Reduction of Bacteriuria and Pyuria After Ingestion of Cranberry Juice

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Objective.—To determine the effect of regular intake of cranberry juice beverage on bacteriuria and pyuria in elderly women.

Design.—Randomized, double-blind, placebo-controlled trial.

Subjects.—Volunteer sample of 153 elderly women (mean age, 78.5 years).

Intervention.—Subjects were randomly assigned to consume 300 mL per day of a commercially available standard cranberry beverage or a specially prepared synthetic placebo drink that was indistinguishable in taste, appearance, and vitamin C content but lacked cranberry content.

Outcome Measures.—A baseline urine sample and six clean-voided study urine samples were collected at approximately 1-month intervals and tested quantitatively for bacteriuria and the presence of white blood cells.

Results.—Subjects randomized to the cranberry beverage had odds of bacteriuria (defined as organisms numbering $\geq 10^5$/mL) with pyuria that were only 42% of the odds in the control group (P=.004). Their odds of remaining bacteriuric-pyuric, given that they were bacteriuric-pyuric in the previous month, were only 27% of the odds in the control group (P=.006).

Conclusions.—These findings suggest that use of a cranberry beverage reduces the frequency of bacteriuria with pyuria in older women. Prevalent beliefs about the effects of cranberry juice on the urinary tract may have microbiologic justification.

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FOR DECADES cranberry-derived beverages have been thought to be useful in reducing bacterial infections of the bladder, but controversy exists as to whether this belief has any basis in scientific fact. In 1914, Blatherwick[1] reported that cranberries are particularly rich in benzoic acid, which is excreted as hippuric acid in the urine. Studies from the 1920s to the 1970s suggested that acidification of the urine was the mechanism through which cranberry juice produced a bacteriostatic effect,[2-4] but other studies have yielded conflicting results concerning urinary acidification.[5-7]

More recently, data have been presented on a different potential mechanism of action: the inhibition by cranberry juice of bacterial adherence to mucosal surfaces. Sobota[8] and Schmidt and Sobota[9] demonstrated that both cranberry juice and the urine produced by mice fed cranberry beverage inhibited adherence of *Escherichia coli* to uroepithelial cells by about 80%. Similar antiadherence activity was found in human urine as well. Zafriri et al[10] identified two compounds in cranberry juice that inhibited lectin-mediated adherence of *E coli* to mucosal cells. One was fructose, common to many fruit juices, and the other was a nondialyzable polymeric compound that inhibited certain adhesins associated with pathogenic strains of *E coli*. Ofek et al[11] were able to isolate this compound from cranberry and blueberry juices, but not from grapefruit, orange, guava, mango, and pineapple juices. They hypothesized that exposure of pathogens to this compound in either the gut or the bladder produces a bacteriostatic effect by inhibiting specific adhesins present on the pili of the bacterial surface.

Despite these intriguing findings and the widespread use of cranberry beverage ("cranberry juice cocktail") for its supposed salutary effect on urinary tract infection, no adequately controlled, randomized clinical trial has been published evaluating its clinical utility in preventing urinary tract infection. Previous studies of the effect of cranberry juice on clinical urinary tract infections mostly have been uncontrolled, have been conducted on a small scale, and have yielded conflicting results.[12-15] Our study was designed to address this question.

Bacteriuria is common among elderly women both in and out of institutions.[16,17] Although much bacteriuria in this age group is asymptomatic and does not require treatment,[18] a large proportion of women older than 65 years will experience at least one urinary tract infection per year. Thus, this patient group presents an opportunity to learn whether the regular ingestion of cranberry juice beverage can influence the urinary flora or the host's granulocyte response to it.

METHODS

After approval by institutional review boards, subjects were recruited from a large, multilevel long-term care facility for the elderly (the Hebrew Rehabilitation Center for Aged), as well as from nine housing complexes for elderly residents in the greater Boston, Mass, area. Those who were capable of giving informed consent were invited to participate in the study if they were willing to ingest at least 300 mL of cranberry juice cocktail per day throughout the 6-month study.

Subjects were excluded if they had terminal disease or severe dementia; only women were studied. In all sites, 153 eligible subjects agreed to participate and contributed at least one urine sample after baseline testing. A placebo beverage containing no juice was developed (Ocean Spray Cranberries, Inc, Lakeville, Mass) that used flavorings and color to simulate the taste and appearance of commercially available cranberry juice cocktail. Because glucose intolerance is common among elderly women, both the cranberry and placebo beverages were sweetened with saccharin. Beverages were delivered in identical containers except for coded lot num-

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bers. Subjects providing informed consent were randomly assigned to receive standard, commercially available, low-calorie cranberry juice cocktail or indistinguishable placebo beverage, in most cases after a 1-month trial of placebo beverage to determine that daily intake would be acceptable throughout the study. Subjects were permitted to consume the beverage in single or divided doses.

We randomized subjects by means of odd vs even digits in the subject's institutional identification number or telephone number to determine which coded lot number of beverage would be used throughout the study. Neither participants nor investigators were aware of whether a given subject was receiving cranberry beverage or placebo beverage. Subjects were instructed not to consume any cranberry products other than those distributed to them during the study. To prevent the possibility that subjects in the institutional setting who were randomized to placebo beverage might inadvertently consume standard cranberry beverage elsewhere in the institution, all such beverage was converted to the placebo product throughout the institution during the study. To ensure that each subject continued to receive the correct beverage, patients were interviewed monthly. In addition, all bottle caps were collected from participants each month, and the coded lot number printed on each bottle cap was rechecked by a research assistant.

Sample size calculations were performed before the study began. We assumed that the overall rate of bacteriuria and pyuria in the control group would be about 0.50, and that the reduction attributable to the cranberry beverage in rate of bacteriuric-pyuric urine samples would be 40%, making the rate in the experimental group 0.30. Therefore, power of 0.80 and a confidence level of 95% would require a sample size of 92 subjects in each group; a total of 192 subjects were enrolled in the study. Data are presented on the 153 subjects who provided a baseline urine sample and at least one additional sample after randomization. No data were available for subjects who withdrew from the study without providing any urine samples after the baseline.

At study entry, a geriatric nurse obtained a complete medical history and instructed subjects in the proper method of obtaining a midstream, clean-voided specimen. In those subjects unable to collect an adequate clean-voided specimen themselves, the geriatric nurse assisted in performing the clean-catch procedure. Each month, the geriatric nurse or a research assistant, both of whom were blinded to subjects' study group assignment, collected the urine samples. At the same time, the nurse collected an interval history to determine evidence of symptomatic urinary tract infection as well as any other symptoms occurring in the prior 30 days. If at study intake or during any monthly interval a subject had been prescribed an antibiotic for any indication, the nurse noted this in the study record. No urine was collected, and the subject was deferred from further study until 1 month after the end of any antibiotic course.

Standard urinalysis, bacterial culture, and antibiotic sensitivity testing were performed on each urine sample immediately after collection. Urine samples were collected until each subject had contributed a baseline specimen plus six monthly specimens or had withdrawn from the study. Data analysis included all urine samples contributed by subjects who provided at least one sample after the baseline collection, whether or not they remained enrolled for all six monthly collections. Samples of both the cranberry and placebo beverages were analyzed by Natan Sharon, PhD, Weizmann Institute, Rehovot, Israel, for their capacity to inhibit adhesion by *E coli* to human erythrocytes, as described previously.[10,11] These samples were identified by code number only to ensure blinded assessment.

A second research assistant, unaware of the experimental design or subject assignment, entered data into a relational database. The primary outcome was bacteriuria (organisms numbering $\geq 10^5$/mL, regardless of organism) with pyuria in a given study month. All subjects who continued to contribute urine samples were included in the analysis. We used logistic regression analysis to estimate the odds that this outcome was associated with assignment to the cranberry beverage group. Each participant contributed up to six assessments of this outcome, corresponding to six follow-up intervals. Because replicate assessments from the same participant were not statistically independent, SEs from the logistic regression model that treated assessments as independent were adjusted by the estimating equation approach of Liang and Zeger.[19] Logistic regression models with adjusted SEs were used to examine and adjust for the effect of bacteriuria with pyuria at baseline when examining the effect of cranberry beverage on study outcomes after randomization. An additional variable considered in the regression model was history of urinary tract infection in the 6 and 12 months before the study.

In secondary analyses we evaluated transition probabilities into and out of the state of bacteriuria with pyuria. The goal was to measure separately whether cranberry beverage might promote recovery from existing infection or prevent the development of infection. Probabilities of recovery from and development of infection over each 1-month interval were estimated separately for subjects in the cranberry beverage and placebo beverage groups. Average 1-month transition probabilities in each group were weighted according to the denominators of the month-specific transition probabilities. We used logistic regression with SEs adjusted for replicate assessments to estimate odds ratios (ORs) and 95% confidence intervals for the transitions associated with treatment assignment. The unit of analysis in these logistic models was the 1-month study interval. First, we considered intervals without bacteriuria plus pyuria at the beginning of the interval and predicted the probability of bacteriuria with pyuria at the end of the interval. A second model evaluated intervals with bacteriuria and pyuria at the beginning and predicted the probability of no bacteriuria plus pyuria at the end of the month.

RESULTS

A total of 818 urine specimens were collected from the study subjects after baseline. About one third produced growth of 10^5 organisms per milliliter or more, about one third produced no bacterial growth, and the remainder yielded intermediate growth of organisms. *Escherichia coli* was the most commonly identified organism (43% of isolates), with *Klebsiella* the second most common single organism (7%); mixed flora accounted for 22% of bacteriuric-pyuric urine samples. As in other studies of urinary tract infection in the elderly,[20-22] the proportion of isolates represented by *E coli* was smaller than that seen in urinary tract infection in younger women.

The analyses that follow include data from all 153 subjects who contributed one or more urine samples after randomization; 109 subjects were community dwelling, and 44 were residents of a long-term care facility. Sixty of those randomized to the cranberry group and 61 of those in the placebo group completed the full 6 months of study. As shown in Table 1, both groups were similar in age, number of medications used, and number of medical problems, as well as bacteriuria, pyuria, and urinary tract symptoms at baseline, although subjects randomized to the cranberry group had a lower rate of previous urinary tract infection by history. Only four subjects used estrogen-containing compounds (two in each group). Slightly less than half of all urine samples revealed white blood cells on microscopic examination (44.4%) or had a positive

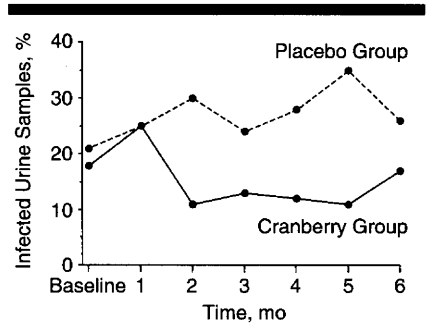
Table 1.—Baseline Measurements of Study Participants

	Cranberry Group	Placebo Group
No. of participants	72	81
Mean±SD age, y	78.1±8.3	79.0±9.4
Mean±SD No. of diagnoses	2.5±2.1	2.5±2.2
Mean±SD No. of medications	3.3±2.7	3.4±2.7
Bacteriuria (organisms ≥10^5/mL) with pyuria present at baseline, No. (%)	13 (18)	17 (21)
Symptoms referable to urinary tract at baseline, No. (%)		
Dysuria or "burning"	1 (1)	1 (1)
Frequency	7 (10)	11 (13)
Flank pain	0	0
Incontinence	5 (7)	0
Foul odor of urine	3 (4)	7 (9)
History of genitourinary abnormalities, No. (%)		
Renal insufficiency	2 (3)	2 (3)
Cystocele	4 (6)	6 (7)
Pessary	1 (1)	1 (1)
Rectocele	3 (4)	1 (1)
Uterine prolapse	2 (3)	4 (5)
Urinary incontinence	11 (15)	18 (22)
Bladder stones	0	1 (1)
Solitary kidney	2 (3)	3 (4)
Renal stone	2 (3)	2 (3)
Urinary retention	2 (3)	0
Other genitourinary pathology	0	2 (3)
Previous urinary tract infection by history, No. (%)		
Ever	33 (46)	36 (44)
In past 12 mo	12 (17)	27 (33)
In past 6 mo	5 (7)	20 (25)
Antibiotic use in 6 mo before study	2 (3)	3 (4)

chemical test for leukocyte esterase (44.0%). Symptoms referable to the urinary tract were noted on 22.0% of all 1-month interval histories. Consumption of study beverages measured by returned bottle caps and subject report exceeded 80.0% of assigned quantities.

Bacteriuria with pyuria was found in 28.1% of urine samples in the placebo group and only 15.0% in the group randomized to the cranberry beverage. We also found a difference in the mean proportion of bacteriuric-pyuric urine samples in each group for each individual (26.1% vs 16.5%, respectively). The difference was not present in the first month after randomization, but appeared most strikingly between months 1 and 2 and then remained fairly stable throughout the rest of the trial (Figure). Adjusting for replicate assessments of the same individuals, we found an OR of 0.42 for bacteriuria with pyuria in subjects randomized to the cranberry beverage relative to control subjects (95% confidence interval, 0.23 to 0.76; P=.004). The effect persisted when we added to the model a variable describing a history of urinary tract infection in the 6 months prior to randomization (OR for infection in cranberry group, 0.53; P=.049) or 12 months prior to randomization (OR, 0.48; P=.01). Subjects in the cranberry group also exhibited a trend toward less bacteriuria irrespective of pyuria (34% of all urine samples in the control group vs 28% in the cranberry group), but this difference was not statistically significant in the replicate assessment analysis (P=.09).

The average 1-month probability of change from bacteriuric-pyuric urine to a sample not meeting criteria for infection was .54 in the cranberry group and .28 in the placebo group (Table 2). The average 1-month probability of change from noninfected to bacteriuric-pyuric urine was .09 in the cranberry group and .12 in the placebo group. As a result, when odds of transition into and out of infection were studied, subjects randomized to the cranberry beverage group were far more likely than controls to make a transition from bacteriuric-pyuric to non–bacteriuric-pyuric urine on successive months (Table 2). For intervals beginning with a bacteriuric-pyuric urine sample, the OR for a bacteriuric-pyuric sample at the end of the interval in the cranberry group was 0.27 (P=.006), indicating that these subjects were only about a quarter as likely as controls to continue to have a bacteriuric-pyuric urine sample. These findings were also unaffected by adjusting for a history of urinary tract infection in the 6 months (OR, 0.31; P=.02) or 12 months (OR, 0.30; P=.01) before the study began. Most subjects with bacteriuria were asymptomatic, and many with symptoms referable to the urinary tract did not have bacteriuria or pyuria. Of the 473 urine samples collected in the cranberry group, only 20 (4%) had bacteriuria and pyuria concurrent with the subject's reporting urinary tract symptoms, compared with 37 (7%) of 498 urine samples in the placebo group, although this did not reach statistical significance.



Percentage of urine samples at each month that had bacteriuria (organisms numbering ≥10^5/mL) with pyuria for subjects randomized to the cranberry beverage (solid line) or the placebo beverage (dotted line).

Antibiotic use after randomization included 16 instances of treatment for urinary tract infection in the control group (3.2 per 100 person-months) vs eight instances in the experimental group (1.7 per 100 person-months). All decisions to use antibiotics were made by subjects' own physicians, who were unaware of the study design or group assignment. No significant difference was observed in the acidification of urine in the cranberry group vs placebo group (median pH=6.0 and 5.5, respectively).

In analyses of the coded study beverages for their effect on bacterial adhesiveness[10,11] conducted by Dr Sharon and colleagues at the Weizmann Institute, 13 of 13 samples of the active cranberry beverage used in the study were found to inhibit *E coli* adhesion in vitro; none of the 15 samples of placebo beverage used exhibited any inhibitory activity.

COMMENT

Despite decades of folk wisdom concerning the effects of cranberry juice on the urinary tract, to our knowledge this study represents the first placebo-controlled, large-scale clinical trial to document the in vivo effect of cranberries on bacteriuria with pyuria. While asymptomatic bacteriuria in elderly women is commonly observed, it does not represent a condition with a negative prognosis[18] or one that requires treatment.[17,23,24] However, demonstration of the capacity of cranberry beverage to reduce the occurrence of bacteriuria with pyuria in elderly women does lend credence to the belief that it contains a substance with biologic activity in relation to the urinary tract. The effect was not seen in the first study

Table 2.—Changes in Urine Samples

	Month					
	1	2	3	4	5	6
Transitions From Bacteriuric-Pyuric to Non–Bacteriuric-Pyuric Urine						
Placebo group, %	24	16	38	35	19	33
Cranberry group, %	31	59	38	75	75	57
Transitions From Non–Bacteriuric-Pyuric to Bacteriuric-Pyuric Urine						
Placebo group, %	11	11	10	16	19	5
Cranberry group, %	15	2	7	10	9	13

month; it appeared only after 4 to 8 weeks of use of cranberry beverage and then persisted at about the same level. This time course could be compatible with modification of gut flora, which are the typical pathogens in urinary tract infections among women. The modest reduction seen in the rate of antibiotics prescribed by experimental group subjects' physicians to treat urinary tract infection suggests that this difference may have manifested itself in important clinical outcomes.

We did not find evidence that urinary acidification was responsible for the observed effect, since the median pH of urine samples in the cranberry group (6.0) was actually higher than that in the experimental group (5.5). While cranberry juice has been advocated as a urinary acidifier to prevent urinary tract infections, not all studies have shown a reduction in urine pH with cranberry juice ingestion, even with consumption of 2000 mL per day.[7,13-15] The amounts used in this trial (300 mL) may not have been large enough to produce this effect. Blatherwick,[1] in 1914, postulated that suppression of bacteriuria by cranberry juice consumption was not related to urine pH or hippuric acid formation but rather to some bacteriostatic properties of cranberry juice or its components.

Although the control group subjects had nearly identical rates of bacteriuria and pyuria at baseline, and baseline status was controlled for in all replicate assessments, control subjects were more likely to have histories of urinary tract infections. The effect of the cranberry beverage persisted even when this information was included in the multivariate regression equation. The rate of attrition differed slightly between the two groups: of those who contributed one or more urine samples following the baseline measurement, 60 (83%) of 72 subjects in the cranberry group completed all 6 months of the study compared with 61 (75%) of 81 in the placebo group. If subjects with sterile urine samples were more likely to drop out before contributing the full 6 months of study, this could have influenced our findings, although such an explanation seems unlikely.

Despite the popularity of use of cranberry juice for prevention of urinary tract infections, the probabilities-of-transition analyses indicate that its effect was more pronounced in converting urine samples out of a state of bacteriuria with pyuria, as compared with preventing the conversion of noninfected urine samples to bacteriuric-pyuric ones. While this does not imply that such a regimen should displace antibiotics as the therapy of choice when treatment is needed, it does suggest important possibilities for the role of bacterial adhesion in the cause and treatment of urinary tract infection. The findings also indicate the need for a trial to determine whether treatment of urinary tract infections with antibiotics plus cranberry beverage would yield outcomes superior to those seen with antibiotics alone.

These findings, if replicated in other settings, would suggest evidence for the bacteriostatic property of cranberry beverage in the bladder. Further studies are needed on the biochemical properties of this substance. Future randomized trials of longer duration in younger women with symptomatic cystitis, as well as other patient groups with recurrent urinary tract infection, will help to clarify the role of cranberry beverage in the prevention and, as an adjunct to antibiotics, in the treatment of this common disorder.

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