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INSIDE

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Guys Need Strong Bones Too: Calcium Is Not Just for Women Anymore

ABSTRACT & COMMENTARY

By David Kiefer, MD

Dr. Kiefer is a Clinical Instructor, Family Medicine, University of Washington, Seattle; Clinical Assistant Professor of Medicine, University of Arizona, Tucson; and Adjunct Faculty at Bastyr University, Seattle; he reports no financial relationship to this field of study.

Synopsis: *This well-designed two-year trial shows that 1,200 mg daily of calcium citrate in healthy middle-aged men translates into higher bone mineral density and fewer falls, expanding on a body of evidence that had been focused primarily on the use of calcium in women and osteoporosis.*

Source: Reid IR, et al. Randomized controlled trial of calcium supplementation in healthy, nonosteoporotic, older men. *Arch Intern Med* 2008;168:2276-2282.

THIS WAS A RANDOMIZED, DOUBLE-BLIND TRIAL COMPARING LUMBAR spine bone mineral density (BMD), the primary endpoint, in 323 healthy, community-dwelling men (average age of 56 years) given two dosages of calcium citrate (600 mg daily or 600 mg twice daily) with placebo over two years. At six-month intervals, a DEXA scan was used to estimate lumbar spine, hip, and total body BMD, and other parameters were measured including number of falls and fractures, grip strength, serum 25-hydroxyvitamin D, serum parathyroid hormone, serum alkaline phosphatase, serum P1NP, urinary calcium, and dietary calcium intake. There was good compliance over the two years, and even though 14 study participants did not complete the clinical trial, all of the data underwent an intention-to-treat analysis.

The study results showed a 1% increase in lumbar spine BMD at six months in the group supplemented with 1,200 mg of calcium daily when compared with placebo, an increase that was sustained

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over the rest of the study period ($P = 0.005$). The group receiving only 600 mg daily did not show any improvement in lumbar spine BMD compared to placebo. The 1,200 mg group also showed an increase in hip BMD, and, unlike for the lumbar BMD, this increase continued throughout the two years (0.9% increase in year 1; 0.5% increase in year 2; $P < 0.001$). Again, the 600 mg group did not show any difference in hip BMD when compared to placebo. Total body BMD increased 1.2% during the first six months, ending at 1.5% above baseline, in the 1,200 mg group ($P < 0.001$); there was no improvement over baseline for either the 600 mg group or the placebo group. All of these results were unchanged when the groups were statistically analyzed as either above or below the median dietary calcium intake of 790 mg daily.

The expected physiological responses to calcium supplementation were seen in the biochemical analyses: There were dosage-related decreases in serum parathyroid hormone, and two markers for bone turnover, serum P1NP and alkaline phosphatase, over the two years of the study. Only in the 1,200 mg group was a statistically significant increase in urinary calcium seen. Of note, the mean level of serum 25-hydroxyvitamin D for all research subjects was 32.05 ng/mL.

Adverse effects occurred with similar frequency for the three groups ($P = 0.16$), including clinical fractures ($P = 0.43$). Following up on concerns about a possible connection between calcium supplementation and serious cardiovascular events in women, the researchers found no significant difference between the treatment and placebo groups for angina ($P = 0.37$), myocardial infarction ($P = 0.37$), or sudden death ($P = 0.61$). The men in the 1,200 mg group had significantly fewer falls when compared to the 600 mg ($P = 0.005$) and placebo ($P = 0.45$) groups.

The authors' conclusion was that supplementation with 1,200 mg of calcium citrate daily in healthy men benefits BMD throughout the body and decreases the incidence of falls, effects that were independent of dietary calcium intake.

■ COMMENTARY

The prevention and treatment of osteoporosis in women is a well-established topic in medical research and clinical medicine, with dozens of clinical trials and years of experience guiding recommendations for lifestyle (i.e., weight-bearing exercise), pharmaceuticals, and dietary interventions such as calcium supplementation. The use of calcium in older men is a more recent but arguably much needed expansion of this topic.

What falls out of this clinical trial (no pun intended) are a few important lessons about the clinical use of calcium in this demographic. Although some physiological changes are seen with 600 mg of calcium citrate daily, the clinical endpoints of changes in BMD and fall rates are only seen at 1,200 mg daily doses; 1,200 mg may in fact be a threshold below which minimal, if any, benefit is seen in healthy older men. In addition, despite concerns about increased nephrolithiasis or cardiovascular events with calcium supplementation, no increased rates of adverse effects were seen in either of the calcium treatment groups. The lack of obvious risk with calcium supplementation in this well-designed trial is an important part of the risk-benefit analysis that accompanies the decision about whether to incorporate calcium, as with any possible medical intervention, into clinical practice.

There is, however, some epidemiological evidence that calcium can increase the incidence of prostate cancer. The Physicians' Health Study (a cohort of 20,885 male U.S. physicians) demonstrated a trend toward increased prostate cancer risk with increased calcium intake as estimated from five dairy foods; the high calcium intake group (> 600 mg/d) had a 32% higher risk of prostate cancer than did the low calcium intake group (< 150 mg/d).[1] This result agrees with other epidemiological studies as well as with observations that countries with higher per capita dairy consumption also seem to have higher prostate cancer rates. The mechanism of this effect seems to be that a high calcium intake suppresses the formation of 1,25 dihydroxyvitamin D3 lev-

Alternative Medicine Alert, ISSN 1096-942X, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

ASSOCIATE PUBLISHER: Coles McKagen
DIRECTOR OF MARKETING: Schandale Kornegay
SENIOR MANAGING EDITOR: Paula Cousins
GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to *Alternative Medicine Alert*, P.O. Box 740059, Atlanta, GA 30374.

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els, a vitamin that otherwise inhibits the proliferation of cells in the prostate. Results of the current study are compelling, but further delineation between optimal calcium dosage and long-term safety is required.

There are a few reasons to have confidence in the results of this clinical trial, despite the fact that previous research on the topic of calcium supplementation in men was mostly equivocal, usually showing no difference in BMD nor fracture rates between treatment and placebo groups. In the current trial, the authors argue that the higher dose of calcium used, the more accurate means of detecting changes in BMD (by using the DEXA scan), and the larger numbers of subjects and therefore increased statistical power, all could have accounted for the observed statistically significant results.

More work is needed on this topic. Many people, such as the elderly, especially if they are in nursing homes, are vitamin D-deficient, which compromises their ability to utilize calcium and improve BMD. The subjects in this trial were relatively vitamin D-replete, so it is difficult to generalize to the effect of calcium supplementation in people who are vitamin D-deficient. In the current trial, while the subjects' mean vitamin D level was in the normal range it was low-normal, and higher levels are currently thought by many to confer optimal bone health benefits. Studies addressing this issue will also be welcome. Furthermore, though information was collected about the dietary intake of calcium, other aspects of people's lives that are relevant to fracture and fall rates and BMD, such as exercise, were not taken into account. It will be interesting to see what comes out of research into calcium supplementation in people of other demographics and when used as part of an integrative treatment approach. ❖

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Editor's Note

LOOK FOR CONTINUED COVERAGE OF VITAMIN D in the April and May issues of *Alternative Medicine Alert.* A two-part series, entitled "Vitamin D and Fracture Prevention: Have We Seen the Light?" will review the role of vitamin D on bone and periodontal health.

Should Vitamin D Screening Be Routine in All CVD Patients?

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Dr. Karpman is Clinical Professor of Medicine, UCLA School of Medicine; he reports no financial relationship to this field of study. This article originally appeared in the Feb. 29, 2009, issue of Internal Medicine Alert. *For that publication, it was peer reviewed by Gerald Roberts, MD, Assistant Clinical Professor of Medicine, Albert Einstein College of Medicine, Bronx, NY; Dr. Roberts reports no financial relationship to this field of study.*

Synopsis: *Hypovitaminosis D was found to be highly prevalent in U.S. adults with CVD, particularly those with both coronary heart disease and heart failure.*

Source: Kim DH, et al. Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). *Am J Cardiol* 2008;102:1540-1544.

VITAMIN D DEFICIENCY OCCURS IN ONE-THIRD TO ONE-half of otherwise healthy middle-aged and elderly adults in the United States and worldwide. There is a growing body of evidence that hypovitaminosis D is highly prevalent in patients with various cardiovascular diseases (CVDs)[1-4] and, in fact, it may actually play a role in the pathogenesis of these illnesses.[5-9] Inadequate exposure to sunlight and/or inadequate vitamin D intake will result in abnormally low serum vitamin D levels, which have been found to be associated with cardiovascular risk factors such as hypertension, diabetes mellitus, obesity, and dyslipidemia;[10,11] however, it must be recognized that many of these observations were from the results of relatively small studies.

Because the degree of occurrence of hypovitaminosis D in adults in the United States with a diagnosis of CVD was largely unknown, Kim and his colleagues examined its prevalence in U.S. adults with CVDs using data from the National Health and Nutrition Examination Surveys (NHANES) from 2001 to 2004.[12] Hypovitaminosis D was found to be present in 74% of the 8,351 adults who had 25-hydroxyvitamin D (25-OH D) blood levels measured. Among CVD patients it was more common in blacks than it was in Hispanic or Caucasian patients and it did not differ by gender. However, although it was found to be present in 68% of persons at low risk for

CVDs, low vitamin D levels were more prevalent in high-risk patients (75%), in patients with coronary heart disease (77%), and in subjects with both coronary heart disease and heart failure (89%) after controlling for age, race, and gender.

■ COMMENTARY

Several lines of evidence have suggested that hypovitaminosis D may contribute to CVDs by stimulating renin expression,[13] proliferation of cardiomyocytes,[14] and smooth muscle cells[15] and by producing secondary hyperparathyroidism[16] and inflammation.[17] Although the higher prevalence of hypovitaminosis D in patients with coronary heart disease and heart failure may have been caused by limited physical activity and sunlight exposure, studies have demonstrated that patients with heart failure compared to healthy controls differed in their lifestyle factors even in their earlier years, suggesting that hypovitaminosis D may occur earlier in life and precede the onset of CVDs.[18]

The Kim observational study revealed that hypovitaminosis D was highly prevalent in U.S. adults with CVDs, particularly those with both coronary heart disease and heart failure.[12] In addition, the results raise the clinical possibility that treatment of vitamin D deficiency with vitamin D supplements and/or lifestyle measures might reduce the frequency of CVDs; however, it must be clearly recognized that treatment strategies suggested by observational data are not always supported by randomized trials. Despite the positive results in small clinical trials in which vitamin D supplementation has promoted reductions in blood pressure,[19,20] left ventricular hypertrophy,[21] and inflammatory cytokines,[22] vitamin D supplementation was not associated with a reduction in cardiovascular events in the Woman's Health Initiative,[23] although it should be noted that that particular trial was not designed to evaluate cardiovascular risk.[24] Obviously, although well constructed, randomized, double-blinded clinical studies are needed to conclusively determine whether correction of vitamin D deficiency is able to contribute to the prevention and treatment of CVDs, at the present time there seems to be little risk for clinicians to recommend at least 800 IU of vitamin D daily for their adult (and especially elderly) patients and to consider prescribing even higher doses of vitamin D if needed to correct persistently abnormally low vitamin D blood levels, especially for those patients whose lifestyle and/or illnesses prevent them from being outdoors. ❖

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Flexible? Yoga and Rheumatoid Arthritis

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD

Synopsis: *Results of this pilot trial of structured yoga therapy for people with rheumatoid arthritis suggest potential therapeutic benefits, but severe methodological flaws relegate the findings to the realm of suggesting the need for further research, not that of a change in therapeutic approach.*

Source: Badsha H, et al. The benefits of yoga for rheumatoid arthritis: Results of a preliminary, structured 8-week program. *Rheumatol Int* 2009 Jan 31; Epub ahead of print.

To determine the effects of a structured yoga program on measures of rheumatoid arthritis (RA) disease activity, disability, and quality of life, the authors of this eight-week pilot controlled intervention trial recruited patients with the disorder from an RA database as developed by two regional rheumatology centers. Potential participants older than age 18 years were contacted by e-mail and asked to join the study, and a total of 47 people did. They were then divided into two groups; a control group who were wait-listed for yoga therapy to be provided at a later date, and who received only information about yoga therapy and RA support groups (n = 21); and an active intervention group who twice weekly, for a total of 12 sessions, received a structured program of yoga that emphasized stretching, strengthening, meditation, and deep breathing (n = 26). Subjects in the active intervention group were also required to perform yoga exercises at home.

All subjects received standard rheumatologic care by their doctors throughout the study. Rheumatologists collected data at baseline and at study completion on the use of disease-modifying anti-rheumatic drugs (DMARDs), disease duration, demographics, disease activity score using the 28 joint count (DAS28), and erythrocyte sedimentation rate. Subjects completed questionnaires at baseline and at 12 weeks, including health assessment questionnaires (HAQ) and the SF-36 quality of life (QOL) measure. They were also asked to fill in visual analog scales relating to pain, global assessment, and fatigue indices. The primary outcomes of interest were changes in DAS28 and HAQ.

About Yoga

Yoga is a mind-body practice with origins in ancient Indian philosophy. The various styles of yoga that people use for health purposes typically combine physical postures, breathing techniques, and meditation or relaxation. There are numerous schools of yoga. Hatha yoga, the most commonly practiced in the United States and Europe, emphasizes postures (*asanas*) and breathing exercises (*pranayama*). Some of the major styles of hatha yoga include Iyengar, Ashtanga, Vini, Kundalini, and Bikram yoga.

The 2002 National Health Interview Survey found that yoga is one of the top 10 CAM modalities used. Nearly 8% percent of those surveyed (more than 15.2 million adults) have used yoga for health purposes. ❖

Source: National Center for Complementary and Alternative Medicine. Available at: http://nccam.nih.gov/health/yoga/.

At trial's end, those who had participated in the structured yoga program reported improvements in most measures of disease activity, especially on the HAQ. Interestingly, however, QOL measures were no different between the two groups. Two subjects in the control group developed RA flares requiring medical attention, while none in the intervention group experienced a disease flare. Three people in the yoga group were taken off some of their medications due to significant clinical improvement. The researchers conclude that a structured yoga program may reduce disease activity scores, the need for medication, and levels of fatigue in people with RA.

■ COMMENTARY

Prior small trials of yoga therapy in the treatment of RA have likewise suggested therapeutic benefit, and studies of dynamic exercise and Tai Chi have also pointed to clinical efficacy in this setting. Improvements in mood and functional capacity have been associated with fitness activities in people with RA, but the problem is that many people with RA do not exercise regularly. The current article adds to the evidence of physical motion's benefits for those with autoimmune disorders, but only slightly, as the results are tainted by severe methodological flaws.

The study sample size is quite small, and the subjects that did enter into the trial were recruited via e-mail contact. Of the 320 people in the RA database only 87 replied to the e-mail, and only the final 47 agreed to participate. Those who became part of the control group did so because they were interested in yoga but could not commit to regular practice, largely due to time constraints. At baseline a larger proportion of subjects in the control group were on DMARDs, suggesting that they may have had more active disease. Subjects who were unable to perform the yoga exercises were not permitted entry into the study, but the authors later state that modifications to the program were suggested for those who could not complete certain exercises. This latter point is important, as most yoga therapists believe that almost anyone can participate in yoga therapy, whether the focus be on postures, breath work, and/or meditation, provided the approach is individualized. While those in the active group came together regularly, members of the control group had no added interpersonal intervention. In addition, there was no blinding of the rheumatologists, so bias is an issue. It should be noted that the authors of this study were up front about its shortcomings.

Of interest is where this study was performed—Dubai. The United Arab Emirates is home to a multiethnic population, yet the participants in the study included only one Arab together with 26 Indians and 15 Caucasians, among others. The individuals' frame of reference could have had an impact on the decision to participate in the trial, as well as the trial's results.

On the up side, the program was jointly developed by the yoga therapist and rheumatologists, intention-to-treat analysis was employed, and even though the trial was of short duration there were suggestions of meaningful clinical improvement for some of the participants. Questions regarding generalizability would be appropriate (the yoga therapist was Master's qualified in Yoga and Ayurveda) except for the fact that the authors kindly provide all the postures and other interventions used during the study for readers to use for themselves and their patients, or to modify as deemed appropriate.

Yoga therapy has been recommended as an adjunctive treatment for mild-to-moderate musculoskeletal disorders on the basis of experience and, in some instances such as carpal tunnel syndrome, good data. The current article in question plants the seed of using yoga therapy for more severe musculoskeletal disorders but little more. Then again, what are pilots for? In and of themselves they are not meant to alter treatment but to kindle a spark for further investigation. It is fair to say that in this regard, at least, these authors succeeded. ❖

Sleep Quality and the Common Cold: Where Are the Data?

ABSTRACT & COMMENTARY

By Joseph Varon, MD, FACP, FCCP, FCCM

Dr. Varon is Clinical Professor of Internal Medicine, University of Texas Health Science Center, Houston, and Adjunct Professor of Medicine, University of Texas Medical Branch, Galveston; he reports no financial relationship to this field of study. This article originally appeared in the Feb. 15, 2009, issue of Internal Medicine Alert. *For that publication, it was peer reviewed by Gerald Roberts, MD, Assistant Clinical Professor of Medicine, Albert Einstein College of Medicine, Bronx, NY; Dr. Roberts reports no financial relationship to this field of study.*

Synopsis: *Lack of sleep impairs the immune system and lowers resistance to viral illness. The quality of*

sleep is important. Those volunteers who spent less than 92% of their time in bed asleep were five-and-a-half times more likely to become ill than those who were asleep for at least 98% of their time in bed.

Source: Cohen S, et al. Sleep habits and susceptibility to the common cold. *Arch Intern Med* 2009;169:62-67.

THIS STUDY WAS AIMED AT EVALUATING WHETHER SLEEP habits are associated with resistance to the common cold. The investigators obtained estimates of sleep habits of volunteers that reported sleep duration, sleep efficiency, and "feeling rested" the next day for a period of 14 consecutive days. In addition, virus-specific neutralizing antibody titers, demographics, and height and weight were obtained in these previously healthy volunteers. Once the baseline sleep assessments were completed and the antibodies titers were obtained, volunteer participants were exposed to a rhinovirus (RV-39) and were closely monitored on a daily basis to see whether they developed the clinical syndrome of the "common cold." All signs and symptoms of illness were assessed the day before and for a period of five days after the viral challenge.

The study data were collected over a four-year period and the study included 78 healthy men and 75 women (age range, 21-55 years). All participants were interviewed by phone on 14 consecutive evenings utilizing questions from the Pittsburgh Sleep Quality Index. To avoid bias, viral immunity was assessed by the pre-challenge antibody titer and age considerations, as well as body mass index, gender, race, income, level of education, season of exposure, and pre-existing psychological variables. Of the 153 subjects enrolled, 135 (88.2%) were infected by the RN-39; 54 (35.3%) developed a common cold (defined as infection and the objective common cold criteria) and 66 (43.1%) developed a common cold (defined as infection and the subjective [Jackson] criteria). In this cohort, a shorter sleep duration and lower sleep efficiency were associated with increased risk for the development of a common cold by both objective and subjective criteria. The percentage of nights that the participants responded as "feeling rested" had no correlation with the presence of infection. Interestingly, sleep efficiency, but not sleep duration, was associated with the total symptom score of these volunteers.

■ COMMENTARY

This study showed a direct association between poorer sleep efficiency and shorter sleep duration prior to RV-39 exposure with an increased probability of developing a common cold. A number of theories exist as to why good sleep efficiency and duration could be protective for viral illness. There is a direct correlation of sleep with the regulation of a variety of pro-inflammatory cytokines, histamines, and other symptom mediators that are commonly released in response to a viral infection.[1] It is well documented that people who sleep 7-8 hours a night have the lowest rates of heart disease.[2] On the basis of the present study, the authors suggest a minimum of 7 hours of sleep on daily basis.

The reader must be cautious, however, when looking at the data presented in this article. All the volunteers were healthy prior to enrollment in this trial. In reality, in a busy clinical practice, many of our patients have other significant comorbidities that may adversely affect their chances of developing a common cold besides good sleep efficiency. ❖

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Forget the Munchies: Can Calorie Restriction Improve Memory?

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD

Synopsis: *Self-reported modest reduction of caloric intake by 30% for a duration of three months improves cognitive function in healthy elderly subjects.*

Source: Witte AV, et al. Caloric restriction improves memory in elderly humans. *Proc Natl Acad Sci U S A* 2009;106:1255-1260; doc: 10.1073/pnas.0808587106.

THE AUTHORS OF THIS PAPER DESIGNED A PROSPECTIVE interventional trial to study the effects of calorie restriction (CR) or a diet high in unsaturated fatty acids (UFA) on cognition in healthy, normal to overweight elderly people. A total of 50 subjects (29 women) were enrolled in the study with an average age of 60.5 years

and an average body mass index (BMI) of 28 kg/m^2. At the end of three months, data were evaluable on 49 participants.

At baseline, a routine physical examination, including neurologic examination with Mini-Mental State Examination (score had to be higher than 26 for study participation), was performed. Subjects were then placed into one of three groups based on age, gender, and BMI: CR (caloric intake to be reduced by 30% from previous habits); "UFA enhancement" (increase amount of UFA ingested by 20% compared with previous intake, while keeping total fat intake constant); and control group (no change to eating habits). The active intervention groups received training by nutritionists blinded to the underlying study hypothesis and received phone instruction if needed (the CR group was privy to a small number of extra sessions of instruction). All participants were required to fill out nutrition diaries and were interviewed at intervals by trained dietitians regarding their diets.

The primary outcome measure of interest was the ability to learn and remember new information. Before and after the three-month intervention subjects were tested on memory performance by a trained neuropsychologist. Participants were asked to learn and remember as many words as possible out of a list of 15, and then to recall the words 30 minutes later. The total number of words recalled was called the memory score. Different exams were given at baseline and at three months.

Blood tests were assessed at baseline and at trial's end for a wide variety of measures including fasting peripheral serum insulin and glucose levels, highly specific C-reactive protein (hs-CRP), TNF-alpha, IGF-1, and brain-derived neurotrophic factor (BDNF).

By the end of the trial, subjects in the CR group had experienced both significant weight loss and a decrease in BMI. While all groups increased their proportional intake of UFAs according to dietary records, seafood intake did not change significantly across the groups, and the ratio of UFAs:saturated fat intake improved only in the UFA enhancement group. There were no significant changes in measures of lipid metabolism or waist-to-hip ratio.

There were, however, significant improvements in memory scores in the CR group at the end of the three-month intervention. Subjects in the CR group remembered more words and made fewer mistakes after calorie restriction. In addition, those in the CR group had decreased fasting insulin levels, decreased hs-CRP levels, and trended toward decreased fasting blood glucose levels. When analysis focused solely on those who most closely adhered to the CR diet (weight loss > 1 SD of mean weight loss of the control group, or weight loss > 2 kg, n = 9), a significant inverse association between memory scores and fasting insulin levels became apparent. Again using this focused analysis, the same inverse relationship was found for memory scores and hs-CRP levels. No memory improvements were found for the UFA enhancement and control groups. No association was found for neurotrophic factors and any of the groups' memory scores.

The authors conclude that moderate calorie restriction over three months time improves memory performance in healthy, normal to overweight elderly people. They posit that the mechanisms of action of CR are increased insulin sensitivity and reduced inflammation.

■ COMMENTARY

Results of a significant number of animal trials, and some human epidemiologic data, suggest that moderate CR could improve the chances for healthy aging, retained cognitive function, and enhanced longevity. Some studies using animal models of aging and neurodegeneration showed that CR protects against functional decline; other trials, however, were not quite so positive, dampening initial enthusiasm. Still, it is known that obesity in later years is associated with cognitive dysfunction. A few of the micronutrient studies that focused on essential fatty acid intake offered some promise for beneficial effects on the aging brain, especially in the animal models, but results have been contradictory.

The authors of the current trial did a very good job assessing the potential impact of the dietary interventions in question using refreshingly simple methodology. They also, however, investigated multiple laboratory parameters and identified interesting inverse relationships between memory scores and fasting insulin and hs-CRP levels in the CR group. Specifically as relates to insulin, the authors state that lower fasting insulin levels due to CR should create less insulin resistance and higher insulin sensitivity, resulting in improved cortical insulin signaling in the brain and neuronal survival. They propose that insulin and inflammatory changes play roles in cognitive impairment in the elderly.

The study is not without its weaknesses: Dietary changes were self-reported by questionnaire with meals prepared independently at subjects' homes, and although subjects in the CR group did lose weight and have decreased BMI at trial's end, it is likely that protocol adherence was not as strong as reported; simply being enrolled in a study often leads to changes in diet and lifestyle, so the report of no change in exercise activity could likewise be overstated; and subjects in the CR

group received more interpersonal attention than did members of the other groups.

The results for UFA enhancement are disappointing but could be related to the relative lack of marine fatty acid intake, insufficient overall UFA intake, or simply non-adherence to the UFA enhancement diet.

Practitioners considering the merits of CR for their middle-aged and older patients would be wise to show caution, as a significant proportion of elderly people are malnourished due to any number of factors including illness, the inability to prepare meals for themselves, changes in taste and dental issues, to name but a few. The data suggesting that CR may be part of a comprehensive healthy aging strategy are intriguing, but, as with any health care intervention, individualization of care is critically important, and we still lack firm guidelines with which to offer recommendations. Stay tuned, though—clearly there will be more research into the intriguing realm of CR and aging. ❖

B_{12} and Canker Sores

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

Dr. Wilke is Residency Program Director, Associate Professor of Family Medicine, University of Alabama at Birmingham School of Medicine—Huntsville Regional Medical Campus, Huntsville; he reports no financial relationship to this field of study. *This article originally appeared in the Feb. 29, 2009, issue of* Internal Medicine Alert*. For that publication, it was peer reviewed by Gerald Roberts, MD, Assistant Clinical Professor of Medicine, Albert Einstein College of Medicine, Bronx, NY; Dr. Roberts reports no financial relationship to this field of study.*

Synopsis: *Vitamin B_{12} was effective in the treatment of recurrent aphthous stomatitis.*

Source: Volkov I, et al. Effectiveness of vitamin B12 in treating recurrent aphthous stomatitis: A randomized, double-blind, placebo-controlled trial. *J Am Board Fam Med* 2009;22:9-16.

These researchers from the department of family Medicine at Ben-Gurion University in Israel previously reported the observation that treating patients with low serum levels of vitamin B_{12} also cleared their recurrent aphthous stomatitis (RAS).[1] In this randomized, double-blind, placebo-controlled trial, they set out to confirm their observation.

The researchers recruited 84 adult patients with RAS for at least 1 year from the practices of 20 family physicians. After excluding those with Behçet's disease, other inflammatory disorders, or HIV-AIDS; recent recipients of B_{12}; recent treatment of RAS by other means; known B_{12} deficiency; and other conditions, 58 patients remain. All patients had serum vitamin B_{12} levels at study entry. They were instructed in a method of recording severity of pain and filling out the "Aphthous Ulcers Diary." Patients were randomized to receive 1,000 µg of sublingual vitamin B_{12} at bedtime or matching placebo.

The intervention and control groups were similar in all respects. The patients were evenly divided between men and women. The average age was about 30 years. On average they had suffered from RAS for about 10 years. The intervention group was divided into those with an initial B_{12} level less than 250 pg/mL and those with a level greater than that. The two subgroups did not differ statistically.

The trial lasted six months. During the first four months of the study both groups had reductions in the average number of days of duration for an RAS episode (from 11.0 to 5.7 for the intervention group and 8.7 to 4.5 for the control group). During the next two months the average number of days for control group remained steady, but the B_{12} group had a further reduction to 2.0. There was a similar pattern to the reduction in the average number of aphthous ulcers per month (from 27.6 to 14.0 for the intervention group and 21.5 to 13.0 for the control group). After that, the curves diverged dramatically, and at six months the intervention group averaged 3.9 ulcers per month vs 13.4 for the control group. The graph of average level of pain showed a nonsignificant separation at month 4, and further separation at months 5 and 6 that were significant. The results did not depend on the initial serum vitamin B_{12} level. No patient reported an adverse reaction.

■ COMMENTARY

Aphthous ulcers (commonly known as canker sores) are the most common inflammatory lesions of the mouth, occurring in up to 10% of the population with more women afflicted than men.[2] Their cause is unknown. They are associated with anemia, gastrointestinal disease such as Crohn's disease and ulcerative colitis, HIV infection, and Behçet's disease. Acidic, salty, and spicy foods can trigger an attack. Treatment is symptomatic with topical anesthetics. Topical tetracycline has been effective, as have sucralfate solution and topical steroids. For severe lesions, thalidomide,

antimetabolites, and immunomodulating agents have all been employed.[3] The association of aphthous ulcers and vitamin B_{12} deficiency has been recognized for many years.[4-6] What set this study apart is that the majority of patients were not B_{12}-deficient.

As you digest the findings of this study, there are some things you should consider: 1) These patients had severe ulcerative disease (I can't think of any patients that I've treated that have had that many ulcers per month); 2) This also was a small study and, therefore, there weren't enough subjects to identify harm; and 3) The investigators' method of recruitment (advertising to local family physicians) may have biased their study to patients with more severe disease. The study also raises a question: Why did both groups show improvement in the first four months? Despite my comment about low number of subjects, you should also consider that vitamin B_{12} is infrequently associated with adverse side effects, and it's cheap. If you have a patient who fits the profile of patients in this study, vitamin B_{12} may be the answer. ❖

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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 credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

CME OBJECTIVES

After completing the program, physicians will be able to:

a. present evidence-based clinical analyses of commonly used alternative therapies;
b. make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
c. describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

CME Questions

9. Clinically significant changes in bone mineral density and fall rates were seen in which of the following groups?
a. The calcium group receiving 600 mg/d
b. The calcium group receiving 1,200 mg/d
c. The placebo group
d. Both the 600 mg/d and the 1,200 mg/d groups

10. Hypovitaminosis D:
a. was more common in Caucasian patients than in black or Hispanic patients.
b. was found to be present in only 35% of persons at low risk for CVDs.
c. was found to be present in 89% of patients with both coronary heart disease and heart failure.
d. need not be treated in patients older than age 85 years.

11. The researchers of the yoga study concluded that a structured yoga program may result in which of the following effects on rheumatoid arthritis?
a. Reduced disease activity scores
b. Reduced need for medication
c. Reduced levels of fatigue
d. All of the above

12. In the study on caloric restriction, the group that reduced caloric intake by 30% reported which of the following outcomes at the end of the trial?
a. Improved memory
b. Reduced body mass index
c. Decreased fasting blood glucose levels
d All of the above

Answers: 9. b, 10. c, 11. d, 12. d.

NIHSeniorHealth Web Site Adds CAM Information

Visitors to NIHSeniorHealth, the National Institutes of Health (NIH) web site designed especially for older adults, now have the opportunity to learn about complementary and alternative medicine (CAM).

Older adults who go to http://nihseniorhealth.gov/cam/toc.html will find easy-to-understand information on the basics of CAM, as well as useful tips on how to be an informed consumer, choose a CAM practitioner, and talk candidly with their doctor about CAM use.

NIHSeniorHealth is a joint effort of the National Institute on Aging (NIA) and the National Library of Medicine (NLM). The site is based on the latest research on cognition and aging. It features short, easy-to-read segments of information that can be accessed in a number of formats, including various large-print type sizes, open-captioned videos, and an audio version. Topics coming soon to the site include dry eye and substance abuse among older adults. ❖

CAM Conference to Be Held May 12-15 in Minneapolis

The North American Research Conference on Complementary & Integrative Medicine will be held in Minneapolis, MN, May 12-15, 2009. This conference is sponsored by the Consortium of Academic Health Centers for Integrative Medicine (CAHCIM), which consists of 42 leading academic medical centers from across North America. This is a follow-up to the first conference presented in Edmonton, Alberta, in May 2006, which was itself the third in a series of international meetings initially co-sponsored by Harvard Medical School and the University of California, San Francisco.

The North American Research Conference on Complementary & Integrative Medicine is international in scope and invites and encourages the submission of scientific abstracts and proposals for sessions from corporate scientists, academic researchers, educators, and health care providers worldwide.

The conference will showcase original scientific complementary, alternative, and integrative medical research (CAIM) through keynote and plenary presentations, oral and poster presentations, and innovative scientific sessions. Areas of CAIM research presented and discussed at this conference will include: research in basic science, clinical research, methodological research, health services research, and education research.

The goal of the directors of this conference is to provide a single event that attracts a critical mass of cutting-edge, peer-reviewed science, and discussion in the broad field of complementary and integrative medical research, organizers say. "The conference invites and benefits enormously from collaboration with many major professional organizations, publishers, and granting agencies, which focus on aspects of the CAIM field. Events throughout the four-day meeting are designed to foster the development of new collaborations and to strengthen existing partnerships." ❖

FDA Warning Expands to Include 69 Weight-loss Products

The FDA expanded an alert to consumers about weight-loss supplements that contain undeclared pharmaceutical ingredients and/or natural or herbal ingredients. Many of the weight-loss products analyzed contain potentially harmful ingredients that are not listed on product labels or in promotional materials. On Dec. 22, 2008, FDA warned consumers about 28 weight-loss products. Since that time, FDA analysis identified 41 additional tainted weight-loss products that may jeopardize consumers' health. A list of these products can be found at: www.fda.gov/bbs/topics/NEWS/2008/NEW01933.html. The recent analysis found that the following active pharmaceutical ingredients, often in amounts far exceeding FDA recommended levels, were present in some of these products:

- **Sibutramine**, a controlled substance that can cause high blood pressure, seizures, tachycardia, palpitations, heart attack, or stroke;
- **Rimonabant**, a drug not approved for marketing in the United States; in Europe, the drug has been associated with increased risk of depression and suicidal thoughts;
- **Phenytoin**, an antiseizure medication;
- **Phenolphthalein**, a solution used in chemical experiments and a suspected cancer-causing agent;
- **Bumetanide**, a diuretic.

Many of the weight-loss supplements are promoted and sold on various web sites and in retail stores. Although some of the products claim to be "natural" or to contain only "herbal" ingredients, they actually contain potentially harmful ingredients not stated on the

product labels or in promotional advertisements. The products are not FDA-approved and may be potentially harmful to unsuspecting consumers.

"These tainted weight-loss products pose a great risk to public health because they contain undeclared ingredients and, in some cases, contain prescription drugs in amounts that greatly exceed their maximum recommended dosages," said Janet Woodcock, MD, director, Center for Drug Evaluation and Research, FDA. "Consumers have no way of knowing that these products contain powerful drugs that could cause serious health consequences. Therefore FDA is taking this action to protect the health of the American public."

FDA has inspected many of the companies associated with the sale of these illegal products, and currently is seeking product recalls *(see below)*. Based on the FDA's inspections and the companies' inadequate responses to recall requests, if necessary, FDA may take additional enforcement steps, such as issuing warning letters or initiating seizures, injunctions, or criminal charges.

Information for consumers can be found at: www.fda.gov/cder/consumerinfo/weight_loss_products.htm. ❖

FDA Warns Against Taking Venom HYPERDRIVE 3.0

THE FDA IS WARNING CONSUMERS NOT TO TAKE VENOM HYPERDRIVE 3.0, a product sold as a dietary supplement and containing sibutramine. Sibutramine, a controlled substance with risks for abuse or addiction, poses potential safety risks. Sibutramine can substantially increase blood pressure and heart rate, and may present a significant risk for people with a history of heart disease, heart failure, irregular heart beats, or stroke, according to Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research.

Venom HYPERDRIVE 3.0 is marketed by Applied Lifescience Research Industries (ALR Industries), Oak View, CA. On Dec. 24, 2008, ALR Industries initiated a recall of all lots of Venom HYPERDRIVE 3.0 after the FDA laboratory analysis showed samples of the product contained undeclared sibutramine. Although ALR Industries claims on its web site that only "trace amounts" of sibutramine were found in this product, the FDA laboratory tests showed that Venom HYPERDRIVE 3.0 contains a significant amount of sibutramine per dosage unit.

The product was sold via distributors and in retail stores nationwide as well as in Canada, Poland, Sweden, Hungary, South Africa, the Netherlands, Australia, France, and the United Kingdom. The product was packaged in red plastic bottles containing 90 capsules each with the UPC# 094922534743.

Consumers who have this product should stop taking it immediately and contact their health care professional if they have experienced any adverse effects. Consumers can contact the company at legal@alrindustries.com to receive further instructions for returning the product and to ask any questions. Health care professionals and consumers may report serious adverse events or product quality problems with the use of this product to the FDA's MedWatch Adverse Event Reporting program either on-line: www.fda.gov/medwatch/report/hcp.htm; by fax: (800) FDA-1078; or by phone: (800) FDA-1088. ❖

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