

Comparative Value of Orange Juice *versus* Lemonade in Reducing Stone-Forming Risk

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Foods that are high in citrate content generally are assumed to deliver alkali load when consumed irrespective of the accompanying cation. The object of this randomized, crossover study was to compare the effects of orange juice with those of lemonade on acid-base profile and urinary stone risks under controlled metabolic conditions. Thirteen volunteers (nine healthy subjects and four stone formers) sequentially received distilled water, orange juice, or lemonade while on constant metabolic diet. Twenty-four-hour urine samples were collected for acid-base parameters and stone risk analysis. Orange juice but not lemonade provided alkali as evidenced by higher net gastrointestinal alkali absorption and higher urinary pH and citrate compared with control. Urinary calcium was not significantly different, but urinary oxalate was higher during the orange juice phase. The calculated supersaturation of calcium oxalate was lower in the orange juice phase compared with control. Calculated undissociated uric acid was lower in the orange juice phase compared with both control and lemonade phases. The calculated supersaturation of brushite was significantly higher in the orange juice phase compared with both control and lemonade phases. Despite comparable citrate content, this study showed that orange juice has greater alkalinizing and citraturic effects than lemonade. Consumption of orange juice was associated with lower calculated calcium oxalate supersaturation and lower calculated undissociated uric acid. This short-term study suggests that orange juice consumption could result in biochemical modification of stone risk factors; however, additional studies are needed to evaluate its role in long-term prevention of recurrent nephrolithiasis.

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Management of recurrent kidney stones requires both diet/lifestyle modification and medical therapy, and one of the important elements of medical therapy is the administration of potassium alkali such as potassium citrate. Potassium citrate has been shown to decrease stone formation rate in patients with idiopathic hypocitraturic calcium nephrolithiasis (1,2), hyperuricosuric (3), and thiazide-unresponsive patients (4). Potassium citrate is believed to exert its beneficial effect through its citraturic and urinary alkalinizing actions. The increase in urinary citrate retards spontaneous nucleation and agglomeration of calcium oxalate crystals (5). Moreover, by increasing urinary pH and decreasing urinary content of undissociated uric acid, this treatment is useful in preventing uric acid stones (6).

There are patients who are not able to tolerate potassium citrate, however, because of gastrointestinal adverse effects. Some may prefer nonpharmacologic therapy. In such cases, dietary sources of citrate may be considered an option or alternative to pharmacologic agents. Fruits and fruit juices with high citrate content generally are assumed to deliver an alkali

load. However, previously published studies on the influence of different citrate-rich fruit juices/beverages on the risk for stone formation have provided conflicting results, with some beverages decreasing the risk for stones whereas others have either no effect or increase the risk (7–16). One reason might be the different constituents of various beverages. For instance, citrate in products such as orange and grapefruit juice is complexed mainly by potassium, whereas citrate in lemonade and cranberry juice is accompanied by proton. Potassium citrate and citric acid are very different in terms of acid-base profiles. It has been shown that the renal effects of orange juice resemble those of potassium citrate and potentially can reduce the stone risk factors (7). Lemonade and cranberry juice, conversely, do not confer the alkali load that orange juice provides, presumably because the accompanying proton negates the effect of bicarbonate that is generated by intrahepatic metabolism of citrate. This study was undertaken to compare the effects of orange juice and lemonade on acid-base profile and urinary stone risk factors while on constant metabolic diet with each participant serving as his or her own control.

Materials and Methods

Study Participants

We recruited healthy volunteers and calcium stone formers who were between 20 and 65 yr of age for this randomized, crossover study that compared the effects of distilled water (as control), orange juice, and lemonade on urinary citrate and pH. Screening medical history, physical examination, serum chemistry, and complete blood count

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were obtained in all potential participants before entry into the study. Subjects were excluded when they had recurrent or active urinary tract infection, renal tubular acidosis, primary hyperparathyroidism, hyperkalemia, any diseases or medications that potentially could affect acid-base status, gouty diathesis, gastrointestinal disease, renal insufficiency, chronic diarrhea, or pregnancy or were women who were nursing. Patients with hypercalcemia, calcium phosphate stones with secondary etiology, struvite, and uric acid stones also were excluded. All participants were instructed to stop all medications for at least 2 weeks before and during each phase of the study. This study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center, and all participants provided written informed consent before enrollment.

Study Protocol

The study was conducted partly in an outpatient and partly in an inpatient setting at the General Clinical Research Center. Participants were provided with frozen metabolic diet during the 4-d outpatient period. The last 3 d of each phase were performed in the inpatient setting. Each participant underwent three phases of the study, each lasting 1 wk. The three phases, chosen in random order according to a scheme developed by our statistician, included the distilled water, or control, phase; orange juice phase; and lemonade phase. For all participants, a 3-wk interval between phases was imposed for washout. During the orange juice phase, participants were asked to consume 400 ml of orange juice (Minute Maid, Houston, TX) three times a day with meals. The source of orange juice was frozen orange concentrate from the same lot. Content of citrate, potassium, calcium, and magnesium was analyzed before use. The frozen concentrate was diluted with an appropriate amount of distilled water so that each 400-ml portion would deliver 33.3 mEq of citrate and 14 mEq of potassium corresponding to 100 mEq of citrate and 42 mEq of potassium/d. The orange juice and lemonade used were not calcium fortified.

During the lemonade phase, participants drank 400 ml of lemonade (Minute Maid) three times a day with meals. The source of lemonade was frozen concentrate from the same lot. The frozen concentrate was diluted with distilled water so that each 400-ml portion would deliver 33.3 mEq of citrate. From our analysis, virtually no potassium would be delivered.

During the control phase, participants drank 400 ml of distilled water using the same dosing interval. During all phases, participants were maintained on a constant low-calcium, low-oxalate, metabolic diet with daily composition of 400 mg of calcium, 150 to 200 mg of oxalate, 800 mg of phosphorous, 100 mEq of sodium, 50 mEq of potassium, and 200 mg of magnesium. Total fluid intake was fixed at 3 L/d.

On days 5, 6, and 7, each participant collected 24-h urine samples for biochemical assessments of stone risk factors that included urinary pH, creatinine, calcium, sodium, magnesium, citrate, oxalate, sulfate, uric acid, and total volume using established techniques. Indices of acid-base balance such as titratable acid, net acid excretion, ammonium, and net gastrointestinal alkali absorption (NGIA) also were determined. Urinary concentration of titratable acidity was measured directly using an automated burette end-point titration system (Radiometer, Copenhagen, Denmark). Net acid excretion was calculated as the sum of urinary titratable acidity and ammonium minus the calculated urinary bicarbonate and ionized citrate, expressed as mEq/d. NGIA was calculated from urinary mineral cations and anions using the method described by Oh (17). Relative saturation ratios (RSR) for calcium oxalate, brushite, and undissociated uric acid were calculated using the EQUIL 2 program (18).

Fasting venous blood samples were drawn in the morning of days 6

and 7. Blood samples were analyzed using a systemic multichannel analyzer.

Statistical Analyses

Repeated measures ANOVA models were used to assess phase and order effects in this crossover design. A repeated measures ANOVA model with a grouping factor also was used to estimate any between-group effects of interactions. Analysis was performed using SAS statistical software version 9 (SAS Institute, Cary, NC). Data are expressed as mean \pm SD. Orange juice, lemonade, and control conferred similar changes in nine healthy volunteers and four stone formers; therefore, data for all 13 participants were combined.

Results

Participants

Fourteen participants (10 healthy volunteers and four stone formers) were recruited for this study. One healthy volunteer withdrew from the study because of personal reasons. Nine healthy volunteers (five men and four women) completed the study. The stone former group consisted of three men and one woman. The mean age was 44.7 ± 9.6 and 40.3 ± 9.5 yr for the healthy volunteers and stone formers, respectively. Body mass index was comparable between the two groups: 31.1 ± 4.5 kg/m² for the healthy volunteers and 31.3 ± 5.0 kg/m² for the stone formers.

Effect on Acid-Base Status

Serum electrolytes did not differ significantly among the three phases (Table 1). NGIA was significantly higher in the orange juice phase with a mean of 52.7 mEq/d compared with 7.6 and 11.1 mEq/d in the lemonade and control phases, respectively (Figure 1). Orange juice consumption resulted in significantly lower ammonium as well as lower titratable acidity (Figure 2) and net acid excretion compared with the control phase (Table 2). These findings were not seen during the lemonade phase.

Effect on Urinary Stone Risk

Orange juice consumption resulted in a significantly higher urinary citrate excretion, whereas lemonade had no significant effect on urinary citrate (Figure 3). The mean increase in urinary citrate per 240 ml of orange juice consumed was 88 ± 30 mg compared with an increase of only 11 ± 23 mg per 240 ml observed during lemonade consumption. Urinary oxalate was significantly higher with the orange juice compared with control, a finding that was not seen with lemonade consumption (Table 2). Despite higher urinary oxalate, the calculated RSR of calcium oxalate was significantly lower in the orange juice phase compared with control. The calculated RSR of calcium oxalate tended to be lower during the orange juice phase compared with the lemonade phase, but the difference was NS.

Urinary pH was higher by 0.6 unit in the orange juice phase compared with the lemonade and control phases (Figure 4). Urinary uric acid and sodium were not statistically different in the three phases. Administration of orange juice resulted in lower calculated undissociated uric acid (77 mg/d in orange juice versus 184 mg/d during the control phase) and higher urinary potassium and magnesium compared with the control

Table 1. Serum chemistries of the study participants according to intervention period^a

Parameter	Control	Lemonade	Orange Juice	ANOVA <i>P</i>
BUN (mg/dl)	11 ± 3	10 ± 3	11 ± 3 ^b	<0.05
Cr (mg/dl)	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.61
Na ⁺ (mEq/L)	138 ± 2	138 ± 2	137 ± 2	0.31
K ⁺ (mEq/L)	4.2 ± 0.3	4.3 ± 0.3	4.4 ± 0.3	0.22
Cl ⁻ (mEq/L)	105 ± 2	105 ± 3	104 ± 2	0.35
CO ₂ (mEq/L)	28 ± 2	29 ± 2	29 ± 2	0.11
Ca ²⁺ (mg/dl)	9.3 ± 0.3	9.3 ± 0.3	9.3 ± 0.2	0.95
P _i (mg/dl)	3.4 ± 0.4	3.2 ± 0.6	3.4 ± 0.4	0.10
Mg ²⁺ (mg/dl)	2.2 ± 0.2	2.2 ± 0.1	2.2 ± 0.1	0.19
UA (mg/dl)	6.6 ± 1.6	6.2 ± 1.6	5.6 ± 1.5 ^{b,c}	<0.0001

^aData are mean ± SD. BUN, blood urea nitrogen; Ca²⁺, calcium; Cl⁻, chloride; CO₂, total carbon dioxide; Cr, creatinine; K⁺, potassium; Mg²⁺, magnesium; Na⁺, sodium; P_i, inorganic phosphorus; UA, uric acid.

^b*P* < 0.05 *versus* lemonade.

^c*P* < 0.05 *versus* control.

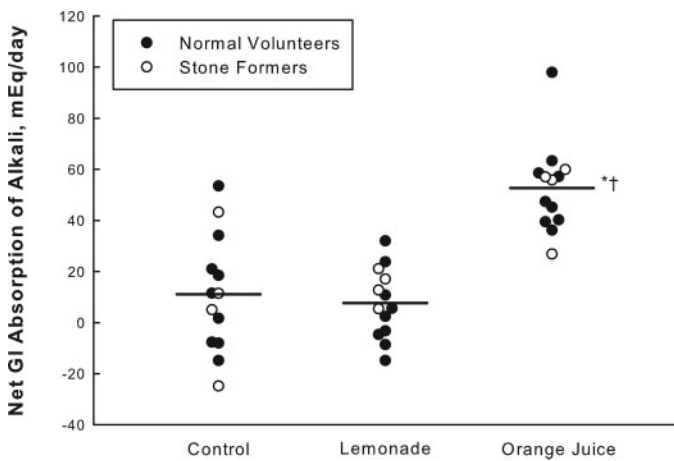


Figure 1. Effect of lemonade and orange juice on net gastrointestinal absorption of alkali. Horizontal lines indicate group means. ●, normal volunteers; ○, stone formers. **P* < 0.05 *versus* control; [†]*P* < 0.05 *versus* lemonade.

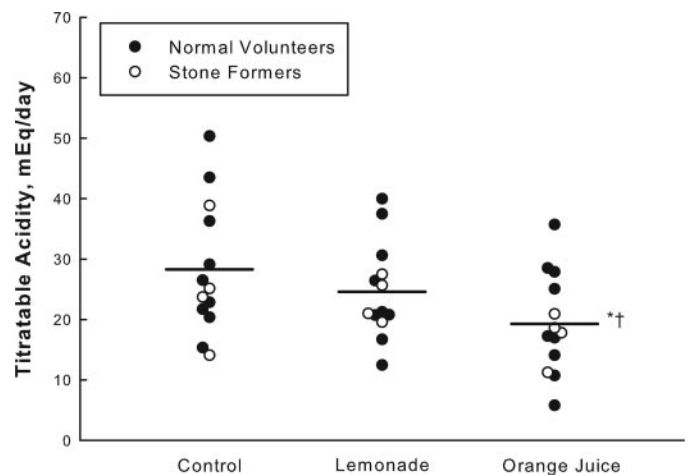


Figure 2. Effect of lemonade and orange juice on titratable acidity. Horizontal lines indicate group means. ●, normal volunteers; ○, stone formers. **P* < 0.05 *versus* control; [†]*P* < 0.05 *versus* lemonade.

phase (Table 2). These findings were not observed during the lemonade phase.

The calculated RSR of brushite was higher in the orange juice phase compared with lemonade and control phases (0.82 during the orange juice phase *versus* 0.32 and 0.42 during the lemonade and control phases, respectively; Table 2).

Discussion

The main goal of this study was to compare orange juice and lemonade with respect to their effects on acid-base balance and stone risk factors. This study provided evidence that orange juice provides an alkali load, promotes hypercitraturia, and reduces the propensity for crystallization of calcium oxalate and uric acid, whereas lemonade does not.

Orange juice provided an alkali load, based on the rise in NGIA, urinary pH, and citrate, and reduction in urinary ammonium, titratable acidity, and net acid excretion. These find-

ings are consistent with a previous study that showed that administration of orange juice, grapefruit juice, and apple juice increased urinary pH and citrate (9) and with a three-phase study that used placebo, orange juice, and potassium citrate (7). Compared with potassium citrate, orange juice delivered an equivalent alkali load and resulted in a comparable increase in urinary pH and citrate. Citrate retards the crystallization of stone-forming salts through two mechanisms. First, it forms a soluble complex with calcium and reduces ionized calcium concentration, thereby reducing calcium oxalate and calcium phosphate supersaturation (6). The second mechanism is the direct inhibitory effect of citrate on spontaneous nucleation, crystal growth, and crystal agglomeration of preformed calcium oxalate crystals (19). Although both orange and grapefruit juices have citraturic and alkalinizing effects, earlier studies showed that they do not affect calcium oxalate supersaturation (7,10). This likely is due to the increase in urinary oxalate

Table 2. Twenty-four-hour urine values according to intervention period^a

Parameter	Control	Lemonade	Orange Juice	ANOVA <i>P</i>
Total volume (L/d)	2.55 ± 0.54	2.61 ± 0.31	2.51 ± 0.35	0.51
Ca ²⁺ (mg/d)	159 ± 42	154 ± 58	146 ± 52	0.32
Mg ²⁺ (mg/d)	83 ± 23	86 ± 21	108 ± 28 ^{b,c}	<0.0001
Cr (mg/d)	1589 ± 349	1565 ± 364	1585 ± 315	0.81
Na ⁺ (mEq/d)	70 ± 37	58 ± 31	66 ± 48	0.28
K ⁺ (mEq/d)	38 ± 11	39 ± 7	85 ± 21 ^{b,c}	<0.0001
Ammonium (mEq/d)	37 ± 10	36 ± 9	23 ± 8 ^{b,c}	<0.0001
Oxalate (mg/d)	31 ± 10	30 ± 7	35 ± 6 ^{b,c}	<0.005
UA (mg/d)	527 ± 123	491 ± 81	533 ± 116	0.22
Calculated RSR CaOx	4.50 ± 1.51	4.26 ± 1.84	3.71 ± 1.58 ^b	0.06
Calculated RSR Br	0.42 ± 0.27	0.32 ± 0.21	0.82 ± 0.56 ^{b,c}	<0.0001
Calculated undissociated UA (mg/d)	184 ± 97	181 ± 88	77 ± 67 ^{b,c}	<0.0001
NAE (mEq/d)	55.5 ± 16.3	48.9 ± 15.7	17.3 ± 20.8 ^{b,c}	<0.0001

^aData are mean ± SD. Br, brushite; CaOx, calcium oxalate; NAE, net acid excretion; RSR, relative supersaturation.

^b*P* < 0.05 versus control.

^c*P* < 0.05 versus lemonade.

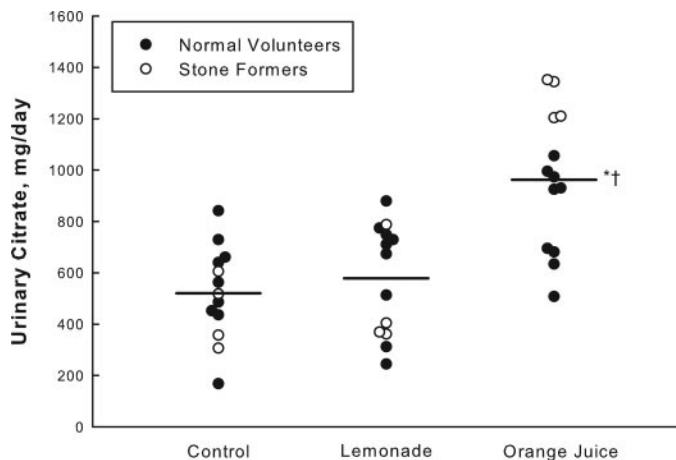


Figure 3. Effect of lemonade and orange juice on urinary citrate excretion. Horizontal lines indicate group means. ●, normal volunteers; ○, stone formers. **P* < 0.05 versus control; †*P* < 0.05 versus lemonade.

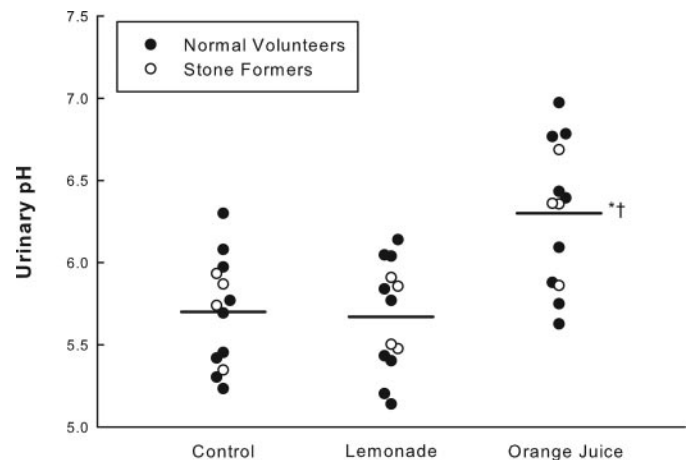


Figure 4. Effect of lemonade and orange juice on urinary pH. Horizontal lines indicate group means. ●, normal volunteers; ○, stone formers. **P* < 0.05 versus control; †*P* < 0.05 versus lemonade.

excretion that was observed during consumption of the two fruit juices.

Despite comparable citrate content, lemonade did not have a significant effect on urinary citrate, pH, ammonium, titratable acidity, net acid excretion, and NGIA. This observation emphasizes the importance of the accompanying cation when providing alkali load. Alkali load enhances urinary citrate excretion by reducing renal tubular reabsorption and metabolism of citrate (19–22). The lack of alkalinizing and attenuated citraturic effects of lemonade probably is due to its accompanying proton, which could have neutralized the effect of citrate. Citraturia, however, could also develop through an alternative mechanism, unrelated to changes in acid-base status. A small fraction of administered citrate may escape *in vivo* metabolism and appear directly in the urine (23). The mechanism may be re-

sponsible, in part, for the observed rise in urinary citrate in hypocitraturic calcium stone formers after consuming 2 L/d lemonade for 1 wk (12). Alternatively, dietary compositions may have influenced the response to lemonade administration.

Through its alkalinizing effect, orange juice also lowered the calculated amount of poorly soluble undissociated uric acid, which could reduce the propensity to form uric acid stones. However, calculated RSR of brushite was significantly higher as a result of the increase in urinary pH. Unlike orange juice, lemonade had no effect on excretion rate of undissociated uric acid and calculated supersaturation of calcium oxalate and brushite.

Despite the alkali load, administration of orange juice did not result in significantly lower urinary calcium excretion. It was shown previously that administration of potassium alkali de-

creases urinary calcium, and this hypocalciuric effect seems to be unique to potassium alkali (potassium citrate or potassium bicarbonate) (24–26). The lack of hypocalciuric effect may be due, in part, to a small amount of additional calcium (100 mg/L) provided by orange juice and, in part, to the effect of carbohydrate load (27). A significant increase in urinary oxalate was observed during the orange juice phase, which probably was due to the presence of a small amount of oxalate in orange juice and/or to *in vivo* conversion of ascorbic acid to oxalate. Calculated calcium oxalate supersaturation was lower in the orange juice phase despite a significant increase in urinary oxalate. Another inhibitor of calcium oxalate complexation is magnesium (28). Our study showed that orange juice increases urinary magnesium, perhaps a reflection of magnesium (110 mg/L) provided by the juice.

Two longitudinal studies by Curhan *et al.* (13,14) refuted the influence of various beverages/fruit juices on the risk for stone formation. Population-based studies have the definite advantage of having a large sample size and long observation period. However, there is a potential problem with inconsistent information on dietary intake that is gathered using food frequency questionnaires (29). Another reason that could have contributed to the conflicting results between the longitudinal and the short-term studies is the study design. Whereas the longitudinal studies used the incidence of symptomatic kidney stones as the main outcome measure, most of the short-term studies evaluated the effects of various fruit juices/beverages on urinary composition. Last, variable diets during the long-term study also could have contributed to the differences. It was shown previously that different diets could significantly affect the urinary composition and the propensity for calcium oxalate crystallization (30).

The results of our study showed that an alkali load is delivered by administration of orange juice but not by lemonade despite equivalent citrate content. There is an absolute need to consider the accompanying cation whenever one assesses the citrate content of a diet. Because an increase in urinary citrate and pH could provide protection against calcium and uric acid stone formation, orange juice but not lemonade potentially could play an important role in the management of recurrent nephrolithiasis and may be considered an option in patients who are intolerant of potassium citrate. One limitation of this study is the short observation period. Additional studies clearly are needed to determine the patients' compliance during and the effectiveness of long-term use of orange juice in the prevention of recurrent kidney stones. Moreover, because fruit juices could provide approximately 21 (lemonade) to 26 g (orange juice) of carbohydrates per cup, the possible calciuric effect of carbohydrate load (27) needs to be considered and discussed when recommending fruit juices as part of the management of kidney stones.

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