Cardiovascular Disease - Toward a Unified Approach

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Abstract

Much information has been disseminated in the past two decades regarding nutrition and cardiovascular disease, mainly atherosclerotic disease. A great deal of this information has addressed cholesterol and fat intake (saturated vs. poly-and-mono-unsaturated fats) and their impact on blood lipids and the development of heart disease. In addition to these studies, a number of scientists have been investigating the connection between micro-nutrients (vitamins, minerals, amino acids, flavonoids, co-enzymes) and heart disease. The oxidation of LDL cholesterol has been linked to vascular damage leading to atherosclerotic plaques. Antioxidant activity and subsequent inhibition of LDL oxidation has been attributed to the dietary and supplemental intake of specific micro-nutrients, including vitamin E, vitamin C, vitamin B6, glutathione, flavonoids, beta carotene, lipoic acid, and coenzyme Q10.

Improper metabolism of the amino acid methionine has emerged as another link to LDL oxidation and heart disease in some individuals. Approximately 20-30% of individuals with heart disease have increased levels of the methionine-intermediate-metabolite homocysteine, which may be linked to dietary and/or genetically-induced deficiencies of folic acid, vitamin B12, vitamin B6, or the amino-acid derivative betaine.

There are numerous inter-connections between nutrients (including S-adenosyl methionine, vitamins C, B6, B12, folate, betaine, pantethine, the amino acids glycine, taurine, lysine, and carnitine) and biochemical pathways (homocysteine metabolism, cholesterol synthesis and degradation, carnitine, coenzyme Q10, and taurine synthesis) which have an effect on coronary atherosclerotic disease prevention and treatment. Ensuring more efficient functioning of these pathways by promoting proper diet and/or supplementation can have a significant positive impact on this multi-factorial disease process. (*Alt Med Rev* 1996;1(3):132-147.)

Introduction

Most of the scientific literature published in the past 15-20 years on nutrition and cardiovascular disease, primarily coronary heart disease (a redundant term which will not be used in this article—instead, the term coronary atherosclerotic disease-CAD—will be used, along with the more generic term heart disease) has focused on macro-nutrient intake, mainly fat and cholesterol intake. Although this research has been valuable, in that it has helped to educate the public and create a greater awareness of the connection between diet and health/disease, it may have created a greater-than-necessary emphasis on dietary cholesterol and saturated fat, and has given birth to an entire industry of low-fat or no-fat foods and fads designed to help people "eat right".

Also over the last few years, a number of researchers have studied the relationships of various micro-nutrients and heart disease. The oxidation of LDL cholesterol and micro-nutrients which act to inhibit this oxidation has been a much-researched topic, as well as the amino acid methionine and the impact that its metabolism has on heart disease.

Heart disease is the number one cause of death in the United States, resulting in at least 1,500,000 heart attacks a year and claiming over 489,000 lives (statistics from 1993). Current allopathic treatment mainly consists of balloon angioplasty or coronary artery bypass grafting. The traditional factors associated with an increased risk for CAD are shown in Table 1.

Table 1

Traditional Risk Factors for CAD

- Elevated serum lipids
- Hypertension
- Diabetes mellitus
- Cigarette smoking
- Physical inactivity
- Obesity
- Positive family history for premature CAD
- Male gender

Prevention in the allopathic arena has consisted of treating the hypertension and diabetes, and attempting to get the patient to change dietary and/or lifestyle factors which have been shown to have an impact on the incidence of CAD, including smoking cessation, weight loss, low-fat diets and drugs to decrease elevated serum lipids, and aerobic exercise. However, the traditional risk factors in Table 1 may account for only 50-60% of the disease incidence.

A more pro-active preventative course may be to make the necessary changes which will impact the risk factors mentioned above, along with addressing those dietary micro-nutrients and their biochemical pathways which have been shown to have a significant impact on CAD, and which may account for some of the traditional risk factors and part of the other 40-50% of CAD incidence. These micro-nutrients/pathways include: vitamin E, polyphenols/flavonoids, vitamin C, coenzyme Q10, methionine metabolism, cholesterol metabolism and excretion, taurine, L-carnitine, and their micro-nutrient co-factors. This article will show the interconnections and interrelatedness of these micro-nutrients and their biochemical pathways, and the laboratory and clinical studies showing the connections between these pathways and CAD.

The LDL Cholesterol Connection

A mechanism which has gotten more attention in recent years is an extension of the cholesterol theory of heart disease—the oxidation of LDL cholesterol—and the antioxidant nutrients which have been shown to inhibit this process. High LDL cholesterol levels are an independent risk factor in CAD. However, it seems to be the oxidized LDL which causes endothelial damage and leads to atherosclerosis. Without adequate antioxidant protection, LDL is damaged by radical oxygen species in the serum and from macrophages, creating a chain-reaction of lipid peroxidation. LDL receptors in the endothelium are less likely to take up oxidized LDL. At the same time, macrophages will take in this altered LDL at 10 times the rate of non-oxidized LDL, becoming engorged "foam cells". These LDL-rich foam cells embed themselves in the vascular endothelium and become the "fatty streak," the beginning of an atherosclerotic plaque. Oxidized LDL seems to be directly cytotoxic to endothelial cells and also promotes the growth of arterial smooth muscle cells in vitro, giving credence to the theory that oxidized LDL is atherogenic and that it participates in the structural changes found in the atherosclerotic lesion.[1-4]

Epidemiologic and clinical studies of dietary antioxidant micro-nutrients, including vitamin E, vitamin C, beta carotene, and flavonoids have shown these substances to be potent antioxidants which can affect not only the oxidation of LDL cholesterol, but also the incidence of CAD.

Vitamin E

Vitamin E (alpha tocopherol) seems to be the most important micro-nutrient involved in the protection of LDL from oxidation. Vitamin E inserts itself in the outer phospholipid layer of LDL and sacrifices itself to the ever-present radical oxygen species, preventing or lessening the lipid peroxidative damage to LDL. Vitamin E is then recycled to its reduced form by ascorbic acid, coenzyme Q10, and dehydrolipoic acid (thioctic acid).[2,5,6]

In vitro studies of vitamin E and LDL oxidation have repeatedly shown that vitamin E reduces LDL oxidation. In a recent eight-week dose-response, placebo controlled study, subjects were supplemented with either 60, 200, 400, 800, or 1200 I.U.'s vitamin E per day. Plasma and LDL tocopherol concentrations increased in a dose-dependent manner during the study. The placebo, 60, and 200 I.U. groups showed no significant effect on ex-vivo copper-catalyzed LDL oxidation. However, supplementation with 400 I.U. and above resulted in a significant decrease in LDL oxidation, revealing that 400 I.U. vitamin E may be the minimum daily supplemental dose.[7] In a 3-month study of vitamin E supplementation (800 I.U./d) in 24 men, vitamin E caused a two-fold increase in the lag time before copper-catalyzed LDL oxidation, and a 40% decrease in the oxidation rate compared to placebo.[8]

A number of epidemiologic studies have been performed which point toward a connection between dietary vitamin E intake and heart disease. Two recent studies of U.S. health professionals found an inverse correlation between vitamin E intake and heart disease. One study involving 87,245 female nurses aged 34-59 without diagnosed heart disease found that, comparing the highest fifth of vitamin E consumption versus the lowest fifth, there was a relative risk for heart disease of 0.66, or a 34% decreased risk. These results had been adjusted for smoking, age, and other CAD risk factors.[9] The male counterpart to this study, which involved 39,910 U.S. male health professionals 40 to 75 years of age found that men consuming more than 60 I.U. per day of vitamin E had a relative risk of 0.64 as compared with those consuming less than 7.5 I.U. per day (a 36% decreased risk).[10] Both of these studies state that, for those taking supplements, a minimum of two years of vitamin E supplementation may be necessary to obtain these results.

Vitamin E has also been shown to decrease total cholesterol and positively influence lipoproteins. Sixty-nine patients were supplemented with 500 IU/d of dl-alpha-tocopheryl (250 IU vit E activity) for 3 months. Vit E increased the mean HDL level 13.6% ($p < 0.05$), with only a 3.8% increase in the placebo group. Total cholesterol was not significantly reduced in either group. Apolipoprotein A (Apo A) is the primary protein in HDL, and is favorable, whereas apolipoprotein B (Apo B) is the primary protein in LDL, and is not desirable. Apo A rose significantly, while Apo B decreased. The Apo A/Apo B ratio increased 17.9% in the treatment group. So, besides the beneficial effects of an increased amount of vitamin E in the LDL molecule, the lipoprotein ratio, which has been shown to be an independent risk factor for CAD, showed a favorable increase.[11]

Table 2

Oxidative damage and micro-nutrient defenses

Substances oxidizing LDL:
Reactive Oxygen Species (ROS) (endogenous metabolites, exogenous oxidized fats, pollutants and chemicals)
Homocysteine - creates H_2O_2, damages endothelial cells directly.

Substances inhibiting LDL oxidation:
- vitamin E
- vitamin C
- vitamin B6
- beta carotene
- dehydrolipoic acid
- flavonoids
- glutathione
- coenzyme Q10

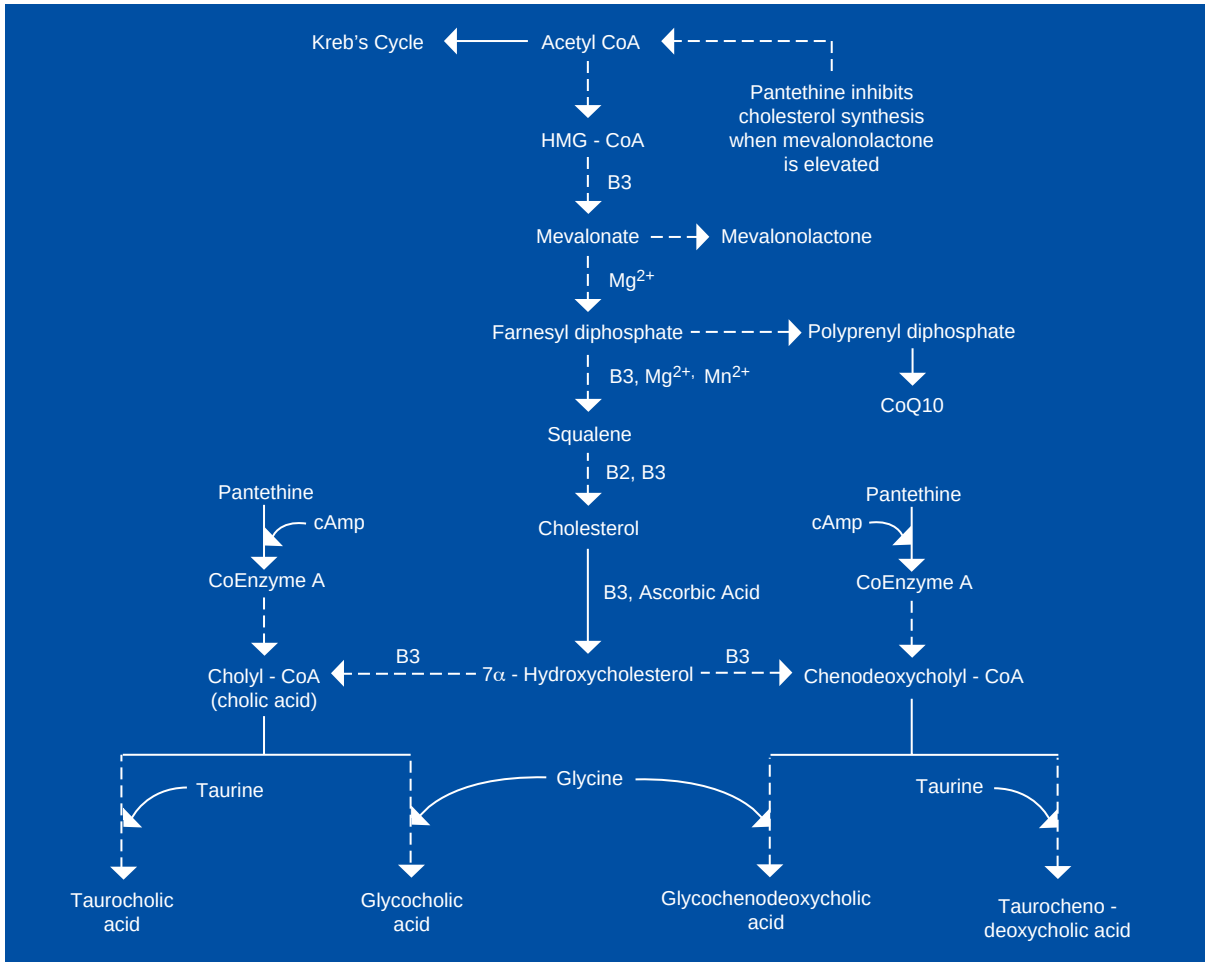


FIGURE 1. Cholesterol metabolism

Vitamin C

Humans, primates, guinea pigs, the fruit bat, and some fish lack the ability to synthesize vitamin C, and must, therefore, derive vitamin C from the diet. Ascorbic acid is an antioxidant and is also involved in cholesterol excretion, as it is necessary for the conversion of 7-alpha-hydroxycholesterol to bile acids via the enzyme 7-alpha-hydoxylase (see Figure 1). In vitamin C-deficient guinea pigs, the transformation of cholesterol to bile acids is decreased, with a concomitant increase in plasma cholesterol and coronary atherosclerosis.[12] Vitamin C is known to participate significantly, along with glutathione and lipoic acid, in the recycling of oxidized vitamin E[2,5] and has been shown to increase red blood cell glutathione.[13] Ascorbate also enhances vascular integrity and reduces vascular permeability due to its influence on the formation and stabilization of vessel wall ground substance.

The evidence for a positive effect on serum lipids and CAD is not as clear-cut for vitamin C as it is for vitamin E. Some supplementation studies do not show a correlation between vitamin C and cholesterol;[14,15] however, the overall evidence shows that an increased vitamin C intake increases HDL cholesterol levels[16-21] and may decrease total cholesterol.[17,22,23]

In the Western Electric Study, dietary vitamin E and vitamin C intake was assessed over a 20+ year span in 1,556 men. For the means of the highest vs. the lowest quartile of vitamin C intake, patients with the higher intake had a 30% decreased risk of death from CAD.[24]

Plasma ascorbic acid (AA) and malondialdehyde (MDA- a marker of lipid peroxidation) were inversely correlated in a study of 172 African-Americans, as was plasma AA and total cholesterol. Serum HDL cholesterol was positively tied to AA levels.[25]

Beta-Carotene

Like vitamin E, the lipid-soluble antioxidant beta carotene also associates itself with lipoproteins. Even though the beta carotene content of LDL cholesterol is less than 1/20th the amount of vitamin E,[26] it has the ability to decrease copper-catalyzed LDL oxidation by 40%.[27] Other studies have shown similar results.[28,29] Epidemiologic studies have shown a reduced risk of CAD in those consuming foods high in beta carotene and vitamin C,[24,30-32] although this does not rule out other unknown factors in those foods which may also be beneficial substances against CAD.

Selenium

The selenium-dependent enzyme glutathione peroxidase also interacts with LDL cholesterol in vivo, and has been shown to exert antioxidant activity on LDL in vitro. Thomas, et al. showed that bovine aortic cells depleted of glutathione or selenium had an increased sensitivity to oxidation by LDL, while incubation of these cells with selenium caused the cells to be more resistant to oxidation. LDL incubated with selenium also reduced its lipid peroxidation and cytotoxicity.[33]

Flavonoids

A group of chemicals found in varying amounts in foods and medicinal plants, flavonoids have been shown to exert potent antioxidant activity against the superoxide radical, hydroxyl radical, hydrogen peroxide, and lipid peroxide radicals. In vitro studies of quercetin, morin, gossypetin, chrysin, myricetin, rutin, catechins, Ginkgo flavone glycosides, and oligomeric proanthocyanidins (OPCs) have shown these flavonoids to have an inhibitory effect on LDL cholesterol oxidation. The mechanism is not entirely clear, but they may directly protect LDL, regenerate LDL-vitamin E, sequester metal ions which may initiate oxidation, or a combination of these.[34-40]

Recent epidemiologic studies indicate an inverse relationship of dietary flavonoids and CAD mortality. A Finnish study found that those with the lowest intake of flavonoids had an increased risk for CAD.[41] The Zutphen Elderly Study also revealed an inverse correlation between dietary flavonoid intake and heart disease.[42]

It is most likely that one mechanism behind the "French Paradox," or the tendency for the French and some other European populations to have a lower risk of CAD even thought they consume a higher fat diet than Americans, is the flavonoid content of the red wine consumed by these people. Fuhrman, et al. showed that red wine flavonoids attach to LDL cholesterol and that they inhibit LDL oxidation. On the other hand, white wine (which contains a very small amount of flavonoids) increased the susceptibility of LDL to undergo oxidation.[39]

Ginkgo flavone glycosides (from Ginkgo biloba) have also been shown to inhibit copper-mediated LDL oxidation in vitro.[38]

The Methionine / Homocysteine Connection

Another significant component in the pathogenesis, prevention, and treatment of CAD involves the amino acid methionine and its metabolites. The degradation or recycling of methionine impacts a number of biochemical pathways involving nutrients known to have an effect on cardiovascular functioning, including coenzyme Q10, cholesterol metabo-

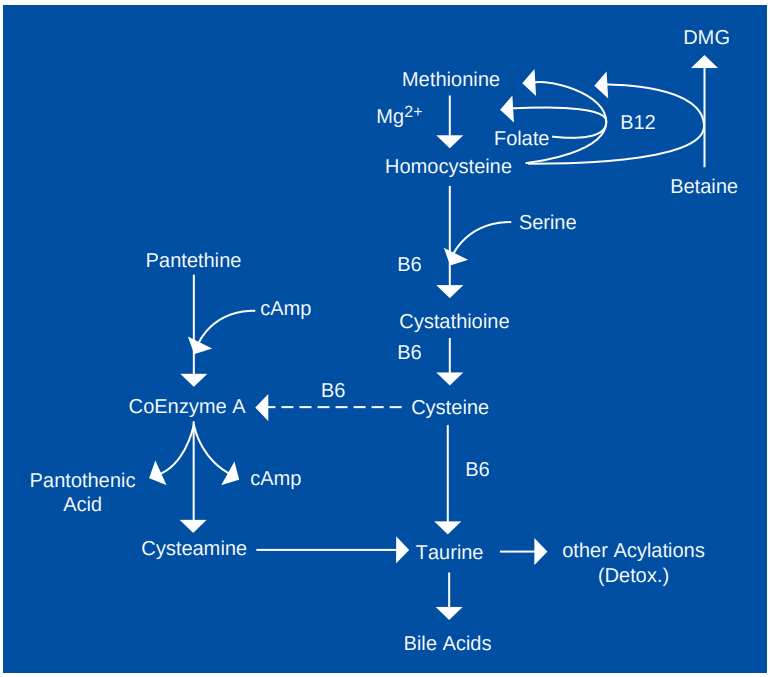


FIGURE 2. Methionine/Homocycteine pathway to Taurine.

lism and excretion, taurine, and L-carnitine. A limiting amino acid in many proteins, methionine is present in higher amounts in meats, legumes, soy products, peanuts, dairy, eggs, and fish. It is also found in garlic, onions, many nuts and seeds, as well as corn, rice, and other grains.

The transsulfuration pathway of methionine degradation produces as its first intermediate the amino acid homocysteine. Homocysteine can either be remethylated into methionine by the vitamin B12-and-folic acid-dependent enzyme methionine synthetase or broken down by the transsulfuration pathway (a vitamin B6-dependent process) into the amino acid cysteine, and then on to the amino acid taurine (see Figure 2). When the enzymes for the breakdown and/or remethylation of homocysteine do not work as they should, due to genetic and/or dietary deficiencies, homocysteine can accumulate, resulting in a condition known as hyperhomocysteinemia. Homocysteine facilitates the generation of hydrogen peroxide,[43-45] which is toxic to vascular endothelium by creating oxidative damage to LDL cholesterol and endothelial cell membranes.

In addition to antioxidant nutrients, native nitric oxide and other oxides of nitrogen released by endothelial cells (also known as endothelium-derived relaxing factor, or EDRF) protect endothelial cells from damage by reacting with homocysteine, forming S-nitrosohomocysteine, which inhibits hydrogen peroxide formation. However, as with the antioxidant mechanisms, as homocysteine levels increase, this protective mechanism can become overloaded, causing damage to endothelial cells and further disruption of the release of EDRF.[44-46] In addition, homocysteine may alter sulfhydryl bonds in collagen, making it unstable.[46] The end result of this oxidative damage and endothelial collagen instability is the formation of atherosclerotic plaques, leading to the conclusion that homocysteine is both a potent and independent risk factor for atherosclerotic vascular disease.

Data gathered by Boers[47] from a number of studies demonstrates that mild hyperhomocysteinemia after a methionine load test occurs in 21%, 24%, and 32% of patients with CAD, cerebrovascular disease, and peripheral vascular disease, respectively. Selhub, et al. found that, from a group of 1160 elderly (ages 67-96) individuals in the Framingham Heart Study, hyperhomocysteinemia (>14 mumol/L by their definition) was present in 29.3%. This study also found that plasma homocysteine increases with age.[48] These increased blood levels of homocysteine are correlated with a significantly increased risk of CAD,[49-52] myocardial infarction,[53,54] peripheral occlusive disease,[48,55-57] cerebral occlusive disease,[48,57] and retinal vascular occlusion.[58]

It has been known for over 25 years that inborn errors of homocysteine metabolism

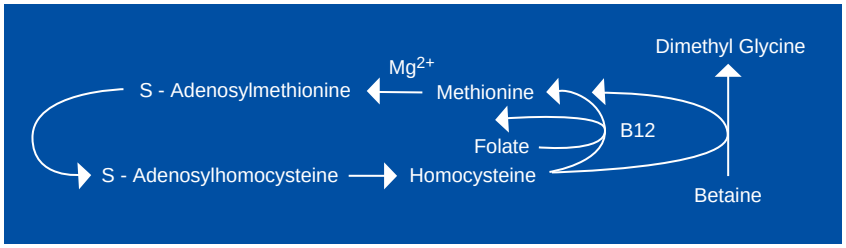


FIGURE 3. Methione-homocysteine -SAM-SAH-Homocysteine loop.

result in high levels of homocysteine in the blood and severe atherosclerotic disease. We now know that, even within the range which is considered normal (4-16 mumol/L), there is a graded increase in risk for CAD. In a group of 304 patients with CAD vs. controls, Robinson, et al. found that the odds ratio for CAD increased as plasma homocysteine increased, even within the normal range. A 5 mumol/L increase in plasma homocysteine was correlated with an increase in the odds ratio of 2.4 ($p<.001$), with no "threshold effect".[52]

The Folate / B12 / B6 Connection

As mentioned above, 5-methyltetrahydrofolate (5-MTHF), a methylated active form of the B-vitamin folic acid, methylates cobalamin (vitamin B12), which is utilized by the enzyme methionine synthetase (also known as N-5-methyltetrahydrofolate:homocysteine methyl-transferase) to re-methylate homocysteine, recycling it back to methionine (see Figure 3). Methionine can then be converted to S-adenosylmethionine, which is vital as a methyl donor to a number of biochemical pathways involved in cardiovascular and neurologic health.

Decreased plasma folate levels are correlated with increased levels of homocysteine, and a subsequent increased incidence of CAD. In a fifteen-year Canadian study of CAD mortality in 5056 men and women 35-79 years of age, lower serum folate levels were correlated with a significantly increased risk of fatal CAD.[59] In a cohort from the Framingham Heart Study, Selhub, et al. found that concentrations of folate and pyridoxal 5'-phosphate (the active, co-enzyme form of vitamin B6) were inversely correlated with homocysteine levels and the risk of extracranial carotid-artery stenosis.[48] Low pyridoxal 5'-phosphate and low vitamin B12 were also linked with hyperhomocysteinemia and a significantly increased risk of CAD in another study.[52]

It makes sense that, if a dietary and/or genetic deficiency of folic acid, B6, or B12 can cause hyperhomocysteinemia, treatment with these micro-nutrients should reduce those increased levels. In a recent placebo-controlled clinical study of 100 men with hyperhomocysteinemia, oral therapy with 650 mcg folic acid, 400 mcg vitamin B12, 10 mg vitamin B6, or a combination of the three nutrients was given daily for six weeks. Plasma homocysteine was reduced 41.7% ($p<0.001$) during folate therapy and 14.8% ($p<0.01$) during B12 therapy, while 10 mg B6 did not reduce plasma homocysteine significantly. The combination reduced homocysteine 49.8%, which, while statistically significant, was not significantly greater than for folic acid therapy alone.[60] In 68 patients with recent myocardial infarction, 18% had increased plasma homocysteine. Oral folate therapy (2.5 mg) reduced this hyperhomocysteinemia in 94% of treated patients (mean decrease 27%).[53]

In a group of 48 patients with peripheral atherosclerotic vascular disease, 50% had abnormally high fasting plasma homocysteine levels, while 100% had abnormal plasma homocysteine after a methionine load. Treatment with 5 mg folic acid and 250 mg pyridoxine for 12 weeks normalized 95% of the fasting levels and100% of post-load homocysteine levels.[55] Other studies confirm that oral folate supplementation will almost always lower high homocysteine, while B6 and B12 will lower homocysteine only in those with a genetic metabolic defect and/or dietary deficiency in those nutrients.[61,62]

A deficiency of the B-6-dependent

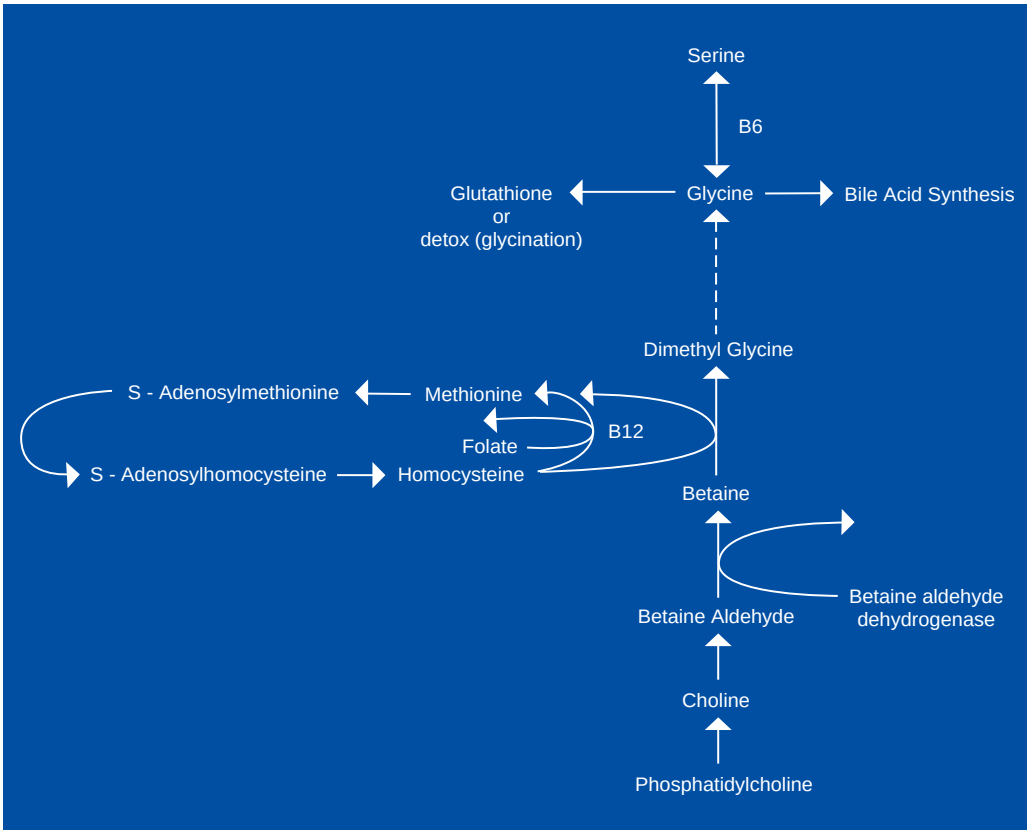


FIGURE 4. Betaine pathway and its interaction with homocysteine

enzyme cystathione synthase is the most common genetic abnormality affecting the transsulfuration pathway of homocysteine breakdown. Fortunately, B-6 supplementation stimulates this enzyme and usually corrects the hyperhomocysteinemia in these individuals, though sometimes folate or betaine needs to be added to the treatment.[62,63] Figure 2 shows the transsulfuration pathway and its reliance on vitamin B6.

As mentioned above, the choline metabolite betaine (trimethylglycine) is another nutrient which may have a positive effect on the re-methylation pathway of homocysteine recycling to methionine. Via the enzyme betaine-homocysteine methyltransferase, betaine gives up a methyl group to homocysteine, and is de-methylated to dimethylglycine (DMG) (see Figure 4) This appears to be a secondary pathway of homocysteine re-methylation which can be stimulated by betaine supplementation. Studies utilizing betaine alone or in combination with B12, B6, or folate have been shown to normalize homocysteine levels,[55,57,62] regardless of whether those individuals originally responded to B6 or folate therapy.[63,64]

The CoEnzyme Q10 Connection

Coenzyme Q10 (CoQ10, ubiquinone) is a ubiquitous lipid-soluble human micro-nutrient that functions as an antioxidant which assists in the recycling of vitamin E,[65,66] along with its significant role in ATP production in the mitochondrial respiratory chain. CoQ10 is synthesized in the body from the amino acid tyrosine and precursor molecules from the cholesterol synthesis pathway (see Figure 5). Two of the final steps in the biosynthesis of CoQ10 involve methylation by S-adenosylmethionine (SAM). The re-methylation of homocysteine should provide adequate methionine for the formation of S-adenosylmethionine. However, a genetic or dietary folate or B12 deficiency can cause a decrease in homocysteine conversion and subsequently a decrease in SAM production, theoretically reducing the ability of SAM to be used in CoQ10 synthesis. Animal

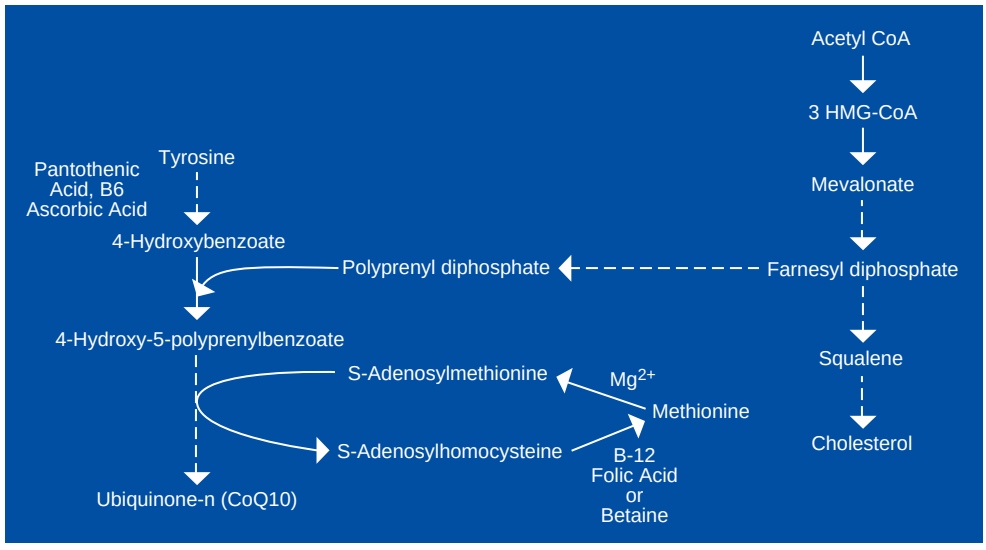


FIGURE 5. Coenzyme Q10 synthesis

studies suggest that depletion of SAM may inhibit CoQ10 synthesis.[67,68]

Looking at the cholesterol-synthesis pathway, it is interesting to note that cholesterol-lowering drugs which inhibit HMG-CoA reductase also lower plasma CoQ10 levels. Supplementation with 100 mg CoQ10 along with 20 mg Simvistatin prevented this drug-induced reduction in plasma CoQ10 in 34 patients.[69]

CoQ10's role in cardiac health stems from its antioxidant activity and its effects on the energy production of the mitochondria. Clinically CoQ10 has been used in the treatment of angina, heart failure, prevention of reperfusion injury after coronary artery bypass grafting, and cardiomyopathy. For a more complete treatise on this subject, please see Alan Gaby's article in this edition of this journal (*Alt Med Rev* 1996;1(3):168-175).

The Carnitine Connection

A trimethylated amino acid roughly similar in structure to choline, carnitine is a cofactor for transformation of free long-chain fatty acids into acyl-carnitines, and their transport into mitochondrial matrix, where they undergo beta-oxidation for cellular energy production. Mitochondrial fatty acid oxidation is the primary fuel source in heart and skeletal muscle. Synthesis of carnitine begins with the methylation of the amino acid L-lysine by SAM, so once again we have a connection to the methionine/homocysteine pathways. Vitamin C, iron, vitamin B-6, and niacin are cofactors in carnitine synthesis, along with the cofactors responsible for creating SAM from homocysteine; folate, B12, and betaine (see Figure 6). Another connection to homocysteine detoxification is that a pivotal enzyme in carnitine synthesis, betaine aldehyde dehydrogenase, is the same enzyme responsible for synthesis of betaine from choline. Two recent studies suggest that this enzyme has a preference for the choline-betaine conversion, and that choline supplementation may decrease carnitine synthesis; therefore, it may be of greater benefit to supplement with betaine rather than its precursor, choline.[70,71]

In acute myocardial ischemia, carnitine levels decrease. L-carnitine supplementation in acute MI patients has been shown to reduce ventricular arrhythmias and decrease the size of the necrotic area.[72,73] Positive effects of reducing angina with 1 g bid carnitine have also been noted in 44 patients with chronic stable angina in a multicenter, double-blind, randomized, placebo controlled crossover trial.[74] Another post-MI study (L-carnitine 4 g/day PO x 12 months) noted improvements in heart rate ($p<0.005$), systolic arterial pressure ($p < 0.005$), a decrease of anginal attacks ($p < 0.005$), and a clear improvement in the lipid pattern ($p < 0.005$). The most dramatic

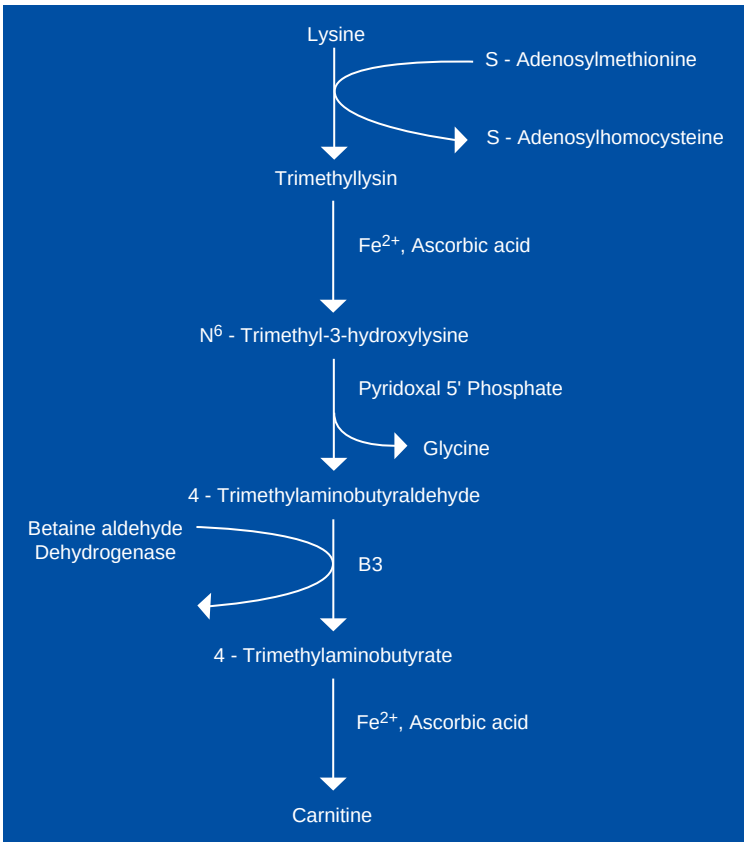


FIGURE 6. Carnitine synthesis

result of this trial, however, is that the mortality of the control group was 12.5%, while patients on L-carnitine had a mortality rate of 1.2%, a 90% decrease in mortality.[75]

The Taurine Connection

The amino acid taurine is one of the end-products of methionine metabolism, and thus is regulated by the micro-nutrient cofactors involved in this pathway (see Figure 2). The most essential micro-nutrient necessary for taurine synthesis is the active coenzyme form of vitamin B6, pyridoxal-5'-phosphate, as it is essential for all the reactions after methionine is converted to homocysteine. Taurine comprises at least 50% of the free amino acid content of the heart, and may act as an antioxidant in cardiac tissue.[76] Taurine also conjugates molecules in the form of bile salts, and is responsible, along with glycine, for conjugating cholesterol for excretion (see Figure 1). Taurine has another connection with homocysteine metabolism, in that betaine is converted into serine, which is necessary for taurine synthesis. Treatment of hyperhomocysteinemia with betaine (the alternate homocysteine re-methylation pathway) decreases homocysteine levels, and additionally has been shown to normalize serum serine and cysteine (the immediate precursor to taurine) levels.[63,77] B12 and Folate supplementation does not have this effect.

The Pantethine Connection

Pantethine, the stable disulfide derivative of vitamin B5 (pantothenic acid), is a precursor to Coenzyme A. In the mitochondria, pantethine increases beta-oxidation of FA, fueling the Kreb's cycle, and has been found to have a favorable effect on blood lipids, including reducing total cholesterol and triglycerides, while increasing HDL cholesterol synthesis.[78-81] Pantethine inhibits cholesterol synthesis when the cholesterol-intermediate mevalonolactone is increased, and is also involved in the formation of the bile acids necessary for cholesterol excretion (see Figure 1).

Table 3

Pantethine seems to have the following impact on enzymes:

ENZYME	EFFECT
Acetyl-CoA synthetase	increase
Cholesterol esterase	decrease
HMG CoA reductase	decrease with high mevalolactone
Lipoprotein lipase	increase
Pantethine and lipid impact:	
Cholesterol	decrease
HDL	increase
Triglycerides	decrease

Laboratory Diagnostics

Unfortunately, very few diagnostic laboratories are offering tests which will be helpful in uncovering the risk factors and nutrient imbalances which have been presented in this article. Your local lab will most likely not currently be offering these tests, but you may be able to have them put together a package. See Table 4 for names and phone numbers of three labs which currently offer comprehensive cardiovascular risk profile tests which may include antioxidant activity, LDL oxidation, homocysteine, lipids and lipoproteins, and nutrients such as folic acid, B6, and B12.

Table 4

National BioTech Laboratory (Seattle, WA) 800-846-6285
SpectraCell Laboratories (Houston, TX) 800-227-5227
Metametrix, Inc. (Norcross, GA) 800-221-4640
Vascular Disease Intervention and Research Laboratory (Oaklahoma City, OK) 405-793-8338

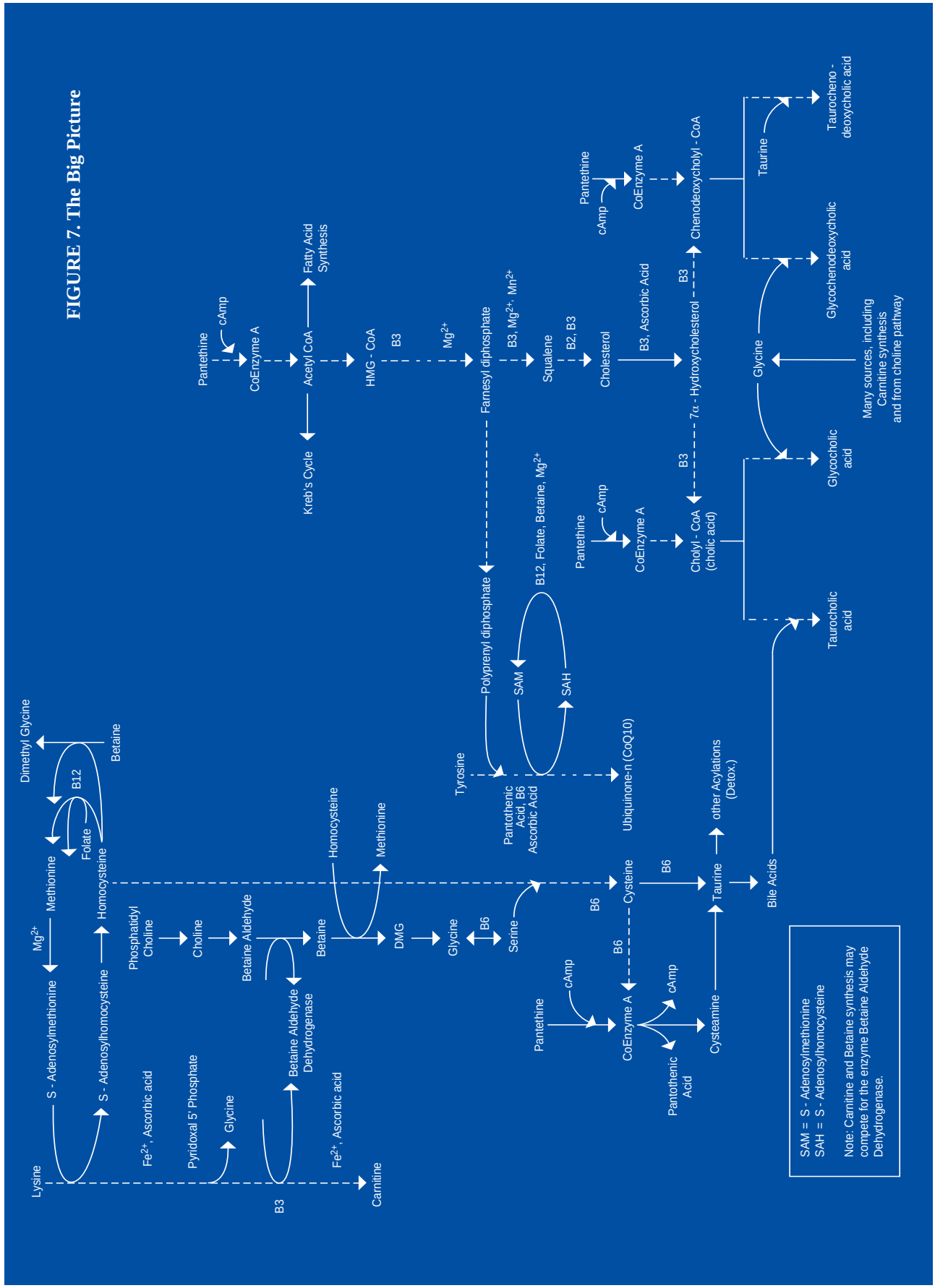
Conclusion

Coronary (and peripheral) atherosclerotic disease is obviously a multi-factorial disease process, with many nutritional, lifestyle, and genetic components. The traditional risk factors listed in Table 1 are valid concerns as independent risk factors. However, they may not be so "independent", as many of them can be connected to the information presented in this article: elevated serum lipids means more lipids which can become oxidized, diabetics have altered lipid profiles, cigarette smoking increases oxidative processes, and positive family history of premature CAD may be related to lipid disorders or homocysteine metabolism defects. In fact, elevated serum lipids, hypertension, and family history of premature CAD may not be a problem unto themselves, but an end-result of micro-nutrient deficiencies caused by inadequate dietary intake or genetic predisposition toward decreased micro-nutrient utilization and/or decreased enzyme activity.

We can address the lipid issue by lowering total and LDL cholesterol, and increasing anti-atherogenic HDL by natural means, including exercise, diet, and micro-nutrients such as pantethine, vitamin C, and vitamin E. But real prevention also includes prevention of LDL oxidation with a healthy cross-section of antioxidants, including vitamin E, vitamin C, coenzyme Q10, flavonoids, selenium, and beta carotene.

Hyperhomocysteinemia is common in patients with "premature" CAD (many authors use this term, as if we will all have it eventually), referring to those under the age of 50 with a diagnosis of CAD. Increased homocysteine (even within the normal range), decreased folate, and decreased pyridoxal-5'-phosphate levels have all been shown to be independent risk factors for CAD. The detoxification of homocysteine by promoting its conversion to essential metabolites is a vital issue which will be the subject of much further research in years to come. However, there is enough current information correlating homocysteine, folic acid, vitamins B6, B12, and the antioxidant micro-nutrients with CAD that these should be screened for in the adult population, or at least in those presenting with heart disease symptomatology or a confirmed diagnosis.

The beauty of the information presented here is that we have scientifically-proven, statistically-significant independent risk factors for CAD which can be prevented or treated with something as simple as proper diet and/or nutritional supplementation. With the direct correlation of folate, B12, and B6 on homocysteine levels, and the proof that homocysteine levels can be effectively lowered by supplementation of these nutrients, we can investigate levels of homocysteine and these nutrients to follow our treatment of CAD patients. If all we do is improve the functioning



of the methionine/homocysteine pathways, other biochemical pathways which have an effect on cardiac health can be favorably affected, including taurine, cholesterol excretion, bile acid synthesis, coenzyme Q10 synthesis, and carnitine synthesis (see Figure 7).

With this approach we can address some of the underlying metabolic conditions which influence the development of CAD and other atherosclerotic processes, with the end-result of decreasing the use of drug-based lipid-lowering therapy, reducing the personal and societal costs of coronary artery bypass and angioplasty surgeries, and ultimately preventing thousands of needless deaths due to CAD, the number one killer in our society.

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