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INSIDE

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Russell H. Greenfield, MD (executive editor) and Paula Cousins (senior managing editor) have no financial relationships with companies having ties to the material presented in this continuing education program.

Glucosamine Sulfate for Osteoarthritis

By Dónal P. O'Mathúna, PhD

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OSTEOARTHRITIS IS THE MOST COMMON FORM OF ARTHRITIS AND A leading cause of disability in the United States.[1] As many as 40% of those older than 65 years may have symptomatic osteoarthritis of the hip or knee, the large joints most commonly affected by osteoarthritis.[1] It is estimated that almost everyone 75 years of age or older is affected by osteoarthritis in at least one joint. However, only about half of the people who show evidence of the disease on X-ray report having any symptoms.[2] The prevalence of osteoarthritis is expected to double in the next 20 years.[3]

Osteoarthritis was once viewed as a consequence of aging, but is now known to develop due to complex interactions involving genetics, age, gender, obesity, joint injury, and muscle weakness.[3] Osteoarthritis tends to affect women at an earlier age than men, making it an important area of investigation for women's health.

Background

Medically speaking, osteoarthritis refers to a disease in which the cartilage inside joints gradually degenerates. This exposes the bone inside the joint and causes narrowing of the joint space leading to stiffness and pain. In the end, the joint may become so immobile and painful that joint replacement surgery is the best alternative. *(See Figures 1 and 2, page 15.)* Osteoarthritis is only one of a number of arthritic diseases, resulting in the term arthritis being used commonly to refer to any pain and stiffness in the muscles and joints. For this reason, some who have osteoarthritis refer to it as arthritis. Technically speaking, arthritis involves inflammation in the joints and osteoarthritis is a non-inflammatory degenerative disease. All of the studies reviewed here were carried out with older adults diagnosed with osteoarthritis.

Currently, osteoarthritis does not have a cure.[4] Management of symptoms includes pharmacological and non-pharmacological

strategies.[1] Weight control, pain relief, exercise to maintain and improve the range of motion and stability of the joints, and limiting functional disability are important strategies in treating osteoarthritis. Frequently, drug therapy, including analgesics like acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), is needed. The newer cyclooxygenase-2 (COX-2) inhibitors are recommended widely as perhaps being safer than older NSAIDs. Although all of these are important for managing symptoms, they do not treat the underlying pathology.

Concerns about the toxicity and side effects of pharmaceutical drugs have fueled interest in complementary approaches to managing osteoarthritis symptoms. Some dietary supplements are alleged to treat the underlying condition. Foremost among these are glucosamine sulfate and chondroitin sulfate, which are some of the most popular dietary supplements sold in the United States.[5] Although the two supplements are usually taken together, most of the studies have tested them separately.[3] This review will focus specifically on the use of glucosamine sulfate.

Glucosamine occurs naturally in the body as one component of the cartilage and synovial fluid found within joints.[5] Glucosamine forms part of the structure of some compounds whose levels are reduced with osteoarthritis. A number of salts of glucosamine are available, with some debate over their relative effectiveness. While the exact mechanism of action of glucosamine remains unknown, it is presumed that glucosamine supplementation facilitates the production and regeneration of cartilage.

Clinical Studies

Clinical studies have been conducted on glucosamine sulfate for osteoarthritis for more than 20 years. Many of the early studies were conducted in Europe using a product available there by prescription as 1,500 mg sachets to be dissolved in water (manufactured by Rotta Pharmaceuticals of Italy). These studies were sponsored by its European manufacturer and generally had favorable results. Later independent studies tended to have negative results, raising concerns about bias. However, the differences among various trials are more complicated, involving different glucosamine formulations and study designs. Independent studies have used products available in the United States as dietary supplements, many of which are formulated as capsules and may not be absorbed well.[2]

An important publication in the history of glucosamine was a systematic review and meta-analysis published in 2000.[6] This review identified six double-blind, randomized, controlled trials (RCTs) in which glucosamine sulfate was administered for at least four weeks. The trials were conducted between 1980 and 1997 and all evaluated knee osteoarthritis symptoms. The analysis revealed moderate-to-large benefits from taking glucosamine sulfate. However, all of the trials were of relatively short duration and had methodological limitations that are known to exaggerate beneficial effects. These included inadequate allocation concealment and lack of intention-to-treat analysis. There was also a question of publication bias.[2]

Another meta-analysis was published in 2003 which reviewed trials published between 1980 and 2002.[7] Seven RCTs of glucosamine sulfate for osteoarthritis were included in the analysis. The treatment periods ranged from four weeks to three years, and only high-quality studies were included. Glucosamine was found to significantly improve symptoms as measured by the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index, Lequesne Index (LI), visual analog scale (VAS) for pain, and mobility tests. The effect sizes were less than those found in the 2000 meta-analysis, which was interpreted as being due to the inclusion of only higher-quality studies. The 2003 review also included two studies in which joint space reduction was measured by X-ray. Both found significant improvements which suggested slowing of the joint cartilage degenerative process.

A subsequent review included all RCTs of glucosamine for osteoarthritis published up until 2005.[8]

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
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.

Back Issues: $58 per issue. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Figures 1 and 2

A healthy joint and a joint with osteoarthritis

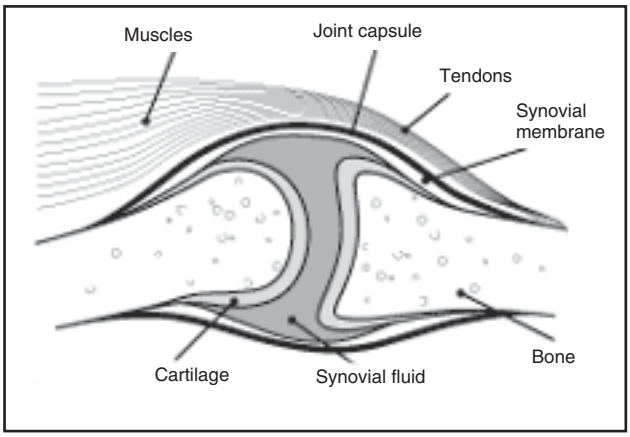

Figure 1: In a healthy join, the ends of bones are encased in smooth cartilage. Together, they are protected by a joint capsule lined with a synovial membrane that produces synovial fluid. The capsule and fluid protect the cartilage, muscles, and connective tissues.

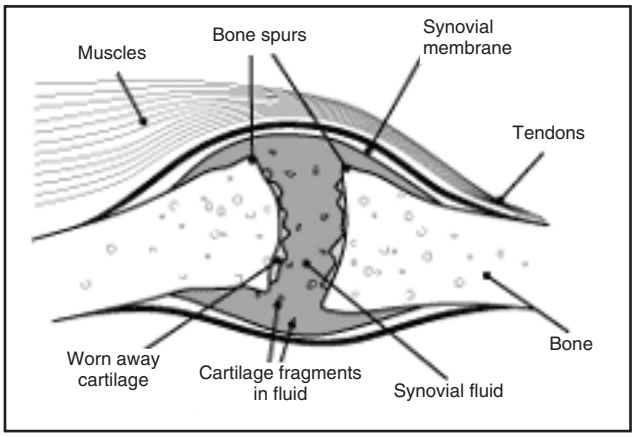

Figure 2: With osteoarthritis, the cartilage becomes worn away. Spurs grow out from the edge of the bone, and synovial fluid increases. Altogether, the joint feels stiff and sore.

Source: National Institutes of Health. Handout on Health: Osteoarthritis. Available at: www.niams.nih.gov/hi/topics/arthritis/oahandout.htm. Accessed Jan. 13, 2008.

Twenty studies were included in the analysis which showed much variability in their results. Overall, glucosamine showed a 28% improvement in pain and a 21% improvement in function as measured by LI. Subgroup analyses shed some light on the sources of variability. The eight studies of highest quality (which had adequate allocation concealment) showed no benefit in pain and WOMAC function scores. Ten of the studies were conducted with the Rotta product and their pooled results found glucosamine superior for pain and function. The 10 studies using non-Rotta products did not show statistical differences between glucosamine and placebo.

Since those reviews were published, the much-anticipated Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) published its results.[9] This study randomized more than 1,500 patients with symptomatic knee osteoarthritis to daily doses of either 1,500 mg glucosamine hydrochloride, 1,200 mg chondroitin sulfate, both glucosamine and chondroitin, 200 mg celecoxib, or placebo. Two-thirds of the participants were women. The primary outcome measure was a 20% reduction in knee pain measured by the WOMAC scale after six months of treatment. No significant reduction in pain occurred for the groups taking glucosamine or chondroitin, alone or together, compared to placebo, while pain was significantly reduced in the celecoxib group. Subanalysis, however, revealed that those participants in the GAIT study with moderate-to-severe pain, had significantly better pain reduction after six months with combination therapy compared to placebo ($P = 0.002$).

Those patients with moderate-to-severe joint damage as revealed by X-ray were asked to continue in a follow-up study focused on joint space width.[3] Patients continued to take the same treatment to which they had been assigned for a total of two years, with X-rays obtained at baseline, 12 months, and two years. No statistically significant differences in joint space width were observed between any of the groups.

Adverse Effects

The GAIT study reported no significant differences in adverse effects between the groups, with a similar number of participants withdrawing from each group because of adverse events.[9] No differences in serious adverse events between groups were reported in the meta-analyses.[7] Its safety profile is thus considered excellent.

Concerns have been raised that glucosamine might interfere with glycemic control in diabetic patients since

animal models have demonstrated such effects. However, a double-blind RCT of Type 2 diabetes patients receiving either placebo or 1,500 mg glucosamine sulfate plus 1,200 mg chondroitin sulfate found no changes occurred in glycemic control after 90 days.[10]

Glucosamine sulfate is obtained from chitin extracted from marine exoskeletons, which has raised concerns about allergic reactions. Those with seafood allergies should probably avoid glucosamine, depending on the severity of their allergy, or be carefully monitored if they try it.[4]

Conclusion

The results of the GAIT study are consistent with previous research on glucosamine hydrochloride: It does not have the effectiveness found for glucosamine sulfate. Only the Rotta brand has consistently demonstrated effectiveness in reducing symptoms and slowing joint deterioration. The glucosamine may be more readily absorbed from this product as it is dissolved in water before consumption. Questions have been raised about the bioavailability of glucosamine in general.[2] In addition, quality varies considerably among those products available in the United States as dietary supplements.[11]

For those with osteoarthritis, a trial of glucosamine sulfate may be warranted, especially for those who do not respond well to conventional treatments. However, even in those trials where glucosamine sulfate has been found effective, participants continued to use other analgesics when pain or discomfort were particularly problematic. Symptoms should be evaluated carefully over 2-3 months, at which time those who are likely to benefit will have responded.[12] As with many chronic conditions, control of weight, exercise, and other symptom-relieving strategies will remain important in the overall management of osteoarthritis. ❖

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De-SELECT? Vitamin E, Selenium, and Prostate Cancer

By Russell H. Greenfield, MD, Editor

Synopsis: *Results of the SELECT trial, a large randomized, placebo-controlled, double-blind trial designed to help determine whether selenium, vitamin E, or both could safely prevent prostate cancer in middle-aged and older men, were not to be published for another four years. Interim analyses, however, revealed no benefit from therapy, and even some potential health concerns.*

Source: Lippman S, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 2009;301:39-51.

The authors of this large phase 3 randomized, placebo-controlled, double-blind trial were interested in determining whether selenium, vitamin E, or both could safely prevent prostate cancer and other diseases in middle-aged and older men who were relatively healthy at time of study initiation. A total of 35,533 men from 427 participating sites in the United States, Canada, and Puerto Rico participated in the trial and were to be followed for 7-12 years. Subjects had to be older than age 50 years if African American, or older than age 55 (all other men), have no prior history of prostate cancer, have a PSA < 4 ng/mL and normal findings on digital rectal examination. Participants were randomly assigned to one of four groups: selenium (200 µg/d from L-selenomethionine) and matched placebo; vitamin E (400 IU/d of all *rac*-alpha-tocopheryl acetate [a synthetic racemic mixture of eight vitamin E stereoisomers]) and matched placebo; selenium and vitamin E; or placebo and placebo. Subjects were followed regularly by their doctor. The main outcome of interest was development of prostate cancer. Secondary outcomes of interest included development of other cancers including lung and colorectal cancer, cardiovascular events, and overall mortality. An independent data and safety monitoring committee met annually and reviewed existing data from the trial. Interim analyses had been planned for years 5, 7, 9, 10, and 11 after the first participant was randomized.

The safety and data monitoring committee met last September to review data as of Aug. 1, 2008, and determined that there was no evidence of benefit from either study agent, and no apparent research benefit to continuing follow-up for subjects enrolled in SELECT. The study was stopped in its seventh year.

The committee reached their decision on the basis of a median 5.46 years of follow-up. There were no statistically significant differences between the four groups for either primary or secondary outcomes of interest. A non-statistically significant increased risk of prostate cancer in the vitamin E group was identified, as was a mildly increased risk for Type 2 diabetes in the selenium group (relative risk = 1.07). Similar risks were not seen in the combined selenium + vitamin E group. The researchers concluded that selenium and vitamin E, alone or in combination, and at the doses and formulations used, did not prevent prostate cancer in a heterogeneous population of relatively healthy older men during a median of 5.5 years follow-up.

■ COMMENTARY

The study authors state that the genesis of SELECT was the findings from secondary analyses of the Nutritional Prevention of Cancer (NPC) study and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study that showed significant prostate cancer risk reductions with selenized yeast or alpha-tocopherol. Further data suggesting chemopreventive effects of selenium and vitamin E came from epidemiologic evidence and preclinical data. At the SELECT study's initiation there were high hopes that an effective method of helping prevent the most common non-skin epithelial malignancy in U.S. men might be found. Many anxiously awaited the year 2013 when results were to be published and we'd learn if the early promise of selenium and vitamin E bore fruit; we gained access to the data early, unfortunately. The results are certainly disappointing, but the negative conclusions drawn from this trial need not be overly broad when considering issues of timing and the specific agents employed.

First, it's important to comment on the strengths of this trial, and they are many. From the very large sample size, to unique methods of pre-trial compliance assessment, to supplement quality measures, to intensive statistical analyses and a study population that included a large proportion (13%) of African-American men, the research team put together an exemplary model of research methodology.

Now, a word of caution in interpreting the results. The subjects enrolled in SELECT were all older than age 50 years at the time of supplement regimen initiation, so we don't know whether earlier administration of selenium, vitamin E, or both might have offered chemoprotective effects against much later development of prostate cancer. The authors point out the next area of concern themselves—they chose one specific formulation each of selenium and vitamin E, and results are tied specifically to the formulations employed. This is an important consideration, as the NPC trial used high selenium yeast, and some researchers suggest that gamma-tocopherol might offer the most active chemoprotective effects, and that all *rac*-alpha-tocopheryl acetate may be significantly less potent than other forms of vitamin E.

Prior studies suggested that selenium's effects might be more noticeable in selenium-deficient populations, but the subjects in SELECT were largely selenium-replete. Other data point to more of a protective effect against prostate cancer for vitamin E in smokers, but subgroup analysis of smokers in SELECT did not reveal a protective benefit for vitamin E.

Concerns about an association between high levels of selenium intake and later development of Type 2 diabetes have been raised previously, but there is no consensus yet, as data are conflicting. The results presented in SELECT merit additional concern in this regard. The

nonsignificant increase in prostate cancer in the vitamin E group also warrants close attention. The authors do state, however, that 400 IU vitamin E appears to be safe in otherwise healthy men, since they detected no increased incidence of cardiovascular events or overall mortality in the vitamin E group.

What are practitioners to make of these data? It seems clear that vitamin E alone, selenium alone, or the two in combination should not be recommended to middle-aged and older men for the specific purpose of preventing prostate cancer. Whether administration of selenium and vitamin E earlier in life, or the use of other formulations, might have benefits in this regard remains unknown.

For the conclusions that can be safely drawn from this trial, it is an exquisite piece of research, one worthy of a place in your file cabinet. ❖

Carnitine Shows Promise Against Risk Factor for Cardiovascular Disease

ABSTRACT & COMMENTARY

By Dónal P. O'Mathúna, PhD

Synopsis: *Carnitine supplementation produced beneficial changes in endothelial function as measured by flow-mediated dilation (FMD) after a high-fat meal. No significant differences were found for other biomarkers of inflammation and oxidative stress. Carnitine may have a role in reducing risk factors for cardiovascular disease, although this research is still at a very early stage.*

Source: Volek JS, et al. Effects of carnitine supplementation on flow-mediated dilation and vascular inflammatory responses to a high-fat meal in healthy young adults. *Am J Cardiol* 2008;102:1413-1417.

Because carnitine has been shown to decrease oxidative stress and improve endothelial cell functioning, the investigators examined the effects of carnitine supplementation on postprandial flow-mediated dilation (FMD) and circulating biomarkers of inflammation and oxidative stress after a high-fat meal. A randomized, double-blind, placebo-controlled, crossover study design was used. Thirty men and women (age 30 ± 8 years, body mass 72.9 kg ± 17.1 kg, body fat 13.0% ± 6.4%) participated in two vascular testing days, each preceded by three weeks of supplementation with either 2 g/d of L-carnitine (L-carnitine L-tartrate) or placebo with a three- to five-week washout period between trials. Brachial artery FMD in response to 5 minutes of upper arm occlusion and circulating markers of oxidative stress and inflammation were measured in the fasting state and after a standardized high-fat meal. After three weeks of supplementation, peak FMD in the fasting state was similar between the carnitine and placebo trials, averaging 6.6%. Peak FMD during the postprandial period decreased to 5.8% at 1.5 hours during placebo and increased to 7.7% during the carnitine trial ($n = 30$: $P = 0.043$ for supplement by time interaction effect). This improvement in postprandial vascular function was most dramatic in subjects who showed a decrease in peak FMD in response to the meal ($n = 15$: $P = 0.003$ for supplement by time interaction effect). There was a significant increase in postprandial lipemia and plasma interleukin-6 but no effect of supplementation. There were no significant postprandial changes or supplement effects for plasma tumor necrosis factor-alpha and malondialdehyde. In conclusion, consistent with other work showing a beneficial effect of carnitine on vascular function, these findings indicate that carnitine supplementation in healthy individuals improves postprandial FMD after a high-fat meal.

■ COMMENTARY

Carnitine is a quaternary amine found primarily in meat and fish. It was once thought to be a vitamin, but is now regarded as a conditionally essential nutrient (CEN).[1] A CEN is a compound normally produced in sufficient quantities in the body, but which can be required in the diet under certain conditions. Carnitine is required for transport of long-chain fatty acids into the mitochondria of muscle cells where they are oxidized to release their energy. Carnitine is concentrated in tissues that utilize fatty acids as their primary dietary fuel, which includes skeletal and cardiac muscle.[2]

The physiological basis for the study reviewed here is that myocardial ischemia leads to loss of carnitine from endothelial cells. Reduced tissue levels of carnitine are associated with increased oxidative stress and compromised blood flow. Earlier studies showed that intravascular carnitine administration can counteract oxidative stress and improve blood flow via several mechanisms that impact endothelial function. Several other studies showed that oral carnitine supplementation has beneficial effects on cardiovascular risk factors and in patients with different forms of cardiovascular disease, including angina, dysrhythmia, chronic heart failure, myocardial infarction, or peripheral vascular disease.[1]

Flow mediated dilation (FMD) is a method used to quantify endothelial function.[3] Impaired endothelial function is involved in the pathophysiology of atherosclerotic cardiovascular disease. FMD represents endothelium-dependent vascular relaxation, and is typically measured at the brachial artery due to ease of access. As such it is a marker for increased risk of cardiovascular disease. Various stimuli can be used to elicit flow-dependent dilation of the arteries, with a single high-fat meal being used in this trial.[4]

The study used a randomized, double-blind crossover design. However, no details were given about the method of randomization or how well the allocation was concealed. The crossover design allows participants to serve as their own controls, but must ensure an adequate washout period between interventions. This trial used three weeks for men and about five weeks for women. Women were given a longer time to ensure they would be tested in each phase in the same menstrual phase. Using the same washout period for all participants would have been preferable. No discussion of the adequacy of either time period for complete washout was given. Neither was there discussion of the rationale for three weeks of supplementation vs any other period. Such details would have provided important background for the design of the study. Compliance with protocol was stated to be 100% based on signed log sheets. Collection of unused capsules would have provided an additional objective method of assessing compliance.

Great detail was given, however, on the procedures used, including how FMD was measured. Recent calls have been made to standardize these procedures before FMD can be usefully applied in research and clinical practice.[3]

The results showed a clear difference in vascular reactivity between those taking carnitine compared to placebo. Not only was the difference numerically significant, but the direction of change was opposite. At 1.5 hours after the meal, peak dilation decreased to 5.8% in the placebo group, but increased to 7.7% in the carnitine group ($P = 0.043$). A subgroup analysis was conducted on those found to have greater postprandial vascular impairment. It was not stated if this analysis was preplanned or conducted ad hoc. Those with greater impairment were identified as having a decrease in peak dilation 1.5 hours after the meal when taking the placebo (n = 15). Their average peak dilation decreased from 7.2% pre-meal to 3.3% 1.5 hours postprandial. When taking carnitine, the average peak dilation increased from 5.5% to 6.9% ($P = 0.003$). However, significant differences were not found at 3 and 4.5 hours postprandial. None of the other outcomes measured showed significant differences between placebo and carnitine supplementation.

The clinical and research implications of this study are difficult to assess, and were not discussed by the authors. Other research has demonstrated that increased FMD is most likely associated with improved nitric oxide metabolism. While this study demonstrates that carnitine supplementation improves endothelial vasodilation after a high-fat meal, further research is needed to demonstrate the clinical relevance of this finding. ❖

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Old and New Treatments for Irritable Bowel Syndrome: Effective or Not?

ABSTRACT & COMMENTARY

By Bridget S. Bongaard, MD, FACP

Dr. Bongaard is Director of the NorthEast Internal & Integrative Medicine Program, CMC-NorthEast Medical Center in Concord, NC; she reports no financial relationships to this field of study.

Synopsis: *This article was a systematic review and meta-analysis of high-quality randomized controlled trials determining the effect of fiber, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome, and demonstrating superiority of the three examined therapeutic modalities as compared to placebo.*

Source: Ford AC, et al. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: Systematic review and meta-analysis. *BMJ* 2008:337:a2313; doi: 10.1136/bmj.a2313.

Prominent international gastrointestinal authorities from six different institutions pooled their assessments of the available literature on treatment options for irritable bowel syndrome (IBS), spanning the years 1950 to April 2008, and combing both English and foreign papers. The selected randomized controlled trials were required to compare fiber, antispasmodics, and peppermint oil with placebo or no treatment in adults older than 16 years of age, excluding patients with organic or other functional gastrointestinal disorders. The goal was to determine whether the modalities rendered for at least one week (to allow achievement of steady state plasma concentrations of the agents) produced either a "global assessment of cure" or improvement of symptoms, or cure or improvement of abdominal pain after treatment.

Twelve studies, containing a total of 591 patients, analyzing fiber vs placebo or no treatment, were found to be acceptable. An array of fiber agents were studied: Dietary fiber and cereals, psyllium/ispaghula, karaya gum, and wheat bran were manifest in the individual studies. This notably includes both soluble and insoluble fiber compounds. Despite the diversity of the products tested, surprisingly, the therapeutic effectiveness was limited to the use of ispaghula/psyllium and not other more common dietary fiber agents utilized in clinical practice.

Twenty-two randomized controlled trials including 1,778 patients, met the criteria for evaluating the effectiveness of various prescribed antispasmodics vs placebo. Again a wide variety of antispasmodic agents were assessed, including: mebeverine, alverine, trimebutine, pinaverium, otilonium, cimetropium, hyoscine, dicycloverine, pirenzipine, prifinium, propinox, and rociverine. Only hyoscine (three trials, 426 patients) and otilonium (four trials totaling 435 patients) showed consistent evidence of efficacy.

Four trials compared peppermint oil or colpermin (the active compound in peppermint oil) with placebo in 392 patients. Both compounds achieved efficacy status in comparison to placebo.

■ COMMENTARY

Irritable bowel syndrome is a common, chronic, relapsing health care issue, not only in the symptomatic experience of the patient, but also in terms of health care system resource strain (multiple expensive diagnostic tests required for exclusion of organic disease, frequent doctors visits, medication expense, and hospitalizations for unrelenting problems). Health care providers and patients alike need an effective and inexpensive strategy to successfully address the problem.

International guidelines and protocols for irritable bowel syndrome are conflicting or equivocal in their recommendations for these three commonly used agents. Traditionally, patients were first instructed to increase dietary fiber to increase intestinal transit time and stool bulk, and, if not efficacious, an antispasmodic prescription was utilized to decrease the symptoms of pain and bloating. Only recently has peppermint oil, an inexpensive over-the-counter treatment for IBS, been utilized as an antispasmodic therapeutic option. The particular best choice for fiber or medication had not been studied; however, this large meta-analysis steps up to offer best therapeutic suggestions.

The study concluded that fiber type mattered in effectiveness of treatment of IBS. Wheat bran was no more efficacious than placebo or a low-fiber diet, and using ispaghula/psyllium did provide improvement over placebo, though many patients had persistent symptoms. Both however confer health benefits as the insoluble fibers increase fecal bulk and decrease intestinal transit time with the resultant potential for increased colonic mucosal health,[1] while the water-soluble fiber supplements promote laxative effects and consequently metabolic benefits. Choosing the correct agent for the patients' clinical symptom complex is critical. Unfortunately, in the meta-analysis only three of the trials reviewed specified the IBS variety treated (constipation, diarrhea, mixed variety). It is therefore difficult to extrapolate which patient population would most benefit from water-soluble fiber, though generally it did improve symptoms. One can therefore make the argument that it should be initiated in any of the IBS subtypes, but with a caution that patients should notify their health care provider if they experience more gas or discomfort.

The type of antispasmodics studied in the meta-analysis were myriad; however, not all are FDA-approved and available in the United States. Such is the case with the two agents recommended as most efficacious in the meta-analysis. Hyoscine and otilonium proved to be the best in class for symptom relief of bloating and pain; however, otilonium is available only in Indonesia, Mexico, Spain, Greece, Brazil, and Italy.

The adverse effects of these drugs need to be taken into consideration when being applied to patient care. They can cause dry mouth, dizziness, and blurred vision compared to placebo; however, in the trials studied, the relative risk of adverse events compared with placebo was 1.62, and none reported any serious adverse events with this class. Trimebutine seemed to have no benefit over placebo, while pinaverium, cimetropium, hyoscine, and otilonium significantly reduced the risk of persistent symptoms after treatment. It is therefore recommended

that if one needs to add an antispasmodic to the patient's IBS regimen after water-soluble fiber, that the first choice be hyoscine, followed by one of the other available medications if hyoscine is not effective in symptom management.

There were no trials evaluated in this meta-analysis comparing peppermint alone either to the sole use of prescription antispasmodics or the singular use of water-soluble fiber. This analysis only addressed the use of the oil opposed to placebo, and this was made somewhat difficult by the inability to mask the smell and taste of the active treatment. Also, the four peppermint trials totaled a patient population less than either of the other two trial agents, so it is difficult to make firm recommendations with the limited data presented. Nonetheless, the studies were of good quality and all indicated that peppermint oil was more effective than placebo.

Peppermint oil decreases smooth muscle spasm, and diminishes colonic contractility and pain due to its calcium channel blocking activity. It is a safe and effective part of the IBS regimen, is an inexpensive alternative to antispasmodic medications, or may be used adjunctively if these medications do not completely dispel the IBS symptoms. Interestingly, peppermint oil can be administered to children with IBS. Buckle,[2] a noted aromatherapy expert, refers to a study by Kline et al using enteric-coated gelatin capsules containing peppermint oil in the treatment of 50 children in a controlled multicenter study.[3] Eight children withdrew for various reasons; however, 76% of the peppermint group showed significant reduction in symptoms compared to 43% in the placebo group. There were no side effects noted, nor change in stool consistency.

More research needs to be done to further clarify the effects of these three treatments in relation to the three subtypes of irritable bowel symptoms. Until that time, however, practitioners can feel confident that they can safely use these inexpensive modalities to help alleviate the suffering of irritable bowel syndrome, and break the cycle of pain and bloating. ❖

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Statins, Sterols, and Stanols

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *Margarines containing plant sterols and stanols can be an effective long-term therapeutic intervention to aid with cholesterol lowering in people already on a stable statin regimen.*

Source: de Jong A, et al. Effects of long-term plant sterol or stanol ester consumption on lipid and lipoprotein metabolism in subjects on statin treatment. *Br J Nutr* 2008;100:937-941.

COMBINING TREATMENTS FOR RECALCITRANT DYSLIPIDEMIA that have differing mechanisms of action could be of greater benefit to patients than simply doubling the dose of standard agents. The authors of this small randomized, double-blind trial examined the effects of long-term plant sterol or stanol consumption on cholesterol levels and apolipoproteins in patients already on a stable statin regimen.

A total of 54 people (32 men) completed this trial (data evaluable on n = 47) where participants were asked to replace their usual spread with a "light" margarine. After a brief run-in period, subjects were randomized to one of three groups for a total of 85 weeks: control margarine; a plant sterol-enriched margarine (2.5 g/d); and a plant stanol-enriched margarine (2.5 g/d). Subjects were asked to weigh the margarine tubs daily to ensure 30 g daily consumption, and to return the tubs for weighing at weeks 5, 50, and 90. During these same times participants completed a Food Frequency Questionnaire regarding the previous four weeks' food intake, and energy intake was calculated by participating dietitians. Fasting blood samples for various lipid parameters were obtained at weeks 0, 4, 5, 9, 10, 29, 30, 49, 50, 69, 70, 89, and 90.

Results showed that subjects in both the sterol and stanol groups experienced a significant additional decrease in total and LDL cholesterol. At weeks 45 and 85, total cholesterol declined in the plant sterol group by 0.49 (8.8%) and 0.29 (5.1%), respectively. Total cholesterol declines in the plant stanol group for the same time periods were 0.82 (6.9%) and 0.50 (9.4%). With respect to LDL-C measures at 45 and 85 weeks, levels decreased by 0.40 (11.6%) and 0.28 (8.7%) in the plant sterol group, and by 0.31 (8.7%) and 0.42 (13.1%) in the plant stanol group. ApoB decreased only in the plant stanol group. The study authors concluded that both

plant sterols and plant stanols effectively lower cholesterol levels when regularly consumed by people already on a stable statin regimen.

■ **COMMENTARY**

Previous studies of the effectiveness of sterols and stanols for management of high cholesterol have reported promising results, but most were short-term trials. In this 85-week trial subjects tolerated therapy with their supplemented margarines well, and experienced significant improvements in their lipid profiles while on statins.

Both sterols and stanols have a chemical structure similar to cholesterol, and it is believed that they act by limiting intestinal absorption of cholesterol. Both are most commonly found as components of functional foods, especially margarines marketed to those with high cholesterol.

de Jong's group put together a very nice trial notable for its duration and the frequency of lipid level measurement. On the flip side, the sample size is small, and while subjects were asked not to change their dietary and exercise patterns during the trial there was no objective verification of this. Research suggests that simply being enrolled in a study can promote lifestyle and dietary changes, some of which may have impacted study results.

The good news is that this paper adds to a sizable amount of data supporting the use of plant sterols and stanols as adjunctive therapy for the treatment of high cholesterol. Keep in mind that it behooves patients to read labels when buying their margarines, however, as many still contain *trans* fats. ❖

What's That Herb Again ... ? Ginkgo for Dementia

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *A well-regarded, standardized extract of* Ginkgo biloba *does not appear to help prevent development of dementia in seniors with baseline normal or mildly impaired cognitive function. Whether use of ginkgo earlier in life has a primary preventive effect on development of dementia remains to be determined.*

Source: DeKosky ST, et al. *Ginkgo biloba* for prevention of dementia: A randomized controlled trial. *JAMA* 2008;300:2253-2262.

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

6. **The clearest evidence of effectiveness in relieving symptoms of knee osteoarthritis is available for:**
   a. glucosamine sulfate.
   b. glucosamine hydrochloride.
   c. glucosamine sulfate plus chondroitin sulfate.
   d. chondroitin sulfate.
7. **Researchers recently found which intervention to reduce the risk of prostate cancer?**
   a. Vitamin E
   b. Selenium
   c. Vitamin E + selenium
   d. None of the above
8. **Which of the following is *false*?**
   a. Peppermint oil is superior to placebo in the treatment of IBS.
   b. Peppermint oil decreases smooth muscle spasm and diminishes colonic contractility and pain.
   c. More adverse events were reported with peppermint oil than with antispasmodics.
   d. Peppermint oil is safe to use in children.

Answers: 6. a, 7. d, 8. c.

The authors of this multicenter, randomized, double-blind trial (The Ginkgo Evaluation of Memory study) sought to determine whether use of a standardized extract of *Ginkgo biloba* over time would decrease the incidence of all-cause dementia, especially Alzheimer's disease, in people older than age 75 years. Participants (n = 3,069 total, n = 482 of whom with mild cognitive impairment; mean age of all subjects = 79.1 years) had to have either normal cognitive function or mild cognitive impairment at baseline. Subjects were randomized to receive either 120 mg *Ginkgo biloba* extract (EGb-761) or an identical placebo tablet twice daily. They were then assessed every six months for incident dementia using multiple tests and scales, and employing DSM-IV criteria. If a diagnosis of dementia were being considered, additional neurologic work-up was undertaken, including MRI scanning, to exclude atypical etiologies of dementia.

After a median follow-up of 6.1 years, a total of 523 people developed dementia, with 92% of them being classified as having Alzheimer's disease or Alzheimer's disease with concomitant vascular disease. Overall dementia rates were 3.3/100 years in the active group and 2.9/100 years in the placebo group. The hazard ratio (HR) for ginkgo use and all-cause dementia was 1.12, and 1.16 for Alzheimer's disease compared with placebo. Adverse events were similar in both groups, and rates of major bleeding did not differ statistically, but there were twice as many hemorrhagic strokes in the ginkgo group than in the placebo group (16 vs 8); however, the numbers were very small. The authors conclude that a standardized extract of *Ginkgo biloba* given in a commonly used dose does not reduce the overall incidence of dementia in seniors with normal cognitive function or those with mild cognitive impairment.

■ COMMENTARY

This is a very well-done trial using a well-standardized extract of *Ginkgo biloba* (EGb-761) and employing comprehensive assessments of cognitive status to support or refute a diagnosis of dementia in senior citizens. The methodology is sound even though compliance was only about 60% by trial's end. The sample size is significant, follow-up was superb, and lots were tested individually and identified. EGb-761 has been well studied and is considered by most experts the standard by which other ginkgo extracts must be measured. The problem comes in how to interpret the data in the context of younger patients who might be at risk for dementia.

Since the study only addressed individuals older than age 75 we do not know, as the authors rightly point out, whether a longer duration of ginkgo administration started earlier in life would have offered a primary preventive effect. Thus, the results seem clear only in that older individuals should not use ginkgo to try to stave off dementia. As for those of us still in our prime, whether that's true or just in our minds (cognitively, of course), the question of ginkgo's potential utility remains to be answered.

Truly effective treatments to prevent or delay the onset of dementia, and to preserve cognitive function, have yet to be identified. The current study contributes to our understanding in a select population but not to younger people, where preventive strategies may be most effective. ❖

News Briefs

Overall Use of CAM by U.S. Adults Remains Steady, but Some Therapy Use Varies

Approximately 38% of adults in the United States aged 18 years and older and nearly 12% of U.S. children aged 17 years and younger use some form of complementary and alternative medicine (CAM), according to a nationwide government survey conducted in 2007. In a similar 2002 survey, 36% of U.S. adults reported using CAM, but there has been substantial variation between the two surveys in the use of some specific CAM therapies.

The survey, conducted as part of the 2007 National Health Interview Survey (NHIS), was developed by the National Center for Complementary and Alternative Medicine (NCCAM), a part of the National Institutes of Health, and the National Center for Health Statistics (NCHS), a part of the Centers for Disease Control and Prevention. The survey included questions on 36 types of CAM therapies commonly used in the United States—10 types of provider-based therapies, such as acupuncture and chiropractic, and 26 other therapies that do not require a provider, such as herbal supplements and meditation.

The 2007 survey results, released in a National Health Statistics Report by NCHS, are based on data from more than 23,300 interviews with American adults and more than 9,400 interviews with adults on behalf of a child in their household. The 2007 survey marks the first time questions were included on children's use of CAM.

According to the 2007 survey, the most commonly used CAM therapies among U.S. adults were (the 2002 percentages are included for those therapies that showed significant increases):

- Nonvitamin, nonmineral, natural products (17.7%). The most common were fish oil/omega-3/DHA, glucosamine, echinacea, flaxseed oil or pills, and ginseng. (The reference period for the use of specific nonvitamin, nonmineral, natural products was reduced from 12 months in 2002, to 30 days in 2007.)
- Deep breathing exercises (12.7% vs 11.6% in 2002)
- Meditation (9.4% vs 7.6% in 2002)
- Chiropractic or osteopathic manipulation (8.6%)
- Massage (8.3% vs 5.0% in 2002)
- Yoga (6.1% vs 5.1% in 2002)

Adults used CAM most often to treat pain including back pain or problems, neck pain or problems, joint pain or stiffness/other joint condition, arthritis, and other musculoskeletal conditions. Adult use of CAM therapies for head or chest colds showed a marked decrease from 2002 to 2007 (9.5% in 2002 to 2.0% in 2007).

Consistent with results from the 2002 data, in 2007 CAM use among adults was greater among:

- Women (42.8% compared to 33.5% of men)
- Those aged 30-69 (30-39 years: 39.6%; 40-49 years: 40.1%; 50-59 years: 44.1%; 60-69 years: 41.0%)
- Those with higher levels of education (Master's, doctorate, or professional: 55.4%)
- Those who were not poor (poor: 28.9%; near poor: 30.9%; not poor: 43.3%)
- Those living in the West (44.6%)
- Those who have quit smoking (48.1%)

The survey showed that overall CAM use among children is nearly 12%, or about one in nine children. Children are five times more likely to use CAM if a parent or other relative uses CAM. Other characteristics of adult and child CAM users are similar—factors such as socioeconomic status, geographic region, the number of health conditions, the number of doctor visits in the last 12 months, and delaying or not receiving conventional care because of cost are all associated with CAM use.

Among children who used CAM in the past 12 months, CAM therapies were used most often for back or neck pain, head or chest colds, anxiety or stress, other musculoskeletal problems, and attention deficit/hyperactivity disorder.

The most commonly used CAM therapies among children were:

- Nonvitamin, nonmineral, natural products (3.9%). The most common were echinacea, fish oil/omega-3/DHA, combination herb pill, flaxseed oil or pills, and prebiotics or probiotics.
- Chiropractic or osteopathic manipulation (2.8%)
- Deep breathing exercises (2.2%)
- Yoga (2.1%)

"The 2007 NHIS provides the most current, comprehensive, and reliable source of information on Americans' use of CAM," says Josephine P. Briggs, MD, director of NCCAM. "These statistics confirm that CAM practices are a frequently used component of Americans' health care regimens, and reinforce the need for rigorous research to study the safety and effectiveness of these therapies. The data also point out the need for patients and health care providers to openly discuss CAM use to ensure safe and coordinated care."

For the full report and downloadable graphics, visit http://nccam.nih.gov/news/camstats.htm. ❖

In Future Issues:

Vitamin D Deficiency

Integrated Back Stability Programs for Chronic Back Pain