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Sodas, Soup, and Tea: The Effect of Liquids on Caloric Intake and Metabolism

By Adriane Fugh-Berman, MD

MANY NORTH AMERICANS ARE STRUGGLING TO CONTROL THEIR weight. Several recent studies suggest that eliminating liquid calories may be a simple way to cut total caloric intake. Apparently, one must chew calories to trigger satiety signals, so liquid calories simply add to the day's energy intake without affecting food intake.

Even highly caloric drinks taken before or with meals do not cause people to eat less food. A crossover study in eight women and seven men tested the effect of 1,880 kJ/d carbohydrate loads as liquid (soda) or solid (jelly beans), each given for four weeks with a four-week washout period between phases.[1] Diet records were obtained at baseline and on random days throughout the study; body composition was measured weekly; and physical activity was assessed before and after treatments. Physical activity and hunger were unchanged. During the jelly bean phase, subjects adjusted their food intake to compensate for the extra calories. In contrast, subjects did not decrease their caloric intake during the soda period. Not surprisingly, body weight and body mass index (BMI) increased significantly only during the liquid period.

A study of 42 men compared the effects of several liquids given before or with meals on caloric intake. Subjects received no drink, water (8 or 16 oz), or lemonade (8 or 16 oz sweetened with either aspartame or sucrose).[2] Drinks were given 30 or 60 min before lunch or with lunch. None of the liquids decreased food intake, so all caloric drinks increased total energy intake.

Soft Drinks and Weight Gain

Juice and milk supply nutrients along with calories; the same cannot be said for soft drinks, which are far more popular. In 2000, Americans bought more than 15 billion gallons of soft drinks. More than half of eight-year-olds drink soft drinks every day.[3] Children and adolescents are especially big customers and have easy access:

60% of all middle and high schools sell soft drinks, and some schools even provide them free with purchased meals.[3]

Sugar-sweetened drinks may be a significant factor in childhood weight gain; a prospective 19-month study of 548 ethnically diverse school children in Massachusetts found that frequency of obesity and BMI both increased significantly with sugar-sweetened drink consumption. Each additional serving increased frequency of obesity (odds ratio 1.60; 95% confidence interval [CI] 1.14-2.24; P = 0.02) and BMI (mean 0.24 kg/m^2, 95% CI 0.1-0.39, P = 0.03). The researchers adjusted for demographic, dietary, and lifestyle variables, and anthropometric measurements. Consumption of sugar-sweetened drinks at baseline also was significantly associated with increased BMI (mean 0.18 kg/m^2 for each daily serving; 95% CI 0.09-0.27; P = 0.02).[4]

The Center for Science in the Public Interest (CSPI), a consumer advocacy group, notes that drink sizes have gotten larger and larger over the years, so a drink meant for an individual today is bigger than some family-size drinks in the 1950s.[5] Some movie theaters serve 44-oz drinks; a 42-oz drink is available at McDonald's; and the largest size drink at a 7-11 convenience store is 64 oz (eight cups).

Table 1

Calorie content in popular beverages

Beverage	Serving Size	Calories
Water		0
Diet cola	20 oz	5
Coffee (with 1 liquid creamer)	8 oz	30
Tea (with 2 packets sugar)	8 oz	50
V8	11.5 oz	70
Fat-free milk	8 oz	90
1% milk	8 oz	100
Apple juice	8 oz	110
Cranberry juice	8 oz	140
Ginger ale	20 oz	200
Starbucks cappuccino	20 oz	200
Ultra Slim-Fast	11 oz	220
Arizona iced tea	20 oz	230
Snapple lemonade	16 oz	240
Sunny delight	20 oz	300
Odwalla future shake Vanilla A'lmondo	16 oz	380
McDonald's coke (super size)	42 oz	410
Baskin-Robbins chocolate shake	24 oz	1,130

Adapted from: Center for Science in the Public Interest. Drink to me only. *Nutr Action Healthletter* 2000;November:9.

Soup

While caloric drinks add calories without dimming appetite, a soup appetizer does decrease food intake. A controlled study of 24 lean women tested the effect of a premeal of chicken rice casserole (with or without a glass of water) vs. chicken rice soup on intake of calories at lunch. The casserole and soup contained the same ingredients, but were different in volume, form, and appearance. Compared to chicken rice casserole, eating soup significantly increased fullness, decreased hunger, and decreased caloric intake at lunch. Drinking a glass of water with the casserole did not affect satiety. The number of calories eaten at lunch was 1,209 (± 1 kJ) after the soup; 1,657 ± 148 kJ after the casserole with a glass of water, and 1,639 ± 148 kJ after the casserole without water. The reduced caloric intake at lunch did not cause the women to eat more at dinner. Other studies have also found that soup decreased subsequent intake. One study compared vegetable soup (blended or chunky) with vegetables (eaten with a glass of water) and found that soup decreased subsequent intake more than vegetables with water; the chunky soup was more

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effective than the blended soup.[6] Another study found that tomato soup decreased subsequent intake more than melon or cheese and crackers.[7]

CSPI suggests that those watching their weight order small sizes of drinks, share beverages, put lots of ice in drinks, or consume low-calorie beverages (water, tea, coffee, or diet soda).

Tea

Tea may be particularly beneficial to the weight-conscious; a crossover study in 10 healthy men compared green tea extract (50 mg caffeine and 90 mg epigallocatechin gallate), caffeine (50 mg), or placebo given with meals, and found that ingestion of green tea extract increased thermogenesis, significantly increasing 24-hr energy expenditure (EE) (4%, $P < 0.01$) and decreasing 24-hr respiratory quotient (RQ) (from 0.88 to 0.85, $P < 0.001$) without changing urinary nitrogen.[8] Norepinephrine excretion was 40% higher during treatment with green tea than with placebo ($P < 0.05$). The effect was not due solely to caffeine (known to be thermogenic); the caffeine control had no effect on EE, RQ, urinary nitrogen, or urinary catecholamines. Catechins in tea are thought to inhibit COMT, the enzyme that degrades norepinephrine, which helps to control thermogenesis and fat oxidation. Capsaicin (the compound that provides the heat in chili peppers) also has been shown to stimulate thermogenesis and fat oxidation in humans.

Given the drastic measures people are willing to take to lose weight, jettisoning caloric drinks, eating soup before meals, drinking tea, and eating spicy food seem like benign dietary modifications. ❖

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Cranberries and Urinary Tract Infections

By Lynn Keegan, RN, PhD, HNC, FAAN

WOMEN FREQUENTLY USE THE JUICE OR EXTRACT OF cranberry (*Vaccinium macrocarpon*) to prevent and treat urinary tract infections (UTIs). It is estimated that 25% of women have at least one UTI in their lifetime and others may have many more.[1] The majority of women referred to specialists are prescribed long-term, low-dose antibiotics. However, given the magnitude of this problem, it is safe to state that large numbers of women are experimenting with alternative remedies such as drinking cranberry juice or ingesting herbal remedies to enhance their immune response. Attempts to scientifically validate this practice have produced conflicting results.

Mechanism of Action

Cranberry extracts and juices contain quinic acid, which cause hippuric acid to be excreted in the urine; since bacteria prefer an alkaline pH for growth, acidification was thought to be the mechanism of action.[2] However, in a 1984 study, Sobota et al showed that cranberry prevents the adhesion of *Escherichia coli* to the bladder epithelium, thus making it easier to wash bacteria out with the urine.[3] Two different constituents of cranberries inhibit *E. coli* adhesion: Fructose inhibits the type 1 fimbrial adhesion and proanthocyanidins seem to inhibit the P fimbrial adhesion of uropathogenic strains.[4]

Cranberry Juice Inhibits Bacterial Adherence

Attempts to account for the potential benefit derived from cranberry juice have focused on urine acidification and bacteriostasis. In the study mentioned above, Sobota demonstrated that cranberry juice is a potent inhibitor of bacterial adherence.[3] Seventy-seven clinical isolates of *E. coli* were tested. Cranberry juice inhibited adherence by at least 75% in more than 60% of the clinical isolates. Cranberry cocktail also was given to mice in place of their normal water supply for a 14-day period. Urine

collected from these mice inhibited adherence of *E. coli* to uroepithelial cells by approximately 80%. Anti-adherence activity also could be detected in human urine. Fifteen of 22 subjects showed significant anti-adherence activity in the urine one to three hours after drinking 15 oz of cranberry juice cocktail.

In a follow-up study based on Sobota's results, researchers examined the effect of cranberry cocktail and juice on the adherence of *E. coli* expressing surface lectins of defined sugar specificity to yeasts, tissue culture cells, erythrocytes, and mouse peritoneal macrophages.[5] Cranberry juice cocktail inhibited the adherence of urinary isolates expressing type 1 fimbriae (mannose specific) and P fimbriae, but had no effect on a diarrheal isolate expressing a CFA/I adhesion. The cocktail also inhibited yeast agglutination by purified type 1 fimbriae. The inhibitory activity for type 1 fimbriated *E. coli* was dialyzable and could be ascribed to the fructose present in the cocktail; this sugar was about 10% as active as methyl alpha-D-mannoside in inhibiting the adherence of type 1 fimbriated bacteria. The inhibitory activity for the P fimbriated bacteria was nondialyzable and was detected only after preincubation of the bacteria with the cocktail. Cranberry, orange, and pineapple juice also inhibited adherence of type 1 fimbriated *E. coli*, most likely because of their fructose content. However, the two latter juices did not inhibit the P fimbriated bacteria. The conclusion is that cranberry juice contains at least two inhibitors of lectin-mediated adherence of uropathogens to eucaryotic cells.

Clinical Trials

A six-month study in elderly women suggests that drinking 300 ml/d of cranberry juice cocktail reduced bacteriuria and pyuria by nearly 50%.[6] This study showed that consumption of cranberry juice is more effective in treating than preventing bacteriuria and pyuria. Along with earlier reports on the ability of cranberry juice to inhibit bacterial adherence to urinary epithelial cells in cell culture, this work found that drinking cranberry juice each day is clinically useful.

In the Program for the Analysis of Clinical Strategies, Brigham and Women's Hospital researchers sought to determine the effect of regular intake of cranberry juice beverage on bacteriuria and pyuria in elderly women.[7] In a randomized, double-blind, placebo-controlled trial, a volunteer sample of 153 women (mean age, 78.5 years) were randomly assigned to one of two groups. They either consumed 300 ml/d 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. A baseline urine sample and six clean-voided urine samples were collected at approximately one-month intervals and tested quantitatively for bacteriuria and the presence of white blood cells. 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 ($P = 0.004$). 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 ($P = 0.006$). These findings suggest that ingestion of cranberry beverage reduced the frequency of bacteriuria with pyuria in older women.

The Cochrane Renal Group, a subset of the Cochrane Database System Review Company in Edinburgh, UK, developed a search strategy to assess the effectiveness of cranberries for the treatment of UTIs.[2] Companies involved with the promotion and distribution of cranberry preparations were contacted; electronic databases and the Internet were searched using English and non-English language terms; and reference lists of review articles and relevant trials also were searched. The selection criteria included all randomized or quasi-randomized controlled trials of cranberry juice or cranberry products for the treatment of UTIs. Trials of men, women, and children were included. Reviewers independently assessed whether the studies met the inclusion criteria. Further information was sought from the authors of papers containing insufficient information to make a decision about eligibility. The reviewers found no trials that fulfilled all of the inclusion criteria and concluded that no well-designed randomized trials assessing the effectiveness of cranberry juice for the treatment of UTIs have been conducted.

In a second Cochrane investigation on UTI prevention, a small number of poor quality trials gave no reliable evidence of the effectiveness of cranberry juice and other cranberry products.[8] The large number of dropouts/withdrawals indicated that cranberry juice may not be acceptable long-term. Other cranberry products, such as cranberry capsules, may be more acceptable. On the basis of the available evidence, the researchers could not recommend cranberry juice for the prevention of UTIs in susceptible populations.

The use of cranberries also has been tried in other groups. One study examined the effect of cranberry prophylaxis on rates of bacteriuria and symptomatic UTI in children with neurogenic bladder receiving clean intermittent catheterization.[9] The double-blind, placebo-controlled, crossover study included 15 children who received cranberry concentrate or placebo concentrate for six months (three months receiving one concentrate, followed by three months of the other). During each

weekly home visit, a sample of bladder urine was obtained by intermittent catheterization. Signs and symptoms of UTI, medication usage, and juice consumption were recorded. During consumption of cranberry concentrate, the frequency of bacteriuria remained high. Of the 151 samples obtained during consumption of placebo, 75% (114) were positive for a pathogen (≥ 10^4 colony-forming units/ml) compared with 75% (120) of the 160 samples obtained during consumption of cranberry concentrate. *E. coli* remained the most common pathogen during placebo and cranberry periods. Three symptomatic infections each occurred during the placebo and cranberry periods. No significant difference was observed in the acidification of urine in the placebo group vs. the cranberry group (median, 5.5 and 6.0, respectively). The frequency of bacteriuria in patients with neurogenic bladder receiving intermittent catheterization was 70% and cranberry concentrate had no effect on bacteriuria in this population.

In another study, seven juices (cranberry, blueberry, grapefruit, guava, mango, orange, and pineapple) were examined; only cranberry and blueberry prevented bacterial bladder adhesion.[10] Although blueberries have not been studied as thoroughly as cranberries, they also may prove to be an alternative treatment for UTI.

Conclusion and Recommendation

Cranberry juice and extract have biologic effects against bacterial adhesion in the bladder. No significant adverse effects have been noted in this long-used folk remedy that is both safe and well tolerated. For those concerned about the high sugar content of cranberry juice, oral capsule extracts are an available option. (*See page 56 for more information.*)

To assess cranberry juice's effectiveness in treating UTIs, well-designed, parallel-group, double-blind trials comparing cranberry juice and other cranberry products vs. placebo are needed. Outcomes should include reduction in symptoms, sterilization of the urine, side effects, and adherence to therapy. Dosage (amount and concentration) and duration of therapy should also be assessed. This area is ripe for more investigation. Studies could relate to dose intake, use of cranberry products in control and experimental groups combined with antibiotics, or contrasting and comparing the effects of cranberry in children, adults, and the elderly. ❖

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Chinese Red Yeast Rice: A Natural Statin?

By John McPartland, DO, MS

RED YEAST RICE IS A CONFUSING BUT ACCURATE NAME for a dietary supplement that lowers cholesterol and triglyceride levels. The product consists of cooked, nonglutinous white rice fermented by the yeast *Monascus purpureus*, which is subsequently sterilized, dried, pulverized, and packed into capsules. Red yeast rice is a dietary staple in many Asian countries, with typical dietary consumption ranging from 14 to 55 g/d.[1] The product has been used for at least 13 centuries in China, where it is known as *hong qu*. In China, red yeast rice is used as a table condiment, a culinary spice, and for food coloring (e.g., the color of Peking Duck). Red yeast rice also is prescribed in traditional Chinese medicine to promote blood circulation.

A double-blind, placebo-controlled study of 83 California men and women found that subjects taking 2.4 g/d red yeast rice significantly lowered their cholesterol from 250 mg/dL to 208 mg/dL (17%) after eight weeks.[1] LDL levels dropped from 173 to 134 (22%), triglycerides dropped from 133 to 118 (12%), and HDL levels did not change. There were no significant changes in the control group. Dietary intake also was monitored, and there were no differences between the two groups in total calories, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, and fiber. There were no serious adverse effects and no changes in liver function tests. This study was funded by Pharmanex, the manufacturer of Cholestin, a standardized extract of red yeast rice. At least six animal studies and less rigorous clinical trials previously have been conducted in China; most of them report more impressive results (30-60% reduction in cholesterol).

In 1979, the primary active ingredient in red yeast rice was identified as monacolin K.[2] Monacolin K inhibits HMG-CoA reductase, a liver enzyme that initiates sterol biosynthesis. This mechanism is shared by synthetic "statin" pharmaceuticals, such as atorvastatin (Lipitor), pravastatin (Pravachol), simvastatin (Zocor), and lovastatin (Mevacor). Indeed, monacolin K proved to be identical to lovastatin, and in 1997 the FDA banned imports of red yeast rice, specifically Cholestin.[3] The FDA claimed Cholestin constituted an unapproved use of a patented drug; Pharmanex countered by saying Mevacor should have its patent revoked because Merck did not "invent" lovastatin, a naturally occurring compound. The FDA claimed that Pharmanex altered the traditional fermentation process to produce a lovastatin-rich product. There were rumors of genetically altered organisms; none of these allegations appear to be true. A year later, the ban was reversed in Federal District Court; Judge Dale Kimball cited "substantial and serious questions regarding the lawfulness of the FDA's actions."[4] The FDA has appealed the decision.

Table 1

Monacolin K and citrinin content of red yeast rice supplements

Supplement/ Manufacturer	Monacolin K (lovastatin) (mg/capsule)	Citrinin (mcg/capsule)
Cholesterex/ Oralabs	1.35	4.87
Cholestene/ HPF, LLC	2.87	2.22
Cholactive/ Herbscience	1.80	6.06
Cholester-Reg/ Nature's Sunshine	3.37	3.23
Beyond Cholesterol/ TwinLab	0.15	< 0.04
Hongqu/ Nature's Sunshine	2.86	11.82
Cholesterol Power/ Nature's Herbs	2.51	< 0.47
RYR/ Solaray	1.56	64.7
Cholestin/ Pharmanex	2.46	0.04

Adapted from: Heber D, et al. An analysis of nine proprietary Chinese red yeast rice dietary supplements: Implications of variability in chemical profile and contents. *J Altern Complement Med* 2001;7:133-139.

Red yeast rice reduces cholesterol by a greater proportion than can be attributed to its lovastatin content alone.[1] If lovastatin can be likened to a "silver bullet" against hyperlipidemia, then red yeast rice is best characterized as a "synergistic shotgun." It contains a complex array of potential lipid-lowering agents, including monacolin K and 10 other monacolin analogs, omega-3 fatty acids, isoflavones, and plant sterols.[3] In addition to therapeutic synergism, a second benefit of herbal medicines may be that of a reduced side effect profile; herbs often are weaker than drugs. Herbalists claim that polypharmaceutical herbs contain compounds that mitigate the side effects of their primary active ingredients,[5] but this concept has not been proven. Extensive animal studies of red yeast rice have shown no acute or chronic toxic effects.[1] Lovastatin, on the other hand, can cause rare cases of liver damage and rhabdomyolysis. The difference may be simply a matter of dose; 2.4 g red yeast rice contains about 5 mg of lovastatin, whereas a daily Mevacor dose ranges from 20-80 mg.[3] A one-month supply of Cholestin costs about $20-30; cholesterol-lowering drugs average $187/month.[6]

Red yeast rice occasionally causes heartburn or flatulence, which can be avoided by taking the supplement with meals. Pregnant or nursing women should consult with their physician before taking any lipid-reducing agent. Individuals are cautioned from taking any lovastatin product if they have liver disease or if they are taking gemfibrozil (Lopid) or other lipid-lowering agents. Side effects from Mevacor may arise when it is taken with compounds that inhibit the drug-metabolizing enzyme cytochrome P-450 3A4, such as antifungal medicines (fluconazole, ketoconazole, etc.) macrolides

(erythromycin, azithromycin), quinolones (ciprofloxacin, norfloxacin), protease inhibitors (indinavir, nelfinavir), cimetidine, and even grapefruit juice.[7] Lastly, statins can deplete Coenzyme Q_{10} levels,[8] so individuals concerned about heart disease may want to add 50 mg CoQ_{10} bid when taking red yeast rice supplements.

After Pharmanex won its case against the FDA and Merck, several other manufacturers have released red yeast rice products. These products, however, may contain other strains of *Monascus* and undergo different fermentation and manufacturing processes. The beneficial effects of red yeast rice have been shown only with the manufacturer-funded trials of Cholestin. The me-too products have not been evaluated in clinical trials.

Commercial products vary substantially. A recent chemical analysis of nine commercially available red yeast rice dietary supplements found that total monacolin content ranged from 0% to 0.58%; levels of monacolin K (lovastatin) ranged from 0.15 mg to 3.37 mg/capsule.[6] Citrinin, a nephrotoxic mycotoxin that can form if fermentation conditions are not carefully controlled, was detectable in seven of nine preparations in amounts ranging from 0.47 to 64.7 mg/capsule.

Some products compensate for suboptimal doses of red yeast rice by adding other lipid-lowering agents, such as gugulipid (from the Ayurvedic herb *Commiphora mukul*). This looks good on the label, but discerning consumers will note that these accessories are provided at sub-therapeutic levels. ❖

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News Briefs

Norplant and Vitamin E

Endometrial bleeding is a common reason for discontinuing use of Norplant (a levonorgestrel subdermal contraceptive implant). A randomized, double-blind, placebo-controlled trial tested 200 mg/d vitamin E or placebo (10 days/month for two months) in 72 Norplant users with bleeding problems. Compared to baseline, the number of days with bleeding decreased significantly in both the treated and placebo groups (from 18.1 ± 1.0 to 7.7 ± 1.4 in the vitamin E group and from 20 ± 1.13 to 12.1 ± 1.3 days in the placebo group). The benefit of vitamin E was seen in both the first and second month. It is not clear, however, that the difference between the treated and placebo group is clinically significant. The study was supported by the World Health Organization and the Department of Education and Culture of the Republic of Indonesia.

Source: Subakir SB, et al. Benefits of vitamin E supplementation to Norplant users—in vitro and in vivo studies. *Toxicology* 2000;148:173-178.

CME Questions

1. **Drinks ingested before or during a meal:**
   a. reduce caloric intake.
   b. increase caloric intake.
   c. have no effect on caloric intake.

2. **The primary mechanism of cranberry juice is:**
   a. acidification of the urine.
   b. inhibition of bacterial adhesion to bladder epithelium.
   c. cell lysis.

3. **Red yeast rice contains:**
   a. no statins.
   b. simvastatin.
   c. lovastatin.

4. **Ingestion of cranberry concentrate tablets:**
   a. increases urinary oxalate.
   b. has no effect on urinary oxalate.

5. **Ipriflavone has been associated with which of the following side effects?**
   a. Anemia
   b. Lymphocytopenia
   c. Thrombocytopenia

With Comments by Adriane Fugh-Berman, MD

Cranberry and Urinary Oxalate

Source: Terris MK, et al. Dietary supplementation with cranberry concentrate tablets may increase the risk of nephrolithiasis. *Urology* 2001;57:26-29.

Design and Setting: Uncontrolled trial in five healthy volunteers (two women and three men, age 26-37) with no history of renal stones, consuming usual diet.

Treatment Dose/Route/Duration: Cranberry tablets administered according to manufacturers recommended dosage for seven days.

Outcome Measures: 24-hour urine collection for pH, volume, creatinine, oxalate, calcium, phosphate, uric acid, sodium, citrate, magnesium, and potassium.

Results: Urinary oxalate levels increased significantly (P = 0.01) by an average of 43.4%. All volunteers experience elevation of urinary oxalate levels. Urinary sodium, magnesium, and potassium all increased significantly, as did calcium oxalate supersaturation; uric acid supersaturation did not increase. Urinary calcium, phosphate, uric acid, and citrate did not differ significantly from baseline.

Funding: Not stated.

Comments: Oxalate content of the cranberry preparation was not specifically analyzed, but the authors estimate that commercially available high-dose cranberry concentrate tablets taken in a manufacturer-recommended dose could increase dietary intake of oxalate by 142% (363 mg). Urinary oxalate concentration is very important in stimulating stone formation; the authors note that as little as 10% increase in urinary oxalate can cause calcium oxalate crystallization. The clinical implications of cranberry concentrate consumption are somewhat unclear as the preparation increased magnesium and potassium (which inhibit stone formation). Also, the authors note that their volunteers had relatively high urine output and urinary calcium levels and may not be representative of the general population or stone-forming individuals.

This is a small and imperfect study. It would have been interesting to include stone formers and it would have been helpful to analyze oxalate levels in the preparation used. Still, it raises an important issue. Cranberry juice is a popular home treatment or prophylactic against urinary tract infections. (*See page 51*). While it is difficult to increase oxalate intake substantially with cranberry juice (which contains 1.89 mg oxalate/30 ml juice), cranberry concentrate tablets may contain significant amounts of oxalate. Patients should be advised to drink juice rather than take tablets. Alternatively calcium, which binds oxalate in the gut, can be administered concurrently with concentrated cranberry products. ❖

Ipriflavone for Osteoporosis

Source: Alexandersen P, et al. Ipriflavone in the treatment of postmenopausal osteoporosis. *JAMA* 2001;285:1482-1488.

Design and Setting: A randomized, double-blind, placebo-controlled, multicenter trial (The Ipriflavone Multicenter European Fracture Study) conducted in Belgium, Denmark, and Italy.

Subjects: 474 postmenopausal white women (age 45-75) with osteoporosis (< 0.86 g/cm^2) of the lumbar spine. Exclusion criteria included body mass index lower than 30 kg/m^2, previous vertebral fractures, significant concomitant disease, alcohol abuse, or use of any medication known to affect bone metabolism. Two hundred ninety-two women completed the study.

Treatment Dose/Route/Duration: Ipriflavone, 200 mg tid for three years. Both treatment and placebo groups received 500 mg/d of calcium.

Outcome Measures: Bone mineral density at spine, hip, and forearm (assessed by dual-energy radiograph absorptiometry) and biochemical markers of bone resorption (including serum alkaline phosphatase, fasting urinary hydroxyproline corrected by creatinine, serum calcium, serum phosphorus, and urinary excretion of calcium corrected for creatinine) assessed every six months. Adverse events, hematology, blood chemistry, and urinalysis were assessed every three months. Non-traumatic vertebral fractures were assessed by lateral radiography at years 1, 2, and 3.

Results: Intent-to-treat analysis showed no difference in annual percentage change in bone mineral density at any site (compared to baseline) between the treated group and the placebo group (lumbar spine ipriflavone 0.1% [95% CI -7.9% to 8.1%] vs. 0.8% [95% CI -9.1% to 10.7%], P = 0.14). Biochemical markers were similar between groups as were new vertebral fractures. The ipriflavone-treated group experienced a significant decrease in lymphocyte concentrations; this effect occurred after six months of treatment. Twenty-nine women in the ipriflavone group developed lymphocytopenia (< 500 mcL) during the study; two additional subjects had lymphocytopenia at 36 months. After discontinuation of ipriflavone, 52% recovered by one year and 81% by two years. The lymphocytopenia was subclinical; there were no significant differences in opportunistic infections, cancers, or other adverse effects between the two groups. Compliance was similar between groups.

Funding: Cheisi Farmaceutici, SpA, which manufactures ipriflavone.

Comments: Ipriflavone, a synthetic isoflavone available over-the-counter as a dietary supplement, has been promoted for prevention and treatment of osteoporosis. Previous smaller trials have indicated a benefit for ipriflavone (see *Alternative Therapies in Women's Health*, September 2000, pp. 67-70.) but this trial is the largest, longest, and methodologically the best of all trials performed to date. There appears to be no benefit of using ipriflavone in postmenopausal women with osteoporosis, and lymphocytopenia is a significant adverse effect. Patients should be counseled against using this dietary supplement. ❖