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Calcium and Bone Health

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Dr. Keegan reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

RECENT ANALYSES FROM THE WOMEN'S HEALTH INITIATIVE HAVE shed new light on the importance of adequate calcium and vitamin D intake to women's bone health. (*See article on page 29.*) This is especially important considering that women's calcium requirements significantly increase not only with menopause, but also pregnancy, post-pregnancy, and lactation.[1] Despite the dissemination of this important information, many women still do not comply with the calcium requirement recommendations.[2]

For example, an investigation in Taiwan found that 80.6% of young adult women (n = 265) were very likely to have accurate knowledge about osteoporosis but also typically had a low calcium intake (454 mg/d).[3] The factors that most strongly affected the intake of calcium by women were knowledge, number of children, self-rated health score, body mass index, graduation from high school, experience of bone density examination, and family history. Findings from three studies conducted from 1994 to 2000 examining the determinants of calcium intake among women at midlife suggest that there is a high level of awareness among women that consuming an inadequate amount of calcium increases their risk of developing osteoporosis, but that this awareness is not being translated into long-lasting behavior change.[4] Even when individuals are interested in increasing their calcium intake, perceived barriers often appear to prevent them from acting or lead to recidivism.

Mechanism of Action

During perimenopause, both the quantity and quality of bone decline rapidly, resulting in a dramatic increase in the risk of fracture in postmenopausal women.[5] The osteoporosis that may occur as a result is a disorder in which loss of bone strength leads to fragility fractures. The fundamental pathogenetic mechanisms underlying this disorder include: (a) failure to achieve a skeleton of optimal strength during growth and development, (b) excessive bone resorption resulting in loss of bone mass and disruption of architecture,

and (c) failure to replace lost bone due to defects in bone formation.[6] Estrogen deficiency is known to play a critical role in the development of osteoporosis, while calcium and vitamin D deficiencies and secondary hyperparathyroidism also contribute. There are multiple mechanisms underlying the regulation of bone remodeling, and these involve not only the osteoblastic and osteoclastic cell lineages but also other marrow cells, in addition to the interaction of systemic hormones, local cytokines, growth factors, and transcription factors. Polymorphisms of a large number of genes have been associated with differences in bone mass and fragility. Bone loss with age and menopause are universal, but rates vary among individuals. Both peak bone mass and subsequent bone loss can be modified by environmental factors, such as nutrition, physical activity, and concomitant diseases and medications.[7]

Clinical Trials

Calcium supplementation appears to increase bone density. In one meta-analysis, calcium was shown to be more effective than placebo in reducing bone loss rates in postmenopausal women.[8] There also was a trend toward improvement in vertebral fracture risk. A review of clinical trials found that increased calcium intake in postmenopausal women led to a slight decrease in fracture risk.[9]

Two U.S. national databases were used to assess the adequacy of calcium intake in patients with osteoporosis. Quantity of calcium intake, both from supplements and food, among individuals with osteoporosis (n = 38 men, n = 376 women) was estimated using the 1999-2002 National Health and Nutrition Examination Survey (NHANES).[10] Physician visits for osteoporosis in the United States increased 4.5-fold between 1994 (1.3 million visits) and 2004 (5.8 million visits). During this time the proportion of osteoporosis visits in which bisphosphonates were prescribed increased from 14% to 81%, while reported calcium use fell from 43% to 23%. Among osteoporosis patients in NHANES, 64% reported using calcium-containing supplements. Reported median calcium intake was 433 mg/d for calcium supplement nonusers and 1,319 mg/d for calcium supplement users. Overall, only 40% of osteoporosis patients had calcium intake exceeding 1,200 mg/d. These researchers concluded that as osteoporosis increasingly is identified and treated with effective medications, calcium is being neglected as a component of osteoporosis management. Despite the fact that the efficacy of new osteoporosis medications depends on adequate calcium intake, reported calcium intake in osteoporosis patients is far below recommended levels.

Another study examined the association of exercise frequency and calcium intake with change in regional and total bone mineral density (BMD) in a group of postmenopausal women completing four years of progressive strength training.[11] Researchers followed 167 calcium-supplemented (800 mg/d) sedentary women (56.1 ± 4.5 years) randomized to a progressive strength training exercise program or to control for four years. Fifty-four percent of the women were using hormone therapy at baseline. The final sample included 23 controls, 55 crossovers, and 89 randomized exercisers. The study showed a significant, positive, association between BMD change and exercise frequency, supporting the long-term usefulness of strength training exercise for the prevention of osteoporosis in postmenopausal women, especially hormone therapy users. The positive relationship of calcium intake to change in BMD among postmenopausal women not using hormone therapy has clinical implications in light of recent evidence of an increased health risk associated with hormone therapy.

A Japanese study compared BMDs among subjects in the same age ranges, but attained by different birth cohorts in 1990 or in 2000.[12] The mean value of the lumbar spine BMD (L2-4) in women in the birth cohort of 1940-1949, when they reached the age stratum 50-59, was significantly higher than that of the cohort born in 1930-1939 when in the same age stratum ($P < 0.05$). The

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Education for Prevention of Osteoporosis

OSTEOPOROSIS PREVENTION REQUIRES ADEQUATE CALCIUM and vitamin D intake, regular physical activity, and avoiding smoking and excessive alcohol ingestion. Risk of fracture determines whether medication is also warranted. A previous vertebral or hip fracture is the most important predictor of fracture risk. Bone density is the best predictor of fracture risk for those without prior adult fractures. Age, weight, certain medications, and family history also help establish a person's risk for osteoporotic fractures. All women should have a bone density test by the age of 65 or younger (at the time of menopause) if risk factors are present. Guidelines for men are currently in development. Medications include both antiresorptive and anabolic types. Antiresorptive medications—estrogens, selective estrogen receptor modulators (raloxifene), bisphosphonates (alendronate, risedronate, and ibandronate), and calcitonins—work by reducing rates of bone remodeling. Teriparatide (parathyroid hormone) is the only anabolic agent currently approved for osteoporosis in the United States. It stimulates new bone formation, repairing architectural defects and improving bone density. All persons who have had osteoporotic vertebral or hip fractures and those with a bone mineral density diagnostic of osteoporosis should receive treatment. In those with a bone mineral density above the osteoporosis range, treatment may be indicated depending on the number and severity of other risk factors.[1]

Clinician offices are the best locations for patients to access reading material, videos, and web sites on bone health, effective prevention measures, treatments for osteoporosis, and the importance of adequate calcium throughout the life cycle. The annual examination should be the time when evaluation and identification of patient risk factors for osteoporosis are done and the patient is counseled on the need for adequate calcium, either through diet or supplement, vitamin D, and weight-bearing exercise. Women depend on their physicians for advice and counseling regarding both prescription and nonprescription interventions and therapies for bone health. The clinician's office should have a comprehensive sampling of educational materials that are of use to patients both for educating them about general preventive health practices as well as for giving them background information that will equip them to ask the physician health questions that directly pertain to them.[2] When working with patients, clinicians should solicit patient concerns about trying to increase their calcium intake and barriers that the patient has experienced in the past or may anticipate in the future.[3]

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same tendency was observed in BMD at the femoral neck. The comparatively higher levels of BMD observed in women in the 1940-1949 birth cohort when they reached their fifties, may reflect nutritional improvements in Japan. The nationwide nutritional survey reports mean values of calcium intake as 253 mg/d in 1946, 338 mg/d in 1955, 465 mg/d in 1965, and 552 mg/d in 1975, a dramatic increase, although still low. Both men and women in later birth cohorts showed higher BMDs in middle-age, which may predict a future decrease in the incidence and prevalence of osteoporosis.

An Australian study assessed whether a lifestyle intervention delivered to mothers might impact osteoporosis preventive behaviors in their children.[13] A two-year randomized controlled trial of individualized BMD feedback was done with either an osteoporosis information leaflet or small group education in a population-based sample of 354 mothers. Receiving small group education was associated with mothers' report of increasing children's calcium intake, as was low t-score feedback. Mothers who increased their own physical activity more often reported an increase in both physical activity and calcium intake in their children. Mothers who commenced calcium supplements more often reported increasing children's calcium intake but not physical activity. Both BMD feedback and small group education delivered to mothers are effective at inducing maternally reported osteoporosis preventive behavior change in their children. These results require confirmation by studies with objective outcome measures.

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 be 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).[14] This condition was termed milk alkali syndrome, and has been reported at calcium supplement levels from 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.[15]

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 their beneficial effect of decreasing intestinal oxalate absorption.

Dosage Recommendations

Based on the adverse effects above, as well as the potential for decreased absorption of other essential minerals, 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.[15]

As part of any osteoporosis treatment program, it is important to maintain adequate calcium and 25-hydroxyvitamin D levels either through diet or supplementation. Among the available pharmacologic therapies, the bisphosphonates alendronate and risedronate have demonstrated the most robust fracture risk reductions—approximately 40-50% reduction in vertebral fracture risk, 30-40% in nonvertebral fracture risk, and 40-60% in hip fracture risk.[17] Ibandronate, a new bisphosphonate, has demonstrated efficacy in reducing vertebral fracture risk. Salmon calcitonin nasal spray and raloxifene demonstrated significant reductions in vertebral fracture risk in pivotal studies. Teriparatide significantly reduced vertebral and nonvertebral fracture risk. Drugs on the horizon include strontium ranelate, which has been shown to reduce vertebral and nonvertebral fracture risk, and zoledronic acid, an injectable bisphosphonate that increased bone density with once-yearly administration. In essence, both pharmacological and nonpharmacological strategies need to be employed.[18]

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 in females. Only about 25% of boys and 10% of girls ages 9-17 are estimated to 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.[14,15]

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. The table below 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.[19]

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

Table

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	1.5 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
Fruit punch with calcium citrate malate	8 oz	300	0.62

Source: http://lpi.oregonstate.edu/infocenter/minerals/calcium/index.html. Accessed March 6, 2006.

potato and dried beans. Phytic acid is a less potent inhibitor of calcium absorption than oxalate. Yeast possesses an enzyme (phytase) which 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.[14]

Recommendations and Conclusion

Osteoporosis, a major public health problem and often the result of poor bone health, is becoming increasingly prevalent in our aging population. A skeletal disorder characterized by compromised bone strength, osteoporosis predisposes individuals to increased risk of fractures of the hip, spine, and other skeletal sites. The clinical consequences and economic burden of this disease suggest that we need measures to assess individuals who are at high risk to allow for appropriate intervention. Adequate calcium throughout a woman's life span is a critical step to achieving and improving bone health. The most critical time periods include adolescence, pregnancy, lactation, perimenopause, and menopause, in which adequate calcium intake is most important. ❖

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Boning Up on Calcium: Does it Help Prevent Fractures?

By Mary Hardy, MD

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Dr. Hardy reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

Source: Jackson RD, et al. Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006;354:669-683.

Abstract: The efficacy of calcium with vitamin D supplementation for preventing hip and other fractures in healthy postmenopausal women remains equivocal. The authors recruited 36,282 postmenopausal women, 50-79 years of age, who were

already enrolled in a Women's Health Initiative (WHI) clinical trial. Participants were randomly assigned to receive 1,000 mg/d of elemental calcium as calcium carbonate with 400 IU/d of vitamin D3 or placebo. Fractures were ascertained for an average follow-up period of 7.0 years. Bone density was measured at three WHI centers. Hip bone density was 1.06% higher in the calcium plus vitamin D group than in the placebo group ($P < 0.01$). Intention-to-treat analysis indicated that participants receiving calcium plus vitamin D supplementation had a hazard ratio of 0.88 for hip fracture (95% confidence interval [CI] 0.72-1.08), 0.90 for clinical spine fracture (CI 0.74-1.10), and 0.96 for total fractures (CI 0.91-1.02). The risk of renal calculi increased with calcium plus vitamin D (hazard ratio 1.17; CI 1.02-1.34). Censoring data from women when they ceased to adhere to the study medication reduced the hazard ratio for hip fracture to 0.71 (CI 0.52-0.97). Effects did not vary significantly according to prerandomization serum vitamin D levels. Among healthy postmenopausal women, calcium with vitamin D supplementation resulted in a small but significant improvement in hip bone density, did not significantly reduce hip fracture, and increased the risk of kidney stones.

■ COMMENTS

MOST WOMEN IN THE UNITED STATES KNOW THAT THEY are supposed to take calcium and vitamin D to prevent osteoporosis and fractures, a major cause of morbidity and mortality in postmenopausal women. This is the most widely recognized public health message in the United States today. However, physicians, and their patients, may be surprised to hear that the medical literature on this topic has not been uniformly positive. On the one hand, two recent Cochrane reviews reported small but positive effects. In the first, calcium supplementation alone showed a statistically significant, albeit small, increase in bone mineral density but only a non-statistically significant trend toward a decrease in vertebral body fractures.[1] No effect was demonstrated on the rate of non-vertebral fractures. A second review, focused on vitamin D, concluded that high-risk patients (frail elderly) may sustain fewer fractures overall if given vitamin D (at least 700 IU/d) in conjunction with adequate calcium.[2] There was no clear cut benefit for vitamin D alone with respect to fracture prevention. However, a recent publication from the Women's Health Initiative (WHI) study cast doubt on this conclusion[3]—or does it?

The WHI study, a very large prospective controlled trial of almost 40,000 American women, assigned subjects to receive either calcium carbonate, equivalent to 1,000 mg/d of elemental calcium, plus 400 IU/d of vitamin D or placebo for the duration of the trial (an average of seven years). The women were postmenopausal, between 50 and 79 years of age, and were not necessarily at high risk for the development of osteoporosis. Throughout the trial, women were allowed to take their own personal calcium supplementation, regardless of group assignment, as well as bisphosphonates, if prescribed. The majority of women also were taking hormone replacement therapy until that portion of the study was stopped several years ago. The authors found a 1% increase in bone mineral density in the treatment group ($P < 0.01$) but an intention-to-treat analysis showed no decrease in the fracture risk, at any site, compared to placebo. A 17% increase in the incidence of renal calculi also was reported in the treatment group. The authors therefore concluded that despite the small increase in bone density, calcium and vitamin D, at the levels tested, did not decrease the risk of fracture and seemed to increase the risk of kidney stones. This study raises the question of whether we should continue to recommend routine calcium and vitamin D supplementation to postmenopausal women.

This trial was reported in the popular press as "proving" that calcium doesn't help bones, but a closer look and a consideration of additional factors paints a more complicated picture. First, the dose of vitamin D in this study was likely too low. Trials conducted after the start of the WHI study showed that less than 700 IU/d vitamin D was much less likely to be effective and a dose of 400 IU/d was considered ineffective to prevent fractures.[4] Second, there may have been some issues with the calcium formulation chosen. Calcium carbonate is less bioavailable in general compared to other calcium salts.[5] This effect is even more pronounced in patients, like many elderly, with low stomach acid. So, the dose of the vitamin D was too low and the calcium formulation may not have been optimal.

Although this study was well conducted and appropriately designed, there were some inherent problems with its design. More than half of the women were on hormone replacement therapy, itself a potent antiresorptive agent, which could have masked a milder effect of calcium and vitamin D. Also, 64% of the women in the placebo group took at least 800 mg/d of calcium through diet and supplementation and 42% also took vitamin D. This use decreased the differences between the placebo and treatment groups, making it harder to demonstrate a statistically significant difference between groups. The authors further reported that the expected rate of hip fractures in the placebo group was half of what they had expected, and so this study may not have been sensitive enough to demonstrate a difference in hip fractures, the most debilitating type of fracture. However, there were large enough numbers of fractures at other sites to show a lack of difference overall between groups for all other kinds of fractures. The most telling analysis may be of

the patients who were the most compliant with their supplements. The women who took calcium and vitamin D more than 80% of the time for the duration of the study did show a significant decrease in their risk of hip fracture (hazard ratio 0.71; 95 % confidence interval 0.52-0.97). So apparently, calcium and vitamin D work better if you actually take them.

Finally, it is important to remember that vitamin D has additional positive benefits. It has been shown to decrease falls in the frail elderly,[6] probably by increasing muscle mass, and also has been associated with a decreased risk of colon cancer in conjunction with calcium supplementation.[7,8]

Unfortunately, the WHI has not given the definitive answers regarding calcium and vitamin D supplementation it was intended to provide, but it does suggest that the effects of supplementation are modest. Therefore, in advising our perimenopausal patients, it is important to continue to reduce all possible risk factors for osteoporosis and to encourage exercise, both weight-bearing and resistance training. To accrue the benefits of supplementation, patients must continue to take adequate doses of appropriate formulations, so we need to continue to reinforce the directive to be adherent with supplementation. Further, we should not depend on calcium and vitamin D alone to prevent osteoporosis, but should monitor patients to start more aggressive therapy if needed. Finally, despite the increase it renal calculi, the benefits of adequate vitamin D (800 IU/d at least) and appropriate calcium supplementation (citrate or malate if elderly and/or achlorhydric) likely outweigh the small risk and should be continued until further data clarifies which patients are the most likely to benefit from supplementation. ❖

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CME Questions

13. When do calcium requirements significantly increase in women?

a. Menopause
b. Pregnancy
c. Post-pregnancy
d. Lactation
e. All of the above

14. Data from the National Health and Nutrition Examination Survey (NHANES) indicate that calcium use among osteoporosis patients decreased from 43% to 23% between 1994 and 2004.

a. True
b. False

15. A recent review concluded that frail elderly patients may sustain fewer fractures overall if given what dose of vitamin D in conjunction with adequate calcium?

a. 500 IU/d
b. 600 IU/d
c. 700 IU/d

Answers: 13. e, 14. a, 15. c.

News Briefs

CAM Conference to be Held in May

The Consortium of Academic Health Centers for Integrative Medicine, which consists of 30 leading academic medical centers from across North America, is sponsoring an educational opportunity for health professionals interested in complementary and alternative medicine (CAM).

The North American Research Conference on Complementary and Integrative Medicine will be held in Edmonton, Alberta, Canada, May 24-27. The conference is international in scope and invites and encourages participation from CAM researchers, educators, and providers, as well as conventional practitioners from around the world. The conference will showcase original scientific CAM research through keynote and plenary presentations, oral and poster presentations, and innovative scientific sessions. Areas of CAM research presented and discussed at this conference will include research in basic science, clinical research, methodological research, health services research, and education research.

The conference represents the first occasion that all 30 academic Consortium centers and other leading national and international CAM networks and organizations are invited to come together to meet and share their research, conference organizers say. This conference is intended to foster the development of new collaborations and to strengthen existing partnerships.

Keynote Speakers Scheduled

Conference organizers have scheduled five keynote speakers. (This information is subject to change.)

David Moher, PhD. "So you want the evidence: Challenges facing its generation, synthesis and reporting." Moher is director of clinical research and the Chalmers Research Group, both at the Children's Hospital of Eastern Ontario Research Institute. Moher has been substantively involved in many CAM research studies and training opportunities for several years.

Margaret Chesney, PhD, NCCAM, NIH. "Integrative medicine: Be bold in what you try, cautious in what you claim." Chesney is the first deputy director of the National Center for Complementary and Alternative Medicine (NCCAM) and leads the center's Division of Extramural Research and Training. Chesney partners with NCCAM's director in planning, directing, and managing the programs and resources of the center. Prior to joining NCCAM, Chesney's clinical practice and research focused on mind-body medicine.

Richard Davidson, PhD. "Buddha's brain: The transformation of mind, brain and body through meditation." Davidson is the William James and Vilas Research Professor of psychology and psychiatry and director of the W. M. Keck Laboratory for Functional Brain Imaging and Behavior at the University of Wisconsin-Madison.

Brian M. Berman, MD. "Acupuncture for osteoarthritis: Trials and tribulations." Berman is the director of the University of Maryland Center for Integrative Medicine. Berman is a professor of family medicine as well as a licensed acupuncturist and homeopath. He is currently principal investigator of two National Institutes of Health center grants to evaluate traditional Chinese medicine and was lead author of the *Annals of Internal Medicine* landmark 2004 study of the effectiveness of acupuncture for osteoarthritis.

Peter Lipsky, MD, NIAMS, NIH. "Thundergod vine: From the countryside to the bedside to the bench." Lipsky performed residency training in internal medicine at Strong Memorial Hospital, Rochester, NY, before becoming a clinical associate at the NIH studying macrophage-lymphocyte interactions. He has been involved in research on Chinese herbal remedies for more than 15 years and working closely with Chinese colleagues has published many papers on this subject.

Pediatric CAM Sessions Scheduled

The conference is also devoting a day to pediatric CAM research. This event, hosted by the Canadian PedCAM Network, will be held on May 24 and will feature speakers who are leaders in the field of pediatric CAM research. Participants may choose from concurrent sessions on skills for pediatric CAM research as well as from experiential sessions on traditional Chinese medicine, naturopathy, and massage therapy for children. PedCAM invites participants to stay for a reception hosted by the Sick Kids Foundation at the conclusion of the day.

For more information about the pediatric CAM session or the conference in general, visit the web site www.imconsortium-conference2006.com. ❖

In Future Issues:

Acupuncture and Obesity

Ginger and Nausea

Melatonin and Migraine Headache