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ORIGINAL PAPER

Effects of *Lactobacillus casei* and *Bifidobacterium breve* on urinary oxalate excretion in nephrolithiasis patients

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Abstract It had been suggested that lactic acid bacteria (LAB) may degrade oxalate in the intestinal lumen, reducing urinary oxalate excretion. We aimed to evaluate the effect of a LAB mixture containing *Lactobacillus casei* (LC) and *Bifidobacterium breve* (BB) (LC + BB) upon urinary oxalate reduction in stone-forming (SF) patients without hyperoxaluria under conditions of an oxalate-rich diet. After an oxalate restriction period (7 days washout), 14 SF patients consumed an oxalate-rich diet during 4 weeks (200 mg/day) and a lyophilized LC + BB preparation was given t.i.d. after meals during the last 2 weeks. Twenty-four-hour urine samples were collected for determination of oxalate, calcium, magnesium, citrate, sodium, potassium and creatinine at baseline, after 2 weeks (DIET) and 4 weeks (DIET + LC + BB). The mean urinary oxalate excretion was significantly higher after DIET versus baseline (27 ± 8 vs. 35 ± 11 mg/24 h), but the mean decrease was not significant between DIET + LC + BB and DIET periods (35 ± 11 vs. 33 ± 10 mg/24 h). Seven out of 14 patients presented a reduction in oxaluria after LC + BB versus DIET, being the reduction higher than 25% in 4, and up to 50% in 2 of them. The latter two patients were those who had presented the greatest increase in oxaluria in response to dietary oxalate. In conclusion, this mixture of *L. casei* and *B. breve* was shown to possess a variable lowering effect upon urinary oxalate excretion that may be dependent on dietary oxalate intake.

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Introduction

Hyperoxaluria is one of the major risk factors of calcium oxalate stone formation due to urinary calcium oxalate supersaturation, since the latter is directly correlated with urinary oxalate concentration [1–3]. Secondary hyperoxaluria is due to either increased availability of substrate (ascorbic acid, ethylene glycol, methoxyflurane) [4] or to intestinal hyperabsorption of oxalate caused by a high-oxalate diet, enteric hyperoxaluria, or an imbalance between intraluminal calcium and oxalate as in a low-calcium diet [5–9]. Under physiological conditions, the majority of urinary oxalate is derived from endogenous metabolism (40–50% from hepatic synthesis and 40% from the breakdown of ascorbic acid). However, our understanding about the sources of urinary oxalate is still incomplete and the relative proportion from diet is uncertain. While some authors report that the contribution of diet to urinary oxalate excretion is around 10% [7, 10], Holmes et al. [11] in a very elegant study, have shown that the contribution of dietary oxalate may be much higher than the previously estimated, achieving values up to 50%. Nevertheless, recent epidemiological studies have not shown a significantly different oxalate intake between stone formers and non-stone formers, so that the relation between dietary oxalate and stone risk remains unclear [12]. In addition, the quantity of free oxalate in the gastrointestinal tract may be affected not only by the intake of dietary oxalate but also by its binding to magnesium, fatty acids, bile salts and calcium [13–15]. Dietary calcium has been associated with lower risk of stone

formation [6] and recurrence rates [16], possibly due to a decreased absorption of dietary oxalate that is bound by calcium in the intestinal lumen, as shown by our group [9, 17] and others [18].

A study performed by Sidhu et al. [19] has demonstrated that the presence of an anaerobic bacterium in the human intestine, *Oxalobacter formigenes*, which extracts metabolic energy exclusively from the decarboxylation of oxalate [20], may be found in 70–80% of healthy subjects as opposed to 20% of stone-forming (SF) patients who exhibited high rates of recurrence. However, the association between intestinal colonization and urinary oxalate levels was not addressed in this study. Subsequently, Kwak et al. [21] have shown that urinary oxalate decreased significantly with increasing colonization of *O. formigenes* in the intestinal lumen. On the other hand, more recent data do not confirm an inverse correlation between its intestinal colonization and oxaluria [22].

Because not all individuals who test negative for *O. formigenes* are hyperoxaluric [21, 22], other components of the gastrointestinal flora also could be important in terms of oxalate-substrate utilization. Some lactic acid bacteria (LAB) used in the dairy industry also use oxalate as an energy source, potentially limiting its absorption from the intestinal lumen hence contributing to decreased oxaluria [23]. In 2001, Campieri et al. [24] showed that a freeze-dried preparation, composed of five different organisms, given for 30 days and chosen based on the results of their in vitro ability to degrade oxalate (*Lactobacillus acidophilus*, *L. brevis*, *L. plantarum*, *Bifidobacterium infantis* and *Streptococcus thermophilus*) induced a significant reduction on oxalate excretion in a small number of hyperoxaluric patients. The underlying mechanism for such reduction remains uncertain since these bacteria lack the gene present in *O. formigenes*'s DNA responsible for oxalate uptake. Lieske et al. [25] have tested the same mixture of LAB in a set of ten subjects with enteric hyperoxaluria and observed a reduction of up to 24% on mean urinary oxalate excretion. Conversely, a more recent randomized and controlled trial performed by Goldfarb et al. [26] did not observe a significant reduction of urinary oxalate in subjects with idiopathic hyperoxaluria given LAB. Therefore, responses to LAB are still controversial.

Since *Lactobacillus casei* is present in a very popular probiotic beverage consumed in some parts of the world, aimed to regulate intestinal habit, the purpose of the present study was to determine if a mixture of lyophilized *L. casei* and *Bifidobacterium breve* could reduce urinary oxalate excretion in stone-forming subjects with normal levels of oxalate excretion, under conditions of a controlled oxalate diet.

Subjects and methods

Subjects

Fourteen stone-forming subjects with normal renal function from the Renal Lithiasis Unit of the Nephrology Division of Universidade Federal de São Paulo, were included in the present study. The diagnosis of stone disease was based on renal colic with confirmed hematuria and voiding of a calculus and/or previous surgical or endoscopic removal of stone(s), and/or radiographic evidence of stone(s). Four patients have voided calculi in the past, but their stones were not available for analysis. On enrollment, all patients presented uni or bilateral radio-opaque stones. The data concerning the definition of distinct metabolic diagnosis in SF subjects were obtained from the results of 24-h urine samples contained in the medical records. Hypercalciuria was defined as urinary calcium >250 or 300 mg/24 h (for female and male, respectively), hyperuricosuria as urinary uric acid >750 or 800 mg/24 h (for female and male, respectively), hypocitraturia as urinary citrate <320 mg/24 h, hyperoxaluria as urinary oxalate >45 mg/24 h and hypomagnesiuria as urinary magnesium <70 mg/24 h, as described elsewhere [27]. Subjects with inflammatory bowel disease, taking dietary supplements, antibiotics, vitamins or those submitted to ileal/colonic resection or bariatric surgery were not eligible. The study was approved by the Ethics Committee of the institution and an informed written consent was obtained from all participants.

Study design

A washout period of 7 days was initiated before the first 24-h urine collection, during which subjects were asked by the dietician to abstain from consuming oxalate-rich foods (a listing of these foods was provided), limiting the amount of oxalate intake to 100 mg/day. Dairy products were also restricted limiting the amount of calcium to around 400 mg/day (300 mg of calcium from milk plus 100 mg from vegetable sources). A 7-day dietary record was obtained to ensure that compliance with diet had been achieved.

On the 7th and last day of the washout period, subjects collected the first 24-h urine sample. They were asked to document their diet in a dietary record to ensure compliance with respect to calcium and oxalate ingestion, recommended for the washout period. On the second period (DIET), the subjects received frozen meals (lunch and dinner) for 7 days, containing a total of 200 mg of oxalate of vegetable origin (boiled spinach, sweet potato, carrot or beetroot) and around 400 mg of calcium, as dairy products were again limited to 240 ml/day of milk. On the 7th day of this period, they collected a second 24-h urine sample. On the third period (DIET + LC + BB) which lasted

14 days, the participants received the same frozen diet and took a granulated oral preparation containing 50 mg of lyophilized *L. casei* Shirota, 2×10^7–10^9 CFU, and *B. breve*, 5×10^7 to 10^9 CFU (Yakut SA Indústria e Comércio - Brazil), t.i.d., after the major meals. On the last day taking the assigned preparation, the subjects again collected the third and last 24-h urine sample. Resuspension of the bacterial cells in saline gave viable counts on MRS (Mann Rogosa Sharpe) agar, comparable to the original cell concentrations (data not shown). Nutrient intake was calculated with a computerized program developed in our Service, which employed a food table from the United States Department of Agriculture [28]. The oxalate content in foods was based on a recent table from Harvard Medical School [29].

Urine chemistries

Calcium, oxalate, sodium, potassium, magnesium, citrate and creatinine were determined in the 24-h urine samples. Calcium and magnesium were determined by atomic absorption spectrophotometry (Perkin Elmer Atomic Spectrophotometer 3110, Norwalk, Connecticut, USA); oxalate by an enzymatic method [30] using a commercial kit (Sigma Diagnostics, St. Louis, MO, USA), and citrate by an enzymatic assay using citrate lyase [31]. Creatinine was determined according to a modified Jaffé reaction through the method of isotope dilution mass spectrometry (IDMS) traceable. Sodium and potassium were determined by an ion-selective electrode. The variation coefficient (CV) of our laboratory was: 1.3% for sodium, 2.6% for potassium,1.5% for uOx, 2.5% for uCa, 6.9% for uMg, 8.4% for uCreat, and 13.4% for uCit. The values of oxalate, calcium, magnesium and citrate were used to calculate the risk of calcium oxalate crystallization as defined by Tiselius [32], according to the formula: $1.9 \times Ca^{0.84} \times Ox \times Mg^{-0.12} \times Cit^{-0.22} \times V^{-1.03}$ (Tiselius index).

Statistical analysis

Non-parametric Wilcoxon's test was used to compare the results obtained after DIET versus BASELINE or versus DIET + LC + BB. Statistical significance was defined by a $P < 0.05$.

Results

The participants included seven men and seven women and the mean age was 42.1 ± 10.8 years. No adverse effects were observed while on the use of LAB. Hypercalciuria and hypocitraturia were present in 64 and 36% of subjects respectively, whereas hyperuricosuria was seen in 14% of them. These disturbances appeared isolated or in association. Hyperoxaluria and hypomagnesiuria were absent.

Table 1 Urinary parameters in each period

	Baseline	Diet	Diet + LC + BB
Volume (ml/24 h)	1,955 ± 1,024	2,041 ± 798	2,133 ± 595
Oxalate (mg/24 h)	27 ± 8	35 ± 11*	33 ± 10
Calcium (mg/24 h)	212 ± 105	202 ± 90	244 ± 65
Sodium (mEq/l)	181 ± 75	209 ± 48	226 ± 87
Potassium (mEq/l)	54 ± 29	60 ± 14	57 ± 26
Magnesium (mg/24 h)	98 ± 35	99 ± 36	111 ± 31
Citrate (mg/24 h)	525 ± 212	491 ± 216	389 ± 147†*
Creatinine (mg/24 h)	1,199 ± 286	1,292 ± 346	1,272 ± 221
Crystallization index	0.85 ± 0.5	0.87 ± 0.5	0.96 ± 0.5

* $P < 0.05$ vs. baseline; † $P < 0.05$ vs. diet

Table 1 shows the results of mean urinary parameters at BASELINE, and after DIET and DIET + LC + BB periods. Mean urinary oxalate excretion was significantly increased after DIET but did not decrease significantly after DIET + LC + BB. After LC + BB use, all other urinary parameters did not present statistically significant differences compared to BASELINE or DIET period, except for urinary citrate, which was significantly lower compared to DIET period (491 ± 216 vs. 389 ± 147, $P < 0.05$).

Figure 1 illustrates the individual values of urinary oxalate throughout the three periods of the study. After DIET + LC + BB period, 7/14 (50%) SF subjects presented a reduction in oxaluria compared to the DIET period (dotted lines). Table 2 lists the results of urinary oxalate excretion at DIET and DIET + LC + BB periods and the percentual variation between them both. As seen, in four subjects the reduction was higher than 25% in comparison to DIET period, achieving almost 50% in two of them. In the remaining three subjects, the reduction in urinary oxalate excretion was around 11–15%. Urinary oxalate almost did not change in two, and even increased in the remaining five subjects.

Discussion

Previous investigations have demonstrated that lactic acid bacteria degrade oxalate in vitro [24] and reduce urinary oxalate excretion [24, 25]. In the present study, we aimed to investigate the effects of a mixture of LAB, not previously tested, on urinary oxalate excretion of normooxaluric stone formers, under conditions of a controlled oxalate diet.

Our results have not shown a significant reduction in the mean value of urinary oxalate in the group as a whole with the use of LAB. Nevertheless, individual reductions in oxaluria varying between 11 and 50% were observed in seven

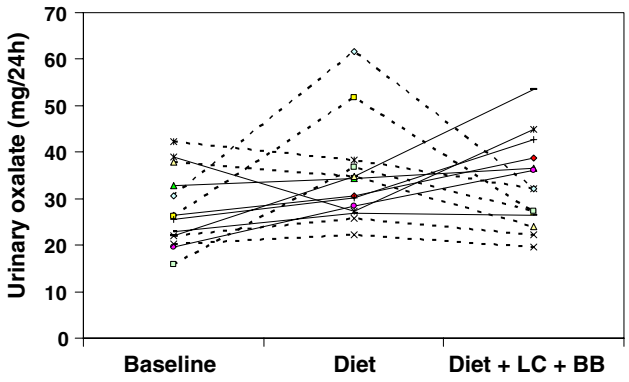

Fig. 1 Individual urinary oxalate excretion of 14 SF patients after DIET and DIET + LC + BB periods

Table 2 Mean value of urinary oxalate in both periods and percentual variation (Δ%) between them

Urinary oxalate excretion (mg/24 h)			
Patient	DIET	DIET + LC + BB	Δ%
1	30.7	38.7	+26.1
2	51.8	27.1	−47.7
3	34.4	36.5	+6.1
4	25.7	22.3	−13.2
5	38.3	32.2	−15.9
6	28.4	36.1	+27.1
7	30.2	42.8	+41.7
8	26.9	26.5	−1.5
9	34.8	53.5	+53.7
10	61.7	32.1	−48.0
11	36.8	27.2	−26.0
12	34.9	24.1	−31.0
13	22.2	10.5	−11.9
14	27.3	45.0	+64.8

subjects, being of a greater magnitude in two of them. Urinary oxalate almost did not change or even increased in the remaining subjects.

Although previous studies by Campieri et al. [24] and Lieske et al. [25] have shown a substantial reduction of mean oxaluria after ingestion of a LAB preparation in subjects with enteric hyperoxaluria (40 and 24% respectively), a recent randomized double-blind placebo-controlled trial performed by Goldfarb et al. [26] in subjects with idiopathic hyperoxaluria did not observe a reduction in urinary oxalate excretion, using the same bacteria.

In the current series of subjects, there has been a wide variation of individual responses to either the diet alone or to its association with the bacterial preparation. Such findings of a wide variation of oxalate in response to oxalate intake agree well with the observations pointed out by Holmes and Kennedy [33] that the absorption of intestinal oxalate is not linearly related to the amount of oxalate ingested, ant that it may vary tremendously between individuals with a range of 10–72%. The variability of oxalate excretion in response to both dietary or non-dietary factors [34] also emphasizes how hard it is to conduct studies relying on distinct impacts on urinary oxalate.

Nevertheless, it is noteworthy that the greater reduction in oxaluria after LAB in the present series had occurred in the same two subjects who exhibited the greatest responses to dietary oxalate in terms of increase in oxaluria, suggesting the presence of absorptive hyperoxaluria in these otherwise normooxaluric subjects. Therefore, the individual intestinal sensitivity to absorb oxalate might have determined the response to probiotics. Curiously, looking into individual responses to LAB in subjects with malabsorptive diseases or those submitted to bypass surgery, in the series of Lieske et al. [25], one may see that the greater reductions on urinary oxalate also occurred in four out of the ten subjects with enteric hyperoxaluria who exhibited the highest baseline levels of urinary oxalate. In the same way, their findings could be ascribed to a higher degree of fat malabsorption by these subjects leaving a higher amount of free oxalate in intestinal lumen to be absorbed [15], hence allowing the degradation by bacteria.

A potential limitation of our study is that the colonization status with *O. formigenes* was not determinated, since the oxalate absorption as well as oxalate excretion could have been influenced by the presence of such bacteria [19, 21]. Nevertheless, a recent trial conducted by Kaufman et al. [22] in 247 recurrent calcium oxalate kidney stone cases (CaOx) versus 259 individuals without stone disease has shown that in spite of a higher prevalence of *O. formigenes* in stool cultures from SF patients than in controls, the median urinary oxalate excretion did not differ with the presence or absence of colonization as expected. Additionally, an intrastool and interstool sample variability in the amount of *O. formigenes* has been reported by Prokopovich et al. [35]. Although the techniques employed in studies focused on *O. formigenes* colonization status are different and difficult to compare, the controversial results indicate that there may be other factors that influence urinary oxalate excretion that have not been identified yet. Another factor that might also have contributed to the variation of the results is related to the 24 h sample collection variability indicated by the increase of urinary creatinine by 10%, although not statistically significant.

Individual metabolic disturbance of each patient did not influence urinary oxalate reduction provided by LAB supplementation, since isolated or associated hypercalciuria was present respectively in 4/7 and 5/7 of subjects that reduced or not oxaluria after LAB. Similarly, isolated or associated hypocitraturia was present respectively in 2/7 and 3/7 of subjects that reduced or not urinary oxalate

levels. Anyway, it is important to emphasize that metabolic disturbances based on defined thresholds, albeit well accepted in the literature, are arbitrary since the risk for stone formation appears to be continuous as recently shown [36].

In our experiment, there had been a significant decrease in urinary citrate following the use of LAB. Although we did not measure urinary pH in the present study, we can hypothesize that the reduction in citraturia might have resulted from an increased tubular citrate reabsorption due to a reduction in urinary pH, as suggested by other investigators who observed lower urinary pH levels after LAB consumption [25]. Nevertheless, the slightly lower citraturia did not increase the urinary crystallization risk estimated by the Tiselius index.

In conclusion, present data suggested that *L. casei* and *B. breve* possesses a variable lowering effect on urinary oxalate excretion, that may be dependent on dietary oxalate. We recognize that this is a small study of feasibility and that future prospective trials under controlled diet enrolling more stone-forming subjects should be important to confirm the hypothesis that LAB is indeed effective in the reduction of urinary oxalate.

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