

SELECTED ABSTRACTS

CALGENEX

OMEGA-3 PUFAS, PHYTOSTEROLS, TOCOTRIENOLS, AND COENZYME Q10

OMEGA-3

Fish and Omega-3 Fatty Acids



In 1996 the American Heart Association released its Science Advisory, "Fish Consumption, Fish Oil, Lipids and Coronary Heart Disease." Since then important new findings have been reported about the benefits of omega-3 fatty acids on cardiovascular disease. These include evidence from randomized, controlled clinical trials. New information has emerged about how omega-3 fatty acids affect heart function (including antiarrhythmic effects), hemodynamics (cardiac mechanics) and arterial endothelial function. These findings are outlined in our November 2002 Scientific Statement, "Fish Consumption, Fish Oil, Omega-3 Fatty Acids and Cardiovascular Disease."

Evidence from prospective secondary prevention studies suggests that taking EPA+DHA ranging from 0.5 to 1.8 grams per day (either as fatty fish or supplements) significantly reduces deaths from heart disease and all causes.

n-3 fatty acids and serum lipoproteins: human studies.

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Am J Clin Nutr. 1997 May;65

The effects of n-3 fatty acids from fish oils (eicosapentaenoic acid and docosahexaenoic acid) and plant oils (alpha-linolenic acid) on human serum lipids and lipoproteins are reviewed. Studies were included in this review if they were placebo-controlled, crossover, or parallel design studies providing < 7 g n-3 fatty acids/d and with treatment periods of > or = 2 wk duration. Only three studies were available for evaluation of the effects of alpha-linolenic acid on serum lipid concentrations. From these studies it appeared that alpha-linolenic acid (18:3n-3) was equivalent to n-6-rich oils vis-vis lipid and lipoprotein effects. Only when very large amounts of flaxseed oil were fed did the hallmark effect of marine n-3 fatty acids-reduced triacylglycerol concentrations-appear. Thus, in terms of effects on lipoprotein metabolism, the plant-derived n-3 fatty acid is not equivalent to the marine-based acids. More studies using the marine-based acids were examined and summarized. Both crossover (n = 36) and parallel (n = 29) design studies reached the same conclusions: total cholesterol is not materially affected by n-3 fatty acid consumption, low-density-lipoprotein cholesterol concentrations tend to rise by 5-10% and high-density-lipoprotein cholesterol by 1-3%, and serum triacylglycerol concentrations decrease by 25-30%. These effects of marine n-3 fatty acids are now well-established; what remains is to determine the mechanisms behind these effects and, more importantly, their health consequences.

Tocotrienols in cardioprotection.

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Vitam Horm. 2007;76:419-33.

Tocotrienols, a group of Vitamin E stereoisomers, offer many health benefits including their ability to lower cholesterol levels, and provide anticancer and tumor-suppressive activities. Several recent studies determined the cardioprotective abilities of tocotrienols, although the number is only 1% compared to the study with tocopherols. Both in acute perfusion experiments and in chronic models, tocotrienols attenuate myocardial ischemia-reperfusion injury, atherosclerosis, and reduced ventricular arrhythmias. Apart from the antioxidative role of tocotrienols, it appears that tocotrienols mediated cardioprotection is also achieved through the preconditioning-like effect, the best yet devised method of cardioprotection. Hence, tocotrienols likely fulfill the definition of a pharmacological preconditioning agent and give a tremendous opportunity to place tocotrienols as an important therapeutic option in cardiovascular system.

Insig-dependent ubiquitination and degradation of 3-hydroxy-3-methylglutaryl coenzyme A reductase stimulated by delta- and gamma-tocotrienols.

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Sterol-regulated ubiquitination marks 3-hydroxy-3-methylglutaryl coenzyme A reductase, a rate-determining enzyme in cholesterol synthesis, for endoplasmic reticulum (ER)-associated degradation by 26 S proteasomes. This degradation, which results from sterol-induced binding of reductase to ER membrane proteins called Insigs, contributes to the complex, multivalent feedback regulation of the enzyme. Degradation of HMG-CoA reductase is also stimulated by various forms of vitamin E, a generic term for alpha-, beta-, delta-, and gamma-tocopherols and tocotrienols, which are primarily recognized for their potent antioxidant activity. Here, we show that delta-tocotrienol stimulates ubiquitination and degradation of reductase and blocks processing of sterol regulatory element-binding proteins (SREBPs), another sterol-mediated action of Insigs. The gamma-tocotrienol analog is more selective in enhancing reductase ubiquitination and degradation than blocking SREBP processing. Other forms of vitamin E neither accelerate reductase degradation nor block SREBP processing. In vitro assays indicate that gamma- and delta-tocotrienol trigger reductase ubiquitination directly and do not require further metabolism for activity. Taken together, these results provide a biochemical mechanism for the hypocholesterolemic effects of vitamin E that have been observed in animals and humans.

Plant stanol and sterol esters in the control of blood cholesterol levels: mechanism and safety aspects.

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Am J Cardiol. 2005 Jul 4;96(1A):15D-22D.

Incorporation of plant stanol esters into margarine is among the first examples of a functional food with proven low-density lipoprotein (LDL) cholesterol-lowering effectiveness. Recently, there have been many studies on the effects of plant stanols/sterols on cholesterol metabolism. It has been found that the serum LDL cholesterol-lowering effect of plant stanols/sterols originates from reduced intestinal cholesterol absorption, a process in which changes in micellar composition are thought to play a major role. However, recent findings suggest that there is an additional process in which plant stanols/sterols actively influence cellular cholesterol metabolism within intestinal enterocytes. Furthermore, in response to the reduced supply of exogenous cholesterol, receptor-mediated lipoprotein cholesterol uptake is probably enhanced, as shown by increased LDL receptor expression. At recommended intakes of about 2 to 2.5 g/day, products enriched with plant stanol/sterol esters lower plasma LDL cholesterol levels by 10% to 14% without any reported side effects. Thus, plant stanols/sterols can be considered to be effective and safe cholesterol-lowering functional food ingredients.

Plant sterols: factors affecting their efficacy and safety as functional food ingredients.

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Lipids Health Dis. 2004 Apr 7;3:5.

Plant sterols are naturally occurring molecules that humanity has evolved with. Herein, we have critically evaluated recent literature pertaining to the myriad of factors affecting efficacy and safety of plant sterols in free and esterified forms. We conclude that properly solubilized 4-desmethyl plant sterols, in ester or free form, in reasonable doses (0.8-1.0 g of equivalents per day) and in various vehicles including natural sources, and as part of a healthy diet and lifestyle, are important dietary components for lowering low density lipoprotein (LDL) cholesterol and maintaining good heart health. In addition to their cholesterol lowering properties, plant sterols possess anti-cancer, anti-inflammatory, anti-atherogenicity, and anti-oxidation activities, and should thus be of clinical importance, even for those individuals without elevated LDL cholesterol. The carotenoid lowering effect of plant sterols should be corrected by increasing intake of food that is rich in carotenoids. In pregnant and lactating women and children, further study is needed to verify the dose required to decrease blood cholesterol without affecting fat-soluble vitamins and carotenoid status.

Coenzyme Q10 in cardiovascular disease.

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Mitochondrion. 2007 Jun;7 Suppl:S154-67.

In this review we summarise the current state of knowledge of the therapeutic efficacy and mechanisms of action of CoQ(10) in cardiovascular disease. Our conclusions are: 1. There is promising evidence of a beneficial effect of CoQ(10) when given alone or in addition to standard therapies in hypertension and in heart failure, but less extensive evidence in ischemic heart disease. 2. Large scale multi-centre prospective randomised trials are indicated in all these areas but there are difficulties in funding such trials. 3. Presently, due to the notable absence of clinically significant side effects and likely therapeutic benefit, CoQ(10) can be considered a safe adjunct to standard therapies in cardiovascular disease.

Effect of coenzyme q10 on myopathic symptoms in patients treated with statins.

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Am J Cardiol. 2007 May 15;99(10):1409-12.

Treatment of hypercholesterolemia with statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) is effective in the primary and secondary prevention of cardiovascular disease. However, statin use is often associated with a variety of muscle-related symptoms or myopathies. Myopathy may be related in part to statin inhibition of the endogenous synthesis of coenzyme Q10, an essential cofactor for mitochondrial energy production. The aim of this study is to determine whether coenzyme Q10 supplementation would reduce the degree of muscle pain associated with statin treatment. Patients with myopathic symptoms were randomly assigned in a double-blinded protocol to treatment with coenzyme Q10 (100 mg/day, n = 18) or vitamin E (400 IU/day, n = 14) for 30 days. Muscle pain and pain interference with daily activities were assessed before and after treatment. After a 30-day intervention, pain severity decreased by 40% ($p < 0.001$) and pain interference with daily activities decreased by 38% ($p < 0.02$) in the group treated with coenzyme Q10. In contrast, no changes in pain severity (+9%, $p = \text{NS}$) or pain interference with daily activities (-11%, $p = \text{NS}$) was observed in the group treated with vitamin E. In conclusion, results suggest that coenzyme Q10 supplementation may decrease muscle pain associated with statin treatment. Thus, coenzyme Q10 supplementation may offer an alternative to stopping treatment with these vital drugs.

Coenzyme Q10 supplementation and heart failure.

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the Western world. Oxidative stress appears to play a pivotal role in atherosclerosis. Coenzyme Q10 (CoQ10), one of the most important antioxidants, is synthesized de novo by every cell in the body. Its biosynthesis decreases with age and its deficit in tissues is associated with degenerative changes of aging, thus implicating a possible therapeutic role of CoQ10 in human diseases. There is evidence to support the therapeutic value of CoQ10 as an adjunct to standard medical therapy in congestive heart failure. However, much further research is required, especially in the use of state-of-the-art techniques to assess functional outcomes in patients with congestive heart failure.