Title
Vitamin C and the Risk of Coronary Heart Disease

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Introduction

Cardiovascular disease is the leading cause of death in the United States, and more than half of these deaths are related to atherosclerotic pathology. In addition to traditional risk factors, such as cholesterol and smoking, increasing evidence in experimental studies suggests that low intake of dietary antioxidants may play a role in the development and consequences of heart disease (9). Several experimental studies suggest that oxidation of low-density lipoprotein (LDL) is important in atherogenesis. In pathological states, oxidized LDL may be taken up by macrophages to create foam cells (2). In addition, LDL oxidation may lead to endothelial cell death and decrease motility of tissue macrophages. Antioxidants, including vitamin C, have been implicated in preventing or diminishing the atherosclerotic process by inhibiting LDL oxidation (9).

Vitamin C Biochemistry

Vitamin C is an electron donor for enzymes involved in collagen hydroxylation, biosynthesis of carnitine and norepinephrine, tyrosine metabolism, and amidation of peptide hormones. A deficiency in vitamin C may result in scurvy (2). However, the amount of vitamin C necessary to prevent scurvy may not be adequate to maintain optimal health. Its ability to donate electrons makes it a potent water-soluble antioxidant that readily scavenges free radicals such as molecular oxygen, superoxide, hydroxyl radical, and hypochlorous acid (1).

In most animals, ascorbic acid (vitamin C) can be synthesized from glucose. However, humans are not able to make L-ascorbic acid and therefore must obtain vitamin C in the diet. Humans can perform the different reactions required for the biosynthesis of the vitamin from D-glucose except for one step-the conversion of L-gluconogammalactone to L-ascorbic acid. The enzyme that catalyzes this reaction, L-gluconolactone oxidase, is defective because of a mutation; thus the need for vitamin C in the diet is the result of an inherent error in carbohydrate metabolism (2).

L-ascorbic acid readily undergoes reversible oxidation and reduction:

L-ascorbic acid " dehydro-L-ascorbic acid + 2H+ + 2e-
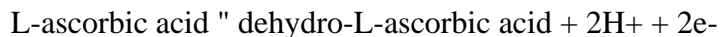
This unique property of the vitamin is the crucial to understanding its role as a redox agent for biologic oxidation. However, ascorbic acid does not act as a conventional cofactor because its requirement can usually be replaced by other compounds with similar redox properties (2). The vitamin has, for example, has the ability to reduce the prosthetic metal ions in many enzymes and exhibit other antioxidant functions by removing free radicals:
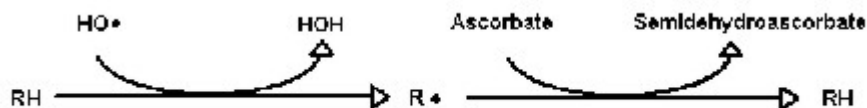
In this setting, several mechanisms could explain a connection between vitamin C and heart disease. For example, vitamin C in vitro can recycle vitamin E, which can donate electrons to

prevent LDL oxidation in vitro. As the lipid-phase vitamin E is oxidized, it can be regenerated by aqueous vitamin C (3). Other possibilities are that vitamin C decreases cholesterol by mechanisms not well characterized, or could improve vasodilatation and vascular reactivity, perhaps by decreasing the interactions of nitric oxide with oxidants (10).

Early Studies of Vitamin C deficiency in atherosclerotic heart disease patients

Vitamin C has been associated with stress ever since Albert Szent-Gyorgi isolated it from the oxen adrenal gland. In the seventies, investigators including Hume et al. and Machtey et al., showed that plasma and tissue vitamin C concentrations declined within one day and increased again after one week in patients with the stress of an acute myocardial infarction (AMI) (8). In the early eighties, Ramirez et al. showed that vitamin C concentrations in leukocytes were diminished in patients with angiographically-proven coronary artery disease than in those without disease (6). Despite suggestions that the findings were due to changes in the ratio of circulating neutrophils to lymphocytes, which have two- to three-fold different vitamin C concentrations, the discovery of low plasma vitamin C remained unexplained until the past decade.

More recently, there has been strong evidence that oxidative free radicals play a role in the development of degenerative diseases, including coronary heart disease. Studies have shown that oxidative free radicals increase the peroxidation of low-density lipoprotein, thereby increasing its uptake by macrophages and leading to increased foam cell formation and atherosclerosis (10). Vitamin C, although not found in appreciable concentrations in LDL, has strong antioxidant capacity, and may function to regenerate or spare vitamin E and lead to reduced LDL oxidization (3). Recent focus on the epidemiological studies rather than experimental data, however, has raised important questions about Vitamin C's role in decreasing the risk of MI.

Studies Implicating No Association

A study by Riemersma et al. examined whether a low plasma vitamin C concentration was correlated with an increased risk of AMI, irrespective of smoking status, socioeconomic factors, and acute phase response. Their results showed that patients with AMI had lower plasma vitamin C concentrations than did control subjects (14.5 and >60.5 µmol/L, respectively). However, the elevated risk of AMI in patients with low vitamin C concentrations during the acute phase would decline three months after an AMI (relative risk: 1.02). The authors concluded that recovery concentrations reflected pre-hospitalization plasma concentrations, and therefore subjects with low vitamin C concentrations did not have an increased risk of infarction (7).

Klipstein-Grobusch et al. investigated whether vitamin C was associated with increased risk of MI in an elderly population between ages 55 and 95 in Rotterdam, Netherlands. In this study, the authors examined 4802 subjects over a four-year period and assessed their dietary data by a semi-quantitative food frequency. Although no association between dietary vitamin C with the risk of MI was observed, there was an inverse relationship of ß-carotene intake with risk of MI was noted. The authors therefore proposed that not all antioxidants may play a role in decreasing the risk of MI (4).

Studies Implicating Cardioprotective Effect

In a prospective study of myocardial infarction on Finnish men, Nvyssonen et al. examined 1605 middle-aged Finnish men without coronary disease when enrolled in a study designed to investigate risk factors for heart disease and related outcomes, including myocardial infarction. During the period March 1984-1992, 70 of the men in the sample experienced MIs. A significantly higher percentage (13.2%) of the 91 men with plasma vitamin C concentrations less than 11.4 µmol/l (2.0 mg/L) experienced MIs, compared with the remaining men with plasma vitamin C above this level, among whom 3.8% suffered from MIs. On a population basis, plasma vitamin C provides a reliable index of tissue stores of the vitamin; levels less than 11.4 µmol/L reflect deficiency. For the group of men with plasma vitamin C greater than 11.4 µmol/L, there were no differences in MI outcomes by plasma vitamin C concentration. They concluded that Vitamin C deficiency, as assessed by low plasma ascorbate concentration, demonstrates a risk factor for coronary heart disease ([5]).

Vita et al. measured antioxidant status and oxidative damage in men and women with existing coronary artery disease. The authors investigated the correlation between antioxidant status, extent of atherosclerosis, and clinical expression of the disease. In this study, the extent of atherosclerosis and low plasma ascorbate represented significant predictors of an unstable coronary status (p=0.008 and 0.01, respectively). For the 128 patients with significant atherosclerosis (defined as one stenosis >50%), low plasma ascorbate and total thiol concentrations, but not the extent of atherosclerosis, were significant predictors of unstable coronary syndrome (p=0.008 and 0.004, respectively). The authors concluded that their findings support the hypothesis that antioxidant status may affect coronary artery disease through an effect on lesion activity rather than by a reduction in the overall development of disease. Furthermore, they suggested that the antioxidant property of vitamin C could affect the clinical activity of the atherosclerotic condition ([10]).

Conclusion

Recent experimental studies on rat cardiomyocytes may help end this long debate seen in epidemiological investigations. Last September, Rinne T et al. found that pre-treatment with vitamin C reduced the number of hypercontracted cells after exposure to free radicals. The authors proposed that their findings implicate a direct protective action of vitamin C on heart muscles cells against oxidative damage. The observations also suggested promising results for two recent and small interventional trials following this investigation. In one trial, antioxidant vitamins decreased the incidence of angina pectoris, arrhythmias, and poor left ventricular function in patients with suspected myocardial infarction. In another trial, vitamin C supplementation in patients with AMI prevented electrical function abnormalities, as observed in electrocardiogram ([9]).

Although vitamin C is a strong antioxidant, the epidemiological evidence to support its role in lowering risk of cardiovascular disease is inconsistent. Some results from studies from different regions of the world suggest a strong inverse correlation between plasma levels of vitamin C and cardiovascular mortality. These data are important in supporting the antioxidant hypothesis and for stimulating further research. However, other dietary and lifestyle characteristics also differ

among the regions studied. One cannot definitively attribute the differences in cardiovascular disease specifically to dietary antioxidants without considering a multitude of other potential coronary heart disease risk factors.

On the basis of mechanistic, physiological, and epidemiological studies, vitamin C's beneficial effect in coronary artery disease has not been resolved. In fact, the evidence for a cardioprotective effect of vitamin C, based on epidemiological studies alone, is rather weak and inconsistent. In order to learn definitively whether vitamin C plasma concentration affects cardiovascular risk, subjects with high concentrations should be compared with those with low concentrations immediately before and at the time of myocardial infraction. Properly designed interventional studies can test this hypothesis and eliminate other risk factors, including lifestyle variations. With properly designed models, epidemiological studies can be evaluated with experimental evidence to determine vitamin C's role in cardiovascular disease prevention. If vitamin C does indeed have a cardioprotective effect, the clinical value of antioxidant therapy in acute myocardial ischemia may then be realized.

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