Current AWARENESS

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DAIRY CALCIUM IS ASSOCIATED WITH REDUCED INCIDENCE OF STROKE AMONG MIDDLE-AGED JAPANESE

This prospective study examined the association between calcium intake and incidence of stroke or coronary heart disease (CHD) among Japanese with a low average calcium intake. More than 41,000 Japanese men and women (40-59 years) without a history of cardiovascular disease or cancer were followed from 1990 to 2003 and incidence of stroke and CHD were documented. The researchers assessed dietary intake with a food frequency questionnaire administered at the beginning of the study and after 5 years of follow-up (1995). Results showed that the highest vs. lowest intake of total calcium was associated with a significant 30% lower risk of total stroke. Intake of calcium from dairy foods was associated with a significant 31% lower risk of both total and ischemic stroke. Dietary calcium intake was not significantly associated with the risk of CHD. The authors mention that several other prospective studies have examined the association between calcium intake and incidence of or mortality from stroke or cardiovascular disease – and the totality of these results "suggest that calcium intake, especially calcium intake from dairy products, has a protective effect against ischemic stroke." The researchers say that previous studies suggest that calcium may reduce risk of stroke and ischemic stroke by reducing blood pressure, platelet aggregation, and cholesterol levels. The authors conclude, "Dietary calcium intake, especially calcium from dairy products, was found to be associated with a reduced incidence of stroke among middle-aged Japanese." [Umesawa M, et al., *Stroke*, 39(9): 2449-2456, 2008]

MILK-DERIVED TRIPEPTIDES HAVE BLOOD PRESSURE LOWERING EFFECTS

High blood pressure is a known risk factor for cardiovascular diseases, including coronary heart disease, peripheral arterial disease, and stroke. "Recently peptides from milk protein have attracted the attention of researchers and the public because of their hypotensive ability", say the authors of this meta-analysis. "Biologically active peptides are produced when milk proteins are broken down by digestive enzymes," they explain. The casein-derived tripeptides that are the most studied are IPP (isoleucine-proline-proline) and VPP (valine-proline-proline).

Chinese researchers identified 9 randomized controlled trials (provide strong causal evidence) that investigated the effect of IPP and VPP on blood pressure and conducted a meta-analysis of the results. Since some of the trials contained multiple parts, the meta-analysis included 12 individual trials. Seven of the trials were conducted in Japan and 5 were conducted in Finland. When results from all 12 trials were pooled, "milk tripeptides IPP and VPP significantly decreased systolic blood pressure by 4.8 mmHg and diastolic blood pressure by 2.2 mmHg",

report the authors. The effect was seen in prehypertensive and hypertensive subjects, though systolic blood pressure lowering was greater in those with existing hypertension. The amount of IPP and VPP used in these trials ranged from 2.6-5.6 mg per day, but the researchers were unable to provide a dose recommendation to reduce blood pressure based on the meta-analysis.

All of the studies in the meta-analysis attributed the blood pressure lowering effects of IPP and VPP to ACE (angiotensin-converting enzyme) inhibition. The authors explain that "ACE catalyzes the conversion of angiotensin I to angiotensin II, which is a strong vasoconstrictor that induces the release of aldosterone and therefore increases the sodium concentration and increases blood pressure. ACE inhibitors not only decrease the production of angiotensin II but also inhibit the degradation of bradykinin, a potent vasodilator." There are other milk-derived peptides that have also shown blood pressure lowering ability. The authors call for more randomized controlled trials testing the blood pressure lowering effectiveness of milk peptides other than IPP and VPP. They say, "Increasing consumption of dairy products containing hypotensive components also avoids undesirable side effects from antihypertensive drugs and saves on the cost of drug therapy." [Xu J-Y, et al., *Nutrition*, 24: 933-940, 2008]

CALCIUM AND VITAMIN D HAVE A KEY ROLE IN PREVENTION OF COLORECTAL CANCER

Researchers at the Strang Cancer Research Laboratory at Cornell University in New York previously demonstrated that a Western style diet with low levels of calcium and vitamin D and high in omega-6 polyunsaturated fatty acids increased the incidence of colon tumors compared to a standard diet in mice. The present study compared the effects of feeding a standard mouse ration, a Western style diet (WD), and a Western style diet supplemented with calcium and vitamin D (WD/Ca/VitD3) on cellular and molecular changes in the colons of mice with a mutation making them a model for human colon cancer. The diets were fed for 24 weeks, then the researchers measured the effects of the diets on cyclin D expression (a cell cycle regulating protein), apoptosis (programmed cell death), and colon tumor development. Results showed that the WD diet, when compared with standard mouse ration, enhanced cyclin D expression, and decreased the ability of colon cells to undergo apoptosis. WD treatment also resulted in the formation of colon polyps and a cancerous tumor. In contrast, the WD/Ca/VitD3 diet blunted the growth promoting cellular and molecular changes in the cells lining the colon induced by the WD diet. In addition, this special strain of mice prone to developing intestinal tumors fed the WD/Ca/VitD3 diet did not develop colon polyps or cancerous tumors. The authors say these results "further strengthen the view that these micronutrients (calcium and vitamin D) play an important role in chemoprevention of intestinal cancers." [Yang K, et al., *J Nutr*, 138: 1658-1663, 2008]

REVIEW OF DAIRY PRODUCTS AND RISK OF COLORECTAL CANCER

The author, recognizing that "prospective cohort studies suggest that higher intakes of dairy products, in particular milk, are associated with a decreased risk of colorectal cancer," reviewed the current epidemiological evidence investigating the relationship between dairy product consumption and risk of colorectal cancer. Data pooled from prospective studies "suggests a significant protective effect of calcium on colorectal cancer risk," states the author. Results from randomized controlled trials looking at the effect of calcium supplements on the development of colon polyps (adenomas) or colorectal cancer suggest that a calcium intake of 1,000-2,000 mg/day reduces adenoma recurrence in individuals with a previous adenoma, but has no effect

on the incidence of colorectal cancer. This evidence for calcium suggests that the protective effect of milk is due in part to its calcium content. However, other milk-associated factors may also confer protection. For example, animal studies have shown that dietary calcium and vitamin D act synergistically to modify colorectal cancer risk. Other components of dairy products under investigation for the prevention of colorectal cancer are conjugated linoleic acid, probiotic bacteria in fermented dairy foods, sphingolipids, and dairy proteins – though most of the evidence of benefit comes from animal studies and replication in human subjects is needed. [Pufulete M, *Nutr Res Rev*, 21: 56-67, 2008] [Editor's note: This review, supported by the UK Dairy Council, was published in June. Since it has just come to our attention, I have included it in this issue.]

CALCIUM, VITAMIN D AND TESTOSTERONE LEVELS HELP REDUCE THE RISK OF FALLING IN OLDER MEN AND WOMEN

Falling is a primary risk factor for hip fracture among older individuals. This study selected 445 men and women over age 65 from those enrolled in the Boston Stop-It trial, a 3 year double-blind randomized controlled trial on the effect of vitamin D3 (700 IU/day) plus calcium (500 mg/day) on bone mineral density and fractures, to investigate sex hormone levels and fall risk. The participants were followed for 3 years after baseline assessment of sex hormones. Results showed that men and women in the highest quartile of testosterone (for their gender) had a decreased risk of falling. Fall reduction was further enhanced in those who took calcium and vitamin D supplements (intervention arm of the study). Specifically, "Higher testosterone levels in both genders and higher DHEA-S (dihydroepiandosterone sulfate) levels in women predicted a more than 60% lower risk of falling. With vitamin D + calcium, the anti-fall benefits of higher physiologic testosterone levels is enhanced from 78% to 84% among men and from 66% to 85% among women." The authors say, "Fall prevention may be further improved by providing vitamin D plus calcium supplementation to individuals with higher physiologic testosterone levels." [Bischoff-Ferrari HA, Orav EJ, and Dawson-Hughes B, *Osteoporos Int*, 19: 1307-1314, 2008]

CLA MILK ISOMER HAS NEUTRAL EFFECT ON MARKERS OF INFLAMMATION

Increased blood levels of markers of inflammation are a strong predictor of cardiovascular disease. Researchers in Denmark compared the effects of two supplementations with different contents of CLA (conjugated linoleic acid) isomers on cardiovascular risk markers (i.e., plasma lipids, inflammatory risk markers, and lipid peroxidation) in postmenopausal women. The effect of CLA was compared to olive oil (control). CLA is naturally produced by ruminant animals. Dairy and ruminant fat contribute >70% of dietary CLA, with the *cis*-9, *trans*-11 CLA isomer contributing from 0.5-2% of the fat in the human diet. This 16-week double-blind, randomized parallel study evaluated the effects of supplementation with a commercial CLA mixture (~40% each of *trans*-10, *cis*-12 and *cis*-9, *trans*-11 isomers), *cis*-9, *trans*-11 isomers (the predominant CLA isomer in milk), or olive oil (control) on blood lipids and markers of inflammation. Results showed that women supplemented with the CLA mixture had significantly higher blood triglycerides and lower HDL-cholesterol than those supplemented with olive oil. The ratio of total:HDL-cholesterol and markers of inflammation were significantly higher in women supplemented with the CLA mixture than in those supplemented with CLA milk. Both CLA supplements increased lipid peroxidation, but the CLA mixture increased it more than did CLA milk. The researchers conclude, "Our results confirm that the

mixture containing *trans*-10, *cis*-12 has a cluster of adverse effects on cardiovascular markers, whereas *cis*-9, *trans*-11 CLA isomer appears to be more neutral." [Tholstrup T, et al., *J Nutr*, 138: 1445-1451, 2008]

IMPACT OF MODERATELY HIGH AND LOW SALT INTAKES ON CALCIUM METABOLISM IN POSTMENOPAUSAL WOMEN

This randomized cross-over trial investigated adaptive mechanisms in calcium and bone metabolism in response to changes in salt and calcium intake in 11 postmenopausal women (<75 years). The women were randomly selected to four successive 5-week periods of controlled dietary intervention, each separated by 4 weeks: 1) low calcium/low sodium; 2) high calcium/low sodium; 3) low calcium/high sodium; and 4) high calcium/high sodium. Moderately low and high calcium (518 versus 1284 mg/day) and sodium (1,600 versus 4,400 mg/day) diets reflecting lower and upper intakes in postmenopausal women consuming a Western style diet were provided. Stable isotope labeling techniques were used to measure calcium absorption/excretion, bone calcium balance was estimated, and markers of bone formation/resorption were measured in blood and urine. Results showed that "salt has a significant effect on calcium urinary excretion and bone calcium balance only on the high calcium diets." The authors say, "It seems that both dietary calcium and sodium play a major role in the maintenance of bone health in postmenopausal women. Low calcium intake (518 mg/day) was associated with negative bone calcium balance with both high and low salt diets, but with a moderately high calcium intake (1284 mg/day), the bone balance was positive when the salt intake was low, but not when it was moderately high." They explain that extended periods of low calcium intake maximize adaptive mechanisms to conserve calcium (greater calcium absorption, less calcium excretion), "which may explain why the salt challenge on the low calcium diet seems to be less pronounced and did not reach significance in terms of calcium kinetics." [Teucher B, et al., *J Bone Min Res*, 23(9): 1477-1485, 2008]

LESS ACCULTURATED LATINOS MAY HAVE MORE HEALTHFUL DIETS

This comprehensive literature review examines the relationship between acculturation and diet by examining national, quantitative, and qualitative studies involving Latinos living in the United States. It examined the extent to which various measures of acculturation, such as acculturation score, years in the United States, birthplace, generational status, and language use, were associated with macronutrient/micronutrient intake, and dietary behaviors. Results based on five studies using data from the Hispanic Health and Nutrition Examination Survey and National Health and Nutrition Examination Survey found that "being less acculturated was associated with more healthful levels of nutrient consumption." For example, one study found, "a higher percentage of Mexican-born men and women, compared to US-born English and Spanish-speaking Mexican/Mexican-American men and women, were more likely to meet dietary guidelines for total fat, saturated fat, fiber, and potassium, as well as consume the recommended dietary allowance of vitamin C, vitamin B-6, folate, calcium, and magnesium." It was interesting to note that across several studies dietary fat and percent energy from fat were not associated with any measure of acculturation. Although more acculturated individuals consume more fast food, fatty snacks, and added fats than the less acculturated, they are more likely to engage in fat avoidance behaviors. Less acculturated individuals were more likely to consume whole milk and more likely to fry food with lard and other meat fat. The authors conclude, "Messages to less acculturated Latinos may need to stress maintenance of healthful

lifestyle behaviors such as eating recommended quantities of vegetables, portion control to reduce energy intake, and changes to food preparation practices; the more acculturated may benefit from messages that stress moderation of fast food, sugar-sweetened beverages, and other away-from-home foods." [Ayala GX, Baquero B, and Klinger S, *J Am Diet Assoc*, 108: 1330-1344, 2008]

In Brief…

Supplement provides proceedings of a vitamin D meeting

A supplement to the *American Journal of Clinical Nutrition* includes 20 papers that summarize the key findings, strength of the evidence, and research needs identified in the National Institutes of Health (NIH) conference, "Vitamin D and Health in the 21st Century: An Update", which was held on September 5-6, 2007 in Bethesda, MD. The conference was jointly sponsored by the NIH Office of Dietary Supplements, the National Cancer Institute, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the American Society for Nutrition. After the conference, scientists with relevant expertise gathered for a systematic evidence-based review and roundtable discussion. This review addressed five questions on 25-hydroxyvitamin D and functional outcomes across the lifecycle, response to exposure, bone health outcomes of supplementation, risks and benefits of sun exposure, and adverse outcomes. For example, the roundtable discussion revealed that "Researchers have made considerable progress in understanding the relation of 25(OH)D to bone health outcomes in the elderly and in postmenopausal women, but we know less about its impact on other stages of the life cycle and in racial and ethnic groups." Future research should assess the role of vitamin D status in health maintenance and disease prevention throughout the lifecycle. [Brannon PM, et al., *Am J Clin Nutr*, 88(supplement): 483S-490S, 2008]

Calcium should be the first line of treatment for older women with vitamin D insufficiency

This one-year randomized, double-blind, placebo-controlled trial evaluated the relative importance of vitamin D and calcium treatment on bone mineral density (BMD) and bone-related chemistry in 256 elderly women with vitamin D deficiency. All participants received 1,000 mg/day of calcium citrate divided between breakfast and dinner for one year, and then were randomly assigned to receive either 1,000 IU vitamin D_2/day or placebo consumed with the evening meal for one year. Results showed that total hip and total body BMD increased significantly and a marker of bone resorption decreased during the study in both treatment groups. "In patients with a baseline calcium intake of 1,100 mg/day and vitamin D insufficiency," conclude the authors, "vitamin D_2 1,000 IU for one year has no extra beneficial effect on bone structure, bone formation markers, or intestinal calcium absorption over an additional 1,000 mg of calcium." They conclude, "Calcium supplementation should be recommended for all elderly women with vitamin D insufficiency as first line treatment to improve bone structure." However, they say the addition of vitamin D may reduce their risk of falling, a major cause of fractures in the elderly. [Zhu K, et al., *J Bone Min Res*, 23(8): 1343-1348, 2008]

Alkali does not explain the benefit of fruit and vegetable intake on bone

"It has been suggested," say these UK researchers, "that long-term exposure to a diet that produces excess acid, which results in a gradual release of alkaline salts from the bone, may be a cause of osteoporosis." This randomized controlled trial determined the effects of alkali-providing potassium citrate and fruit and vegetable intake on bone turnover in 276 postmenopausal women (55-65 years) over two years. The women were randomly assigned to one of 4 groups: high-dose potassium citrate, low dose potassium citrate, 300 gm additional

fruits and vegetables (equivalent to 18.5 mEq alkali), or placebo. The women consumed about 800-900 mg of calcium daily and were not given calcium or vitamin D supplements. The results showed that "Two-year potassium citrate supplementation does not reduce bone turnover or increase bone mineral density in healthy postmenopausal women, which suggests that alkali provision does not explain any long-term benefit of fruit and vegetable intake on bone." [Macdonald HM, et al., *Am J Clin Nutr*, 88: 465-474, 2008]

It's unlikely that decreased physical activity has fueled the obesity epidemic

Researchers in the Netherlands and Scotland evaluated physical activity energy expenditure and examined trends over time to test the hypothesis that reduced levels of physical activity energy expenditure have driven the obesity epidemic. They compiled data on levels of daily energy expenditure (DEE) by the doubly labeled water method and basal energy expenditure (BEE) by respirometry over time in Europe and North America. They compared levels of expenditure in modern Western societies with those from the third world countries, which generally mirrored physical activity of Western societies in the past. Finally, they compared the levels of expenditure and physical activity level of modern humans with those of wild terrestrial mammals, taking into account body size and temperature effects. Results showed that physical activity expenditure has not declined over the same time period that obesity rates have increased. In addition, conclude the researchers, "daily energy expenditure of modern man is in line with energy expenditure in wild animals, so it is unlikely that decreased expenditure has fuelled the obesity epidemic." [Westerterp KR and Speakman JR, *International Journal of Obesity*, 32: 1256-1263, 2008]

Dietary fat's influence on bone depends on individual genetics

"Between 55% and 85% of the variance in peak bone mass is determined by heritable factors," say the researchers of this study that used a mouse model to elucidate the complicated gene/environment interaction between dietary fat and bone mineral density (BMD). They identified the PPARG (peroxisome proliferator activated receptor γ) gene as influencing peak bone mass in mice and humans. The PPARG gene plays an important role in fat regulation and metabolism. They challenged a genetically altered mouse model (female 6T mice with an altered PPARG gene) with a high fat diet and found that the 6T mouse had a lower areal leg BMD compared to the control mice. They then tested the interaction of the PPARG gene and dietary fat on BMD in human participants in the Framingham Offspring Cohort. That analysis showed a similar interaction of the PPARG gene and diet (fat intake) on BMD in both men and women. The authors conclude that a high fat diet may be detrimental or beneficial to bone mass depending on the presence of specific variations in the PPARG gene. [Ackert-Bicknell CL, et al., *J Bone Min Res,* 23: 1398-1408, 2008]

Consumption of added sugar or sugar-sweetened foods and beverages are not associated with risk of pancreatic cancer

This prospective study of 487,922 men and women (50-71 years) investigated whether the consumption of total added sugar and sugar-sweetened foods and beverages is associated with pancreatic cancer risk. Sugar-sweetened foods and beverages were grouped into sugar sweetened beverages (i.e., regular soft drinks and regular fruit drinks), sugar added to coffee and tea, sweets (i.e., candy, cookie, cake, pie, donut, and sweet roll), dairy desserts (i.e., ice cream and frozen yogurt), and other sugar-sweetened foods (i.e., muffin, cornbread, and pancake). After seven years of follow-up, results showed "No overall greater risk of pancreatic cancer was observed in men or women with high intake of total added sugar or sugar-sweetened foods and beverages." The authors say that further studies are needed to

understand the role of body mass index, physical activity, and insulin resistance, and to provide a more in-depth understanding of the association. [Bao Y, et al., *Am J Clin Nutr*, 88: 431-440, 2008]

Prevalence of spinal fractures differ between black and white women

Fractures of the spihne are the most common osteoporotic fracture. Researchers studied 7,860 white and 472 black women 65 years or older who were enrolled in the Study for Osteoporotic Fractures and compared prevalence of spinal fracture. Results showed that the prevalence of spinal fractures was 10.6% in black and 19.1% in white women. A one standard deviation decrease in hip bone mineral density was associated with a 47% increased odds of fracture in black women, and an 80% increased odds in white women. This lower risk for fracture was not due to hip bone density or other risk factors. Although the prevalence of spinal fractures is lower in black compared to white women, the prevalence increased in both groups with increases in age, low body mass index, and other risk factors. [Cauley JA, et al., *J Bone Min Res*, 23: 1458-1467, 2008]

Low vitamin D status is associated with mortality from all causes

Researchers at Johns Hopkins University School of Medicine in Baltimore, MD used data from the Third National Health and Nutrition Examination Survey (NHANES III) to test the association of low vitamin D (25(OH)D) levels with all-cause, cancer, and cardiovascular disease mortality in more than 13,000 adults. Factors associated with a higher risk for vitamin D deficiency were increasing age, female sex, nonwhite race/ethnicity, diabetes, current smoking, and higher body mass index. Greater physical activity, vitamin D supplementation, and nonwinter season were associated with a lower risk for deficiency. Having the lowest (<17.8 ng/mL 25(OH)D) compared to the highest vitamin D status (>32.1 ng/mL 25(OH)D) was associated with a 26% increased risk of death from any cause. [Meladed ML, et al., *Arch Intern Med*, 168(15): 1629-1637, 2008]

Other Publications of Interest

- *Vitamin K supplementation does not significantly impact bone mineral density and biochemical markers of bone in pre- and perimenopausal women. [Volpe SL, Leung MM, and Giordano, Nutr Res, 28: 577-582, 2008]*
- *The developmental origins of sarcopenia. [Sayer AA, et al., J Nutr Health & Aging, 12(7): 427-432, 2008]*
- *Sarcopenia: Diagnosis and treatment. [Morley JE, J Nutr Health & Aging, 12(7): 452-456, 2008]*
- *Impact of peer nutrition education on dietary behaviors and health outcomes among Latinos: A systematic literature review. [Perez-Escamilla R, et al., J Nutr Educ Behav, 40: 208-225, 2008]*
- *Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. [Shai I, et al., N Engl J Med, 359(3): 229-241, 2008]*
- *Oxidative stress-induced risk factors associated with the metabolic syndrome: a unifying hypothesis. [Grattagliano I, et al., J Nutritional Biochemistry, 19: 491-504, 2008]*
- *Association of insulin resistance and inflammation with peripheral arterial disease: The National Health and Nutrition Examination Survey, 1999 to 2004. [Pande RL, et al., Circulation, 118: 33-41, 2008]*
- *Project M.O.M.: Mothers & Others & MyPyramid. [Wansink B, J Am Diet Assoc, 108(8): 1302-1304, 2008]*
- *Natural history and risk factors for bone loss in postmenopausal Caucasian women: a 15-year follow-up population-based study. [Zhai G, et al., Osteoporos Int, 19: 1211-1217, 2008]*