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The Use of Omega-3 Fatty Acids for Cardiovascular Disease

By Susan T. Marcolina, MD, FACP

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THE VOLATILITY OF THE INVESTMENT MARKETS ON WALL STREET should make us consider our own investment in overall health, especially our cardiovascular health. For women in the United States, the leading cause of death continues to be coronary heart disease (CHD) and the mortality in women has shown no decline for the past 20 years as it has in men.[1] In fact, most women who die suddenly of CHD had no previous symptoms but did have a high prevalence of CHD risk factors *(see Table 1, page 3)*.[2] Another complication is the finding by Khot et al that 20% of all coronary events occur in individuals without any of the established risk factors identified in the Framingham risk score.[3] Such statistics require primary care physicians to reallocate and diversify strategies to decrease risk by ensuring that current established guidelines from the American Heart Association[4-6] *(see Table 2, page 3)* are implemented and individualized for all female (and male) patients as well as by identifying and treating those women (and men) at risk who may not fit the traditional profiles.

Cardiovascular Disease Risk Prediction for Women

Over the past 10 years, prospective epidemiologic studies such as the Women's Health Study (WHS) have identified chronic inflammatory states, evidenced by elevations in plasma high sensitivity C-reactive protein (hs-CRP) levels, as independent risk factors for cardiovascular disease (CVD) along with the typical risk factors identified in Table 1. The WHS followed more than 15,000 initially healthy women older than age 45 over 10 years for the occurrence of CV events. Of all of the laboratory data compiled over this time, levels of non-HDL cholesterol and total/HDL-C were most predictive of CV events and hs-CRP levels added prognostic information to all lipid fractions. Based on these data, the Reynolds Risk Point Score (RRPS) was created to estimate the risk of myocardial infarction (MI) in women. This score predicted risk of MI as well as the Framingham risk score did for women at high and low risk. However, for

women identified as intermediate risk, it proved to be a better tool due to the incorporation of two additional risk factors: 1) having a parent with a myocardial infarction prior to age 60, and 2) having a hs-CRP level greater than 2 mg/L.[7]

For these intermediate-risk patients, the new scoring re-classified 50% of the women from the intermediate group into either the high- or the low-risk group so they could be appropriately identified for early intervention to decrease the chronic inflammatory state or reassured regarding their low risk for CVD. Subsequently, these new classifications accurately predicted the clinical outcomes of these women over the ensuing 10 years.[8] Ridker et al, in the recent JUPITER trial, affirmed the value of hs-CRP in the global CV risk assessment of both middle-aged men and postmenopausal women, especially those who would otherwise be categorized as low-to-intermediate risk based on acceptable levels of lipid fraction determinations and, therefore, not offered inflammation-lowering treatment, which were statins in this study.[6]

Association of CAD with Chronic Inflammatory Diseases

Certain patient groups such as those with psoriasis, rheumatoid arthritis, and periodontal disease are known to have an increased risk for CVD due to chronic inflammatory states. Addressing the underlying inflammatory state through the use of medications such as methotrexate (psoriasis, RA), intake of dietary omega-3 fatty acids and dietary antioxidants (RA), and subgingival and supragingival removal of dental plaque (as well as scaling, root planning, and local antibiotic administration for periodontal disease) may diminish inflammation and mitigate CV risk as suggested by observational studies.[9-13] Such interventions, particularly the dietary incorporation of omega-3 fatty acids, are low-cost strategies relatively easily implemented into a patient's daily routine.

Summary Points

- Modest increases in dietary intake of omega-3 PUFAs can modulate lipid values and inflammatory markers such as hs-CRP levels to significantly diminish risk from clinical CV endpoints of myocardial infarction, stroke, and CV death from both a primary and secondary prevention standpoint.
- Increased dietary intake of omega-3 PUFAs has the potential to improve overall general medical health by mitigating the course of systemic inflammatory illnesses such as rheumatoid arthritis, inflammatory bowel disease, and psoriasis.
- Functional foods such as viscous fibers, plant stanol/sterol esters, soy protein, nuts, and omega-3 PUFAs have important nutritional and medicinal values.

Functional Foods for CV Health

Since everyone has to eat to live, new dietary approaches to reduce CV risk by incorporating cholesterol- and inflammation-lowering functional foods into daily eating plan makes sense. As a matter of fact, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and the American Heart Association (AHA) recommend the use of a variety of foods high in components that reduce cholesterol *(see Table 3, page 3)*.[14,15] Jenkins et al found such a portfolio diet to be as effective as lovastatin in decreasing the LDL-cholesterol to the goal levels of 130 mg/dL in a group of hyperlipidemic, healthy middle-aged outpatients (41% women).[16] The omega-3 polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found in fish and fish oils and alpha linolenic acid (ALA) found in plant sources, are a fifth group of functional foods to be added to Table 3 for their favorable effects on lipid and trigylceride profiles. They are, however, much more versatile for improving both general and cardiovascular health due to

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Table 1

Established risk factors for CAD[2]

- Dyslipidemia
- Hypertension
- Smoking
- Diabetes/insulin resistance
- Age
- Family history of CAD

Table 2

AHA recommendations for primary prevention of CVD in women[4-6]

- Blood pressure < 120/80 mm Hg
- LDL-cholesterol < 100 mg/dL
- HDL-cholesterol > 50 mg/dL
- Triglycerides < 150 mg/dL
- Non-HDL-cholesterol < 130 mg/dL
- Avoidance of smoking as well as environmental tobacco exposure
- hs-CRP levels < 2 mg/L*

*Per results of the JUPITER trial

their antithrombotic, antiarrythmic, anti-inflammatory, and vasodilating properties.

The omega-3 and omega-6 fatty acids are considered essential fatty acids because the human body cannot manufacture them and they must be obtained through the diet. Therefore, they are an excellent (and essential) way to diversify the portfolio of dietary strategies to decrease CV risk.[17]

Pharmacologic Actions of Omega-3 Fatty Acids

EPA and DHA are precursors to a group of eicosanoids (prostaglandins, leukotrienes, and thromboxanes), which have anti-inflammatory, antithrombotic, and vasodilatory effects (leukotriene B5, thromboxane A3, and prostaglandin E3). Although EPA and DHA can be endogenously produced from dietary ALA, the conversion process is limited and inefficient since ALA and omega-6 fatty acids are competitive substrates for the rate-limiting enzyme delta 6 desaturase, which controls the metabolic conversion of the omega-6 and omega-3 PUFAs into their respective eicosanoids. The greater dietary concentration of omega-6 fatty acids, particularly arachidonic acid, favors its formation into a group of eicosanoids that has proinflammatory, prothrombotic, and vasoconstricting effects such as tumor necrosis factor alpha (TNF alpha), thromboxane A2, prostaglandin E2, and leukotriene B4 (LTB4). The EPA in fish oil and fish competitively inhibits arachidonic

Table 3

Portfolio diet components[14-16]

Food Group	Examples	Amount (per day)
Viscous (soluble) fiber	Oats Barley Psyllium Okra Eggplant	12-25 g from a variety of sources
Plant sterols/stanols	Enriched spreads (Benecol®)	2 g
Soy protein	Soy milk Soy meat analogues	20-30 g
Nuts	Almonds Walnuts	14 g (~ 12 almonds) 14 g (~ 7 halves)

metabolism, resulting in the synthesis of less thrombogenic and less inflammatory eicosanoids.[18] Generally, the eicosanoids derived from omega-3 fatty acids have biological potencies for the induction of cellular inflammatory responses that are 1/10 to 1/100 of those derived from the omega-6 fatty acids.[19]

Factors Affecting hs-CRP Levels

Although smoking, obesity, and aging can elevate hs-CRP levels, clinical studies that control for these factors continue to show a significant association with CVD. Since intercurrent illness can cause transient increases in hs-CRP, a single measurement may not represent the true basal level and two determinations are currently recommended.[20]

Clinical Studies of Omega-3 Fatty Acids and CVD

Dyerberg et al initially described the epidemiologic connection between high dietary fat intake and low incidence of CHD in Greenland Eskimos (Inuit). This study sparked both scientific and public interest in the role of various types of fatty acids in the prevention and treatment of chronic diseases, particularly CHD.[21] Subsequently, both epidemiological[22] and randomized controlled studies of omega-3 fatty acid dietary supplementation have shown decreased CHD morbidity and mortality, particularly the secondary prevention trials.

Secondary Prevention Trials. In the GISSI Prevenzione Study, more than 11,000 post MI patients in the Italian public health system were randomized to receive either omega-3 PUFA (1 g/d) alone, vitamin E (300 mg/d alpha tocopherol), omega-3 PUFA + vitamin E, or placebo for 3.5 years. The group receiving the omega-3 fatty acids alone had a 20% reduction in CV death as well as nonfatal MI and stroke. Importantly, the risk of sudden cardiac death also decreased 45% in this group compared

to vitamin E alone and placebo.[23] The DART trial compared three dietary interventions (increased dietary polyunsaturated/saturated fats vs increased fatty fish intake vs increased dietary cereal fiber) in 2,033 post infarction men for two years. The omega-3 PUFA consumption in the form of fatty fish was the only intervention to significantly reduce mortality by 29%. Interestingly, the CV benefits were seen with consumption of only two fish meals per week or as little as 1 g/d of omega-3 PUFA (EPA + DHA) supplements (GISSI Trial).[24]

Primary Prevention Trials. Micallef et al, in a three-week, randomized, placebo-controlled, double-blind parallel study of 60 hyperlipidemic, community-dwelling, healthy patients (35-70 years of age), demonstrated that subjects assigned to a combined marine fish oil capsules (1.4 g/d) and plant sterol supplement (2 g/d) had a significant decrease in the inflammatory markers hs-CRP (39%), TNF alpha (10%), interleukin-6 (10.7%), and LTB4 (15.3%) compared to baseline and to the placebo group on sunola oil (sunflower oil, i.e., monounsaturated high oleic acid oil) after only three weeks of treatment. This represented a 22.6% reduction in overall CV risk with the plant sterols acting synergistically to produce a greater anti-inflammatory effect when used in combination with the omega-3 fatty acid supplementation. Interestingly, use of the plant sterols alone had no anti-inflammatory effect in this study.[25]

Characteristics of Fish Oil Supplements and Dosage

Lovaza®, a standardized omega-3 fatty acid ethyl esters product, is available via prescription as a liquid filled gel capsule. Each gel capsule is 1 g and contained at least 900 mg of the ethyl esters of omega-3 fatty acids, predominately a combination of EPA (approximately 465 mg) and DHA (approximately 375 mg).[26] Dosage of over-the-counter fish oil supplements should be based upon the amount of EPA and DHA in the product. Commonly, supplements contain 0.18 g of EPA and 0.12 g of DHA; they should be sourced from wild not farm-raised fish. Supplements should also be chosen from a reliable brand that has the Consumer Lab (CL) seal of approval, which designates that CL has evaluated and verified the product's EPA and DHA content, tested it for purity (i.e., contains no methylmercury, polychlorinated biphenyls, or dioxin) and for freshness (i.e., oxidation of the fish oil generates free radicals and renders it unsuitable for ingestion).[27]

Storage and Cooking Considerations

Omega-3 fatty acid supplements are subject to denaturation by light and heat. Check cooking temperatures for all oils to be certain that the smoke point is not exceeded during the cooking or baking process. They should be maintained in dark containers and in cool, dry places for maximum shelf-life. Some products like flax oil should be refrigerated and completely used within a few weeks of opening.[27]

Adverse Effects of Omega-3 Fatty Acids

Persons allergic or hypersensitive to fish should avoid products containing fish oil or omega-3 fatty acid products derived from fish. Gastrointestinal symptoms are common with the use of fish oil supplements. The most common symptoms are nausea, increased eructation, reflux, indigestion, and a fishy aftertaste. Such side effects can be minimized if the fish oils are taken with a meal and initial dosages are low and gradually increased.

Omega-3 PUFAs have antiplatelet properties and can cause prolongation of bleeding times, particularly in high doses (> 3 g/d) and in persons taking concomitant anticoagulants or antiplatelet medications such as warfarin, aspirin, clopidogrel, etc.[28] Although some concern was raised regarding in vitro studies that demonstrated an increased susceptibility to oxidation of LDL-cholesterol by omega-3 PUFA supplementation, the effect can be reduced by supplementation with vitamin E.[29]

Dosage of Omega-3 Fatty PUFAs for CAD

Recommendations from the symposium Beyond Cholesterol: Prevention and Treatment of Coronary Heart Disease with omega-3 Fatty Acids are for a daily intake of 250-500 mg DHA and EPA from either dietary or supplement sources for the primary prevention of CHD death and after a coronary event to reduce risk of CHD death. Lovaza is currently FDA-approved for treatment of very high triglycerides and the dosage for this indication is four 1 g gel capsules taken once or twice daily with a meal.[30]

The AHA recommendations for persons with known CHD are to eat one fatty fish meal at least twice a week or take 1 g/d of omega-3 PUFAs (EPA + DHA). There are no specific recommendations for those at increased risk for CHD without known disease.[31] Clinical trials have used a range of doses from 1-3 g of EPA + DHA daily and the duration has been from three weeks to 3.5 years.

Dietary Sources of Omega-3 Fatty Acids

Fish is an important source of omega-3 fatty acids in the U.S. diet, especially salmon, mackerel, and sardines; however, vegetable sources including flaxseeds and flaxseed oil, soybean and canola oils, walnuts, leeks, and

enriched eggs offer alternatives for those unable to consume fish.[18]

Conclusion

The use of dietary manipulations as therapy to diminish both primary and secondary CV risk is a cost-effective, well-tolerated, and multifaceted approach to a complex problem amenable to customization by the physician-patient team. Omega-3 fatty acid supplementation has broad implications for reducing the risk of CVD as well as modifying the course of other inflammatory disorders such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease.

Recommendation

A dietary portfolio consisting of 10-25 g of soluble fiber from a variety of sources combined with 20-30 g of soy protein, one-half ounce serving of nuts, 2 g of plant sterol/stanol spread rounded out with 250-500 mg supplemental DHA + EPA per day or two fatty fish meals weekly is a diversified, cost-effective, and interesting way to balance risk and maximize overall health returns. ❖

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Vitamin D Supplementation: Timing and Dosage Still Uncertain

By Dónal P. O'Mathúna, PhD

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Source: Chlebowski RT, et al; for the Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of breast cancer. *J Natl Cancer Inst* 2008;100:1581-1591.

ALTHOUGH SOME OBSERVATIONAL STUDIES HAVE ASSOCIated higher calcium intake and especially higher vitamin D intake and 25-hydroxyvitamin D levels with lower breast cancer risk, no randomized trial has evaluated these relationships.

Postmenopausal women (n = 36,282) who were enrolled in a Women's Health Initiative clinical trial were randomly assigned to 1,000 mg of elemental calcium with 400 IU of vitamin D_3 daily or placebo for a mean of 7.0 years to determine the effects of supplement use on incidence of hip fracture. Mammograms and breast exams were serially conducted. Invasive breast cancer was a secondary outcome. Baseline serum 25-hydroxyvitamin D levels were assessed in a nested case-control study of 1,067 case patients and 1,067 control subjects. A Cox proportional hazards model was used to estimate the risk of breast cancer associated with random assignment to calcium with vitamin D_3. Associations between 25-hydroxyvitamin D serum levels and total vitamin D intake, body mass index (BMI), recreational physical activity, and breast cancer risks were evaluated using logistic regression models. Statistical tests were two-sided.

Invasive breast cancer incidence was similar in the two groups (528 supplement vs 546 placebo; hazard ratio = 0.96; 95% confidence interval = 0.85-1.09). In the nested case-control study, no effect of supplement group assignment on breast cancer risk was seen. Baseline 25-hydroxyvitamin D levels were modestly correlated with total vitamin D intake (diet and supplements) ($r = 0.19$, $P < 0.001$) and were higher among women with lower BMI and higher recreational physical activity (both $P < 0.001$). Baseline 25-hydroxyvitamin D levels were not associated with breast cancer risk in analyses that were adjusted for BMI and physical activity ($P_{trend} = 0.20$).

Calcium and vitamin D supplementation did not reduce invasive breast cancer incidence in postmenopausal women. In addition, 25-hydroxyvitamin D levels were not associated with subsequent breast cancer risk. These findings do not support a relationship between total vitamin D intake and 25-hydroxyvitamin D levels with breast cancer risk.

■ COMMENTARY

Breast cancer is the most common cancer in women in the United States. In spite of important developments in screening for and treating breast cancer, it remains the second leading cause of cancer-related deaths among U.S. women.[1] Therefore, much attention has been given to methods of preventing breast cancer, including the use of various dietary supplements.

In the 1980s, it was proposed that higher levels of vitamin D would reduce the risk of colon cancer, breast cancer, ovarian cancer, and other cancers.[2] The hypothesis was based on observations that sun exposure increases vitamin D levels and people living in areas with less sun exposure had higher incidences of these cancers. Biochemical studies confirmed that vitamin D metabolites induced several anticancer systems in the body. A number of epidemiological studies, including the Nurses' Health Study, investigated potential connections between vitamin D levels and risk of cancer. The strongest association was with risk of colon cancer, with breast cancer having the second largest reduction in risk. In the Nurses' Health Study, plasma levels of 25-hydroxyvitamin D were significantly lower in women with breast cancer compared to controls, with the strongest association in postmenopausal women. However, vitamin D intake was associated with risk of cancer only in premenopausal women, and not in postmenopausal women. Thus, the age at which supplementation begins may be significant, and may have impacted the results of the Women's Health Initiative (WHI) trial reviewed here because only postmenopausal women were enrolled.

Some observational studies have supported a connec-

tion between vitamin D intake and risk of breast cancer, but others have not. Similarly, the results of observational studies examining calcium intake or calcium levels and risk of breast cancer have been variable, with not all studies finding an association. Hence the motivation for this randomized controlled trial of calcium with vitamin D supplementation and the incidence of breast cancer.

The results presented here from the WHI were planned secondary endpoints from a highly complex and rigorously designed trial. The primary endpoint was reduction in risk of hip fracture, with risk of colon cancer being another secondary endpoint. The risk of colon cancer was not reduced by calcium and vitamin D supplementation.[3] The results reported here also found no benefit from supplementation in reducing the risk of breast cancer. However, there were some limitations to the study, which has led other commentators to suggest that further study of these supplements is still warranted.[1]

The dose of vitamin D used in the WHI trial was 400 IU/d, which is that recommended by the Institute of Medicine. However, more recent investigations have suggested that 1,000-2,000 IU/d may be necessary for cancer prevention.[4] The researchers acknowledged this limitation and noted that approximately half of the women in the WHI trial took an additional 400 IU vitamin D themselves. The participants were permitted to use dietary supplements in additional to whatever they were assigned in the trial. This non-protocol use of calcium and vitamin D is another limitation with the WHI study. The authors monitored total supplement intake and found in was comparable between groups. However, about 15% of the placebo group took vitamin D themselves at the dose used in the trial. The analysis was conducted on an intention-to-treat basis, with the authors claiming this non-protocol use did not overly influence the results.

An interesting finding in the WHI trial was the correlation between 25-hydroxyvitamin D levels and lower BMI and higher recreational physical activity. When analyses were adjusted for these two factors, 25-hydroxyvitamin D levels were no longer associated with risk of breast cancer. This suggests that observational studies which did find an association may have been confounded

CME Objectives

After reading *Alternative Therapies in Women's Health*, the health care professional will be able to:

1. evaluate alternative medicine and complementary therapies for women's health concerns;
2. identify risks and interactions associated with alternative therapies;
3. discuss alternative medicine options with patients;
4. offer guidance to patients based on latest science and clinical studies regarding alternative and complementary therapies.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. 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, you must complete the evaluation form provided and return it in the reply envelope provided at the end of the semester to receive a certificate of completion. Upon receipt of your evaluation, a certificate will be mailed.

CME Questions

1. **An elevation in hs-CRP levels is considered an independent risk factor for coronary artery disease.**
   a. True
   b. False
2. **Omega-3 fatty acid supplementation can potentiate the effects of anticoagulants.**
   a. True
   b. False
3. **Omega-3 fatty acids have which of the following effects?**
   a. Anti-inflammatory
   b. Lipid-lowering
   c. Antiarrythmic
   d. All of above
4. **Which of the following factors affects plasma hs-CRP levels?**
   a. Age
   b. BMI
   c. Smoking
   d. All the above
   e. None of the above

Answers: 1. a, 2. a, 3. d, 4. d.

by BMI and exercise levels. Since exercise and leanness are associated with breast cancer risk, these factors will need to be taken into account in future studies.

The main findings do not support a causal relationship between calcium with vitamin D supplementation and breast cancer risk. However, further studies are warranted, especially to examine whether higher doses may be beneficial, or whether supplements are beneficial when begun at an earlier age. This study provides an excellent model for further examination of these questions. ❖

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News Briefs

Disclosure to physicians is higher for users of provider-based CAM

PATIENTS ARE MORE LIKELY TO TELL MEDICAL providers about using provider-based complementary and alternative medicine (CAM) than self-care CAM, according to recent research.

In this study, researchers wanted to see if disclosure was higher for CAM modalities that are perceived to have greater legitimacy, such as provider-based domains. They also wanted to see if relative to non-Latino whites, racial/ethnic minorities were less likely to disclose CAM use to medical doctors, or whether access to and quality of conventional medical care accounted for racial/ethnic differences in CAM disclosure.

Researchers at Richard and Hinda Rosenthal Center for Complementary and Alternative Medicine, College of Physicians and Surgeons, Columbia University, New York, NY, performed bivariate and multiple variable analyses of the 2002 National Health Interview Survey and 2001 Health Care Quality Survey.

They found that disclosure of CAM use to medical providers was 47% for provider-based CAM vs 34% for self-care CAM. Disclosure of any CAM was associated with factors of access to and quality of conventional care, including insurance status, source of conventional care, postponing care due to cost, having a regular doctor, and satisfaction with conventional care, the researchers say. CAM disclosure was higher among non-Latino whites relative to minorities (44% vs 30-37%). Controlling for confounding factors, having a regular doctor and a quality patient-provider relationship mitigated racial/ethnic differences in CAM disclosure.

The researchers concluded that disclosure of CAM use can be improved through consistent provider relationships, better patient-physician communication, and quality of health care across racial/ethnic groups. For more information about this study, see the November 2008 issue of the *Journal of the National Medical Association*. ❖

In Future Issues:

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