Most fatal acute myocardial infarctions result from a fracture of the plaque’s fibrous cap. We proposed the hypothesis some years ago that the level of collagen in the fibrous cap depends on a dynamic balance of synthesis and degradation.1 We further showed that inflammatory cytokines can regulate both the expression of genes that direct interstitial collagen synthesis in vascular smooth muscle cells and the interstitial collagenases (matrix metalloproteinases 1, 8, and 13) required to initiate the breakdown of collagen fibrils.2-5 Given the capital importance of collagen in protecting the plaque from rupture and hence thrombosis, the metabolism of this complex molecule merits consideration in depth.

See p 1485

The formation of mature fibrillar collagen involves many steps beyond gene transcription (Figure). The initial translation product, the procollagen peptide chain, undergoes extensive posttranslational modification: an especially noteworthy point during this period of exploration of the proteome. Collagen contains unusual amino acids, hydroxyproline and hydroxylysine, formed by a vitamin C–dependent process that entails enzymatic transfer of hydroxyl groups to selected proline and lysine residues in the nascent procollagen chains. Glycosyl transferases then add sugar moieties to the procollagen chains. The hydroxylated and glycosylated monomers then self-assemble into helical trimers as they traverse several intracellular compartments. Trimming the nonhelical tails (the telopeptides) from both ends of the procollagen molecule by proteinases yields the mature interstitial collagen triple helix secreted by smooth muscle cells in arteries. These building blocks then further self-aggregate into multimers and form interstitial collagen fibrils, linear structures as strong as steel wires.

The ascorbate-dependent addition of polar hydroxyl groups to the side chains of proline and lysine may aid the self-assembly and stability of the collagen fibril by forming interchain hydrogen bonds. The absence of sufficient ascorbic acid (vitamin C), a required cofactor for prolylhydroxylase, thus impairs the formation of stable collagen. The human phenotype of vitamin C deficiency, scurvy, classically involves fragility of blood vessels. In 1753, James Lind described the skin of scurbitics as “...covered with several reddish, bluish... spots... resembling an effusion of blood.”6 Lind’s discovery that food rich in vitamin C provided a cure for scurvy spurred England’s subsequent naval supremacy and putatively changed the course of history. Of course, chemical characterization of vitamin C as the antiscorbutic factor did not occur until the 1930s. (Interested readers may find Albert Szent-Györgi’s dispute with the editor of the Biochemical Journal regarding publication of the structure of vitamin C amusing.7 Cardiologists know Szent-Györgi better for his later discovery of the biochemical basis of muscle contraction).

Study of vitamin C’s role in vivo has proven challenging. Unlike humans, usual experimental animals can synthesize vitamin C and thus cannot be made scurbitic. Maeda’s group has recently introduced a targeted mutation that makes mice dependent on dietary vitamin C, allowing manipulation of ascorbate levels. In this issue of Circulation, Nakata et al8 studied atheroma in hypercholesterolemic and scurbitic mice. They find no change in lesion size, but they observe decreased collagen content in the lesions. Such changes should impair the biomechanical strength of the plaque and make it more prone to rupture. This finding extends the burgeoning evidence that changes in collagen metabolism can influence crucial characteristics of the atherosclerotic plaque. Our recent in vivo studies also showed that alterations in collagen synthesis and catabolism induced by lipid lowering or statin treatment influence the collagenous structure of atheroma in rabbits.9-11 It would have been of interest to evaluate overall protein content in these lesions, as we showed almost 2 decades ago that ascorbate can augment noncollagen protein synthesis by cultured arterial smooth muscle cells.12

We do not know whether scurbitic humans with atherosclerosis would experience increased plaque rupture, a curious but currently clinically irrelevant question. In addition to its antiscorbutic action, vitamin C has potent antioxidant properties. Physiological concentrations of ascorbic acid can inhibit in vitro oxidative modification of LDL, a critical event during atherogenesis.13 For this reason, many individuals take this and other antioxidant vitamins in hope that combating oxidative stress can forestall atherosclerosis and its complications. Vitamin C has other antiinflammatory effects as well, including decreased leukocyte adhesion to the endothelium and increased bioavailability of atheroprotective nitric oxide (NO). Administration of vitamin C for 10 days (2 g/d) reduces adhesion of monocytes obtained from cigarette smokers to cultured endothelial cells.14 Vitamin C’s potency generally exceeds that of vitamin E as an antiinflammatory and antiatherogenic agent. For example, intake of vitamin C, but not vitamin E, inhibits oxidized LDL-induced leukocyte adhesion to endothelium in hamsters.15 Physiological concent-
trations of ascorbic acid also increase synthesis and activity of NO in vitro. Vitamin C also inhibits activation of nuclear factor-κB (NF-κB), a key regulator of inflammatory gene expression. Administration of vitamin C can improve endothelial dysfunction in hypercholesterolemic patients. Ascorbate’s effect on plaque collagen content adds another theoretical rationale for using vitamin C in patients at risk for atherosclerotic events.

Unfortunately, we lack clinical evidence that would permit us to translate this basic science into practice. The recently reported (but as yet unpublished) Heart Protection Study (HPS) administered a cocktail of antioxidant vitamins (vitamin C 250 mg, vitamin E 600 mg, beta-carotene 20 mg/d) to a large group of individuals at high risk for atherosclerotic events for a period of 5 years. The vitamins had absolutely no effect on a variety of end points, including coronary events (see also The Heart Protection Study Investigators at http://www.hpsinfo.org). Brown and colleagues recently reported acceleration of coronary atherosclerosis in patients treated with a combination of statins and a cocktail of antioxidant vitamins (vitamin C 1000 mg, vitamin E 800 IU, beta-carotene 25 mg/d) in the HDL-Atherosclerosis Treatment Study (HATS).

To what may we attribute this apparent failure of a plausible and widely used therapeutic approach? First, these studies may have employed suboptimal doses of the vitamins used, or interactions among them may have mitigated a beneficial effect of one or the other supplements. In this regard, vitamin E monotherapy showed no benefit on atherosclerotic events in both the Heart Outcomes Prevention Evaluation (HOPE) and GISSI studies. In these various studies, the degree of preexisting disease or inadequate duration of treatment might have limited the benefit of the antioxidants. Yet, the striking beneficial effects observed in the statin treatment arms of both the HPS and HATS and of the angiotensin converting enzyme inhibitor in the HOPE study establish the mutability of outcomes measured in these patient populations in the same trials. Partition of fat-soluble vitamin E into the lipid phase of plaque or lipoproteins might shield it from the cooperative antioxidant effect of water-soluble ascorbate, excluded from these lipid milieux. Thus, more potent or amphipathic antioxidants might interrupt oxidative stress during atherogenesis more effectively than the vitamins. Although vitamin deficiencies lead to disease, consumption of pharmacological amounts of these substances in individuals who maintain vitamin-sufficient diets may not prevent disease. Indeed, malnutrition hardly applies to our patients with atherosclerosis. Contemporary developed societies seem at much higher risk of dietary surfeit than lack.

It is curious indeed that many remain suspicious of pharmacological lipid-lowering, a strategy now proven un-
equivocally to prevent myocardial infarction and stroke and to prolong life as well. Yet, many individuals readily consume costly vitamin supplements devoid of benefit in clinical trials. This situation may reflect in part a failure of the medical community to communicate effectively with the public regarding evidence-based medicine and the life-saving benefits of preventive strategies. The present results of Nakata et al8 reinforce the importance of collagen metabolism in determining the structure of atherosclerotic plaques. However, current clinical and experimental evidence suggests that the best way to influence favorably the balance of collagen synthesis and degradation in atheroma at hand today remains lipid-lowering, not vitamin C.

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References


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Vitamin C, Collagen, and Cracks in the Plaque
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