REVIEW

Probiotics and Other Key Determinants of Dietary Oxalate Absorption[1]

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ABSTRACT

Oxalate is a common component of many foods of plant origin, including nuts, fruits, vegetables, grains, and legumes, and is typically present as a salt of oxalic acid. Because virtually all absorbed oxalic acid is excreted in the urine and hyperoxaluria is known to be a considerable risk factor for urolithiasis, it is important to understand the factors that have the potential to alter the efficiency of oxalate absorption. Oxalate bioavailability, a term that has been used to refer to that portion of food-derived oxalate that is absorbed from the gastrointestinal tract (GIT), is estimated to range from 2 to 15% for different foods. Oxalate bioavailability appears to be decreased by concomitant food ingestion due to interactions between oxalate and coingested food components that likely result in less oxalic acid remaining in a soluble form. There is a lack of consensus in the literature as to whether efficiency of oxalate absorption is dependent on the proportion of total dietary oxalate that is in a soluble form. However, studies that directly compared foods of varying soluble oxalate contents have generally supported the proposition that the amount of soluble oxalate in food is an important determinant of oxalate bioavailability. Oxalate degradation by oxalate-degrading bacteria within the GIT is another key factor that could affect oxalate absorption and degree of oxaluria. Studies that have assessed the efficacy of oral ingestion of probiotics that provide bacteria with oxalate-degrading capacity have led to promising but generally mixed results, and this remains a fertile area for future studies. *Adv. Nutr. 2: 254–260, 2011.*

Introduction

Oxalate is the anion of a strong dicarboxylic acid ($C_2O_4H_2$) that arises in the body from a combination of dietary sources and endogenous synthesis from precursors such as ascorbate and various amino acids (1). Approximately 75% of all kidney stones are composed primarily of calcium oxalate (2), with hyperoxaluria considered to be a primary risk factor for this type of stones (3). Urinary oxalate is a key determinant of the level of calcium oxalate saturation (4). Although it was reported that dietary oxalate contributes no more than 10–20% of the oxalate excreted in urine under normal conditions (1,2), more recent work (5,6) suggested that even in the absence of gastrointestinal disorders, intestinal absorption of dietary oxalate can make a more considerable contribution to urinary oxalate output. Because hyperoxaluria is a considerable risk factor for urolithiasis, it is important to understand which dietary sources of oxalate can raise urinary oxalate levels under what types of conditions. The propensity of a specific food to raise urinary oxalate is dependent both on oxalate content and efficiency of absorption, because it is well established that little oxalate catabolism occurs after absorption and >90% of absorbed oxalate can be recovered in the urine within 24–36 h (7).

Oxalate is a common component in many plant foods, including nuts, fruits, vegetables, grains, and legumes, and is typically present as a salt or ester of oxalic acid (1). In food, oxalic acid is typically found as either sodium or potassium oxalate, which are water soluble, or calcium oxalate, which is insoluble. Magnesium oxalate is also poorly soluble in water, although the contribution of this salt to the insoluble fraction of oxalate in food is unclear. In terms of the analytical determination of food oxalate content, when only water is used in the extraction step, the oxalate released is referred to as soluble oxalate. Using a strong acid solution in the extraction step will solubilize all oxalate salts, including calcium oxalate, and thus yields an assessment of total oxalate content. Insoluble oxalate, presumed to be primarily calcium oxalate, is computed as the difference between total and soluble oxalate.

Oxalate absorption appears to occur throughout the gastrointestinal tract (GIT) with both paracellular and transcellular (active and passive) uptake mechanisms (8). The timing of the peak recovery of urinary oxalate following

[1] Author disclosures: M. Liebman and I. A. Al-Wahsh, no conflicts of interest.

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oxalate ingestion is typically between 2 and 6 h, which suggests the small intestine is a key absorptive site. A peak recovery of urinary oxalate during this period does not preclude significant oxalate absorption in the stomach and it has been argued that a greater proportion of the food-derived oxalate would be solubilized at the normal gastric pH of 2 and thus becomes available for absorption (9). The overall contribution of colonic oxalate absorption in healthy individuals is unclear. However, it is well established that the colon is an important site for the increased oxalate absorption in individuals with enteric hyperoxaluria related to intestinal disease or intestinal surgery (10).

The term oxalate bioavailability has often been used in the literature to refer to that portion of food-derived oxalate that is absorbed from the GIT. Oxalate absorption rates from different foods have been estimated to range from ~2 to 15% (10,11). Oxalate bioavailability is likely dependent on a number of factors, including absorptive properties of the intestines, gut transit time, presence of divalent cations such as calcium and magnesium that can bind oxalate within the GIT, and presence of oxalate-degrading bacteria (12,13).

Two methods, previously summarized by Holmes et al. (10), have been used to assess food oxalate bioavailability. The first, referred to as the load method, involves a comparison of urinary oxalate excreted after ingestion of an oxalate load (usually an oxalate-rich food) with the amount excreted over 2–3 h immediately prior to ingestion of the oxalate load (baseline period). A 10- to 12-h fast is typically imposed prior to collection of the baseline urine sample. Any increase in urinary oxalate above baseline levels during the postoxalate ingestion period, typically varying from 6 to 24 h depending on the study design, is assumed to represent absorbed oxalate. The oxalate increment above baseline can be divided by total oxalate ingested to yield an estimate of oxalate absorption. Use of this method requires the assumption that oxalate excreted during the 2- to 3-h baseline period is primarily of endogenous origin. A key limitation is the lack of constancy in baseline urinary oxalate due to either fluctuations in endogenous synthesis or in the contribution of colonic absorption of oxalate consumed prior to the institution of a 10- to 12-h fast (10).

The importance of obtaining a valid estimate of endogenous oxalate excretion from the baseline urine sample is illustrated by results from a study in which the load method was used to assess oxalate absorption from 2 almond and 2 black bean treatments (14). Mean urinary oxalate for the 2-h baseline period ranged from 1.7 to 2.0 mg across the 4 treatments. A comparison of computed 24-h oxalate absorption levels was made by using each treatment's 2-h baseline oxalate level for each participant compared to using the mean of the 4 treatments' 2-h baseline oxalate level for each participant. For each of the 4 treatments, there was a markedly lower SEM for the overall mean estimate of 24-h oxalate absorption when each participant's mean 2-h baseline oxalate was used. Thus, these data suggested that the most accurate estimate of each participant's oxalate absorption is obtained when care is taken to obtain the most valid estimate of baseline oxalate excretion.

The second method, referred to as the daily excretion method, involves a comparison of urinary oxalate excretion for a defined period (typically 6–24 h) after ingestion of an oxalate-containing food with excretion during a control period of the same duration during which a low-oxalate diet is imposed. Oxalate absorption is approximated by dividing the difference in oxalate excretion during the test period and the control period by the total oxalate ingested. Validity is enhanced by allowing adequate time for equilibration of the test and control diets (i.e. feeding these diets for a number of days before the day in which urine is collected) (10). Inability to allow adequate equilibration is a limitation of the majority of studies that employed this method. Similar to the load method, there is also the assumption of a relative constancy in endogenous oxalate excretion, in this case, between the test and control periods.

The results of one study that employed this latter method may have been skewed due to a possible violation of the assumption of relative constancy in endogenous oxalate excretion. This study utilized the collection of a 6-h urine sample after participants ingested varying quantities of oca (also known as yam) (15). Total urinary oxalate was compared to levels in a 6-h control urine sample. The low oxalate bioavailability estimates for the 3 oca treatments, ranging from 1.2 to 1.8%, may have been at least partially due to the surprisingly high mean urinary oxalate (9.08 mg) for the 6-h control period. Extrapolating this 9.08-mg figure out to 24 h leads to an estimated daily oxalate excretion of >36 mg, a level that is markedly higher than expected for healthy participants who are consuming a low-oxalate diet.

Current status of knowledge

Oxalate bioavailability: effect of concomitant food or nutrient ingestion

As stated previously, dietary oxalate absorption expressed as a percentage of the oxalate ingested is generally quite limited. There is much higher absorption of radiolabeled oxalate given in the fasting state (e.g. as sodium oxalate) compared to when oxalate-rich foods are ingested or when the isotopic dose is given with food (10). Thus, oxalate absorption appears to be decreased by interactions between oxalate and coingested food components within the GIT. Additional support for this assertion is provided by the consistent finding of higher absorption from sodium oxalate compared to oxalate in foods, even those with a high soluble oxalate content such as spinach (16,17). The overall data suggest that oxalic acid is most efficiently absorbed as the free-charged anion rather than as a complex with divalent cations such as calcium or magnesium (10,18). It is well established that oxalate absorption can be markedly reduced by simultaneous ingestion of either calcium or magnesium (12), presumably due to the ability of these minerals to bind to oxalate in the gut, leaving less available for absorption. It is unclear whether sodium oxalate can be absorbed intact or dissociation generally occurs before absorption.

There was also one study conducted with rats that suggested that small amounts of calcium oxalate can be absorbed in an undissociated form (19), although the physiological significance of this finding and whether this absorptive route can occur in humans are unclear.

In sum, it is important to acknowledge that oxalate absorption figures for foods provided in the fasting state are likely to be an overestimate of absorption that occurs from these foods consumed as part of mixed meals. This should be considered when assessing the ability of various oxalate-rich foods to cause a clinically significant rise in urinary oxalate.

Oxalate bioavailability: importance of proportion of soluble to insoluble oxalate

There is a lack of consensus as to whether oxalate absorption is dependent on the proportion of total dietary oxalate that is soluble (13,20). The assertion that the proportion of soluble oxalate in a food is an important determinant of oxalate absorption is supported by the results of some studies (14,17,21,22) but not by others (15,23,24). Starting with studies that are judged to be positive in this regard are those that assessed oxalate absorption from milk chocolate and/or dark chocolate (16,21,25,26). Because only milk chocolate is made with milk powder, it has a markedly higher calcium content than dark chocolate and thus would be expected to have a much higher proportion of the insoluble calcium oxalate salt (i.e. a lower proportion of soluble oxalate). We recently found that the soluble oxalate content represents 82% of the total in a sample of dark chocolate but only 50% of the total in milk chocolate (M Liebman, unpublished results).

A study by Brinkley et al. (16) obtained a 2.6% oxalate bioavailability estimate for milk chocolate bars, whereas Balcke et al. (25) reported oxalate absorption figures of 12.2 and 7.5% for 50- and 100-g chocolate servings, respectively. Although not specifically stated, it can be assumed that the chocolate used in this study was dark chocolate because of the low-calcium content reported. Because none of these studies involved a direct comparison of milk chocolate and dark chocolate, the reported oxalate absorption estimates are only suggestive of an oxalate bioavailability difference between these 2 products.

We found only one study in which the 2 types of chocolate were directly compared (21). In a large population of calcium stone formers, consuming a 200-g milk chocolate bar (providing 94 mg oxalate and 428 mg calcium) between meals led to a 24-h urinary oxalate level of 35 vs. 32 mg during the 24-h control period. The corresponding figures for the 67-g dark chocolate treatment (providing 94 mg oxalate and 26 mg calcium) were 36 vs. 30 mg. Although significance between the chocolate and control trials was reached only for the dark chocolate, it is unclear whether the difference in oxalate increment between the 2 trials (3 mg for milk chocolate vs. 6 mg for dark chocolate) was clinically significant.

Other studies that are supportive of the importance of soluble oxalate content compared oxalate absorption between foods that either appeared or were demonstrated to have very different ratios of soluble:insoluble oxalate (14,17,22). Using the daily excretion method, Hanson et al. (17) demonstrated that oxalate bioavailability from sugar beet fiber (0.7%) was lower than that from spinach (4.5%) and suggested that this may be attributed to the markedly different molar ratios of oxalate:calcium in these products (0.2:1 vs. 2.5:1 in sugar beet fiber and spinach, respectively). These disparate molar ratios, suggestive of a predominance of insoluble oxalate in sugar beet fiber, may partially explain its very low oxalate bioavailability, but a definitive conclusion cannot be drawn because of the possibility of an inhibitory effect of the fiber, per se, on oxalate absorption.

Chai and Liebman (14) used the load method to compare oxalate absorption from 2 almond and 2 black bean treatments that provided 120 mg oxalate. The significantly higher oxalate absorption from almonds (5.9%) than from black beans (1.8%) was consistent with the proportion of soluble oxalate in these 2 foods (31 and 5% for almonds and black beans, respectively). In a similarly designed study, Tang et al. (22) used the load method to compare oxalate absorption from 2 oxalate-rich spices, cinnamon and turmeric, which were ingested in the form of supplements that provided 63 mg oxalate. Computed 22-h oxalate absorption from cinnamon (3.0%) was significantly less than from turmeric (7.7%). Because these spices varied widely in proportion of soluble oxalate (6% in cinnamon vs. 91% in turmeric), the absorption data supported the contention that the relative amount of soluble and insoluble oxalate plays a role in determining efficiency of oxalate absorption.

As stated previously, there are also several studies that do not support a proposed relationship between oxalate solubility and bioavailability (15,23,24). For example, using the daily excretion method over a 6-h period, Albihn and Savage (15) reported that oxalate absorption from 50-, 100-, and 150-g servings of baked yam ranged from 1.2 to 1.8%. Because yam is known to contain predominantly soluble oxalate, higher absorption figures would be expected if soluble oxalate is the more bioavailable fraction. However, a surprisingly high mean urinary oxalate (9.08 mg) for the 6-h control period may have caused an underestimation of actual absorption, because this method involves the determination of the urinary oxalate increment (i.e. the difference between oxalate excretion after consumption of the test food and oxalate excretion during a control period during which a low-oxalate diet is maintained), which is divided by the oxalate dose to estimate percentage absorption.

An important caveat related to this entire discussion is that although it is generally accepted that only soluble forms of oxalate can be absorbed, there are key gastrointestinal factors that can greatly affect how much oxalate remains solubilized and thus available for absorption. Jaeger and Robertson (9) emphasized the importance of pH changes within the GIT as well as the concentrations of key oxalate binding ions such as calcium and magnesium, whose luminal concentrations can dramatically change upon absorption into the mucosal cells. A related point is the overall effect of

concomitant calcium ingestion on oxalate bioavailability. As previously stated, oxalate absorption can be markedly reduced by simultaneous ingestion of either calcium or magnesium (27), presumably due to the ability of these minerals to bind to oxalate in the gut, leaving less in a soluble form available for absorption. Numerous studies have demonstrated a calcium-induced reduction in oxalate absorption (5,15,23,27–29) and some have even demonstrated a dose-dependent reduction (5,23). An ancillary finding of interest is that in the majority of cases, oxalate absorption was not reduced to zero even when a molar excess of calcium was provided (i.e. an amount of calcium with the potential to bind all the soluble oxalate provided by the test meal or supplemental oxalate dose) (5,23,29). For example, Liebman and Chai (5) reported that at least 200 mg (5.0 mmol) of ingested calcium was required to maximize the reduction in oxalate absorption (from a baseline value of 11.3 to 5.9%) in conjunction with a soluble oxalate dose of 198 mg (2.2 mmol). These data suggest that there are likely to be a multitude of interacting factors that are of importance with respect to oxalate bioavailability. For example, pH-induced solubility changes between the stomach and small intestine and the presence of other food components that can bind to calcium with high affinity are likely to be important factors.

In sum, there are inherent methodological limitations associated with the assessment of oxalate absorption that were previously summarized in this paper. Depending on the experimental design, the absolute absorption estimates can be biased in either direction, but there is likely to be some constancy in the bias among the different samples tested. Thus, it can be misleading to compare results from different studies. Rather, directly comparing foods of varying soluble oxalate contents using the same methodology (i.e. within a single study) may be the most ideal way to detect relative differences in oxalate bioavailability and to assess the importance of oxalate solubility. Studies that met this criterion compared dark chocolate to milk chocolate (21), spinach to sugar beet fiber (18), almonds to black beans (14), and cinnamon to turmeric (22). In all 4 cases, a higher proportion of soluble oxalate was associated with a higher estimate of oxalate absorption. Although additional research will be required to confirm these findings, it appears likely that the proportion of soluble to insoluble oxalate present in food is an important determinant of oxalate bioavailability.

Probiotics and oxaluria

As previously stated, another key factor that affects oxalate bioavailability is the presence of oxalate-degrading bacteria. The GIT of humans is colonized with a wide variety of bacterial species, some of which have the ability to degrade oxalate. Oxalate degradation might be expected to reduce oxalate absorption, thereby decreasing the degree of oxaluria. The best known oxalate-degrading species is *Oxalobacter formigenes*, an anaerobic bacterium that inhabits the colon and depends solely on oxalate as a source of metabolic energy. Colonization of the GIT by *O. formigenes* begins in infancy, and by the age of 6–8 y, almost all children test positive for this bacterium, compared to only 60–80% of adults, which could be explained in part by the use of antibiotics (30). A key unanswered question is whether the absence of this bacterium increases the risk of hyperoxaluria and the formation of kidney stones. In an early study, Sidhu et al. (31) linked the absence of *O. formigenes* to hyperoxaluria in 19 of 36 patients with cystic fibrosis. A very recent study demonstrated that the prevalence of *O. formigenes* was 17% in recurrent calcium oxalate stone formers compared to 38% in controls, but patients who tested positive or negative for *O. formigenes* did not differ in median urinary oxalate excretion (32 and 35 mg/24-h urine, respectively) (32). However, 2 earlier studies showed that urinary oxalate excretion was significantly lower in stone formers who tested positive for *O. formigenes* compared to those who tested negative [26.1 vs. 32.4 mg/d (33); 29.4 vs. 38.6 mg/d (34)]. Thus, the overall data suggest that colonization with *O. formigenes* could be a protective factor in terms of predisposition to kidney stones. In addition to *O. formigenes*, other bacterial species may play a protective role in terms of oxalate degradation, including, but not restricted to, *Eubacterium lentum*, *Enterococcus faecalis*, and *Lactobacillus acidophilus* (35).

Several studies have assessed whether providing bacteria with oxalate-degrading potential could reduce urinary oxalate excretion, thereby reducing risk of developing calcium oxalate kidney stones. The following section focuses on in vivo studies that explored the effects of consuming different probiotic preparations on urinary oxalate excretion in humans. These studies are summarized in **Table 1**.

In a preliminary study, Campieri et al. (36) reported a mean decrease of 40% (range of 20–86%) in urinary oxalate excretion in 6 participants with calcium oxalate stones and idiopathic hyperoxaluria (>40 mg/d) after 4 wk of daily ingestion of 2 doses of freeze-dried lactic acid bacteria consisting of 5 strains. The decrease in urinary oxalate excretion was sustained after 1 mo of discontinuation of the probiotic treatment. The probiotic treatment was successful in lowering urinary oxalate excretion to normal levels (<40 mg/d) in 5 of the 6 participants. The 6th participant started with a very high oxalate excretion of 95 mg/d, which decreased to 56 mg/d after treatment.

In a follow-up study, Lieske et al. (37) examined the effect of increasing the dose of a probiotic preparation that was slightly different from the one used previously by Campieri et al. (36) (one strain of bacteria was not included and the remaining 4 strains were mixed in a different ratio) on urinary oxalate excretion in a group of 10 patients with calcium oxalate stones, fat malabsorption, and enteric hyperoxaluria. In spite of marked interindividual variation in urinary oxalate excretion, the mean reductions were 19, 24, and 2% with 1, 2, and 3 doses of the probiotic, respectively. However, none of the 3 doses was successful in bringing hyperoxaluria to normal levels (<40 mg/24-h urine). After 1 mo of stopping the probiotic treatment, mean urinary oxalate excretion remained 20% less than baseline.

Table 1. Summary of in vivo studies dealing with the effects of probiotics on oxaluria

Reference	Study population	Probiotic composition	Method of administration	Length of study	Δ Urinary oxalate excretion, %
36	Six stone formers with idiopathic hyperoxaluria on uncontrolled normal diet	Oxadrop 4×10^{11} CFU 5 strains mixed in 1:1:1:1:1 ratio; *Lactobacillus acidophilus, Lactobacillus plantarum, Streptococcus thermophilus, Bifidobacterium infantis, Lactobacillus brevis*	Suspended in cold water, twice a day before meals	4 wk	−40
37	Ten stone formers with enteric hyperoxaluria on uncontrolled but similar diet during urine collection days	Oxadrop 8×10^{11} or 16×10^{11} or 24×10^{11} CFU, 4 strains mixed 1:1:4:4 ratio; *L. acidophilus, L. brevis, S. thermophilus, B. infantis*	Suspended in cold beverage (not milk), once daily 1–2 h after dinner or the major meal of the day	4 wk on each dose	−19[1] −24 −2
38	Twenty stone formers with idiopathic hyperoxaluria on uncontrolled, low-oxalate, but similar, diets during urine collection days	Oxadrop 10.8×10^{11} CFU, 4 strains mixed in 1:1:4:4 ratio; *L. acidophilus, L. brevis, S. thermophilus, B. infantis*	Suspended in a cold beverage (except milk), once daily 1–2 h after dinner or the major meal of the day	4 wk	−6
39	Sixteen stone formers on a controlled, high-oxalate diet	2×10^{7} to 10^{9} CFU of *Lactobacillus casei* and 5×10^{7} to 10^{9} CFU of *Bifidobacterium breve*	After major meals	2 wk	−6
40	Eleven healthy non–stone formers on controlled, low-oxalate diet	VSL#3 8 $\times10^{11}$ CFU, 8 strains; *S. thermophilus, B. breve, Bifidobacterium longum, B. infantis, L. acidophilus, L. plantarum, L. paracasei, and Lactobacillus delbrueckii* subsp. *bulgaricus*	Once a day, dissolved in water, after the last meal of the day	4 wk	−33
41	Forty stone formers on controlled, low-oxalate diet	Oxadrop 2×10^{11}, 4 strains mixed in 1:1:4:4 ratio; *L. acidophilus, L. brevis, S. thermophilus, B. infantis*		3 wk	+11

[1] The 3 changes in urinary oxalate excretion correspond to the 3 increasing doses of the probiotic, respectively.

Unlike the 2 previously described studies, a recent randomized, double-blind, placebo-controlled study did not demonstrate a positive effect of lactic acid bacteria on urinary oxalate excretion in calcium oxalate stone formers with idiopathic hyperoxaluria (38). Twenty participants received either a daily probiotic preparation identical (made from the same batch) to the one used in the previous study (37) or a placebo for 4 wk. The changes in median urinary oxalate excretion in both the treatment and placebo groups were not significant (–6% and +8%, respectively).

All 3 aforementioned studies used commercially available probiotic preparations containing 4 or 5 different strains of bacteria. Thus, any positive effect on oxaluria could not be traced to a particular strain. A recent study (39) used a mixture of only 2 strains of lyophilized bacteria, namely *Lactobacillus casei* and *Bifidobacterium breve*, for 14 d in 14 stone formers. After a washout period of 7 d of free living, during which the participants were instructed to consume a low-oxalate and low-calcium diet (100 and 400 mg, respectively) and another 7 d on a controlled diet (200 mg oxalate and 400 mg calcium), the participants consumed the bacterial preparation 3 times/d after meals for 14 d. Twenty-four-hour urinary oxalate excretion increased significantly after 7 d of controlled diet (from 27 to 35 mg/d) and no further change occurred after 14 d of probiotic consumption. A 50% probiotic-induced reduction in urinary oxalate excretion was observed in 2 participants with enteric hyperoxaluria, 5 participants had a modest reduction in urinary oxalate excretion, and 7 participants had increased urinary oxalate excretion. Although the participants in this study were described as normooxaluric, it should be acknowledged that the baseline urine samples were taken at the end of 7 d of consuming a low-oxalate diet (100 mg/d) rather than after a normal diet, which contains an average of 200 mg.

Okombo and Liebman (40) examined the effect of a 4-wk daily ingestion of a commercially available probiotic preparation (VSL#3; VSL Pharmaceuticals, Inc.) on urinary oxalate excretion in 11 healthy participants. The participants were challenged with 80 mg of oral soluble oxalate loads from capsulated turmeric at baseline, after 4 wk of probiotic use, and further after 4 wk of discontinuing probiotic use (washout period). The participants continued to consume a low-oxalate diet and used the same foods during each of the 3 load test days. Total urinary oxalate per 22 h following the oxalate loads decreased significantly by 33% from baseline to the probiotic and washout periods (47.0, 31.6, and 31.6 mg, respectively). However, there was no significant

decrease in total oxalate excreted in the urine collected in the first 6 h (typical oxalate absorption peak) after the ingestion of the oxalate loads, suggesting that oxalate degradation by the probiotic bacteria may be limited to the colon. It is also worthy to mention that the reduction in urinary oxalate excretion was largely due to a marked probiotic-induced reduction in oxalate excretion in 4 participants with enteric hyperoxaluria evidenced by their high urinary oxalate excretion between 6 and 22 h after the oxalate loads (compared to normal participants for whom urinary oxalate excretion typically peaks between 2 and 6 h after an oxalate load).

In a randomized, placebo-controlled study, Lieske et al. (41) examined the effect of ingesting 2 preparations, Oxadrop (a probiotic preparation; VSL Pharmaceuticals, Inc.) and Agri-King Synbiotic (a symbiotic with no established oxalate-degrading activity that contains fructooligosaccharide, bacteria, and yeast; Agri-King, Inc.), on urinary oxalate excretion in participants with idiopathic mild hyperoxaluria (>31 mg/d) and a history of calcium oxalate kidney stones. The participants consumed a controlled, metabolic, low-oxalate (80–100 mg) diet for 1 wk followed by 3 wk of daily consumption of 1 of 3 treatments: Oxadrop packet (1/d) plus placebo capsule (2/d), placebo packet (1/d) plus Agri-King Synbiotic capsule (2/d), or placebo packet (1/d) plus placebo capsule (2/d). During the course of treatment, the participants were instructed to avoid high-oxalate foods and live culture dairy products. The results showed a significant reduction in urinary oxalate excretion from 40.5 to 26.1 mg/L at the end of the initial week of the low-oxalate controlled diet. No further reduction in oxalate excretion was observed after 3 wk of using the 2 preparations.

Although 3 of the these described studies used controlled oxalate diets (39–41), the remaining 3 did not provide direct estimates of the amount of oxalate or calcium ingested daily and relied on the assumption that the participants adhered to dietary instructions regarding the consumption of high-oxalate-containing foods and calcium-containing dairy products, as well as live-bacteria-containing food products. Thus, it is likely that dietary factors other than the probiotic could have affected the observed changes in oxaluria. Controlling the diet by providing specific foods that contain known amounts of oxalate may decrease variability in urinary oxalate and increase the probability of detecting any probiotic-induced effects.

One of the studies tested for baseline colonic *O. formigenes* colonization (40) and one tested for lactobacilli and enterococci (41). However, none specifically tested the colonic colonization of the bacterial strains that were used in the corresponding probiotic preparation. Some participants may already have had the bacterial strain inhabiting their GIT and thus no further effect could be observed after ingesting additional bacteria in the probiotic. The specific association between colonic colonization of the bacteria of interest and urinary oxalate excretion was not addressed.

The composition of the probiotic preparations in terms of bacterial strains and mixing ratios differed among the different studies, which makes it difficult to compare results. In addition, the timing of probiotic administration, either before meals (36) or after dinner or the major meal (37–40), or irrespective of meal timing (41), may have contributed to the disparate results. The overall data suggest that the ability of chronic probiotic ingestion to reduce urinary oxalate excretion may be primarily confined to participants with absorptive (enteric) hyperoxaluria. In addition, none of the studied preparations can be recommended as a sole treatment for hyperoxaluria, because, in general, they were not able to consistently bring urinary oxalate excretion to normal levels (<40 mg/d).

Conclusions

Oxalate absorption appears to occur throughout the GIT and absorption of dietary oxalate can make a considerable contribution to urinary oxalate output. Oxalate absorption rates from different foods typically range from 2 to 15% and are dependent on a multitude of factors, including absorptive properties of the intestines, presence of divalent cations that can bind oxalate within the GIT, thereby decreasing the soluble oxalate fraction, and presence of oxalate-degrading bacteria. It is generally accepted that only the fraction of gastrointestinal oxalate that is soluble has the potential to be absorbed. A key question relates to whether the soluble oxalate content of the diet correlates with the amount of soluble oxalate that will be made available for absorption within the intestinal lumen (i.e. whether efficiency of oxalate absorption is dependent on the proportion of total dietary oxalate that is present in a soluble form). Although results obtained from different studies do not provide universal support for this proposition, studies that directly compared oxalate absorption from foods of varying soluble oxalate contents support the importance of this factor. Studies that have assessed the ability of probiotics that provide bacteria with oxalate-degrading capacity to reduce oxaluria, presumably by decreasing the availability of oxalate for absorption, have led to promising but generally mixed results. The current review suggests that the ability of chronic probiotic ingestion to reduce urinary oxalate excretion may be primarily confined to participants with absorptive (enteric) hyperoxaluria. Until now, studies have not examined the acute effect of consuming probiotics on oxalate excretion and whether the simultaneous ingestion of probiotic bacteria with oxalate can lead to increased oxalate degradation within the GIT during transit, a possibility that should be explored.

Acknowledgments

M.L. and I.A.A. conducted the literature research and wrote the manuscript. Both authors read and approved the final manuscript.

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