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INSIDE

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Calcium for Weight Management

By Lynn Keegan, RN, PhD, AHN-BC, FAAN

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OBESITY IS INCREASING IN THE UNITED STATES IN EPIDEMIC PROportions.[1] Overweight Americans are well aware of the plethora of diets and exercise programs for weight management. Most people with weight issues have tried many courses of action.

Recent epidemiologic research suggests that dairy product intake or its components (calcium, vitamin D, and amount or source of protein) are associated with lower body weight or body fat. Clinical intervention trials designed to test this association during weight loss are promising, but still controversial.[2]

Mechanism of Action

The role of calcium in weight loss and management may be dependent upon the dietary environment. It is theorized that during periods of over-consumption of an energy-dense diet a high-calcium diet attenuates body fat accumulation and weight gain; whereas during caloric restriction, a high-calcium diet increases fat breakdown and preserves metabolism, thereby markedly accelerating weight and fat loss. Researchers believe that this effect is mediated primarily by circulating calcitriol, which regulates adipocyte intracellular Ca^{2+}. Studies of human adipocyte metabolism demonstrate a key role for intracellular Ca^{2+} in regulating lipid metabolism and triglyceride storage: Increased intracellular Ca^{2+} stimulates lipogenic gene expression and lipogenesis and suppresses lipolysis, resulting in adipocyte lipid filling and increased adiposity. The increased calcitriol produced in response to low-calcium diets stimulates adipocyte Ca^{2+} influx and, consequently, promotes adiposity, while higher-calcium diets inhibit lipogenesis; promote lipolysis, lipid oxidation, and thermogenesis; and inhibit diet-induced obesity in mice.[3]

It is interesting that dairy sources of calcium exert markedly greater effects in attenuating weight and fat gain and accelerating fat loss. This augmented effect of dairy products versus supplemental calcium has been localized, in part, to the whey fraction of dairy and is likely due to additional bioactive compounds, such as angiotensin

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converting enzyme (ACE) inhibitors and the rich concentration of branched chain amino acids, which act synergistically with calcium to attenuate adiposity. However, these compounds do not fully account for the observed effects, as they are more readily absorbed and therefore have significantly greater bioactivity than do other compounds. These concepts are supported by epidemiological data and recent clinical trials showing that diets that include at least three daily servings of dairy products result in significant reductions in body fat mass in obese humans in the absence of caloric restriction and marked acceleration of weight and body fat loss secondary to caloric restriction compared to low-dairy diets.[3]

Studies in transgenic mice have demonstrated that calcium influences adipocyte metabolism. High-calcium intake depresses levels of parathyroid hormone and 1,25-hydroxyvitamin D. These decreased hormone levels decrease intracellular calcium, thereby inhibiting lipogenesis and stimulating lipolysis. High dietary calcium intakes increase fecal fat excretion and may increase core body temperature. Calcium from dairy products seems to have more of an impact than calcium from dietary supplements.[1] The mechanisms proposed to mediate the putative effect of dietary calcium include the formation of fecal fatty acid complexes to reduce fat absorption and the regulation of energy metabolism, including lipolysis from adipocytes and fatty acid oxidation, through the calciotropic hormones, parathyroid hormone, and 1,25-dihydroxyvitamin D. Increased energy expenditure, increased satiety, or a shift from fat to lean mass must accompany these changes in lipid metabolism to achieve changes in fat mass.[2]

Clinical Trials

Studies suggest that high-dairy and high-fiber/low-glycemic index diets may facilitate weight loss, but data are conflicting.[4] One animal and one human study support the hypothesis, other studies refute or simply do not support it.

Animal Studies

One group of researchers fed low-calcium (0.4% Ca) and high-calcium (1.2% Ca from $CaCO_3$) obesity-promoting (high-sucrose/high-fat) diets to aP2-agouti transgenic mice and assessed regulation of reactive oxygen species (ROS) production in adipose tissue and skeletal muscle. They discovered that mice on the high-calcium diet gained 50% as much body weight and fat as mice on the low-calcium diet. The high-calcium diet significantly reduced adipose intracellular ROS production by 64% and 18% and inhibited adipose tissue nicotinamide adenine dinucleotide phosphate oxidase expression by 49% and 63% in visceral and subcutaneous adipose tissue, respectively. Although this study supports a potential role for dietary calcium in the regulation of obesity-induced oxidative stress,[5] it is one of the few studies showing a positive correlation in support of the use of calcium for weight management, and it was done on mice.

Human Studies

One group of researchers performed two randomized trials in obese African-American adults and found positive effects of dairy consumption on adiposity and body composition. In the first (weight maintenance), 34 subjects were maintained on a low-calcium (500 mg/d)/low-dairy (< 1 serving/d) or high-dairy (1,200 mg Ca/d including three servings of dairy) diet with no change in energy or macronutrient intake for 24 weeks. In the second trial (weight loss), 29 subjects were similarly randomized to the low- or high-dairy diets and placed on a caloric restriction regimen (-500 kcal/d). In the first trial, body weight remained stable for both groups throughout the maintenance study. The high-dairy diet resulted in decreases in total body fat, trunk fat, insulin, and blood pressure and an increase in lean mass, whereas there were no significant changes in the low-dairy group. In the second trial, although both diets produced significant weight and fat loss, weight and fat loss on the high-dairy diet were approximately twice as high, and loss of lean body mass was markedly reduced compared with the low-dairy diet. In essence, substitution of calcium-rich foods in isocaloric diets reduced adiposity and improved

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metabolic profiles in obese African Americans without energy restriction or weight loss and augmented weight and fat loss secondary to energy restriction.[6]

Another group of researchers found no association between calcium intake and weight management in Arizona's obesity-prone population of Pima Indians. Sixty-five Pima Indian adults (35 men/30 women, age 33 ± 8 years) participated in a study of eating behavior and 78 Pima Indian children (36 boys/42 girls, age 10.4 ± 0.3 years) participated in a study of childhood obesity. Height and weight were measured, and body composition was determined by dual-energy X-ray absorptiometry. Food intake in adults was assessed using the Block 1998 Food Questionnaire; food intake in children was assessed using a 24-hour recall with parental assistance. The results found that in adults, mean energy intake was 3,163 ± 1,037 kcal/d, mean percentage of energy from fat was 41% ± 7%, and calcium intake was 914 ± 333 mg/d. In children, mean energy intake was 1,988 ± 733 kcal/d, mean percentage of energy from fat was 36% ± 9%, and calcium intake was 637 ± 352 mg/d, half the recommended daily intake for this age group. There were no significant associations between calcium intake and body weight, or body mass index (BMI) in either adults or children, respectively. One explanation for the lack of association between reported calcium intake and body size in Pima Indians may be that the high-fat, high-energy diet consumed by this population overwhelmed the "anti-obesigenic" effect of calcium.[7]

A cross-sectional study examined possible associations of intakes of calcium and dairy products to BMI in young Japanese women and found no relationship. A total of 1,905 female Japanese dietetic students who were 18-20 years of age had their dietary intake assessed over a one-month period with a validated, self-administered diet history questionnaire. BMI was computed using self-reported weight and height. BMI was compared among quartiles of energy-adjusted intakes (per 1,000 kcal) of calcium and dairy products while controlling for intakes of protein, fat, and dietary fiber, self-reported rate of eating, and other nondietary variables. Results showed a mean BMI (± SD) of 20.8 ± 2.6 kg/m^2. Mean estimated intakes were 268 ± 93 mg/1,000 kcal for calcium and 80 ± 63 g/1,000 kcal for dairy products. Intakes of calcium and dairy products were not significantly associated with BMI. These results were also observed after excluding 481 energy under- and over-reporters for calcium and dairy products. Intakes of calcium and dairy products may not necessarily be associated with BMI among young Japanese women who not only are relatively lean but also have a relatively low intake of calcium and dairy products.[8]

The purpose of yet another study was to compare weight and body fat loss on a calorie-restricted, low-dairy (CR) vs. high-dairy (CR+D) diet. Fifty-four subjects were randomly assigned to calorie-restricted (-500 kcal/d) low-dairy calcium (n = 29; approximately 1 serving dairy/d, 500 mg/d calcium) or high-dairy calcium (n = 25; 3-4 servings dairy/d, 1,200-1,400 mg/d calcium) diets for 12 months. Main outcome measures included change in weight and body fat. There were no significant differences between groups at baseline. At 12 months, weight and body fat loss were not significantly different. These findings suggest that a high-dairy calcium diet does not substantially improve weight loss beyond what can be achieved in a behavioral intervention.[9]

Still another study showed no correlation between weight loss and body fat and diets high in dairy, or high in dairy and fiber and low in glycemic index, when compared to a standard diet. Ninety obese subjects were randomized to one of three diets designed to provide a calorie deficit of 500 calories/d over a 48-week period. The study compared a moderate-calcium diet with a high-calcium diet. Significant weight and fat loss occurred with all three diets. A diet with 1,400 mg of calcium did not result in greater weight loss than a diet with 800 mg of calcium. A diet with 1,400 mg of calcium, increased fiber content, and fewer high-glycemic index foods did not result in greater weight loss than the standard diet with 800 mg of calcium. Lipid profile, high-sensitivity C-reactive protein, leptin, fasting glucose, and insulin improved significantly, but there were no significant differences between the experimental diets and the control diet. These researchers found no evidence that diets containing more than 800 mg of calcium from dairy products, or diets high in fiber and low in glycemic index foods, enhance weight reduction beyond what is seen with calorie restriction alone.[4]

In a related study, overweight postmenopausal women proved to be more susceptible to bone loss with weight reduction than previously studied obese women. The influence of energy restriction and calcium intake on bone mineral density was assessed in 66 individuals. Weight reduction resulted in bone loss at several sites in women consuming 1 g Ca/d and was mitigated with higher calcium intake at 1.7 g/d.[10]

Finally, Bowen et al compared the effects of two high-protein diets that differed in dietary calcium and protein source on weight loss, body composition, glucose and lipid metabolism, liver function, fibrinolysis, endothelial function, and blood pressure.[11] This randomized, parallel study (12 weeks of energy restriction, four weeks of energy balance) of high-dairy protein/high-

calcium (2,400 mg Ca/d) and high mixed protein/moderate-calcium (500 mg Ca/d) diets (5.5 MJ/d, 34% protein, 41% carbohydrate, 24% fat) included 50 healthy, overweight (age 25-64 years; BMI 25-35 kg/m^2) males (n = 20) and females (n = 30). Loss of total weight (-9.7 ± 3.8 kg), fat mass (-8.3 ± 0.4 kg), and lean mass (-1.6 ± 0.3 kg) were independent of dietary group. Improvements in fasting insulin, lipids, systolic/diastolic blood pressure, and markers of liver function, fibrinolysis, and endothelial function were independent of dietary intervention. This study, like others, found that increased intake of dietary calcium/dairy foods in an energy-restricted, high-protein diet does not affect weight loss or body composition.

Dosage and Implementation

It has yet to be learned what amount of calcium would be optimal for weight management and what influence, if any, an individual's current calcium intake and existing weight might play. Additionally, it is still difficult to pinpoint which component(s) in dairy foods have a role in weight reduction and whether they act alone or in synergism with calcium.[12]

The Food and Nutrition Board of the Institute of Medicine set the tolerable upper level of intake for calcium in adults at 2,500 mg/d.[13]

Calcium product labels should state the amount of elemental calcium in each tablet, i.e., 500 mg of elemental calcium in each 1,250 mg tablet. The amount of elemental calcium should be used to calculate true daily intake.

Products made from calcium carbonate are often recommended because they contain the highest percentage of elemental calcium per mg of calcium source.[14] Calcium carbonate is best absorbed when taken with a meal or with a source of additional acid such as orange juice. Calcium citrate, on the other hand, usually provides less calcium per caplet than calcium carbonate, but it does not require extra stomach acid and can be taken anytime, even on an empty stomach.

Safety and Cautions

Abnormally elevated blood calcium (hypercalcemia) resulting from the overconsumption of calcium has never been documented to occur from foods, only from calcium supplements. Mild hypercalcemia may occur without symptoms, or may result in loss of appetite, nausea, vomiting, constipation, abdominal pain, dry mouth, thirst, and frequent urination. More severe hypercalcemia may result in confusion, delirium, coma, and if not treated, death. Hypercalcemia has been reported only with the consumption of large quantities of calcium supplements usually in combination with antacids, particularly in the days when peptic ulcers were treated with large quantities of milk, calcium carbonate (antacid), and sodium bicarbonate (absorbable alkali).[15] This condition was termed milk alkali syndrome, and has been reported at calcium supplement levels of 1.5-16.5 g/d for two days to 30 years. Since the treatment for peptic ulcers has changed, the incidence of this syndrome has decreased considerably.[13]

Although the risk of forming kidney stones is increased in individuals with abnormally elevated urinary calcium (hypercalciuria), this condition usually is not related to calcium intake, but rather to increased excretion of calcium by the kidneys. Overall, increased dietary calcium has been associated with a decreased risk of kidney stones. However, in a large prospective study, the risk of developing kidney stones in women taking supplemental calcium was 20% higher than in those who did not.[16] This effect may be related to the fact that calcium supplements can be taken without food, eliminating the beneficial effect of decreasing intestinal oxalate absorption.

Although dairy products have been found to be associated with an elevated risk of prostate cancer, studies investigating the potential effect of calcium are limited, and findings are inconsistent. A recent French study tested the relationship between the risk of prostate cancer and consumption of dairy products and calcium.[17] The analysis included 2,776 men from the French SU.VI.MAX (Supplementation en Vitamines et Minéraux Antioxydants) prospective study, among whom 69 developed prostate cancer during the follow-up period. Food consumption was assessed at inclusion from repeated 24-hour records and nutrient intake was calculated using a food composition table. A higher risk of prostate cancer was observed among subjects with higher dairy product and calcium intake. Interestingly, they identified a harmful effect of yogurt consumption upon the risk of prostate cancer independent of the calcium content. These data support the hypothesis that dairy products have a harmful effect with respect to the risk of prostate cancer, largely related to calcium content. The higher risk of prostate cancer with linear increasing yogurt consumption seems to be independent of calcium and may be related to some other component.

Others find that higher milk intake has been relatively consistently associated with an increased risk of prostate cancer, especially advanced prostate cancer. Some data suggest that high intake of calcium might account for this association, but this relationship remains controversial. A Harvard study examined calcium intake in relation to prostate cancer risk using data from the Health

Table 1

Calcium content in foods

Food	Serving	Calcium (mg)	Servings needed to equal the absorbable calcium in 8 oz of milk
Milk	8 oz	300	1.0
Yogurt	8 oz	300	1.0
Cheddar cheese	8 oz	303	1.0
Cheese food	1.5 oz	241	1.2
Pinto beans	½ C, cooked	45	8.1
Red beans	½ C, cooked	41	9.7
White beans	½ C, cooked	113	3.9
Tofu, calcium set	½ C	258	1.2
Bok choy	½ C, cooked	79	2.3
Kale	½ C, cooked	61	3.2
Chinese cabbage	½ C, cooked	239	1.0
Broccoli	½ C, cooked	35	4.5
Spinach	½ C, cooked	115	16.3
Rhubarb	½ C, cooked	174	9.5

Source: The Linus Pauling Institute. Available at: http://lpi.oregonstate.edu/info-center/minerals/calcium/index.html. Accessed March 28, 2006.

Professionals Follow-up Study, a prospective cohort study of 47,750 male health professionals with no history of cancer other than nonmelanoma skin cancer at baseline.[18] Researchers assessed total, dietary, and supplementary calcium intake in 1986, 1990, 1994, and 1998, using a validated food frequency questionnaire. Higher calcium intake was not appreciably associated with total or non-advanced prostate cancer but was associated with a higher risk of advanced and fatal prostate cancer. Dietary calcium and supplementary calcium were independently associated with an increased risk. For high-grade prostate cancer (Gleason ≥ 7), an association was observed for high vs. low calcium, but a non-significant, inverse association was observed for organ-confined, low-grade prostate cancer. In a sample of this cohort, higher calcium intake was associated with lower circulating vitamin D levels. These findings suggest that calcium intakes exceeding 1,500 mg/d may be associated with a decrease in differentiation in prostate cancer and ultimately with a higher risk of advanced and fatal prostate cancer, but not with well-differentiated, organ-confined cancers.

A team from Tufts conducted a meta-analysis search of Medline for prospective studies published in English-language journals from 1966 through May 2005.[19] They identified 12 publications that used total, advanced, or fatal prostate cancer as endpoints and reported associations as relative risks. Random-effects models were used to pool study results and to assess dose-response relationships between dairy product or calcium intakes and the risk of prostate cancer. Results showed that men with the highest intake of dairy products and calcium were more likely to develop prostate cancer than men with the lowest intake. Dose-response analyses suggested that dairy product and calcium intakes were each positively associated with the risk of prostate cancer, thus supporting the theory that high intake of dairy products and calcium may be associated with an increased risk of prostate cancer, although the increase appears to be small.

All three of these studies support the hypothesis that a high-calcium diet or supplements are not a good idea for men, especially those already diagnosed with prostate cancer.

Food Sources

Average dietary intakes of calcium in the United States are well below the adequate intake recommendation for every age and gender group, especially for females. Only about 25% of boys and 10% of girls ages 9-17 meet the adequate intake recommendations. Dairy foods provide 75% of the calcium in the American diet. However, it is typically during the most critical period for peak bone mass development that adolescents tend to replace milk with soft drinks.[13,15]

Dairy products represent rich and absorbable sources of calcium, but certain vegetables and grains also provide calcium. However, the bioavailability of that calcium must be taken into consideration.[20] Table 1 lists a number of calcium-rich foods, along with their calcium content and the number of servings of that food required to equal the absorbable calcium from one glass of milk.

Skim milk products provide as much calcium as whole milk with the added advantage of less fat and cholesterol. Some calcium-fortified soy beverages and orange juices may contain as much calcium as milk. Vegetables also provide calcium, as do fish products containing bones (canned salmon and sardines) and meat alternatives such as lentils and beans. However, some foods, such as those with excessive amounts of salt and caffeine, may cause calcium loss via excretion through the urine.

Although the calcium-rich plants in the kale family (broccoli, bok choy, cabbage, mustard, and turnip

greens) contain calcium that is as bioavailable as that in milk, some food components have been found to inhibit the absorption of calcium. Oxalic acid, also known as oxalate, is the most potent inhibitor of calcium absorption, and is found in high concentrations in spinach and rhubarb and somewhat lower concentrations in sweet potato and dried beans. Phytic acid is a less potent inhibitor of calcium absorption than oxalate. Yeast possesses an enzyme (phytase) that breaks down phytic acid in grains during fermentation, lowering the phytic acid content of breads and other fermented foods. Only concentrated sources of phytate such as wheat bran or dried beans substantially reduce calcium absorption.[15]

Table 2

Recommended daily calcium requirement

Age (years)	Daily Calcium Requirement (mg)
4-8	800
9-18	1,300
19-50	1,000
50+	1,500
Pregnant or lactating women	1,000

Source: Osteoporosis Canada. Available at: www.osteoporosis.ca/english/home/default.asp?s=1. Accessed April 11, 2006.

Conclusion

Although the essentiality of calcium to bone health appears well established, the role of calcium and dairy product intake in obesity and weight management remains uncertain.[7] In the studies cited above, however, there seems to be a preponderance of evidence that negates the relationship between calcium intake and weight loss. If dairy products or their components have an effect on altering fat mass, it is likely to be a small change that may have a substantial effect on the incidence of obesity over time.[2] Based on much of the presently reported data, calcium, and even more so dairy foods, might help in weight reduction/maintenance when combined with energy-restricted diet. The scientific community is in agreement that there is a pressing need for large clinical trials to assess the effect of calcium on weight reduction and to investigate whether weight loss could be achieved more easily with calcium supplements or dairy products.

Recommendation

Considering the prevalence of overweight/obesity, its effects on public health, and the economic burden it entails, it is of crucial importance to develop effective weight loss and weight management strategies.

More research in this area is clearly necessary before specific recommendations can be made. However, given the calcium intake levels in the typical American diet and the need for calcium for bone health, a simple strategy to increase intake of low-fat dietary sources of calcium seems reasonable not only for those striving to reduce their weight, but for all patients.[12] Again, men, especially those already diagnosed with prostate cancer, need to consult their health care provider before adding additional calcium to their diets; intakes above 600 mg/d may not be a good idea. Table 2 lists the recommended calcium intakes advocated by Osteoporosis Canada.

The bottom line is that most women should consume about 1,000 mg/d of calcium, while those older than age 50 should strive for 1,500 mg/d. These are basic requirements and lower intake levels (< 600 mg/d) are advisable for men because of prostate cancer concerns. At this time no recommended requirements have been established for those using calcium for weight management. The state of the science for this concept is still too controversial and requires clarification. ❖

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Vitamin D Supplementation to Prevent Colorectal Cancer

By David Kiefer, MD

Dr. Kiefer recently completed a fellowship at the Program in Integrative Medicine, College of Medicine, University of Arizona in Tucson; he reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

EVIDENCE HAS ACCUMULATED ABOUT THE POSSIBLE involvement of vitamin D in the prevention of various types of cancer. From the 1930s and 1940s, with the observation that lower cancer rates may occur with sunlight exposure and in lower latitudes, researchers have demonstrated connections between vitamin D status and ultraviolet-B (UVB) exposure and breast, colon, and ovarian cancer risk.[1] This article will explore details about the use of supplemental vitamin D specifically for the prevention of colorectal cancer.

Physiology

As detailed in a prior article for this publication,[2] the body is able to make its own vitamin D, produced when ultraviolet light (specifically UVB) contacts the skin and converts 7-dehydroxycholesterol to cholecalciferol, also called vitamin D_3.[3-5] Vitamin D_3 is then hydroxylated in the liver to make 25-hydroxyvitamin D (calcitriol, or 25(OH)D), which predominates in the human body;[5] 25(OH)D is the compound most commonly used to check a person's overall vitamin D status.[4] The more potent but less prevalent (0.1% concentration of 25(OH)D) form of vitamin D, 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D), is created through further hydroxylation, primarily in the mitochondria of the renal tubules in the kidney.

Approximately 3,000-5,000 IU of cholecalciferol is necessary for normal daily metabolism;[6,7] a combination of oral intake, sun exposure, and release from tissue stores accounts for this amount. The contribution from diet is usually minimal; for example, in mid-latitudes, 90-95% of circulating 25(OH)D results from UVB exposure.[8] Circulating 25(OH)D levels are an accepted way to measure vitamin D status, and is either reported as nmol/L or ng/mL. Severe vitamin D deficiency and a risk for rickets occurs at levels lower than 8-10 ng/mL (20-25 nmol/L), whereas 10-16 ng/mL (25-40 nmol/L) is common in the winter among populations in northern latitudes and is still associated with physiological alterations that could affect bone health.[6] Serum 25(OH)D levels below 30 ng/mL (75 nmol/L) are associated with increased cancer risk,[9] whereas toxicities occur with levels of 400-1,250 nmol/L (160 to 500 ng/mL).[10]

Basic science research has discovered many possible mechanisms through which the different forms of vitamin D may have anticancer effects *(see Table 1)*.[9,11] Most anticancer effects have been attributed to 1,25-$(OH)_2$D, the more active form, but some conversion from 25(OH)D may take place in tissues other than the kidney (such as the colon), so 25(OH)D itself may also possess anticancer effects.[11]

Research has begun to demonstrate that some of the anticancer effects of vitamin D may be mediated

Table 1

Possible anticancer mechanisms for vitamin D and its metabolites[9,11]

- Inhibition of tumor angiogenesis
- Improving contact inhibition by increasing cell adherence
- Improving contact inhibition by increasing gap junction communication
- Inhibition of mitosis
- Induction of apoptosis and terminal differentiation by enhancing the intracellular release of ionized calcium
- Regulation of cell proliferation in human colon cell lines
- Regulation of cell differentiation in human colon cell lines

Table 2

Number of trials showing benefit or no association for several different types of cancer[9]

Cancer Type	Number of Trials Showing Clear Benefit	Number of Trials Showing No Association
Colon cancer (CC) or adenomatous polyps (AP)	25 (CC = 5, AP = 20)	5
Breast cancer	9	3
Prostate cancer	13	11
Ovarian cancer	5	2

through vitamin D receptors, present in many cell types.[1] When these receptors are bound to 1,25-$(OH)_2D$, the cells are signaled to differentiate and stop proliferating, and are less likely to metastasize or develop new blood vessels. Furthermore, certain neoplastic mouse models show increased tumor formation with high fat, low calcium, and low vitamin D intake within what is normal for Western diets.[12] It may be possible to reverse these trends by supplementing the Western diet with calcium and vitamin D, in some cases showing a return to normal gene expression whether or not the fat content of the diet was changed.

Vitamin D has many other physiological effects, such as facilitating active calcium absorption from the lumen of the intestine, important in maintaining bone density and preventing fractures, and prevention of other conditions such as diabetes and autoimmune diseases.[2-4,8]

Epidemiology

Vitamin D deficiency is thought by many experts to be an epidemic in the United States.[4] One demographic particularly at risk is the elderly; vitamin D deficiency occurs in the elderly because of decreased sunlight exposure, suboptimal nutrition, and skin that is less efficient in producing vitamin D.[13] However, the problem may be more extensive. Data from the Women's Health Initiative (WHI) was used to examine calcium and vitamin D intake from dietary and supplement sources in 223 colorectal cancer cases among 36,976 women.[14] A 131-item food questionnaire was used and estimates were conducted for vitamin D intake from multivitamins; it was unclear if extra vitamin D supplements were accounted for in the analysis. The cohort median intakes were 882 mg daily of calcium and 271 IU daily of vitamin D; of this, 705 mg and 205 IU came from food, respectively. Sunlight exposure was not accounted for in this analysis, but it does tell us that, overall, the intake of vitamin D in this demographic is below what is being recommended for overall health and cancer prevention as discussed below.

Researchers have demonstrated that vitamin D supplementation can improve serum vitamin D. For example, in one study of 553 community-dwelling women aged 65 and older, the women were given 400 IU vitamin D as part of a multivitamin and 1-2 tablets of calcium carbonate (600 mg) plus 200 IU vitamin D, for a total of 400-800 IU vitamin D daily for three months.[15] This was not a placebo-controlled trial, but the supplementation regimen decreased the rate of vitamin D deficiency as measured by serum 25(OH)D.

In another study, 139 men and women aged 40-83 years filled out a food questionnaire, and vitamin D intake was estimated (average per day) while serum 25(OH)D was checked.[16] Of this group, 27 took supplements with vitamin D, which when combined with diet, yielded an average daily vitamin D intake of 374 IU for men and 354 IU for women. There was a slight and significant correlation (coefficient 0.34) between vitamin D intake and serum 25(OH)D, slightly higher for users of supplements during seasons of low light.

It appears that dietary intake influences serum vitamin D more when there is low sunlight exposure. A study in 67 men having only one glass of milk a day and no supplements in Omaha, NE, during the winter were checked for 25(OH)D and given different doses of vitamin D (either no cholecalciferol, 1,000 IU, 5,000 IU, or 10,000 IU daily), leading to a direct correlation between the dose and serum vitamin D levels.[7] The researchers also found that, at a minimum, 500 IU daily was necessary to keep this serum 25(OH)D constant.

Cancer Effects

A comprehensive review of the epidemiological evidence assessed the effect of serum vitamin D markers, serum vitamin D metabolites, or sunlight on the risk or mortality of several different cancers,[9] including both colon cancer and adenomatous polyps *(see Table 2)*. There are several significant associations between vitamin D and colon cancer: Colon cancer mortality rates are higher with lower sunlight, there is increased risk of colon cancer or polyps for people with serum 25(OH)D less than 30 ng/mL (75 nmol/L), and risk of colon cancer is higher in people who consume lower amounts of vitamin D.

Using data from 18 observational studies (four examining serum 25(OH)D and 14 oral vitamin D), one

statistical analysis calculated that an intake of 1,000 IU of vitamin D daily or a serum concentration of 25(OH)D of at least 33 ng/mL (82 nmol/L) would lead to a 50% decrease in the risk of colon cancer.[8] The level of supplementation suggested by this study is higher than most previous recommendations.

Clinical Trials

Many of the clinical trials on the effects of vitamin D supplementation are complicated by the co-administration of calcium. The physiological activities of calcium and vitamin D are closely tied, not only for bone health but also for cancer prevention, so the methodology is sound even as it makes it difficult to sort out the isolated effect of vitamin D.

One randomized, double-blind trial in 36,282 postmenopausal women compared the incidence of colorectal cancer over seven years between two groups receiving either 400 IU daily of vitamin D_3 plus 1,000 mg elemental calcium (as calcium carbonate) daily or placebo.[17] This trial was a continuation of the WHI, the first part of which was to examine the risks and benefits of hormone therapy and dietary changes in menopause. For those who agreed to this part of the WHI, blood initially was drawn to be used in a nested case-control study to examine the odds ratio of cancer risk related to baseline 25(OH)D, and patients received colon cancer screening as their personal physician recommended. An intention-to-treat analysis of the 322 invasive colorectal carcinomas in the study group revealed that the calcium and vitamin D group had the same cancer risk as the placebo group. Furthermore, for these cancer cases, the baseline 25(OH)D did not correlate with any increase or decrease in risk, though a statistically significant trend ($P = 0.02$) did display that lower baseline 25(OH)D was inversely correlated with colorectal cancer risk. Some of the problems with this study include the fact that neither study duration (seven years) nor the vitamin D dose employed may be enough to demonstrate an effect. Also, the demographic studied was generally already healthy and took supplemental calcium and vitamin D in amounts (1,151 mg and 367 IU, respectively) about twice what is average for the U.S. population; this compromises the generalizability of these results.[18]

Another nested case-control study in the Nurses Health Study examined the plasma 25(OH)D levels in 193 colorectal cancer cases.[11] A statistically-significant inverse relationship was observed between cancer risk and serum 25(OH)D level for women older than 60 years; the odds ratio was 0.53 for the women in the group with the highest range of 25(OH)D. The decreased incidence of cancer held for the distal colon and rectum but not for the proximal colon.

Another trial combining calcium and vitamin D randomized 19 patients with adenomatous polyps in the colon or rectum to either partial resection plus placebo or partial resection and supplementation with 1,500 mg three times daily calcium carbonate plus 400 IU vitamin D_3 daily for six months.[19] Various pathological techniques and immunohistochemical stainings were used to estimated the presence of vitamin D receptors, the proliferation and apoptosis of the remaining cells, and the expression of certain oncogenic proteins. The treatment group showed a significant reduction in the number of cells that initially remained behind after the partial resection; there was also a decrease in the proliferation of those cells, though the amount of apoptosis did not change. This is an interesting preliminary study, though it is small and difficult to estimate whether the effect observed was due to calcium, vitamin D, or both.

Dosing and Sources of Vitamin D

The Daily Reference Intakes (DRI) for vitamin D are 200 IU for infants, children, adults through age 50 and pregnant and lactating women; adults age 50-69 years have a DRI of 400 IU, and adults age 70 and older, 600 IU.[20] As alluded to in some of the research reviewed above, the dose of vitamin D necessary to achieve optimal cancer prevention will depend on a person's vitamin D status, diet, geographic location, and sunlight exposure, but anticancer daily intakes probably should be closer to 1,000 IU.

Sunlight exposure generally provides 90-95% of a person's vitamin D needs, and, even though the conversion reaction in the skin upon exposure to UVB radiation is less efficient as a person ages, it is usually sufficient.[4] During the spring, summer, and fall, 5-15 minutes daily of sun exposure during the middle of the day on the arms and legs, or arms, hands, and face is usually sufficient to provide adequate vitamin D, after which people should use sunscreen, cover up, and/or move into the shade or indoors.[4] In the frail elderly, it is also possible to normalize vitamin D status by facilitating time outdoors, with 15-30 minutes daily being adequate in a temperate climate.[5,21]

Most supplements contain either vitamin D2, made by exposing ergosterol from yeast to UVB radiation, or vitamin D_3, both of which are used by the body to make 25(OH)D.[4] There is some evidence that vitamin D_3 in the same doses increases serum 25(OH)D more than vitamin D_2.[22,23] One study randomized 72 people to take either 4,000 IU per day of vitamin D_2 or vitamin D_3 for 14 days during the winter.[24] The serum 25(OH)D was checked at baseline and post-treatment; the vitamin D_3

group displayed a 1.7 times higher rise in serum 25(OH)D (P = 0.03), which translated into an extra 7 nmol/L rise in the serum value. Those individuals with lower baseline 25(OH)D showed a better response to supplemental vitamin D.

In addition to vitamin D-fortified foods such as milk and bread, a few foods naturally contain vitamin D, at a dose of approximately 400-500 IU per serving; these include oily fish (salmon, mackerel, herring) and sun-dried mushrooms.[4]

Adverse Effects

Vitamin D supplementation as described in the above trials is well tolerated, with adverse effect reports similar to those from the placebo groups in most cases. Some sources state that high doses of vitamin D (50 mcg, or 2,000 IU, in both children and adults) can lead to calcinosis and hypercalciuria; therefore, in people with these pre-existing conditions or other conditions where elevated calcium would be a problem, vitamin D supplementation should be avoided.[6,25] Other experts have published that the safe upper limit of 2,000 IU daily is overly conservative and that true adverse effects only surface at much higher doses, such as when 10,000-50,000 IU are consumed on a daily basis for long periods of time.[10] Also, some caution is advised with excessive vitamin D supplementation in people taking thiazide diuretics, as thiazides can decrease the urinary excretion of calcium.

Conclusion

There is convincing basic science for the anticancer effects of vitamin D, corroborating what has been observed for colon cancer risk and mortality with sunlight exposure, geographic location, vitamin D intake, and serum 25(OH)D levels. Serum 25(OH)D levels can be checked and levels below 30 ng/mL (75 nmol/L) are associated with increased cancer risk. Vitamin D_3 seems to be the optimal form of supplemental vitamin D, and cancer protective doses depend on the individual, but some studies point to a vitamin D DRI level of 200-600 IU, though the optimal amount is more likely closer to 1,000 IU daily. A cancer prevention strategy utilizing vitamin D is most effective when combined with adequate intakes of calcium, except for men at risk of prostate cancer due to a possible increased risk with calcium intakes above 600 mg/d.[26] Vitamin D is very well tolerated in doses lower than 2,000 IU daily, except for some individuals with pre-existing conditions involving abnormal calcium metabolism.

Recommendation

Given that vitamin D deficiency is a common problem, especially as people age, health care practitioners should consider checking serum hydroxyvitamin D; optimal levels to help prevent colorectal and other cancers should be above 30 ng/mL. There is good evidence that supplementation with cholecalciferol (vitamin D_3) decreases colorectal cancer risk and mortality. Vitamin D_3 is the preferred form, and the dose should be at least in line with the DRIs; some evidence is accumulating that higher doses, more along the lines of 1,000 IU daily are optimal, but this certainly depends on a person's vitamin D status and sunlight exposure.

The positive effects of vitamin D supplementation appear to occur with simultaneous calcium supplementation, so patients should be counseled about appropriate doses of dietary and supplemental calcium. Regarding calcium supplementation, caution is advised for men at risk of prostate cancer; moderate calcium intakes (less than 600 mg daily from supplements and food) is recommended until this issue is further clarified in the medical literature. Given the evidence accumulating for cancer risk associated with vitamin D deficiency, all people should ensure adequate vitamin D intake, whether from supplementation, enriched or high-vitamin D foods, or prudent sunlight exposure. ❖

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Clinical Briefs

With Comments from Russell H. Greenfield, MD

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Hungry, but Alive—Calorie Restriction

Source: Heilbronn LK, et al. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: A randomized controlled trial. *JAMA* 2006;295: 1539-1548.

Goal: To determine the effects of prolonged significant calorie restriction, with or without exercise, in overweight subjects over six months.

Design: Randomized controlled trial.

Subjects: Sedentary men (< 50 years) and women (< 45 years) with a body mass index (BMI) between 25 and 30 kg/m^2 (n = 48).

Methods: Subjects had total energy expenditure assessed at baseline and were then randomized into one of four groups: weight maintenance group (control), 25% calorie restriction (CR), 12.5% calorie restriction plus structured exercise (CRE), and very low-calorie diet (890 kcal/d) until 15% reduction in weight followed by a weight maintenance diet. Food was provided to all participants in accordance with specified menus assigned to each group. Subjects made mid-week calls to report energy intake and attended weekly group meetings. Weight was determined weekly following a 12-hour fast, and metabolic tests were performed at baseline, three and six months.

Results: In all three intervention groups fasting insulin levels dropped significantly at six months, as did energy expenditure compared with baseline. Subjects in the CR and CRE groups showed reduced core body temperature at trial's end, but no significant changes occurred in dehydroepiandrosterone sulfate (DHEAS) or fasting glucose levels in any group. Plasma T3 levels were decreased in all three intervention groups at trial's end. DNA damage was reduced from baseline in the intervention groups, but not in aggregate when compared to the control group. No association was found between DNA damage and changes in body weight, fat mass, or energy expenditure.

Conclusion: Prolonged calorie restriction in overweight humans results in: 1) a reversal in two of three previously reported biomarkers of longevity (fasting insulin level and core body temperature, but not DHEAS levels), 2) a larger than expected decrease in energy expenditure (metabolic adaptation) associated with lower thyroid hormone levels, and 3) a reduction in DNA damage.

Study strengths: Compliance and participant retention rates; methods employed for determining energy requirements.

Study weakness: Small sample size.

Of note: Theories regarding the anti-aging benefits of calorie restriction abound, and include decreased energy expenditure with consequent reduction

in generation of reactive oxygen species (ROS), modulation of insulin sensitivity, decreased inflammation, and neuroendocrine effects; the oxidative stress theory of aging posits that long-term accumulation of ROS results in disease development, including cancer; subjects received significant monetary compensation for participation in the trial; group allocation was balanced for sex and two categories of BMI (25-27.9 and 28-30 kg/m^2) at screening; save for the very low-calorie diet, all diets were based on American Heart Association recommendations; cognitive behavioral techniques were employed to promote adherence to diet and exercise regimens; subjects in all four groups lost weight (range 1.0-13.9%); no significant changes occurred in any group with respect to spontaneous physical activity; 24-hour energy expenditure data were also compared to data from 865 subjects with comparable baseline characteristics previously studied in a similar metabolic chamber (energy expenditure was again found to be lower in the intervention groups at three and six months); the authors believe no changes in DHEAS levels were found due to insufficient study duration; the results suggest that energy deficit rather than calorie restriction results in decreased energy expenditure; the metabolic adaptation occurred within the first three months of the study.

We knew that: Chronic calorie restriction has been shown to increase lifespan in animal studies; total energy expenditure is comprised of resting energy expenditure, nonresting energy expenditure, and the thermic effect of eating; some data suggest calorie restriction lessens energy expenditure beyond what would be expected metabolically, but the evidence is conflicting; ROS are byproducts of energy metabolism; the Baltimore Longitudinal Study of Aging showed that men with lower plasma insulin levels and oral temperatures, as well as higher DHEAS levels, live longer; fasting glucose level is not consistently altered through calorie restriction; the thermic effect of food accounts for but 10% of daily energy expenditure; recent data suggest that calorie restriction may slow age-related changes in diastolic cardiac function (Meyer, et al. Long-term caloric restriction ameliorates the decline in diastolic function in humans. *J Am Coll Cardiol* 2006;47:398-402.).

Clinical import: The results of this study, phase 1 of the Comprehensive Assessment of the Long Term Effects of Reducing Intake of Energy (CALERIE) trial, are certainly compelling, but the authors are quick to point out that trials of longer duration must be performed to determine whether the impacts of calorie restriction are sustained and positively impact the human aging process. The current environment underscores the importance of such data. As noted in an accompanying editorial and presented in another article in the same edition of *JAMA*, more than 65% of adults are overweight or obese, and 17% of children in the United States are overweight. Some of these same children are developing adult-type diseases at an alarming rate. In addition, consumers can consult with a plethora of "anti-aging" doctors (the alternative to aging does not appeal to this writer…) purveying all manner of therapeutic intervention. Certainly the focus needs to be on healthy aging to promote, as others have coined, long healthspan as well as lifespan. Some of our patients may be drawn to the idea of significant calorie restriction after learning of this trial. As health care providers we should advise that the data are preliminary, while promoting an open discussion regarding healthy dietary and lifestyle choices.

What to do with this article: Keep a hard copy in your file cabinet. ❖

CME Questions

CME Instructions: Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a certificate of completion. When an evaluation form is received, a certificate will be mailed to the participant.

15. The preponderance of evidence:

a. supports a relationship between calcium intake and weight loss.
b. supports a relationship between calcium intake and weight loss, but only for dietary calcium intake.
c. negates a relationship between calcium intake and weight loss.
d. neither supports nor negates a relationship between calcium intake and weight loss.

16. Unless advised differently by a physician, most women should strive to consume 1,000 mg/d of calcium until age 50, then increase to 1,500 mg/d.

a. True
b. False

17. Optimal levels of serum hydroxyvitamin D for preventing cancer should be:

a. 15-20 ng/mL
b. 20-25 ng/mL.
c. 25-30 ng/mL.
d. above 30 ng/mL.

Answers: 15. c, 16. a, 17. d.

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ALTERNATIVE MEDICINE ALERT™

A Clinician's Evidence-Based Guide to Alternative Therapies

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Growing Stronger—Strength Training for Older Adults

RESEARCH HAS SHOWN THAT STRENGTHENING EXERCISES ARE BOTH SAFE AND EFFECTIVE FOR women and men of all ages, including those who are not in perfect health. In fact, people with health concerns—including heart disease or arthritis—often benefit the most from an exercise program that includes lifting weights a few times each week.

Strength training, particularly in conjunction with regular aerobic exercise, can also have a profound impact on mental and emotional health.

Benefits of Strength Training

There are numerous benefits to strength training regularly, particularly as you grow older. It can be very powerful in reducing the signs and symptoms of numerous diseases and chronic conditions.

Arthritis relief. Tufts University recently completed a strength-training program with older men and women with moderate-to-severe knee osteoarthritis. The results of this 16-week program showed that strength training decreased pain by 43%, increased muscle strength and general physical performance, improved the clinical signs and symptoms of the disease, and decreased disability. The effectiveness of strength training to ease the pain of osteoarthritis was just as potent, if not more potent, as medications. Similar effects of strength training have been seen in patients with rheumatoid arthritis.

Restoration of balance and reduction of falls. As people age, poor balance and flexibility contribute to falls and broken bones. These fractures can result in significant disability and, in some cases, fatal complications. Strengthening exercises, when done properly and through the full range of motion, increase a person's flexibility and balance, which decrease the likelihood and severity of falls. One study in New Zealand in women 80 years of age and older showed a 40% reduction in falls with simple strength and balance training.

Strengthening of bone. Postmenopausal women can lose 1-2% of their bone mass annually. Results from a study conducted at Tufts University, which were published in the *Journal of the American Medical Association* in 1994, showed that strength training increases bone density and reduces the risk for fractures among women aged 50-70.

Proper weight maintenance. Strength training is crucial to weight control, because individuals who have more muscle mass have a higher metabolic rate. Muscle is active tissue that consumes calories while stored fat uses very little energy. Strength training can provide up to a 15% increase in metabolic rate, which is enormously helpful for weight loss and long-term weight control.

Improved glucose control. More than 14 million Americans have Type 2 diabetes—a staggering 300% increase over the past 40 years—and the numbers are steadily climbing. In addition to being at greater risk for heart and renal disease, diabetes is also the leading cause of blindness in older adults. Fortunately, studies now show that lifestyle changes such as strength training have a profound impact on helping older adults manage their diabetes. In a recent study of Hispanic men and women, 16 weeks of strength training produced dramatic

improvements in glucose control that are comparable to taking diabetes medication. Additionally, the study volunteers were stronger, gained muscle, lost body fat, had less depression, and felt much more self-confident.

Healthy state of mind. Strength training provides similar improvements in depression as antidepressant medications. Currently, it is not known if this is because people feel better when they are stronger or if strength training produces a helpful biochemical change in the brain. It is most likely a combination of the two. When older adults participate in strength-training programs, self-confidence and self-esteem improve, which has a strong impact on overall quality of life.

Sleep improvement. People who exercise regularly enjoy improved sleep quality. They fall asleep more quickly, sleep more deeply, awaken less often, and sleep longer. As with depression, the sleep benefits obtained as a result of strength training are comparable to treatment with medication but without the side effects or the expense.

Healthy heart tissue. Strength training is important for cardiac health because heart disease risk is lower when the body is leaner. One study found that cardiac patients gained not only strength and flexibility but also aerobic capacity when they did strength training three times a week as part of their rehabilitation program. This and other studies have prompted the American Heart Association to recommend strength training as a way to reduce risk of heart disease and as a therapy for patients in cardiac rehabilitation programs.

Make Strength Training a Part of an Overall Activity Program

Although strength training can be valuable by itself, you can gain even more benefit from an overall physical activity program that includes endurance aerobic activities, stretching activities, and balancing exercises.

Making Sure You're Ready

Being more active is safe for most people regardless of age. Strength training can be very beneficial; however, people with a chronic medical condition should check with a doctor before they significantly increase their level of physical activity.

Getting Started

The following suggestions can help you get started with strength training:

- Community recreation centers, churches, and schools may offer physical activity classes that include strength training.
- Strength-training exercises can be modified to accommodate health problems, for example, by varying whether the exercise is done standing, seated, or lying down.
- Join a health club or work with a personal trainer for instructions on how to use strength-training equipment.
- Try other everyday activities that can help you become stronger. For example, many typical household, gardening, and manual labor activities (such as lifting, carrying, digging, raking, splitting wood, and sawing) strengthen muscles. Although these activities alone do not offer the comprehensive benefits of a strength-training program, they can help you strengthen some muscles.
- Check with your local bookstore or library for a book or video to begin a strength-training program at home.

Maintaining Interest

Strength training provides the most benefits when you adopt it as a regular activity in your daily life. Consider the following tips for maintaining your interest:

- Vary your strength training routine. After engaging in strength training for a few weeks, try alternating muscle groups or adding additional activity components.
- Exercise with friends or family to provide encouragement to each other. For example, go to the gym together or sign up for a community tai chi class.
- Keep a journal of your strength-training activities to track your progress. A record of your activities can help you recognize improvements.

If a new challenge helps maintain your interest, try one of the following tips:

- Gradually increase the difficulty of your training. If one exercise begins to seem too easy, try others that can help you increase your strength.
- Increase the number of sets you do for various exercises. (A "set" is the number of times you repeat an exercise. The recommended number of sets varies with the exercise.) As you become comfortable with a certain exercise, try performing additional sets to add variety to your strength training program.

Source: Centers for Disease Control and Prevention. Available at: www.cdc.gov/nccdphp/dnpa/physical/growing_stronger/spotlight.htm. Accessed April 18, 2006.

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