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ORIGINAL PAPER

Effect of diet orange soda on urinary lithogenicity

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Abstract Studies have shown that certain beverages decrease urinary lithogenicity by increasing urine citrate excretion. Diet Sunkist Orange soda had the highest concentration of citrate and total alkali content among 12 diet sodas previously assayed. We studied the effect of Diet Sunkist Orange soda consumption on urinary chemistry. Nine healthy men and women ages 26–54 years completed the study. During the control period, subjects drank 36 oz of water for 3 days in addition to their own, self-selected diet and recorded a food diary. During the study period, the subjects drank three 12-oz cans of Diet Sunkist Orange soda a day instead of water, and replicated their diets from the control period. In each period, the subjects performed 24-h urine collections on days 2 and 3. Urine chemical analysis was performed, including urinary citrate levels and pH. Diet Sunkist Orange soda increased urinary citrate excretion by 60 mg/day, which was not statistically significant (95% CI −75 to 195, *P* value 0.34). There was no significant change in pH from the control period to the study period (pH: 6.29–6.21; 95% CI: −0.09 to 0.25, $P = 0.30$). Urine volumes and creatinine excretions were not significantly different between the control and study periods. Despite the relatively high citrate and total alkali content of Diet Sunkist Orange soda, the volume consumed in this study (36 oz per day) did not provide sufficient potential base to significantly alter urine composition in healthy subjects with normocitraturia. The effect of Diet Sunkist Orange soda on urinary chemistry in patients with hypocitraturia and nephrolithiasis is not likely to have a clinically significant effect to prevent calcium or uric acid stones.

Keywords Alkalies · Carbonated beverages · Citrates · Nephrolithiasis · Urolithiasis

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Introduction

Patients with kidney stones are advised that increasing fluid intake will increase urine volume and thereby reduce recurrence of nephrolithiasis [1]. In a randomized controlled trial of increased water intake, calcium stone formers who achieved an average urine volume of more than 2.5 L per day had significantly fewer stones than the control group whose average urine volume was about 1 L per day [2]. Increased water intake is effective and economically favorable. However, many patients do not find water palatable and have difficulty increasing intake beyond the volume required to satisfy thirst. In addition, a majority of kidney stone formers prefer altering their diets to pharmacotherapy to alter urine chemistry and prevent

recurrent stone events [3]. Increasing urine citrate excretion by drinking fluids with higher citrate content is the best example of such a beverage strategy. Although most dietary citrate is metabolized in the liver, consuming a proton to yield bicarbonate before it reaches the kidneys, some of that citrate escapes metabolism and is excreted in the urine. If metabolized, the alkaline dietary load also indirectly increases urinary citrate excretion by inhibiting the reabsorption of citrate by the pH-sensitive sodium-citrate transporter in the proximal tubule. A homemade preparation of lemonade became popular after it was shown to significantly increase urine citrate in patients with hypocitraturic calcium oxalate nephrolithiasis [4]. A subsequent retrospective analysis of patients treated with the same lemonade formula in a stone clinic suggested that this treatment reduced recurrent stone events [5]. However, not all studies demonstrate benefit [6]. Though this "lemon juice lore" has been widely disseminated among patients and physicians, other citrate-containing beverages may be preferable for stone prevention because some with higher pH may contain more potential base. For instance, despite similar citrate content, orange juice with a higher pH led to higher citrate excretion and more alkaline urine than a lemon juice preparation [7]. Sports drinks are also popular citrate-containing beverages and may be associated with favorable effects on urine lithogenicity if citrate content and pH are optimal [8].

Another potential citrate-containing drink that could enhance urine chemistry is soda. Soda remains a hugely popular drink among children and adults with recent attention paid to its possible deleterious effects [9]. Given the links between these sugar-containing beverages, obesity and the metabolic syndrome, and the links between metabolic syndrome and kidney stones [10], diet sodas which contain artificial sweeteners may be more attractive therapeutic choices for stone formers seeking higher urine volume and citrate excretion. We recently studied 15 commercially available diet sodas and demonstrated that Diet Sunkist Orange soda contained the most citrate and potential base among a number of diet sodas assayed. It also had more potential base than the popular lemonade preparation [11]. We sought to demonstrate whether this beverage could effect clinically important changes in urine lithogenicity.

Methods

Subjects

We conducted a crossover study in healthy volunteers. The study was approved by the local institutional review board (ClinicalTrials.gov identifier NCT01330940). Participants were recruited through advertisements. Participants were enrolled between November 2009 and April 2010 until the projected sample size of 12 participants was obtained. Men and women between the ages of 18 and 65 years were included in the study. Inclusion criteria were the ability to provide informed consent and the ability to reliably urinate into a vessel and measure urine volume. Exclusion criteria were a prior history of nephrolithiasis, a known history of metabolic bone disease, hyperthyroidism, hyperparathyroidism or chronic kidney disease, current use of diuretics, current use of potassium citrate or other oral alkali supplementation, and use of calcium supplementation that could not be stopped.

Study design

There were two periods in the study. In period 1, the study participants were instructed to drink 36 oz (1.06 L) of water per day for 3 days, while performing 24-h urine collections on days 2 and 3. The water intake was in addition to their usual, self-chosen fluid intake. Study participants also kept a food diary of their self-selected diet. Period 2 began after a week of washout period. Subjects drank 36 oz (3 cans, 1.06 L) of Diet Sunkist Orange soda per day instead of water. Participants repeated their recorded self-selected diet from period 1 during period 2 of the study. Because the diet was replicated to the best of the participants' abilities, the only change from periods 1 to 2 was the drink prescribed. Participants were randomized to two groups, with the first group drinking water in period 1 and orange soda in period 2, and the second group drinking in the reverse order. The Diet Sunkist Orange soda was bought at a local store. Subjects provided their own water and were instructed to drink either tap water or bottled water.

Urine chemistry analysis

During the urine collections, the urine was maintained at room temperature. An antimicrobial and a urine volume marker were added to each urine container and then a 50-ml aliquot of urine was obtained. The participants performed the urine collections at home, and then mailed their urine collections to Litholink Corp (Chicago, IL), a commercial laboratory for analysis [12]. Results of individuals in whom 24-h excretion of creatinine varied between collections by 30% or more were judged to have been inaccurately collected and were excluded.

In each 24-h urine sample, we measured calcium, chloride, creatinine, magnesium, sodium, potassium, phosphate, ammonium and uric acid concentrations by standard laboratory technique using a Beckman Synchron CX5 (Beckman Instruments, Brea, CA, USA). pH was

Table 1 Comparison of urine chemistry during Diet Sunkist and control periods

	Control	Diet Sunkist	Difference	*P* value
Volume (L)	2.02	1.86	−0.16	0.32
Calcium (mg)	129	148	19	0.18
Citrate (mg)	554	613	59	0.34
pH	6.29	6.21	0.08	0.30
Oxalate	31.7	30.1	−1.6	0.59
Sodium (meq)	148	174	26	0.11
Potassium (meq)	64	59	−5	0.23
Phosphate (mg)	831	898	67	0.40
Creatinine (mg)	1,593	1,630	37	0.47
SS CaOx	3.7	4.3	0.6	0.25
SS CaP	0.6	1.0	0.4	0.04
SS UA	0.6	0.6	0	0.64

measured by glass electrode. Oxalate was measured by enzyme assay using oxalate oxidase (Trinity Biotech, Bray, Ireland). Citrate was measured by enzyme assay using citrate lyase (Mannheim Boehringer, Mannheim, Germany). From these analyses, we calculated supersaturation (SS) with respect to calcium oxalate, calcium phosphate and uric acid using the interative computer program EQUIL 2 [13]. For each of the 3-day experimental phases, the mean values of the two 24-h collections were reported.

Statistics

Urine values obtained during the experimental and control periods were compared by paired Student's *t* test and considered statistically different at $P < 0.05$. Statistical data were generated and analyzed with a commercially available software package, Systat (Point Richmond, CA, USA). Results were expressed as mean ± SD.

Results

Of the 12 subjects recruited, 9 completed the study. One subject withdrew during the diet orange soda phase because she could not drink 36 oz of soda per day, one withdrew after signing consent but before starting the study, and another subject's data were discarded because he mailed one of his samples several days after collection. There were no adverse events during the study periods. The 24-h urinary creatinine excretion was similar between study periods (1,593 mg/day in the control period vs. 1,630 mg/day in the study period), which reflects accurate collections of 24-h urine samples. One subject's data had a pair of urines in which creatinine excretion varied by more than 30%. The urines were excluded from analysis and for this one subject there was only a single urine at baseline and during soda consumption.

There was no significant difference in mean urine citrate excretion between the control period (554 mg/day) and the study period (613 mg/day; 95% CI: −75 to 195, *P* value 0.34) (Table 1). There was no significant change in urine pH from the control period to the study period (pH: 6.29–6.21; 95% CI: −0.09 to 0.25, $P = 0.30$). There also was no significant change in urinary excretion of sodium, calcium, uric acid and oxalate between the control and study periods, nor were there changes observed in supersaturation of calcium oxalate or uric acid. A small increase in calcium phosphate supersaturation was statistically significant ($P = 0.04$) despite the slight decrease in urine pH.

The urine volumes ($P = 0.32$), excretion of potassium ($P = 0.23$) and urea nitrogen ($P = 0.36$) were not significantly different between the two periods, which showed that the protocol that used a diet diary to replicate the self-selected diet between study periods was successful in controlling for other variables. Phosphorus excretion was also not different between the periods ($P = 0.40$).

Discussion

Diet Sunkist Orange soda (36 oz or 1,065 ml per day) did not significantly alter any 24-urine constituents in healthy volunteers in our study compared with baseline consumption of water. This negative finding comes despite the fact that we previously showed that Diet Sunkist Orange had more potential base content in a 12-oz can than other citrate-containing soft drinks [11]. Our lack of positive effect is similar to a previous finding that Fresca, another citrate-containing soda, failed to increase urine citrate excretion [14]. These results are in contradistinction to a previous study which demonstrated that drinking 1 L of a sports drink called Performance per day was associated with an increase in urine pH and citrate excretion [8]. A slight increase in urine calcium excretion and decrease in

volume, neither statistically significant, during the soda period compared with the control period, led to a small increase in supersaturation of calcium phosphate, despite no increase in urine pH. This difference is highly unlikely to be clinically meaningful.

Several short-term studies have looked at the effect of beverages on urinary composition that have implications for potentially preventing nephrolithiasis. The mechanism by which they may do so is through their favorable effects on urinary chemistry, specifically increasing citraturia and urinary pH. However, one limiting factor of many beverages studied to date is that they contain a significant amount of calories and carbohydrates. For example, studies have shown that orange, pomegranate and cranberry juice may increase urine citrate, but contain a significant amount of calories per serving [15]. Prescribing patients over a liter per day of such beverages could lead to deleterious side effects such as weight gain, diabetes mellitus and the metabolic syndrome, and as a result might offset any benefit the drink provided. We sought to find a diet beverage (without calories or sugar) that contained a large amount of citrate, specifically as potential base, in the hopes that it would have a favorable effect on urinary chemistry without these potential adverse effects. This study was designed to test the hypothesis that drinking 1 L a day of Diet Sunkist Orange soda would increase citraturia and urine pH. Our findings showed that although there was a slight increase in the amount of citrate excretion from the control period to the study period, the difference was not significant and urine pH was also unchanged.

Diet Sunkist Orange soda probably did not raise urinary pH or increase citraturia despite its high alkali content because an insufficient volume was prescribed. Seltzer et al. [4], found that subjects drinking lemonade increased their citrate excretion by a mean of 204 mg/day, a statistically significant difference. However, participants drank 2 L of lemonade a day compared to the 1 L of Diet Sunkist Orange soda that we prescribed. Another study of lemonade failed to show increased urine pH or citrate when consumption was of less than 750 ml, or about 60 meq citrate per day [6]. We thought that patients would have difficulty adhering to a prescription of 2 L of a carbonated beverage daily. Even with the requirement of only 1 L per day, one subject dropped out of the study because she could not tolerate drinking so much carbonated liquid.

Several studies have had positive effects on urine chemistry with a prescribed volume of only 1 L. We examined the effect of grapefruit juice on urinary chemistry using only 720 ml/day [16], a volume that increased citraturia (505–591 mg/day) and pH. Grapefruit juice, however, has been associated with increased risk of stone formation in epidemiologic studies [17]. Similarly, our sports drinks study showed a positive effect of only 1 L of Performance per day, but not with Gatorade [8]. The results were explained by the fact that Performance has a significantly higher concentration of citrate in an alkaline form (23.6 meq/L) compared to both Gatorade (5.8–8.2 meq/L) and Diet Sunkist Orange soda (10.5 meq/L of total alkali). Drinking twice as much Diet Sunkist (and therefore 21.0 meq/day of total alkali) would presumably have a positive effect on citrate excretion and urine pH, if tolerated. In addition, we are concerned about recent reports suggesting that more diet soda consumption is associated with a risk of chronic kidney disease [18]. Although the causal nature of this relationship has not been demonstrated and the pathophysiologic basis for the finding has not been explained, we were hesitant to encourage higher doses of diet sodas to patients with kidney stones.

Another potential explanation for our findings is that the diets were not accurately replicated from one period to another. Although subjects recorded their self-selected diets during the control part of the study and attempted to replicate their diets during the experimental part, it is possible that by chance the subjects may have eaten a diet containing a higher amount of alkali during the control period, which then offset the alkali provided by the Diet Sunkist Orange soda. Potassium is a reasonable marker of alkali in diet and, although not significant, there was an increase in urine potassium during the control period of about 10 meq compared to the study period. This difference could be explained by a chance occurrence of more alkali in the diet while drinking water, or drinking water with alkali in it. As the concentration of alkali in Diet Sunkist Orange soda was measured to be 10.5 meq/L (with 8.4 meq/L of citrate), subjects were drinking about 10 meq of alkali a day during the study period. Interestingly, the amount of urea and sulfate, markers of protein ingestion, in the two periods was the same. Additionally, there was a slight increase in urinary Na during the soda period, but the Diet Sunkist provided about 14 mmol of Na a day, which accounts for that finding. The small increase in sodium excretion was not sufficient in these non-stone formers to cause an increase in urine calcium excretion.

In summary, the potential of diet sodas to reduce recurrence of kidney stones does not appear to be great at ingested volumes of approximately 1 L per day. Their citrate and potential base content is not adequate to change urine chemistry without imbibing a significantly higher volume than the one tested here.

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