NUTRI NEWS

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# Nutraceutical Approaches to Coronary Artery Disease

*Mitchell J. Ghen, D.O., Ph.D.*

Outside of the medical/surgical model for heart disease, modern practitioners should consider complementary approaches to assist their patients. The stand-out difference between the two approaches is that the complementary strategy attempts to break the underlying pathology perpetuating the disease. The best example is arteriosclerotic cardiovascular disease, an epidemic malady of the industrialized nations. With so many products available today, it is best to approach the discussion by grouping nutraceuticals by their physiologic actions. Our nutritional knowledge base today helps us to recognize key areas of concern that must be addressed simultaneously. It is this concerted effort that should prove to have maximum impact on quality and quantity of life issues for the coronary artery disease patient. Therefore, we will consider the issues of *inflammation, infection, hormones, lipids, platelet aggregation, vasodilation, antioxidants, sympathetic tone, stress, insulin resistance* and *homocysteine*. You may note that several nutrients may be mentioned or noted twice due to their multiple types of action. It is best that you choose at least one from each of these categories, utilize the proper dose, evaluate the efficacy and then add or subtract substances depending on your patient's response. Though this article is focusing on supplemental issues, there is a marked importance in appropriate dietary intervention as well.

## Anticoagulants

One of the primary treatments applied for patients with coronary artery disease are anticoagulants. The aging process lends itself to increased coagulability. The obvious consequence of hypercoagulability is clot formation and subsequent artery occlusion. Increase in blood viscosity can create a hemodymamic state of ischemia, with its own set of circumstances. Ischemia is defined as low blood

*continued on page 2*

## Table 1 – Anticoagulant Activity

| | |
|---|---|
| Alpha-tocopherol | 400-1600 I.U./day |
| Arginine | 2000-6000 mg/day |
| Ascorbic acid | 1000-4000 mg/day |
| Bromelain | 500-3000 mg/day |
| *Curcuma longa* | 200-1200 mg/day |
| E.D.T.A.-Oral or rectal suppository | Dose varies depending on renal fx |
| Essential Fatty Acids (EFAs) | 5000-10,000 mg/day |
| Ginger (powdered) | 1/2 to 1 tspn/3 times a day |
| *Ginkgo biloba* | 40-120 mg/day |
| Inositol hexanicotinate | 400-3000 mg/day |
| Magnesium | 300-1600 mg/day |
| N-acetyl cysteine | 500-3000 mg/day |
| Pancreatin | 300 mg/day |

## Inside This Issue

flow, which may or may not have total obstruction associated with it. Ischemia can lead to apoptosis and inflammation. Evaluation of ischemic potential can be approached with a functional coagulation panel. This composite of tests includes the typical PT, PTT tests and also the more comprehensive combination of fibrinogen, prothrombin fragments one and two, thrombin-anti-thrombin complexes, soluble fibrin monomers and platelet CD62P (Selectin) receptors. A valuable test for evaluation of clotting is platelet aggregation testing. Platelet aggregation occurs with the presence of adenosine, epinephrine, collagen and thrombin. Most anti-platelet aggregation medications work only in the presence of adenosine (aspirin for example). This may explain why type A personalities using aspirin still have clot formation. In contrast EDTA (ethylene diaminetetracetic acid), inhibits aggregation to all of the substances above with the exception of collagen. Acute phase reaction, particularly a high c-reactive protein, is related to vascular inflammation and or infection. Substances, such as coumadin affect prothrombin/thrombin activation. Natural products like vitamin E and magnesium have similar properties. Platelet hyperactivity is minimized by aspirin and similarly by other natural products like ginkgo and ginger. Fibrinogen/fibrin monomers can be addressed with enzymatic therapy like bromelain and pancreatin. Natural substances, that have similar reaction to heparin, are arginine, niacin, bromelain and papain. I have found clinically that increased fibrinogen levels of greater than 400 mg respond quickly and effectively to *Curcuma longa*.

**Table 2 – Vasodilation**

| | |
|---|---|
| Arginine | 3000-6000 mg/day |
| Garlic | 400-600 mg/day |
| Hawthorne | 160-250 mg of the flower (standardized) |
| Horse chestnut | 600-700 mg (standardized to aecins) |
| Capsicum (cayenne) | 40,000-100,000 heat units 1-6 capsules/day |

## Vasodilation

An important component to coronary artery disease treatment is vasodilation. The consequence of vasodilation is improved blood flow and subsequent increase in tissue oxygenation. The object of nitrates or nitrate therapy, a mainstay of both acute and chronic coronary arterial disease care is to increase blood flow to constricted blood vessels, whether this stricture is created by plaque or by vasospasm. The natural substance, arginine, for example, is said to increase nitric oxide, a free radical (part of a group of compounds known as endothelial releasing factor, EDRF) that functions as a vasodilator. Nitric oxide has a secondary effect to potentially reduce the damage created by homocysteine. It has been hypothesized that EDTA's benefit can, to a large degree, be attributed to its release of nitric oxide. Of course, EDTA is an excellent anti-coagulant.

Also worthy of note, cayenne pepper has excellent effects on blood lipids, platelet activity, and vasodilatory action. As a wonderful first aid remedy, one teaspoon of cayenne in a glass of water can quickly relieve the discomfort of acute chest pain caused by angina.

## Lipid Modulation

There are many products that effectively control dyslipidemia without the side effects often associated with conventional medical drugs. For elevated cholesterol, a combination of pantethine and inositol hexacotinate can demonstrate profound improvements in one month. For those patients with elevated triglyceride levels, L-Carnitine, as well as EFAs, can often solve the problem. I prefer the inositol hexanicotinate form of niacin due to its absence of the troublesome side

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## Table 3 – Lipid Modulation

| | |
|---|---|
| Pantethine | 500-1,000 mg/day |
| Inositol hexanicotinate | 3000 mg/day |
| Garlic | 400-600 mg/day |
| L-Carnitine | 1000-3000 mg/day |
| Essential Fatty Acids (EFAs) | 5000-10,000 mg/day |
| MIC (methionine-inositol choline) | 200-400 mg/day of each |
| *Lpa (lipoprotein a) — decreasing agents* | |
| Inositol hexanicotinate | 3000 mg/day |
| CoQ10 | 200-400 mg/day |
| Vitamin C | 1000-2000 mg/day |
| L-Lysine | 1000-2000 mg/day |

effects of flush and liver irritation. Its mechanism of action is similar to all niacin compounds to reduce plasma triglycerides, VLDL, LDL synthesis and total cholesterol. Pantethine is the active hormone of pantethenic acid. It is considered to be one of the most important parts of coenzyme A (CoA) that transports fats to and from the cells. It has a potent effect on cholesterol as well as triglycerides. L-Carnitine is synthesized from lysine with the help of methionine. It improves triglyceride levels, total cholesterol and increases HDL. The n-3-polyunsaturated acids in large enough doses have been shown to be helpful in many studies. The DART study and most recently the GISSI study (published in The Lancet) are good examples. The role of omega-3 fatty acids are several, but recent studies report that their most profound effects may be on arrhythmogenesis as well as inflammation. The GISSI study reported a substantial decrease in cardiovascular events as a result of fish oil supplementation. I believe the study results, although impressive, would have been even more dramatic had the investigation used omega-6 fatty acids as well. In refractory cases of elevated lipids, which have failed to respond to the above regimen, consider the combination of methionine, inositol and choline in doses of 200-400 mg of each taken 3 times daily. Lipoprotein a (Lpa) is an apolipoprotein, i.e. an LDL particle, to which an additional protein is attached. Because of Lpa's similarity with plasminogen, it interferes with fibrinolysis, and of course ultimately speeds up clot formation. Several substances as shown Table 3 can be helpful. Coenzyme Q10 for example, can inhibit the Lpa receptor expression.

## Table 4 – Homocysteine Reduction

| | |
|---|---|
| B6 | 10-50 mg/day |
| B12 | 1000-5000 mcg/day |
| Folate (folic acid) | 800 mcg-5 mg/day |
| TMG (trimethylglycine) | 250-1000 mg/day |
| Choline | 200-1000 mg/day |

Also helpful are: Serine, Glycine, and NAC (n-acetyl cysteine)

### Homocysteine Reduction

There are many published studies supporting homocysteine as a risk factor for vascular disease. Homocysteine has also been considered a good marker for B6, B12 and folic acid deficiency. Even Raloxefen's benefit as seen in the Ruth Study "Raloxefen use for heart study" suggested this drug's action on coronary artery disease, may in part be due to its homocysteine-lowering qualities. Regular supplementation with the three B vitamins (B6, B12 and folate) will control a great majority of elevated homocysteine levels. A simple blood test confirming the patient's level of homocysteine should be performed with their annual routine exam. Although laboratories suggest that a level below 15 is normal, a level of less than 10 is ideal and less than 7 is considered optimal.

### Insulin Resistance Reduction

Receptor sensitivity for insulin decreases and the body compensates by secreting increased amounts of insulin. This is known as 'insulin resistance'. Increased insulin levels promote lipogenesis, increased thrombosis from increase in plaminogen activator/inhibitor, and decreases through a hepatic mechanism, which will decrease HDL while increasing triglyceride production. One of the most devastating effects is the glycosylation process, whereby circulating glucose attaches to proteins. Eventually this leads

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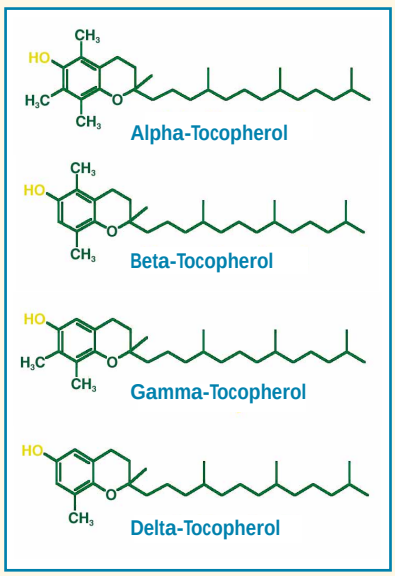
# Gamma-Tocopherol: Its Importance and Unique Properties

When the term "vitamin E" is used, alpha-tocopherol is generally what comes to mind. However, vitamin E is actually a collective term that encompasses 3 other tocopherols (beta, gamma, and delta) in addition to alpha-tocopherol. These molecules are differentiated by the number and placement of methyl groups on their structure (see figure). Recent research has been revealing that gamma-tocopherol possesses some unique properties that allow it to function independently from as well as synergistically with alpha-tocopherol.

Alpha-tocopherol is the major form of vitamin E that can be found in blood as well as many tissues in humans. Due to its abundance in the body research has generally focused on alpha-tocopherol, with less emphasis on the other isomers. However, gamma-tocopherol is the major form of vitamin E consumed in the diet and is found in many plant seeds and the oils made from them. It has been estimated that gamma-tocopherol represents 70% of the vitamin E consumed in the typical US diet. Once in the body, the metabolism of alpha and gamma-tocopherol differs significantly. Alpha and gamma-tocopherol are absorbed similarly from the gastrointestinal tract and secreted into chylomicron particles without selective discrimination. However, when the chylomicron remnant particles are taken up by the liver, alpha-tocopherol is preferentially incorporated into very low-density lipoprotein (VLDL) cholesterol particles. This preferential placement of alpha compared with gamma-tocopherol into VLDL particles is a result of the presence of a protein in the liver called alpha-tocopherol transfer protein. This protein is able to recognize the stereochemistry of the various tocopherols and has the greatest affinity for the d-alpha form. Consequently, alpha-tocopherol becomes selectively located in VLDL particles, which after circulation and metabolism are transformed in to low-density lipoprotein (LDL) particles. An interesting note is that supplementation with alpha-tocopherol in the absence of gamma-tocopherol leads to a reduction of both tissue and plasma levels of gamma-tocopherol. Nonetheless, given its presence in chylomicrons, and presence in other lipoprotein particles (albeit it at levels less than alpha-tocopherol) gamma-tocopherol does reach the circulation and plays an important role.




Alpha-tocopherol is generally thought of as the most powerful antioxidant of the various tocopherols, and due to its structure it can more readily donate electrons compared with gamma-tocopherol. Gamma-tocopherol, however, can better quench certain dangerous reactive nitrogen species such as peroxynitrate and nitrogen dioxide, both of which have been associated with a number of degenerative diseases. In fact, in relation to alpha-tocopherol it has been reported that gamma-tocopherol is superior in detoxifying nitrogen dioxide to less harmful compounds. In addition to its antioxidant properties, gamma-tocopherol has also been shown to possess anti-inflammatory properties and can inhibit the activity of cyclooxygenase-2 (COX-2) and production of prostaglandin $E_2$. Given the role that inflammation plays in the pathology of cardiovascular disease this finding is particularly important. Some researchers have also reported that gamma but not alpha-tocopherol levels are lower in those with cardiovascular disease compared with control subjects. Recent work has also brought to light a relationship between gamma-tocopherol and prostate cancer. In a case-control study, the correlation between alpha-tocopherol, gamma-tocopherol, selenium intake and prostate cancer was examined. The researchers found a significant inverse correlation between the intake of gamma-tocopherol and the incidence of prostate cancer (i.e., the greater the intake of gamma-tocopherol, the lower the risk of disease). Most intriguing was that alpha-tocopherol and selenium intake was only protective when gamma-tocopherol intake was also high.

These interesting scientific findings, coupled with the fact that gamma-tocopherol, but not alpha-tocopherol levels have been shown to decline with age in humans give further credibility to the importance of supplementing with a well-rounded mixed tocopherol supplement that contains significant amounts of gamma-tocopherol.

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## Table 5 – Insulin Resistance Reduction

| | |
|---|---|
| Soluble fibers | 35-45 g/day |
| Chromium | 200-1000 mcg day |
| Vanadium | 1-2 mg/day |
| (higher doses often used for short periods of time) | |
| Cinnamon | 1/2 tspn 3 times/day |
| C.L.A. (conjugated linoleic acid) | 1-3 gm/day |
| EFAs | 1-3 gm/day |
| Magnesium | 800-2000 mg/day |
| Zinc | 15-60 mg/day |

to advanced glycosylation end products (AGE), which can be a precursor to microvascular disease. The abnormal glucose/insulin metabolism augments formation of free radicals. Of course, oxidative stress is often responsible for many of the factors contributing to coronary artery disease. Other than the substances noted in Table 5, caloric restriction is an excellent way to decrease free radical formation and improve insulin sensitivity. Equally as important is a regular exercise program given that insulin receptors are located within muscle tissue. In addition, repletion with antioxidants is also imperative (see Table 6).

### Antioxidants and Biological Enzymes

There are many studies that support the importance of adequate antioxidant levels and the occurrence of coronary artery disease. In several instances, it has been postulated that antioxidant use is more important than the control of lipid levels. It is well known that cholesterol in itself is not problematic, but the exposure of cholesterol to the oxidation process certainly can generate plaque. Grapeseed extract, vitamin E and vitamin C are important components of antioxidant therapy. Grapeseed extract alone has been shown to reduce plaque size. Since most diets have poor consumption of antioxidants and flavanoids, supplementation with larger doses than usual for coronary artery disease (C.A.D.) patients may be helpful.

Bromelain has been shown to have numerous therapeutic benefits, including effects on cytokines such as TNF-alpha, IL-1beta, IL-6 and IL-8. Studies also give evidence that bromelain may inhibit platelet aggregation, an important cardioprotective property. Some have claimed that bromelain can not be effective orally, but this has since been refuted.

Researchers report that soluble fibers have a positive effect on hypertension as well as serum-fasting insulin. Patients should be regularly tested for glycosylated hemoglobin, fasting blood sugar and fasting insulin levels.

### Inflammation and Infection

Presently, most recognize that there are several infectious agents that are associated with coronary vascular disease. Human herpes virus 6, nanobacteria, chlamydia and cytomegalo virus all have been implicated as part of the epigenesis of heart disease. Studies have even shown 89% of patients have chlamydia in their hearts at the time of bypass surgery. Most investigators agree that, although these infectious organisms may not be the primary cause of heart

## Table 6 – Antioxidants & Biological Enzymes

| | |
|---|---|
| *Antioxidants* | |
| Vitamin A | 5000-10000 I.U./day |
| Vitamin C (buffered preferred) | 1000-4000 mg/day |
| Vitamin E (unesterified, natural alpha-tocopherol with mixed tocopherols and tocotrienols) | 800-1600 I.U./day |
| Selenium | 200-1000 mcg/day |
| *Biological enzymes* | |
| SOD (superoxide dismutase) | 2000-3000 MF/units |
| Catalase | 2000-3000 MF/units |

## Table 7 – Inflammation and Infection

| | |
|---|---|
| Bromelain (acid stable) | 500-2000 mg/day |
| Papain | 100-200 mg/day |
| Pancreatin | 300 mg/day |
| Central fatty acids (EFAs) | 5000-10000 mg/day |
| *Curcuma longa* | 200-1200 mg/day |
| Vitamin C (buffered) | 1000-4000 mg/day |

disease, they significantly contribute to a hypercoagulable state. The use of low-dose broad-spectrum antibiotics such as tetracycline has been suggested along with aggressive enzyme usage. It seems that this combination affords the best result of reducing infection and inflammation. Several studies have shown the overall effectiveness of enzyme use is greater than the non-steroidal anti-inflammatories.

**Table 8 – Sympathetic Tone**

| | |
|---|---|
| Melatonin | 0.5-10 mg/night |

### Sympathetic Tone

The sympathetic nervous system (flight or fight) plays an important role in C.A.D. Greater than usual sympathetic tone will increase heart rate and elevate blood pressure. Increased sympathetic activity has often been demonstrated in patients with C.A.D. Increased levels of adrenal medulla hormones, i.e., norepinephrine and epinephrine damage the arterial lining, increase platelet aggregation and increase oxidized cholesterol, all which lead to a faster generation of arthrogenesis. Remember, calcium stimulates sympathetic discharge, whereas, magnesium has antagonistic properties. Therefore, appropriate levels of magnesium and melatonin help to control an imbalanced sympathetic nervous system.

Researchers have demonstrated that patients with C.A.D. have nighttime melatonin levels that are 1/5 lower than healthy controls. Explanatory physiology is likely to be related to increased nighttime sympathetic discharge and the subsequent increase in epinephrine/norepinephrine. Also, melatonin levels could possibly explain why the majority of heart attacks occur in the early morning hours. Melatonin has also been found to inhibit platelet aggregation. Saliva melatonin sampling can be obtained from several laboratories throughout the country.

Table 9 depicts several substances with either ionotropic (increase heart contractibility) or chronotropic (rhythm heart stabilizing) effects on the heart. Regular use of these substances can often augment typical conventional medications of similar nature, i.e., digitalis and antiarrythmics. Several studies have shown magnesium to be an excellent preventative of dysrythmias and can be especially useful in intravenous doses of 2-3 gm in the early stages of heart attack and for several days thereafter. Its use can prevent the serious rhythm disturbances that often accompany myocardial infarction. Long-term use is also suggested since most patients are magnesium deficient. Other studies have determined that the use of coenzyme Q10 in dosages of 300 mg/day one week prior to cardiac surgery improves three-fold the serum levels and tissue levels in the heart of this nutraceutical. This improvement seems to reduce the heart failure associated with low coenzyme Q10. Another study on the usefulness on coenzyme Q10 in clinical cardiology demonstrated large doses over time will reduce overall cardiac medication requirements significantly. (See insert on this page "Coenzyme Q10) Taurine, an amino acid has likewise been shown to have positive cardiac effects and diuretic properties. Hawthorne berry has been used for years by western herbologists as a good ionotropic natural agent.

### Summary

A multiangle assertive approach seems to be appropriate when treating the coronary artery disease patient. Hormonal issues should also be examined and a saliva profile may prove efficacious in determining DHEA, estrogen, progesterone, and testosterone levels. Recently, much has been written about hormones and their inverse relationship with coronary artery disease. By routinely screening with these saliva and blood tests, you will be able to note lipid levels, coagulability, glucose/insulin levels, melatonin level, hormone levels, inflammatory status, and homocysteine levels. A practitioner could then choose, from the tables provided, those nutritional supplements that would address areas of concern revealed by the test results.

**Table 9 – Ionotropic and Chronotropic Augmentation**

| | |
|---|---|
| Magnesium | 1600-3000 mg/day |
| Taurine | 2000-4000 mg/day |
| Hawthorne Berry | 250-500 mg/day |
| Coenzyme Q10 | 200-400 mg/day |

Abnormal tests would be noted and repeated after an appropriate length of treatment and adjustment of the treatment plan, by either increasing doses of already-prescribed nutraceuticals, with or without the addition of new agents. Further adjustment in the program would be necessary when the patient is taking concurrent medicine(s). Drugs that have similar properties to those nutraceuticals, that your patient is already taking, would require appropriate adjustment. For example, patients taking anti-coagulants would require lower doses of those supplements mentioned in Table 1. However, other patients, taking lipid-lowering drugs, may require increased doses of CoQ10. Remember, many coronary-related medications cause other nutritional deficiencies and I suggest that you refer to a text describing drug-herbal and drug-nutrient interactions.

### Final thoughts:

The use of EDTA, although it is considered by the conventional medical community as controversial, has revealed in many studies to have a significant place in the treatment of coronary artery disease along side the nutraceuticals presented in this paper. Heavy metals do play a role in artherogenesis and should be studied further. Don't forget, in the midst of this complex array of nutraceuticals, water itself may improve the outcomes of coronary events. Simply drinking 4 or more glasses of pure water each day, can decrease myocardial infarction by more than 50%.

## Coenzyme Q10: A Brief Description

Coenzyme Q10, (CoQ10) also known as ubiquinone has been receiving an increasing amount of attention over the past 5 years for its cardioprotective abilities. CoQ10 is a fat-soluble molecule synthesized from cholesterol and located predominantly in mitochondria (the cell's powerhouse) where it plays a vital role in energy production. Specifically CoQ10 is crucial for the proper transfer of electrons through the mitochondrial respiratory chain. Given that heart muscle requires a tremendous amount of energy to function properly, it is not unusual that significant levels of CoQ10 can be found in heart muscle. Since CoQ10 levels have been found to be lower under certain circumstances, researchers have been investigating the effect that supplemental CoQ10 can have on heart function. Not surprisingly, numerous clinical studies have demonstrated improvements in functional parameters of the heart in patients with congestive heart failure after supplementation with CoQ10. CoQ10 treatment prior to bypass procedures has also yielded more positive outcomes when compared with patients who did not receive supplementation. CoQ10 levels have also been shown to be reduced in patients taking statin drugs, as cholesterol is required for the synthesis of CoQ10 in the body. CoQ10 has been shown to be an effective antioxidant, protecting against lipid peroxidation, DNA and protein oxidation and is also capable of functioning synergistically to help regenerate other antioxidants. The research community continues to find strong data indicating the benefits from supplementation with CoQ10, especially in the area of cardiovascular health as it relates to congestive heart failure.

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