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Nutrition Bytes

Title

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Permalink

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Journal

Nutrition Bytes, 14(1)

ISSN

1548-4327

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Publication Date

2010-05-06

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Vitamin C and Treating Coronary Artery Disease: More Hype than Hope?

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Introduction

Among the myriad diseases and ailments that exist today, coronary artery disease (CAD) stands out as the single leading cause of mortality and morbidity in the United States and other Westernized nations. CAD results when the arteries supplying the heart are narrowed due to plaque accumulation, resulting in chest pain and encouraging thrombotic events. An imbalance between oxidative stress, caused by reactive oxygen species (ROS), and antioxidant defense mechanisms is believed to play a pivotal role in atherogenesis.¹ ROS are by-products of aerobic respiration and function as signaling molecules that regulate cell growth and adaptation responses. However, at non-physiological concentrations, ROS can induce cellular injury and contribute to atherosclerosis by oxidizing low-density lipoproteins (LDL).¹ The oxidized LDL is preferentially phagocytosed by macrophages and leads to the formation of foam cells that can either return the cholesterol to the liver for removal or continue to pick up lipid and cause greater inflammation. Leukocytes combining with foam cells form fatty streaks which, along with continued ROS generation and inflammation, lead to advanced atherosclerosis.

A potential role for vitamin antioxidant therapy?

Given what we know about the role of ROS in atherosclerosis, the logical conclusion has been that a diet rich in antioxidants could mitigate their harmful effects. An antioxidant can be defined as “any substance that, when present at low concentrations compared to those of an oxidizable substrate (e.g. proteins, lipids, carbohydrates and nucleic acids), significantly delays or prevents oxidation of that substrate”.² Potential diet-derived antioxidants include ascorbic acid (vitamin C), α -tocopherol (vitamin E), polyphenols, β -carotene, lycopene, and other various carotenoids.

Vitamin C is one of the antioxidants that has been studied as a potential treatment for CAD. It is a water-soluble micronutrient required by our bodies for normal metabolic functioning and is obtained through dietary consumption of foods, such as citrus fruits and vegetables. Vitamin C has two main properties that make it an effective antioxidant. One is the low reduction potentials of both vitamin C and the oxidation product it forms after scavenging a ROS, the ascorbyl radical.² These low reduction potentials allow vitamin C and the ascorbyl radical to reduce virtually all physiologically relevant oxidants and free radicals. The other key property is the relative stability of the ascorbyl radical and the fact that it can readily be reduced back to ascorbate by an NADH-dependent semidehydroascorbate reductase.³

How does vitamin C affect the cardiovascular system on a biochemical level?

The experimental studies done to date indicate that vitamin C affects several different components of the cardiovascular system. In vitro experiments have shown that oxidative biomarker formation does not occur until most of the endogenous vitamin C has been depleted.^{4,5} While several clinical trials have shown no effect on LDL oxidation,^{6,7} others have shown an

increase in lag time of LDL oxidation after vitamin C addition;⁸⁻¹² in addition to scavenging ROS, vitamin C may prevent copper-mediated modification of LDL and hence play a protective role.^{13,14}

One of the early steps in atherosclerosis is the impairment of vascular endothelial function through the loss of nitric oxide (NO), a molecule generated by the endothelium that regulates vascular homeostasis.¹⁵ ROS scavenge NO and produce a reactive peroxynitrite intermediate that promotes lipid oxidation and atherogenesis. Human cell studies and mouse models show that vitamin C may increase NO bioavailability by enhancing nitric oxide synthase and its co-factor, tetrahydrobiopterin (BH₄).¹⁶ Clinical trials have also shown that daily administration of vitamin C improves arterial vasodilatation via elevated NO levels in patients with increased oxidant stress, including CAD,^{17,18} hypertension,¹⁹ hypercholesterolemia,²⁰ chronic smoking,²¹ obstructive sleep apnea,²² and estrogen-deficient post-menopausal women.²³ The fact that NO also inhibits platelet aggregation and leukocyte adhesion, two components implicated in atherosclerosis, may explain why some studies have found an association between elevated plasma vitamin C concentrations and reduced platelet adhesiveness²⁴ as well as reduced monocyte adhesion to endothelial cells.²⁵

Inflammatory pathways, mediated in part by ROS formation, play a key role in atherogenesis and elevated plasma levels of several inflammatory markers (i.e. interleukin-6, C-reactive protein, P-selectin) have been predictors of risk for thrombotic events.^{26,27} A cross-sectional study by Wannamethee et al. showed an inverse association between inflammatory markers and vitamin C intake in 3,258 men with no history of CAD or diabetes.²⁸ A randomized, double-blind placebo-controlled trial by Block et al. demonstrated that vitamin C supplementation (515 mg/day) in 216 healthy men and women significantly reduced plasma levels of C-reactive protein.²⁹

What is the epidemiologic evidence for vitamin C's cardioprotective effect?

Results from epidemiologic studies that have studied the relationship between dietary intakes of vitamin C and incident heart disease events have been mixed. A number of prospective cohort studies done in the past several decades indicated a protective cardiovascular effect for vitamin C that correlated with levels of daily intake.³⁰⁻³² The study by Osganian et al. followed 85,118 female nurses for 16 years and used questionnaire data to estimate their vitamin C intake.³³ The study found that women in the highest quintile of vitamin C intake (≥ 360 mg/day) had a 27% reduced risk of adverse cardiovascular events than women in the lowest quintile (≤ 93 mg/day). Several other epidemiologic studies found no beneficial effect even with intakes of vitamin C >200 mg/day in populations without cardiovascular risk.³⁴⁻³⁶ However, a pooled analysis of nine prospective cohort studies, which included 293,172 patients without CAD at baseline and a follow-up average of 10 years, found that those who took >700 mg supplemental vitamin C per day had a reduced CAD incidence rate (RR=0.75; 95% CI: 0.60-0.93) relative to people who did not take vitamin C supplements.³⁷

Other prospective cohort studies that have used the more reliable approach of directly measuring plasma vitamin C levels, as opposed to relying on nutrition questionnaires, have found an association with cardiovascular disease risk.³⁸⁻⁴⁰ A study by Simon et al. found that among the 6,624 men and women enrolled in the second National Health and Nutrition Examination Survey, those with higher vitamin C levels of 63-153 $\mu\text{mol/L}$ compared to lower concentrations of 6-23 $\mu\text{mol/L}$ showed 26% and 27% risk reductions for stroke and coronary artery disease,

respectively.⁴¹ Another study found that participants with plasma concentrations $>89 \mu\text{mol/L}$ compared with $<52 \mu\text{mol/L}$ had a 62% reduction in mortality from heart disease.⁴² The findings from these studies are summarized in Table 1.

How effective has vitamin C supplementation been in clinical trials?

The two major clinical trials looking at the effect of vitamin C intake on incident CAD events have been disappointing. Sesso et al. ran a double-blind, placebo-controlled, randomized trial to evaluate whether long-term vitamin C and vitamin E supplementation decreased risk of major cardiovascular events in men.⁴³ From 1997 until its scheduled completion in 2007, 14,641 male physicians aged 50 or older were randomized to receive vitamin E (400 IU every other day) or its placebo, vitamin C (500 mg/day) or its placebo, multivitamin, or placebo. During a mean follow-up of 8 years, the rate of major cardiovascular events did not differ significantly between vitamin C and placebo or between vitamin E and placebo (10.8 versus 10.9 per 1,000 person years, respectively, for both comparisons). Furthermore, no significant differences were found between individual endpoints (myocardial infarction, stroke, cardiovascular mortality, and all-cause mortality) for either vitamin supplement.

Another double-blind, placebo-controlled, randomized trial by Cook et al. examined both the individual and combined actions of antioxidants on cardiovascular disease risk.⁴⁴ The participants were female health professionals 40 years or older who had a self-reported history of cardiovascular disease or three or more cardiovascular disease risk factors. Beginning in 1995, 8,171 participants were followed for a mean duration of 9.4 years during which they were randomized to receive vitamin C (500 mg/d), vitamin E (600 IU every other day), and beta carotene (50 mg every other day). Vitamin C supplementation had no effect on the combined endpoint of cardiovascular morbidity and mortality (RR=1.02; 95% CI: 0.92-1.13) or in any risk factor subgroup. The endpoints were not affected by antioxidant interactions, but those randomized to both active ascorbic acid and vitamin E did experience fewer strokes (RR=0.69; 95% CI: 0.49-0.98).

Other randomized trials that have included vitamin C in multivitamin regimens have also been unsuccessful. The MRC/BHF Heart Protection Study studied antioxidant supplementation in 20,536 high cardiac risk individuals over a 5-year treatment period in which participants were given a multivitamin pill (250 mg vitamin C, 600 mg vitamin E, and 20 mg β -carotene daily) or matching placebo.⁴⁵ Although this regimen substantially increased the plasma vitamin concentrations, no significant differences were found in rates of fatal and non-fatal cardiovascular events. A separate trial by Hercberg et al. in which 13,017 French adults were given a multivitamin pill (120 mg of vitamin C, 30 mg of vitamin E, 6 mg of beta carotene, 100 μg of selenium, and 20 mg of zinc) or placebo over a 7.5-year treatment period also failed to find any significant effects on all-cause mortality or adverse cardiovascular events.⁴⁶

Future outlook

The evidence gathered from human clinical trials does not support the use of vitamin C antioxidant therapy for preventing adverse cardiovascular events. In particular, the trials by Sesso et al. and Cook et al. found no benefit to vitamin C supplementation, for reasons that are not entirely clear.^{43,44} The 500 mg/day dose used in each trial far exceeds typical dietary vitamin

C levels⁴⁷ and is above the ≈ 100 mg/day that results in tissue saturation in healthy adult men.⁴⁸ The possibility that non-adherence diminished serum vitamin C levels and lowered the treatment efficacy is a potential limitation, but sensitivity analyses that censored follow-up time based on non-adherence did not alter the findings in the two studies.^{43,44}

One possible reason for the failure of these trials is that the wrong group of patients was studied. In theory, antioxidant therapy should be most effective in the earlier stages of atherosclerosis by mitigating LDL oxidation and plaque formation. Given that the population group in each study has an average age >60 years, initiating antioxidant therapy may have been too late to reverse an atherosclerotic process that had been progressing over several decades.

Conversely, it can be argued that only select patients with an objective biochemical assessment of increased oxidative stress should be studied. Analyzing the effects of vitamin C supplementation on people with, for example, angiographically proven atherosclerosis at the study baseline could potentially show more significant results than simply looking at a heterogeneous population of people with varying levels of cardiovascular risk. Although the trial by Cook et al. studied a population at risk for cardiovascular disease, it relied on self-reported histories of cardiac risk factors instead of clinical determination of atherosclerosis.

The emphasis of clinical trials on adverse cardiovascular event rates also neglects to look at the positive effects vitamin C may have on a biochemical level. Inclusion of biochemical markers of oxidative stress and vascular response may show changes that affect cardiovascular event severity and subsequent quality of life, two variables that have not yet been addressed. Furthermore, few of the unsuccessful antioxidant trials have used imaging modalities to assess temporal changes in plaque size and formation while taking vitamin C supplements; such information could reveal what stages of atherogenesis vitamin C might be most efficacious in treating.

Barring any significant changes in how these major clinical trials are conducted, the consensus in the medical community will remain that vitamin C antioxidant therapy for the prevention or treatment of CAD is ineffective. There do not appear to be any other pending clinical trials investigating the impact of vitamin C on CAD at the time of this writing. Nevertheless, the underwhelming clinical evidence for a cardioprotective effect should not negate the conventional advice that increasing consumption of fruits and vegetables can help reduce the risk of cardiovascular disease. The numerous cardiovascular benefits of vitamin C elucidated in experimental studies show the potential for what it can do, but whether a trial can be designed that teases out these benefits remains to be seen.

Table 1. The effect of vitamin C on mortality from CAD

Trial	Study Type	Pop. size (n)	Age (yr)	Intervention	Duration (yr)	Outcome
Sesso [43]	double-blind, placebo-controlled, randomized trial	14,641	64.3 ± 9.2	vit. E (400 IU every other day), vit. C (500 mg/day); 2x2 factorial design	8	RR: 1.07 (95% CI: 0.97-1.18) No significant effects on all-cause mortality or cardiovascular events.
Cook [44]	double-blind, placebo-controlled, randomized trial	8,171	60.6 ± 8.8	vit. E (600 IU every other day), vit. C (500 mg/day); 2x2 factorial design	9.4	RR: 1.02 (95% CI: 0.92-1.13) No significant effects on all-cause mortality or cardiovascular events.
Enstrom [30]	prospective cohort study	men: 4,479 women: 6,869	men: 25-74 women: 25-74	>50 mg/day + regular supplements ¹	10	men: RR: 0.58 (95% CI: 0.41-0.78) ² women : RR: 0.75 (95% CI: 0.55-0.99) ²
Knekt [31]	prospective cohort study	men: 2,748 women: 2,385	30-69	men: >85 mg/day compared to <60 mg/day women: >91 mg/day compared to <61 mg/day	14	men: RR: 1.00 (95% CI: 0.68-1.45) women : RR: 0.49 (95% CI: 0.24-0.98)
Osganian [33]	prospective cohort study	85,118	30-55	>360 mg/day compared to <93 mg/day	16	RR: 0.73 (95% CI: 0.57-0.94)
Pandey [36]	prospective cohort study	men: 1,556	40-55	>113 mg/day compared to <82 mg/day	24	RR: 0.75 (95% CI: 0.52-1.07)
Kushi [34]	prospective cohort study	women: 34,486	55-69	>391 mg/day compared to <112 mg/day	6	RR: 1.49 (95% CI: 0.96-2.30)
Losonczy [35]	prospective cohort study	11,178	67-105	vitamin C supplement compared to no supplement ³	6	RR: 0.99 (95% CI: 0.74-1.33)
Nyyssönen [38]	prospective cohort study	men: 1,605	42-60	<11.4 µmol/l compared to >11.4 µmol/l	8	RR: 2.50 (95% CI: 1.3-5.2) ⁴
Gale [32]	prospective cohort study	730	>65	>27.8 µmol/L compared to <11.9 µmol/L	20	RR: 0.90 (95% CI: 0.6-1.3)
Sahyoun [42]	prospective cohort study	725	60-101	>89 µmol/L compared to <52 µmol/L	12	RR: 0.38 (95% CI: 0.19-0.75)
Singh [40]	cross-sectional study	595	50-84	<15.2 µmol/L compared to >42.6 µmol/L	n/a	OR: 2.21 [95% CI: 1.12-3.15] ⁵
Simon [41]	cross-sectional study	6,624	40-74	63-153 µmol/L compared to 6-23 µmol/L	n/a	OR: 0.73 [95% CI: 0.59-0.90] ⁶

¹Exact value of vitamin C supplements not recorded²Relative risk was obtained using a standardized mortality ratio of 1.00 for all US whites because the study cohort was based on a nationally representative sample in which 82% of participants were white³Exact value of vitamin C supplements not recorded⁴Relative risk of myocardial infarction for vitamin C intake <11.4 µmol/L (defined in the study as vitamin C deficient)⁵Odds ratio of having CAD (lowest quintile/highest quintile)⁶Odds ratio of having CAD (highest quintile/lowest quintile)

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