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Soybean Intake and Bone Density

PART III OF A SERIES
ON PHYTOESTROGENS

By Adriane Fugh-Berman, MD

PHYTOESTROGENS FROM SOY OR FLAX HAVE PROMISE IN TREATING hot flashes (see *Alternative Therapies in Women's Health*, Premiere issue, pp. 1-4), but what effect do they have on bone? Conjugated estrogens help preserve bone density, but phytoestrogens are much weaker in binding assays than pharmaceutical or endogenous estrogens. There is some evidence that phytoestrogens have a beneficial effect on bone, and intriguing animal studies indicate that these effects may involve non-estrogenic mechanisms. There are few clinical trials, however, and long-term human studies are lacking.

Epidemiologically, bone density is lowest in Asian women and highest in African-American women, with white women in the middle. Interestingly, however, hip fracture rates are lower in Asians than in whites,[1] despite the fact that Asians have thinner bones. Compared to white women, Asian women have a 40-50% lower risk of hip fracture, and African-Americans a 50-60% lower risk of hip fracture.[2] The reasons for these differences are unknown, although body mass, differences in hip axis length (distance from the greater trochanter to the inner pelvic brim), and bone quality may all play a role. Fracture risk is also influenced by muscle function; however, this has not been quantified among ethnic groups in the same level of detail as bone density. It is possible that high soy intake contributes to improved bone quality in Asians compared to whites, but this is entirely speculative, since there are many differences between these two groups. It bears noting that bone density measurements are only one indicator of fragility; disordered trabecular microarchitecture probably contributes to fracture risk independently of bone mass.[3]

Clinical Trials

The most thorough human study to date is a double-blind trial in 66 postmenopausal, hypercholesterolemic women, aged 49-73.[4] Subjects were randomly assigned to 40 g protein a day from one of

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three sources: milk (nonfat dried milk and casein), soy protein with medium isoflavone content (equivalent to 55.6 mg isoflavones daily), or isolated soy protein with high isoflavone content (equivalent to 90 mg isoflavones daily). All women also followed a low-fat, low-cholesterol diet. Dual-energy X-ray absorptiometry (DEXA) bone density studies of the lumbar spine, proximal femur, and total body were done at the beginning of the six-month study (after a two-week lead-in) and at the end of the study. *(See Table for isoflavone content of soyfoods.)*

No differences were seen among the three groups in bone density studies of the hip or total body, but subjects receiving the high isoflavone preparation experienced a significant increase in lumbar bone density and mineral content (2%), compared to the milk protein group. This is consistent with an estrogenic effect; conjugated estrogens have a more pronounced effect on trabecular than on cortical bone, and thus affect bone density more in vertebrae than in femoral bone density. Six months is relatively brief for an osteoporosis study. A greater effect may have been observed with a longer study.

An extremely problematic one-year pilot study in eight white women with low bone mass (mean age 56) has been reported in abstract form.[5] This study enrolled subjects in a six-day course emphasizing lifestyle, exercise, intake of whole-grain products, and sufficient calcium, magnesium, and vitamin D intake. Women also received a vitamin and mineral supplement containing calcium, magnesium, silica, zinc, boron, copper, vitamin C, pyridoxine, vitamin D, and vitamin K, and apparently received or were encouraged to drink calcium-enriched soy milk in unspecified amounts. However, six women were concurrently taking HRT or bisphosphonate drugs, and two participants were allergic to soy and were not included in the final analysis. Although researchers noted that five of the six women demonstrated a gain in BMD/BMC (the sixth subject discontinued HRT during the study), DEXA measurements of bone mass were not significantly different from baseline at the end of the study. It is not noted how many of the six subjects analyzed were using HRT or bisphosphonate drugs.

This is an excellent example of how not to do a study. No effort seems to have been made to screen subjects to assure even a minimally homogenous study population. Exclusion criteria obviously should include allergy to the compound to be tested. Allowing the concurrent use of drugs known to affect the endpoint of bone density in a small study is unjustifiable. And the multimodal, individualized approach would have rendered any positive results uninterpretable. It is interesting, however, that even with this panoply of pharmaceutical and non-pharmaceutical interventions, there were no positive results.

Animal Studies

Both soybean intake and genistein (the predominant isoflavone phytoestrogen in soybeans) have been tested on bone density in the oophorectomized rat model. A rat study noted that genistein protects against loss of trabecular bone volume and bone mineral density and appears to increase osteoblastic activity without affecting osteoclasts.[6] As the mechanism of estrogen appears to be suppressing bone turnover (i.e., osteoclastic activity) rather than stimulating bone growth, the effect of genistein on bone may not be an estrogen-like mechanism.

One study compared four groups: oophorectomized rats, sham-operated rats, oophorectomized rats fed a milk protein diet with 17-beta-estradiol, and oophorectomized rats fed soybean protein isolate.[7] Oophorectomized rats showed significant decreases in bone density; both 17-beta-estradiol and soybean protein isolate protected against this bone loss.

Another study in oophorectomized rats compared sham-operated rats with three oophorectomized groups; two were fed casein- (milk protein-) based diets and one group was fed a 22% soybean diet.[8] One of the casein-fed groups received estrogen injections. Rats in the sham-operated, soy-fed, and estrogen-treated groups had significantly higher femur and tibia ash contents than

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Table

Estimated Isoflavone Content of Soyfoods

Food	Serving Size	Isoflavone mg/serving*
Mature soybeans, uncooked	1/2 cup	175.6
Roasted soybeans	1/2 cup	167.0
Green soybeans, uncooked	1/2 cup	70.1
Tempeh, uncooked	4 oz	60.5
Soy isolate, dry	1 oz	56.5
Soy flour	1/4 cup	43.8
Tofu, uncooked	4 oz	38.3
Textured soy protein, dry	1/4 cup	27.8
Soy milk	1 cup	20.0
Soy concentrate, dry	1 oz	12.4

*Values obtained from published literature and analyses of selected products. Isoflavone content varies widely among soybean varieties and from product to product based on manufacturing process and sources of soy protein.

Source: Indiana Soybean Board

casein-fed rats. Markers of bone turnover were not affected.

Two studies compare oophorectomized rats fed casein, reduced-isoflavone soy protein, or normal isoflavone soy protein to oophorectomized or sham-operated rats fed a casein-based diet. The first study[9] found that femoral density did not differ between either soy group and oophorectomized controls (sham-operated controls, as expected, had higher bone mass). The second study[10] found increased femoral bone density with isoflavone-intact soy but no effect of isoflavone-reduced soy. Measures of bone turnover were not affected by any of the soy diets in either study. Both of these studies, reported by the same group, found differing results on femoral bone density but similar findings on lack of effect on bone turnover rates (which are accelerated by oophorectomy).

Another study in which rats were injected subcutaneously with genistein (5 mcg/g body weight) found less bone loss in the genistein-treated group and higher rate of bone formation, again without any effect on bone resorption.[11]

Genistein may have a biphasic effect. In a model of extreme bone loss, it is more effective at lower rather than higher doses. In a total assault on bone mineral stores, lactating oophorectomized rats are fed a low-calcium diet; rats so treated will lose more than 50% of bone mineral mass in two weeks. Three different doses of genistein (0.5 mg, 1.6 mg, or 5.0 mg daily) were compared to conjugated estrogen in this model,[12] endpoints were scanning electron microscopy (SEM) measurements of the proximal tibia, femoral ash weights, and uterine weights. Mean femoral ash weights were significantly higher in the low-dose genistein group than the conjugated estrogen group, and higher than ash weight of those in the intermediate or high genistein group. SEM results showed low-dose genistein to be equivalent to conjugated estrogens in the retention of cancellous bone tissue. However, high doses of genistein were less effective.

A primate study found different results than the rat studies. Forty-one oophorectomized cynomolgus monkeys received one of four treatments: a milk protein diet with or without 17-beta-estradiol or a soy protein based diet with or without 17-beta-estradiol.[13] Histomorphometry on mid-femur cortical bone showed that soy protein did not prevent oophorectomy-induced increase in bone turnover and actually increased bone turnover on the endosteal (inner lining of the bone) surface compared to milk-fed monkeys. On the other hand,17-beta-estradiol suppressed oophorectomy-induced increase in bone turnover.

Conclusion

There is no definitive evidence that dietary soy or isoflavone supplementation benefits bone, but one reasonable human study shows a modest effect of high-isoflavone soy supplementation on vertebral (not femoral) bone. There is enough intriguing animal evidence to recommend further clinical research.

Although most rat studies show beneficial effects of soy or genistein on bone, a primate study did not confirm these results. Results from animal studies are not entirely consistent in terms of preservation of bone density, but a consistent finding is that soy, unlike estrogen, does not reduce oophorectomy-induced bone turnover. Any beneficial effect of soy appears to be due to stimulating bone formation rather than reducing bone resorption.

Additional animal studies should be done to elucidate mechanisms of action. Long-term human studies comparing the effect of HRT or bisphosphonates with soy supplementation on fracture incidence should be done to determine whether phytoestrogens protect bone. ❖

References

1. Lauderdale DS, et al. Hip fracture incidence among elderly Asian-American populations. *Am J Epidemiol* 1997;146:502-509.

2. Cummings SR, et al. Racial differences in hip axis length might explain racial differences in rates of hip fracture. Study of Osteoporotic Fractures Research Group. *Osteoporos Int* 1994;4:226-229.
3. Cooper C. The epidemiology of fragility fractures: Is there a role for bone quality? *Calcif Tissue Int* 1993;53(suppl):23-26.
4. Potter SM, et al. Soy protein and isoflavones: Their effects on blood lipids and bone density in postmenopausal women. *Am J Clin Nutr* 1998;68(suppl):1375-1379.
5. Olsen EL, et al. Bone gain after calcium enriched soy milk, food supplement, and lifestyle changes in women with low bone mass: A pilot project in course form. *Am J Clin Nutr* 1998;68(suppl):1518(abstract).
6. Fanti O, et al. Systematic administration of genistein partially prevents bone loss in ovariectomized rats in a nonestrogen-like mechanism. *Am J Clin Nutr* 1998;68(suppl):1517(abstract).
7. Arjmandi BH, et al. Dietary soybean protein prevents bone loss in an ovariectomized rat model of osteoporosis. *J Nutr* 1996;126:161-167.
8. Harrison E, et al. The effect of soybean protein on bone loss in a rat model of postmenopausal osteoporosis. *J Nutr Sci Vitaminol (Tokyo)* 1998;44:257-268.
9. Arjmandi BH, et al. Role of soy protein with normal or reduced isoflavone content in reversing bone loss induced by ovarian hormone deficiency in rats. *Am J Clin Nutr* 1998;68(suppl):1358-1363.
10. Arjmandi BH, et al. Bone-sparing effect of soy protein in ovarian hormone-deficient rats is related to its isoflavone content. *Am J Clin Nutr* 1998;68(suppl):1364-1368.
11. Fanti P, et al. The phytoestrogen genistein reduces bone loss in short-term ovariectomized rats. *Osteoporos Int* 1998;8:274-281.
12. Anderson JJ, et al. Biphasic effects of genistein on bone tissue in the ovariectomized, lactating rat model. *Proc Soc Exp Biol Med* 1998;217:345-350.
13. Lees CJ, Ginn TA. Soy protein isolate diet does not prevent increased cortical bone turnover in ovariectomized macaques. *Calcif Tissue Int* 1998;62:557-558.

Chocolate Addiction

By Adriane Fugh-Berman, MD

IT'S NOT NEWS TO FEMALE READERS THAT CHOCOLATE contains psychoactive substances. But what those psychoactive ingredients are, however, is still a matter of debate. Chocolate contains a plethora of possibilities: theobromine is a methylxanthine with caffeine-like effects; phenylethylamine has amphetamine-like qualities; and phenylalanine and tyrosine are both precursors to norepinephrine and dopamine.[1] Additionally, eating carbohydrates, especially chocolate, increases uptake of tryptophan by the brain and subsequently increases 5-hydroxytryptophan in the central nervous system.

One case series reported a high rate of chocolate craving among MDMA (Ecstasy) abusers. MDMA causes long-term 5HT depletion and the authors of this case series postulate that eating chocolate may have been an unconscious effort to raise 5HT levels.[1]

However, an experimental study aimed at separating physiological from sensory factors found no evidence for a physiological basis for chocolate craving.[2] This study compared the effect of chocolate bars, cocoa capsules, white chocolate, white chocolate plus cocoa capsules, placebo, or nothing on satiation of chocolate craving in 72 students who served as their own controls. White chocolate is made from a cocoa butter base and does not contain the pharmacological components of chocolate or cocoa.

Only 34 students turned in at least one observation for each treatment (this study is notable for having more dropouts than completers). Milk chocolate was the standard for craving relief. White chocolate produced intermediate scores. Cocoa capsules, however, did not reduce craving any more than placebo.

Cannabinoid Mimics in Chocolate

In 1996, a letter in *Nature*[3] terrified parents and husbands by announcing the isolation of psychoactive compounds in chocolate that act in a similar manner as the psychoactive compounds in marijuana—tetrahydrocannabinol (THC) and related compounds. Actually, it's no use hiding the chocolate; the human brain makes its own version of THC, which explains the presence of receptors that are specific for cannabinoids. Anandamide is a brain lipid that binds to cannabinoid receptors and mimics the psychoactive effects of marijuana.

The chocolate researchers isolated three unsaturated *N*-acylethanolamines from chocolate that may act as cannabinoid mimics. It is unclear whether these compounds directly activate cannabinoid receptors or act indirectly by increasing anandamide levels.

Nestlé Responds: Chocolate No More Addictive Than Oatmeal

A recent research letter to *Nature*[4] sought to reassure those worried that chocolate might lead to the hard stuff.

A multinational group from Naples, Jerusalem, and the Nestlé Research Centre in Lausanne found that NAEs in chocolate were no higher than soybeans, hazelnuts, oatmeal, and millet. Additionally, they tested anandamide and the endocannabinoid 2-arachidonoylglycerol (found in milk and cocoa) in an in vivo test used to assess cannabimimetics and concluded that although the compounds were active in four of five behavioral tests, they were only active at much higher concentrations than delta^9-THC. Another experiment found that most of these compounds are hydrolyzed in the gastrointestinal tract and that less than 5% of orally administered compounds entered the bloodstream.

Beltramo and Piomelli[5] criticized the above study in a reply which implied that Di Marzo et al definitively answered a question that no one had asked. The finding that NAEs do not cause overt cannabis-like effects was hardly a surprise since no one ever claimed that marijuana and chocolate have comparable psychoactive effects. The two most prevalent NAEs in chocolate (*N*-oleylethanolamine and *N*-linoleylethanolamine) weren't tested at all—a particular lapse given that these NAEs are produced in the brain by a similar mechanism to that which produces anandamide. Additionally, substances in chocolate may prevent anandamide degradation rather than act as anandamide agonists. Lastly, Beltramo and Piomelli point out that NAEs may act synergistically, so that individual NAEs should be tested against cocoa.

Conclusion

More research clearly needs to be done. If milk contains relatively high levels of endocannabinoids, would hot cocoa be expected to have potentiated psychoactive effects, and could this be the real reason ski trips put people in a good mood? Updates on the chocolate wars will be provided when available. ❖

References

1. Schifano F, Magni G. MDMA ("ecstasy") abuse: Psychopathological features and craving for chocolate: A case series. *Biol Psychiatry* 1994;36:763-767.
2. Michener W, Rozin P. Pharmacological versus sensory factors in the satiation of chocolate craving. *Physiol Behav* 1994;56:419-422.
3. di Tomaso E, et al. Brain cannabinoids in chocolate. *Nature* 1996;382:677-678.
4. Di Marzo V, et al. Trick or treat from food endocannabinoids? *Nature* 1998;396:636.
5. Beltramo M, Piomelli D. [letter] *Nature* 1998;396:636-637.

Book Review

Rational Phytotherapy, by V Schulz, R Hansel, V Tyler. Berlin: Springer-Verlag; 1998. 306 pp, $49.

By Adriane Fugh-Berman, MD

RATIONAL PHYTOTHERAPY IS AN INVALUABLE RESOURCE for any physician interested in herbal medicine. This scholarly, well-referenced, and thoughtful textbook also contains many interesting tidbits—for instance, the ginkgo, a notoriously hardy tree, was the first green growth to sprout in Hiroshima in 1946.

One frustrating aspect of assessing clinical evidence on specific herbs is that many of these trials appear in German medical literature that are often difficult to find in American medical libraries. This book summarizes the numerous German studies of herbs as well some as studies in English language literature. It includes brief information on production and quality control and a thorough introduction to different dosage forms. The main body uses a systems approach, grouping herbs under central nervous system, cardiovascular, respiratory, digestive tract, urinary tract, gynecology, skin and connective tissues, and agents that increase resistance to disease, which includes adaptogens, immune stimulants, and botanical antioxidants.

For most of the 100 herbs covered, active constituents are listed; pharmacological and toxicological information is included; clinical and animal studies are summarized; and risks, side effects, indications, dosages, and contraindications are covered.

The length of sections covered generally reflects the quantity of literature available. Although the recommendations of Commission E (the German agency charged with assembling herbal monographs, roughly equivalent to a division of the Food and Drug Administration) are often mentioned, this book does not rely on Commission E monographs. Its authors are well-known international authorities in herbal medicine.

The clinical trials summaries are the most valuable part of this book; more detail would have been preferable. An effort is made to critique trial methodology. Descriptions of individual trials are relatively brief but usually informative, containing information on number of patients, dose and duration of therapy, and main outcome measures. Some chapters, however, have less information on clinical trials than others, which is maddening. The ideal herbal reference book would include citations from journals in other languages, but this book constitutes a great leap forward in terms of rendering German trials accessible to North Americans. ❖

CME Questions

11. Compared to milk protein, soy supplementation containing 90 mg isoflavones a day:
a. increased vertebral bone density.
b. increased femoral bone density.
c. decreased vertebral bone density.
d. caused no change in femoral or vertebral bone density.

12. In most animal studies:
a. estrogen and genistein both stimulate bone formation.
b. estrogen and genistein both suppress bone resorption.
c. estrogen stimulates bone formation while genistein suppresses bone resorption.
d. genistein stimulates bone formation while estrogen suppresses bone resorption.

13. In terms of omega-3 fatty acid content, flax oil is most similar to:
a. olive oil.
b. fish oil.
c. evening primrose oil.
d. None of the above.

14. Chocolate contains:
a. theobromine, phenylalanine, tyrosine, and tetrahydrocannabinol.
b. theobromine, phenylalanine, tyrosine, and N-acylethanolamines.
c. theobromine, phenylalanine, tyrosine, and anandamide.
d. None of the above.

15. Chocolate craving appears to be:
a. physiological.
b. psychological.
c. sociological.
d. X-linked.

Label Review

With Comments from Adriane Fugh-Berman, MD

Ann Louise Gittleman's The Essential Woman

Label Information

"Designed for the Special Needs of Women"

"A delicate balance of essential fatty acids and phytochemicals from soy and flax particulate"

"The Essential Woman was especially formulated to address concerns of women during or nearing midlife. Young or 'High risk' women will also want to consider The Essential Woman for its preventative qualities. The Essential Woman combines valuable essential fatty acids from flax and evening primrose oil, with powerful yet gentle phytochemicals identified as lignans, isoflavones, saponins and protease inhibitors isolated from flaxseed particulate and soy. These ingredients have been carefully formulated to provide a balancing effect, while delivering an optimum dose."

One tablespoonful provides apx:

Fatty acids	
Omega-3	5,115 mg
Omega-6	2,330 mg
Omega-9	1,488 mg
Gamma-Linolenic acid	100 mg
Lignans	5 mg
Isoflavones	45 mg
Other	
Flaxseed particulate	2,180 mg
Saponins	55 mg
Rosemary/ascorbic acid	20 mg
Protease inhibitors	9 mg

Ingredients: Organic flaxseed oil, evening primrose oil, flaxseed particulate, isoflavones, saponins and protease inhibitors isolated from soy.

Supplement Facts

Serving size: 1 T (14 ml)

Servings per container: 17

Calories: 110

Calories from fat: 95

	Amount per serving	*% daily value*
Total fat	11 g	15%
Saturated fat	1 g	5%
Polyunsaturated fat	7 g	*
Monounsaturated fat	1 g	*
Dietary fiber	1 g	4%
Omega-3 fatty acids	5 g	*

*Daily value not established

Suggested Dosage

One tablespoonful daily as an addition to a healthy diet.

Manufactured by Barlean's Organic Oils, Ferndale, WA 98248

Price: $14.99/8 fl. oz. (236 ml)

Discussion

The vagaries of the language on the label make it difficult to dispute specific claims. This product apparently aims to gather up consumers who have heard anything good about phytoestrogens, flaxseed oil, or evening primrose oil, but this combination makes little sense. The words "high risk" are not attached to any condition or disease, possibly to maximize the product's attractiveness to any consumer at high risk for anything.

Soy and flax are sources of different types of phytoestrogens (isoflavones for soy; lignans for flax). Lignans

and lignan precursors in flax demonstrate some anticancer effects in animal models.[1] The amount of lignans in this preparation, however, is inconsequential, as it contains 3 g of "flaxseed particulate" (presumably crushed flaxseed) and only 5 mg of lignans. Studies of flaxseed for menopausal symptoms, for example, have used a dose of 10-50 g flaxseed daily.

Flaxseed oil, which constitutes most of this product, is similar to fish oil in terms of being rich in omega-3 fatty acids; this class of compounds inhibits platelet aggregation, has anti-inflammatory effects, and has immunomodulating effects.[2] Most studies of fish oil administered amounts equivalent to 3-4 g daily of omega-3, so this supplement, which provides 5115 mg omega-3 fatty acids, does fall in a therapeutic range.

Evening primrose oil is high in omega-6 fatty acids, especially gamma linolenic acid (GLA), a precursor of prostaglandin E. Evening primrose oil is popular for a variety of inflammatory conditions; there is some evidence of its efficacy for mastalgia.[3] Short-term use appears safe, but there is a theoretical concern that long-term intake could increase inflammation due to slow accumulation of arachidonate in tissues.[4]

Several compounds derived from soy, e.g., purified isoflavones, protease inhibitors, and saponins, have apparently been added to this formula. While isoflavones in food products have a number of beneficial effects (see *Alternative Therapies in Women's Health*, Premiere issue, pp. 1-4), the long-term safety of food-free isoflavones has not been established.

Saponins are steroid or triterpene glycosides widely distributed in plants. Although saponins are active principles in a number of medicinal plants,[5] they are not considered to be the active principles in soybeans.

Rosemary and vitamin C, in tiny amounts, might be preservatives but in the existing doses are inconsequential therapeutically.

The protease inhibitors present in this formulation occur naturally in soybeans, but in soyfood product protease inhibitors are deactivated by heat processing. Protease inhibitors compose an important class of anti-HIV drugs but have no place as a dietary supplement.

In summary, this supplement is predominately flaxseed oil fortified with an odd mix of compounds of dubious therapeutic value. Flaxseed oil is a good source of omega-3 fatty acids and may have some cardioprotective effects. This product also apparently contains some crushed flaxseed. While there is evidence for possible health benefits of lignans in flaxseed, this product does not contain sufficient quantities for any therapeutic effect. "The Essential Woman" probably has no advantage over plain flaxseed oil, which can be purchased more cheaply.

References

1. Thompson LU, et al. Variability in anticancer lignan levels in flaxseed. *Nutr Cancer* 1997;27:26-30.
2. Uauy-Dagach R, Valenzuela A. Marine oils: The health benefits of n-3 fatty acids. *Nutr Rev* 1996;54:102-108.
3. Kleijnen J. Evening primrose oil. *BMJ* 1994;309: 824-825.
4. Phinney S. Potential risk of prolonged gamma-linolenic acid use. *Ann Intern Med* 1994;120:692.
5. Lacaille-Dubois MA, Wagner H. A review of the biological and pharmacological activities of saponins. *Phytomedicine* 1996;2:363-386.

Clinical Abstracts

With Comments from Adriane Fugh-Berman, MD

Calcium Effective for Premenstrual Syndrome

Source: Thys-Jacobs S, et al. Calcium carbonate and the premenstrual syndrome: Effects on premenstrual and menstrual symptoms. *Am J Obstet Gynecol* 1998;179:444-452.

Design and Setting: Randomized, double-blind, placebo-controlled, parallel group multi-center trial at 12 outpatient health centers across the United States.

Subjects: 497 healthy premenopausal women ages 18-45 with moderate to severe, cyclically recurring premenstrual symptoms.

Treatment: Calcium carbonate (TUMS®-EX)

Dose/Route/Duration: 1500 mg calcium carbonate (containing 600 mg elemental calcium) PO bid for three menstrual cycles.

Outcome Measures: Changes in the PMS Diary, a previously validated 17-parameter symptom score. The four categories of symptoms assessed were negative affect, water retention, food cravings, and pain.

Results: By the third treatment cycle, calcium treatment resulted in an overall 48% reduction from baseline in total

symptom scores, compared to a 30% reduction with placebo. The difference was statistically significant in the luteal phase of both the second and third treatment cycles.

Funding: SmithKline Beecham Consumer Healthcare, manufacturers of TUMS®-EX, a calcium carbonate antacid.

Comments: This reasonable study provides evidence that calcium decreases symptoms associated with PMS. Symptoms assessed included mood swings, crying spells, breast tenderness, abdominal bloating, food cravings, and lower abdominal or low back pain. Supplemental calcium is safe and has the added benefit of providing some protective effect against osteoporosis. It can be difficult to persuade young women of the importance of early calcium supplementation (as peak bone mass is laid down prior to age 35). Perhaps this study will provide incentive for younger women to take calcium supplements. ❖

Alternative Therapy Use Among Women with Chronic Vaginal Symptoms

Source: Nyirjesy P, et al. Over-the-counter and alternative medicines in the treatment of chronic vaginal symptoms. *Obstet Gynecol* 1997;90:50-53.

Objective: Survey to investigate the use of over-the-counter (OTC) and alternative medicines in women with chronic vaginal symptoms.

Setting: Temple University Vaginitis Referral Center

Methods: Self-administered questionnaire given to all new patients referred for evaluation of chronic vaginal symptoms between September and December 1994.

Subjects: 105 (mean age 36)

Results: 73.3% of patients had used OTC medications in the preceding year, including miconazole, clotrimazole, povidone-iodine, and hydrocortisone, and 41.9% had used one or more alternative medicines. Of the latter group, 50% had tried supplementing their diet with acidophilus; 20.5% tried yogurt, 9.1% garlic pills, and 9.1% "herbal tea." In addition, 20.6% had tried topical applications of acidophilus or yogurt, 13.6% had tried vinegar douches, and 13.6% had tried topical application of boric acid. Two patients (4.5%) had tried acupuncture. The median yearly expenditure for these treatments was $35 (range $0-$1,200). Approximately 70% reported that their health care providers were aware of the treatment (this number was significantly lower than the 88.3% in the OTC group who reported that their health care providers were aware of the treatment).

Funding: Not noted.

Comments: With the exception of the two patients who tried acupuncture, all of the alternative therapies used by the subjects in this survey were self-administered, "home remedy" type therapies. The therapies listed are harmless and have some theoretical basis for efficacy, at least for candidal infections. Boric acid was once used for yeast infections; garlic has antifungal effects in vitro; vinegar douches acidify the vagina; and the use of yogurt or acidophilus is clearly an attempt to colonize the vagina with beneficial flora. ❖

Eat Your Candy

Source: Lee IM, Paffenbarger RS Jr. Life is sweet: Candy consumption and longevity. *BMJ* 1998;317:1683-1684.

Setting/Methods/Subjects: This subset of the Harvard alumni health study included 7,841 men, free of cancer and cardiovascular disease, who responded to a 1988 health survey that included information on candy consumption.

Results: Between 1988 and 1993, 7.5% of non-consumers of candy died, compared to 5.9% of candy consumers (age-adjusted relative risk was 0.83). Compared with non-consumers, the relative risks of mortality among men who consumed candy 1-3 times a month was 0.64, 1-2 times a week was 0.73, and 3 or more times a week was 0.84.

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Comments: This is cheerier news than one is used to getting from a medical journal. It bears noting that there does not seem to be increased benefit from increased intake; if anything, the opposite is true. Still, candy consumers do better than non-consumers in overall mortality. It is unfortunate that the relevant questions in this survey did not distinguish between chocolate and other types of candy. My favorite part of this report was the competing interests note at the end that states: "The authors admit to a decided weakness for chocolate and confess to an average consumption of one bar a day each." ❖

In Future Issues:

Ginkgo and Memory

Herb-Drug Interactions

Yoga for Back Pain

Alternative Cancer Therapies