Is vitamin C an antiinflammatory agent?[1–3]

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Inflammation is pivotal to atherosclerosis from the nascent fatty streak to the culmination in acute coronary syndromes (1). C-reactive protein (CRP), a stable downstream marker of inflammation, also may participate in atherothrombosis. Thus, strategies directed at attenuating inflammation may prove beneficial with respect to a reduction in cardiovascular disease. Vitamin C is a water-soluble antioxidant that is present in fruit and vegetables in the diet. Recently, the Dietary Reference Intake Panel of the Institute of Medicine recommended a vitamin C dietary allowance of 90 mg/d for men and 75 mg/d for women (2). This recommendation was based on many lines of evidence, including the amount required to maintain near-maximum neutrophil concentrations with minimal urinary excretion of ascorbate. Whereas it is well accepted that vitamin C has antioxidant effects with respect to both reactive oxygen and nitrogen species, its effect on biomarkers of inflammation has not been well studied. In a cross-sectional analysis of the third National Health and Nutrition Examination Survey data, Ford et al (3) reported that CRP concentrations were inversely and significantly associated with concentrations of retinol, retinyl esters, vitamin C, α-carotene, β-carotene, lycopene, cryptoxanthin, lutein or zeaxanthin, and selenium C after adjustment for age, sex, race-ethnicity, education, body mass index (BMI), leisure-time physical activity, and aspirin use. In this issue of the Journal, Wannamethee et al (4) report a significant inverse association of dietary and plasma vitamin C and fruit and vegetable intakes with biomarkers of inflammation in a cross-sectional study of 3258 men aged 60–69 y who had no history of cardiovascular disease or diabetes. Wannamethee et al concluded that vitamin C has antinflammatory effects and is associated with an attenuation of endothelial dysfunction. However, it is important to emphasize that theirs was a cross-sectional study and not a randomized placebo-controlled clinical trial, and thus the authors' conclusion is not firm and cannot be used for policy guidelines. Furthermore, with respect to fruit and vegetable intakes, it is unclear why the authors did not pool the data.

The authors showed that plasma vitamin C correlates inversely with biomarkers of inflammation such as CRP more than does dietary vitamin C. This study was focused on white men aged > 60 y, and thus its findings cannot be translated to men aged < 60 y, women, or people of other races. Furthermore, as shown in Table 2 in Wannamethee et al, the increase in dietary vitamin C with increasing BMI was paradoxically accompanied by a decrease in plasma vitamin C. The dietary intake should have been standardized to energy consumption. No mention is made of

vitamin E and flavanoid intakes, which could also result in antiinflammatory effects. The authors used the tissue plasminogen activator (t-PA) antigen assay as a biomarker of endothelial dysfunction; some have accepted this use of the t-PA antigen assay, but it is not clear whether there is indeed a relation between vitamin C and biomarkers of endothelial function, because the authors did not show a correlation between vitamin C and von Willebrand factor, another biomarker of endothelial dysfunction. It would have been instructive if they had measured other important biomarkers of inflammation, such as E-selectin or soluble vascular cell adhesion molecule and plasminogen activator inhibitor 1. Many believe it is more relevant to measure t-PA activity, and thus the inverse correlation seen with t-PA antigen can be construed as suggesting that a lower concentration of t-PA is beneficial, whereas t-PA activity actually denotes fibrinolysis, and increased plasminogen activator inhibitor 1 concentrations suggest impaired fibrinolysis.

If it is true, as Wannamethee et al concluded, that vitamin C has antiinflammatory effects, then that finding should be borne out in prospective supplementation studies. A review of the prospective studies to date found that 4 of the 5 studies with doses ranging from 250 to 3000 mg vitamin C/d in persons with diabetes, hypercholesterolemia, hemodialysis, or coronary artery disease reported no antiinflammatory effect (5–9). Block et al (5) found a reduction in CRP in active and passive smokers with intakes of 515 mg vitamin C/d. Thus, in summarizing the prospective studies, one cannot arrive at a firm conclusion that vitamin C is antiinflammatory, and indeed most of the studies would support the notion that vitamin C is not antiinflammatory (5–8).

With respect to endothelial dysfunction, many studies have shown that intravenous vitamin C results in an improvement in endothelial vasoreactivity (2). Studies of the effect of oral vitamin C supplementation on endothelial vasoreactivity are few and conflicting. More data are required to confirm whether dietary vitamin C supplementation is beneficial to endothelial function.

In conclusion, whereas the study by Wannamethee et al is provocative with respect to the antiinflammatory effects of vitamin C, it does not allow the drawing of any valid conclusions.

Much further research in a dose-response structure is required to ascertain whether oral vitamin C supplementation is antiinflammatory and whether it improves endothelial dysfunction. Until such studies have been conducted, it is safe to adhere to the guidelines of national organizations to consume ≥5 daily servings of fruit and vegetables.

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