Cranberry juice is popular remedy for many ills; apart from the pleasant tasting many people drink it to help in preventing UTIs and stones. Authors from Cape Town (where there is the added benefit of an excellent climate) assessed the influence of cranberry juice on urinary risk factors for calcium oxalate calculi in a randomized crossover trial, showing that it has anti-lithogenic properties. In the second paper, authors from Jerusalem report on 14 patients with distal ureteric strictures after kidney transplantation, all of whom were treated endourologically. They found transurethral incision of the distal ureteric stricture to be effective.

Influence of cranberry juice on the urinary risk factors for calcium oxalate kidney stone formation

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OBJECTIVE

To investigate the potential influence of cranberry juice on urinary biochemical and physicochemical risk factors associated with the formation of calcium oxalate kidney stones, as this product might affect the chemical composition of urine.

SUBJECTS AND METHODS

Urinary variables were assessed in a randomized cross-over trial in 20 South African men (students) with no previous history of kidney stones. The first group of 10 subjects drank 500 mL of cranberry juice diluted with 1500 mL tap water for 2 weeks, while the second group drank 2000 mL of tap water for the same period. This was followed by a 2-week 'washout' period before the two groups crossed over. During the experimental phase subjects kept a 3-day food diary to assess their dietary and fluid intakes; 24-h urine samples were collected at baseline and on day 14 of the trial periods, and analysed using modern laboratory techniques. Urine analysis data were used to calculate the relative urinary supersaturations of calcium oxalate, uric acid and calcium phosphate. Data were assessed statistically by analysis of variance.

RESULTS

The ingestion of cranberry juice significantly and uniquely altered three key urinary risk factors. Oxalate and phosphate excretion decreased while citrate excretion increased. In addition, there was a decrease in the relative supersaturation of calcium oxalate, which tended to be significantly lower than that induced by water alone.

CONCLUSION

Cranberry juice has antilithogenic properties and, as such, deserves consideration as a conservative therapeutic protocol in managing calcium oxalate urolithiasis.

KEYWORDS

kidney stones, cranberry juice, oxalate, urinary risk factors, calcium oxalate

INTRODUCTION

A low urinary volume is a major determinant in urolithiasis and as such, an increase in fluid intake is routinely recommended for patients with stones [1–3]. The choice of fluid is important and it should be selected cautiously; several studies have investigated the effects of different beverages on the risk of stone formation. Fluids which have been shown to increase the risk of calcium oxalate (CaOx) stone formation are cocoa [2], carbonated beverages [4], grapefruit juice [4] and cola [5]. Conversely, fluids which decrease the risk are some mineral waters [6], fruit and herbal teas [7], orange

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juice [2,8] and lemon juice [9]. In several cases, fluids which had been regarded as harmful have subsequently been shown to have beneficial effects. These include alcohol [4,10], milk [4], tea [11] and coffee [4]. There is conflicting evidence about the effects of blackcurrant juice [12] and apple juice [4,7].

Cranberry juice is an old folk remedy that has been used for decades to treat UTIs [13]; components occurring naturally in cranberries can inhibit the attachment of bacteria to the epithelial lining of the urinary tract [13–15]. Also, preliminary data show that cranberry juice has some direct antibacterial activity [14]. This is regarded as important as it has recently been suggested that calcium-based stones may have an infectious origin, and that the anti-adherence and antibacterial properties may help to inhibit the attachment of CaOx crystals, and stone-promoting bacteria, to renal epithelial cells [16]. However, another recent study involving the ingestion of cranberry concentrate tablets showed a possible increase in the biochemical risk factors for nephrolithiasis [17], but the latter study was limited by the few subjects (five) of both genders (two female and three male), the relatively brief administration of supplementation (7 days) and the unrealistically high dose of cranberry solid used (equivalent to 6 L of cranberry liquid per day). The present study was undertaken to investigate further the effect of cranberry juice on the risk of CaOx stone formation, but using a more rigorous approach in which these limitations were addressed.

TABLE 1 Comparison of mean daily intake of nutrients (from the 3-day diary) while drinking cranberry juice or water

Variable	Cranberry juice	Water	P (cranberry vs water)
Moisture, %	84.85 (0.825)	85.52 (0.825)	0.55
Energy, kJ	12 339 (827.9)	12 009 (827.9)	0.77
Protein, g/day	127.44 (8.368)	126.01 (8.368)	0.90
Animal protein, g/day	89.86 (6.641)	90.06 (6.641)	0.98
Fat, g/day	132.08 (9.19)	129.74 (9.19)	0.85
Carbohydrate, g/day	304.3 (24.82)	282.8 (24.82)	0.52
Fibre, g/day	21.38 (2.09)	21.98 (2.09)	0.83
Added sugar, g/day	32.23 (9.4)	34.10 (9.40)	0.88
Oxalate, mg/day	122.36 (15.10)	71.91 (15.10)	**0.0184**
Calcium, g/day	1 292.6 (123.72)	1 366.6 (123.72)	0.66
Magnesium, mg/day	348.63 (25.45)	362.46 (25.45)	0.69
Phosphate, mg/day	1 917.6 (135.37)	1 971.4 (135.37)	0.77
Potassium, mg/day	3 462.7 (274.72)	3 466.6 (274.72)	0.99
Sodium, mg/day	4 143.1 (284.23)	3 478.9 (284.23)	0.09
Zinc, mg/day	15.71 (1.19)	16.58 (1.19)	0.59
Vitamin A, RE/day	1 059.7 (148.02)	1 068.3 (148.02)	0.97
Vitamin B6, mg/day	2.02 (0.21)	2.21 (0.21)	0.50
Vitamin C, mg/day	204.89 (20.88)	44.01 (20.88)	**< 0.001**
Vitamin D, μg/day	4.42 (0.61)	5.55 (0.61)	0.18

Standard errors given in brackets. Significant differences in bold.

SUBJECTS AND METHODS

Healthy male university students (20) with no previous history of kidney stones were recruited from the authors' institution and divided into two groups (A and B) in a randomized cross-over trial. During the first 2 weeks of the trial, group A ingested a daily volume of 500 mL cranberry juice (Crystal Falls, Black Sheep Beverage Distributors, South Africa) diluted with 1500 mL tap water, while group B drank 2000 mL tap water. The juice was diluted by the research staff. After a 'washout period' of 2 weeks, both groups changed to the other treatment. Subjects did not alter their normal home diets during the trial but were requested to record 3-day food diaries during each of the protocols to assess their dietary and fluid intakes, and to identify potential confounding factors. Data from the food diaries were analysed using Food Composition Tables [18,19] to determine the nutrient content.

For urinary measurements, 24-h urine samples were collected by each subject at baseline ('control') and at the end (14 days) of each drinking protocol. Urinary pH and volume were routinely measured for each sample. Urinary sodium, potassium, calcium and magnesium were determined by atomic absorption spectroscopy, while oxalate, citrate, phosphate, urate, chloride and creatinine were measured using commercially available assay kits. Relative supersaturations of CaOx, uric acid and calcium phosphate were calculated using the computer programme EQUIL [20].

The metastable limit (ML) of each sample was determined by the method of Ryall *et al.* [21]. Briefly, successive aliquots of aqueous sodium oxalate were added in progressively increasing concentrations to urine samples, until CaOx crystallization (as detected by particle counts using a Coulter counter) was initiated. The concentration of exogenous sodium oxalate required to produce detectable crystallization was taken as a measure of the ML. All data were assessed statistically using ANOVA, with differences considered statistically significant at $P \leq 0.05$.

RESULTS

The mean nutrient intake of the subjects during the cranberry juice and water protocols was determined from the 3-day food diaries (Table 1); the oxalate and vitamin C contents were significantly higher while drinking cranberry juice ($P = 0.0184$ and < 0.001, respectively). None of the other nutrients differed significantly.

The mean urinary variables and the computed risk indices are given in Table 2. The ingestion of cranberry juice produced three statistically significant changes in urine composition that were not present while drinking water only. Oxalate excretion decreased relative to control and water-only, citrate excretion increased (all $P < 0.001$) and phosphate excretion decreased relative to the control ($P = 0.0139$). The relative supersaturation of CaOx decreased significantly after both protocols but the value after consuming juice tended to be significantly lower than that after drinking water ($P = 0.0594$). Several urinary risk factors were altered significantly

TABLE 2 Comparison of urinary variables for the control, water and cranberry juice regimens

Variable	Control (I)	Cranberry (II)	Water (III)	P II vs I	III vs I	II vs III
pH	6.10 (0.07)	6.31 (0.05)	6.36 (0.05)	**0.0131**	**0.0022**	0.4600
Volume, ml/24 h	1304.0 (105.6)	1805.0 (77.91)	2018.0 (77.91)	**< 0.001**	**< 0.001**	0.0564
Oxalate, mmol/24 h	0.16 (0.01)	0.11 (0.004)	0.16 (0.004)	**< 0.001**	0.5745	**< 0.001**
Citrate, mmol/24 h	2.83 (0.21)	3.72 (0.15)	2.55 (0.15)	**0.001**	0.2863	**< 0.001**
Calcium, mmol/24 h	4.33 (0.34)	3.03 (0.25)	3.24 (0.25)	**0.0031**	**0.0129**	0.5462
Magnesium, mmol/24 h	3.62 (0.25)	3.35 (0.18)	3.19 (0.18)	0.3789	0.1635	0.5363
Sodium, mmol/24 h	89.42 (11.60)	85.90 (8.56)	99.56 (8.56)	0.8076	0.4843	0.2634
Potassium, mmol/24 h	51.22 (5.39)	48.82 (3.98)	50.67 (3.98)	0.7209	0.9348	0.7431
Urate, mmol/24 h	3.43 (0.20)	3.12 (0.15)	3.13 (0.15)	0.2293	0.2534	0.9424
Creatinine, mmol/24 h	13.87 (0.74)	13.93 (0.55)	12.64 (0.55)	0.9448	0.1874	0.1000
Phosphate, mmol/24 h	29.23 (2.25)	22.18 (1.66)	24.72 (1.66)	**0.0139**	0.1112	0.2838
Chloride, mmol/24 h	122.05 (9.49)	125.19 (7.01)	136.53 (7.01)	0.7907	0.2235	0.2566
ML	0.05 (0.010)	0.07 (0.005)	0.07 (0.005)	**0.0031**	**0.0067**	0.7898
Relative supersaturation:						
Brushite	1.88 (0.19)	0.68 (0.14)	0.75 (0.14)	**< 0.001**	**< 0.001**	0.7468
Uric acid	2.07 (0.19)	0.96 (0.14)	0.72 (0.14)	**< 0.001**	**< 0.001**	0.2460
CaOx	4.28 (0.29)	1.46 (0.21)	2.04 (0.21)	**< 0.001**	**< 0.001**	0.0594

Standard errors given in brackets. Significant differences in bold.

by both protocols, i.e. pH, volume and ML increased, while calcium excretion and the relative supersaturations of brushite and uric acid decreased.

DISCUSSION

As expected, the nutrient content of the diets during the two protocols differed only for oxalate and vitamin C. These differences were attributed to the relatively high content of oxalate (86 mg/L) and ascorbic acid (300 mg/L) in the cranberry juice used in this study. (The oxalate content was determined in our laboratory using a commercially available assay kit; the ascorbic acid value was provided by the juice manufacturer).

The ingestion of cranberry juice favourably and uniquely altered three key urinary risk factors, i.e. oxalate and phosphate excretion decreased, while citrate excretion increased. Several other risk factors were favourably altered by *both* protocols, i.e. pH, volume, ML, calcium excretion and relative supersaturation of calcium phosphate (brushite), uric acid and CaOx.

The reduced oxalate excretion after drinking cranberry juice is important as it is a key risk factor in CaOx stone formation [3,22]. It is particularly remarkable that it decreased despite the high oxalate and ascorbic acid content of the juice, as both of these exogenous factors might have been expected to increase oxalate excretion. The result thus agrees with that previously reported [23], a study which showed that oxalate in cranberry juice is not readily bioavailable [23]. We suggest that cranberry juice may inhibit the absorption of oxalate (from dietary sources other than the juice) and that its possible use in the conservative treatment of hyperoxaluria might be worth exploring.

However, the cited study involving cranberry tablets [17] showed a significant increase in urinary oxalate excretion, although the dose of oxalate delivered per day by the tablets (363 mg) in that study was an order of magnitude higher than in the present study (43 mg). Furthermore, the bioavailability of the oxalate in the concentrate tablets is unknown and may be greater than that of juice.

In the present study, drinking cranberry juice increased urinary citrate while there was no change in previous studies involving juice [12] or tablets [17], respectively. This is an important finding, as citrate is universally regarded as an effective inhibitor of CaOx stone formation [24] and as such, raising the urinary levels of this component is a widely practised therapeutic strategy in managing these stones [25,26].

Urinary phosphate is a risk factor for brushite and apatite saturation [27]; brushite has been mooted as a possible initiating nidus for the formation of calcium phosphate calculi [28]. Thus, protocols in which this component is reduced are favourable for managing these types of stone; there was such a decrease in the present study.

The relative supersaturation of CaOx decreased significantly after both protocols, suggesting dilution effects. However, notwithstanding such effects, the value after drinking juice tended to be significantly lower than after drinking water. As such, we suggest that cranberry juice may have antilithogenic properties (with respect to the relative supersaturation of CaOx) beyond those that can be attributed to dilutional effects alone.

The significantly higher urine volumes produced by the juice and water protocols relative to the control, without the latter being significantly different, is an indication of fluid compliance and gives confidence in these data. Indeed, other significant changes during both protocols (in ML, and relative supersaturations of brushite and uric acid) can be attributed to urinary dilutional effects.

Early studies claimed that cranberry juice caused a decrease in urinary pH [29,30]. Quinic and benzoic acids in cranberries are presumably precursors of the hippuric acid that is excreted by the kidneys, and thereby acidify the urine [30]. Recently, claims about the ability of cranberry juice to acidify urine have been disputed [13,17]. A study of the effect of cranberry juice on bacteriuria and pyuria found that a group drinking cranberry juice had a higher urinary pH than the placebo group [13], while there were no significant changes in urinary pH in the study with cranberry tablets [17]. In the present study, the pH increased after drinking cranberry juice (relative to the control) but drinking water also caused an increase in urinary pH. Similarly, calcium excretion decreased relative to the control after drinking juice or water. These results are puzzling but may have arisen as a result of subtle dietary changes when subjects were drinking the fluids. Clearly, a controlled dietary regimen would have eliminated this possibility. Despite this potential shortcoming, the present results for oxalate and citrate excretion, and for the relative supersaturation of CaOx after drinking cranberry juice, were significantly different from those obtained for water, thereby showing a unique effect of the former.

Thus we conclude that drinking cranberry juice favourably alters important risk factors for CaOx stone formation, and as such it deserves to be considered as a conservative therapeutic protocol in managing this disease.

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Abbreviations: **CaOx**, calcium oxalate; **ML**, metastable limit.