublished data).

Experiments with cultured renal cells indicate that oxalate can activate pathways that either trigger cell growth or produce a cellular injury that can ultimately result in cell death [37]. The crucial factor in such experiments is the oxalate concentration at which these pathways are activated. The lowest concentration of oxalate in the growth medium that triggers a response has been reported to be 200–500 μM. A consideration in such experiments that use supraphysiological oxalate concentrations in growth media that contain mM levels of calcium is whether calcium oxalate crystals form and are more reactive than the oxalate anion. The onus should be on investigators who do such experiments to provide conclusive evidence that crystallization has not occurred. This could be achieved by filtering growth medium incubated with and without cells and measuring the oxalate content of the filters as described by Fan and Chandhoke [38]. This may underestimate crystals that form as they may settle under gravity in the medium and attach to cells or plastic surfaces. Further questions emerge concerning the cell surfaces exposed to oxalate. Many experiments have used cells grown on plastic

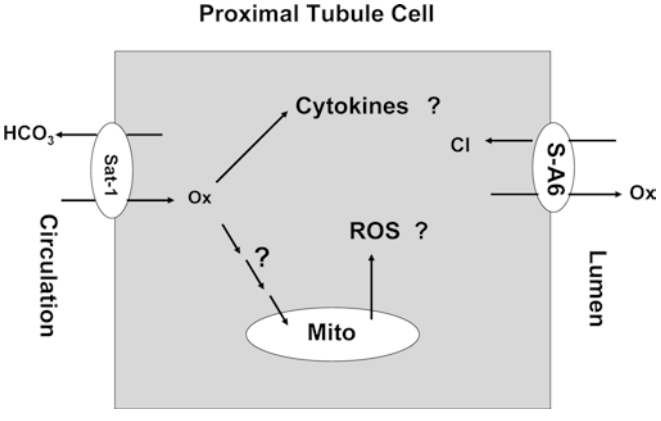


**Fig. 1** Possible responses in proximal tubule cells to increased oxalate secretion

where complete polarization of apical and basolateral proteins may not occur at confluency.

In considering the mechanisms by which the oxalate anion triggers responses within cells, the most plausible hypothesis, we believe, is that it is achieved through a rise in the concentration of intracellular oxalate. An alternative hypothesis is that any response is due to an interaction between oxalate and an external receptor on the cell surface. Notably, however, the response of LLC-PK1 cells to oxalate does not involve the activation of the p42/44 MAP kinase signaling pathway, which includes pathways involving an interaction with an extracellular receptor [39]. Unfortunately, in cell culture experiments the relationship between the extracellular oxalate concentration, the intracellular oxalate concentration, and cellular responses has not yet been investigated. Our initial investigations on the oxalate concentration in a wide range of tissues (unpublished data), indicate that it is close to 60 μM, based on a crude assumption that 1 g of tissue is equivalent to 1 ml of cytoplasm and the further assumption that oxalate is distributed equally throughout the cell. There is no evidence to date that oxalate is sequestered in any subcellular organelle, and we have observed that mitochondria isolated from Hep G2 cells contain very little oxalate (unpublished data).

If changes in gene expression or in signalling or peroxidative pathways in proximal tubule cells are associated with calcium oxalate stone formation, a rise in the intracellular concentration may trigger such changes. It must be stressed that such changes in proximal tubular function and their linkage to calcium oxalate stone disease are entirely speculative and there is little evidence to suggest they occur in vivo. Such evidence will be difficult to obtain. Permanent or long lasting changes may be evident in cortical tissue or proximal tubule cells obtained from stone formers, but transient changes such as those associated with diet-induced renal oxalate loads will require more intense scrutiny.

## Stone formation and growth

Whether the initial events involved in stone formation and stone growth are inter-related or completely divorced is not clear at the moment. Transient rises in the urinary concentration of oxalate associated with the ingestion of an oxalate-rich, calcium poor meal are likely to contribute to stone growth, if other conditions promoting crystallization and aggregation are present. The role of such transient rises in oxalate concentrations in the initiation of stone formation is less certain and will require further investigation. In view of this simplistic deduction, it is clear that to avoid the possibility of stone growth in calcium oxalate stone formers transient increases in oxalate excretion should be suppressed as a means of attenuating stone activity in patients. More rigorous steps to decrease the intake of oxalate-rich foods and to increase the intake of calcium or magnesium when oxalate is ingested appear to be warranted for prevention. Such steps could be as simple as a better education and documentation of the oxalate content of foods and the co-ingestion of a dairy product or calcium supplement with oxalate-containing meals. This approach, in part, underlies the successful decrease in stone formation reported by Borghi and colleagues in their studies of dietary intervention [40]. The limits of acceptable oxalate and calcium intake for both normocalciuric and hypercalciuric stone formers clearly require further investigation.

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