The Potential Role of Antioxidants in the Prevention of Atherosclerosis

D. Roger Illingworth

Division of Endocrinology, Diabetes and Clinical Nutrition
Department of Medicine
Oregon Health Sciences University
Portland, Oregon 97201-3098 U.S.A.

Summary Hypercholesterolemia attributable to increased plasma concentrations of low density lipoproteins is a well recognized risk factor for the premature development of coronary atherosclerosis in both experimental animals and humans. Recent studies have indicated that modifications to low density lipoprotein result in enhanced uptake of the modified lipoproteins by macrophages and lead to accelerated rates of lipid deposition and the creation of foam cells. Oxidation of low density lipoprotein has been shown to be one of the modifications which leads to uptake of this lipoprotein by scavenger receptors present on macrophages and results in intracellular lipid accumulation. Treatment of hypercholesterolemic animals with antioxidant drugs, including probucol, has been shown to reduce the development of atherosclerosis and xanthoma regression has been observed in patients with severe hypercholesterolemia treated with this drug. Epidemiologic studies support the view that low plasma concentrations of antioxidant vitamins, including vitamin E are associated with higher rates of coronary atherosclerosis in humans and that supplementation with vitamin E is associated with a decreased incidence of coronary artery disease. Prospective clinical trials to assess the potential benefit of antioxidant supplementation in high risk patients are currently in progress and these trials, when completed, should provide definitive information concerning the potential benefits to be derived from supplementation with antioxidant vitamins as an adjunctive therapy to prevent the premature development of atherosclerosis.

Key Words lipoproteins, hypercholesterolemia, low density lipoproteins, vitamin E, probucol, antioxidants, atherosclerosis

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INTRODUCTION

Hypercholesterolemia attributable to increased plasma concentrations of low density lipoproteins (LDL) is a well recognized risk factor for the premature development of atherosclerosis in experimental animals and humans (1). Studies conducted in a number of laboratories have, however, indicated that modifications to LDL which result in an alteration in charge lead to facilitated uptake by "scavenger receptors" present on macrophages with the resultant development of foam cells. In contrast to the uptake of native LDL via high affinity LDL receptors, which results in the suppression of intracellular cholesterol biosynthesis, the uptake of modified LDL particles by macrophages is not associated with suppression of cholesterol biosynthesis with the result that the cellular uptake of modified LDL particles leads to progressive intracellular lipid accumulation. Modification of native LDL can occur by a number of different mechanisms but the one that is believed to be most important under physiological conditions is oxidative damage which leads to the formation of oxidized LDL. The latter is readily taken up via the scavenger receptors present on macrophages. In addition to promoting foam cell formation, recent studies have indicated that oxidized LDL may also exert cytotoxic effects, is chemotactic for monocytes, inhibits macrophage mobility, stimulates cytokine release from macrophages, stimulates the formation of autoantibodies and may inhibit arterial relaxation via effects on endothelial derived relaxing factor (1–3). The increased awareness of the potentially detrimental effects which may result from oxidized LDL have led to increased interest in the potential role of antioxidants in the prevention of atherosclerosis. Naturally occurring antioxidants which are lipid soluble include vitamin E, betacarotene, lycopene, ubiquinol-10 and flavonoids. Vitamin C is the major water soluble antioxidant vitamin. In addition to these naturally occurring antioxidants, a number of synthetic antioxidants have been used experimentally; these include butylated hydroxytoluene (BHT) and the hypolipidemic drug, probucol (4).

ANTIOXIDANT VITAMINS AND ATHEROSCLEROSIS

A number of factors may potentially influence the ability of LDL particles to undergo oxidative modification which may in turn result in increased incorporation into foam cells. These factors include the magnitude of oxidative stress, the concentration of lipid soluble vitamins and other antioxidants present in the LDL particle as well as the concentration of water soluble antioxidants present in the aqueous phase of plasma, the fatty acid composition of esterified lipids present in the LDL particle and potentially the serum concentrations of divalent cations including copper or iron (5, 6). Epidemiologic studies which have examined plasma concentrations of vitamin E and mortality from ischemic heart disease in cross-cultural studies support the view that low plasma concentrations of vitamin E are associated with an increased risk of coronary
antioxidants and atherosclerosis. In the studies of Gey et al. (7) a strong inverse correlation was observed between the plasma concentration of vitamin E and mortality from ischemic heart disease in 16 European countries; this correlation persisted after adjustment for other cardiovascular risk factors including hypercholesterolemia and hypertension. Riemersma et al. (8) examined the relationship between the risk of angina pectoris and plasma concentrations of vitamins A, E and C together with betacarotene in 110 Scottish patients with angina pectoris and 395 controls who were selected from a sample of 6,000 men between the ages of 35 and 54. An inverse correlation was observed between the presence of angina pectoris and low plasma concentrations of betacarotene and vitamin C but this association was markedly reduced after adjustment for cigarette smoking. In contrast, the inverse correlation between the risk of angina pectoris and plasma concentrations of vitamin E persisted after adjustment for other known cardiovascular risk factors. The authors concluded that their data supports the view that patients at high risk for the premature development of coronary artery disease may benefit from eating diets enriched in natural antioxidants, particularly vitamin E. These results are supported by data from two recent studies in which the incidence of coronary artery disease was reduced by 35–40% in both men (9) and women (10) who were consuming supplemental vitamin E (median intake 419 IU per day in men and 208 IU per day in women). In these large cohort studies (9, 10) no correlation was observed between the intakes of vitamin C and subsequent risk of coronary artery disease or between the intake of betacarotene and cardiovascular risk in men or women who were non-smokers. Taken together, these results support the view that low plasma concentrations of vitamin E may increase the risk of premature cardiovascular disease whereas supplemental intakes may be cardio-protective.

ANTIOXIDANTS AND THE DEVELOPMENT OF ATHEROSCLEROSIS

A number of studies have demonstrated that the ability of LDL to be oxidized in vitro is influenced by the content of natural antioxidants present in the LDL particle. Thus, LDL isolated from the plasma of patients who have taken supplements of vitamin E, ubiquinol or probucol, show a reduced susceptibility to copper-mediated oxidation (4, 11). These in vitro results are supported by studies in experimental animals with diet-induced or genetic causes of hypercholesterolemia which have demonstrated reductions of 30–80% in the rate of development of atherosclerosis when the animals were receiving antioxidants, including vitamin E, probucol or a probucol analog (MDL29311) that does not exert the hypolipidemic effects known to occur with probucol (12–14).

Several studies in humans lend support to the animal data that supplementation with antioxidants prevents oxidative modification of LDL with a resultant decrease in foam cell formation and/or the risk of atherosclerosis. In patients with familial hypercholesterolemia treatment with probucol, it has been shown to result in the regression of xanthomas (15) which are composed, in part, of foam
cells. The lag phase for oxidative modification of LDL has also been shown to correlate with the extent of coronary atherosclerosis in young male survivors of a myocardial infarction (16); these findings support a link between the ease of oxidation of LDL and the subsequent development of atherosclerosis in humans.

CONCLUSIONS

Evidence from a number of interrelated areas strongly supports the concept that oxidative modification of LDL leads to an enhanced uptake of the oxidatively-modified LDL by macrophages and may lead to an enhanced formation of foam cells with a resultant acceleration in the development of atherosclerosis. Low levels of antioxidants, particularly vitamin E, increase the susceptibility of LDL to oxidation whereas observational studies in humans indicate that the rate of development of coronary artery disease in subjects consuming a supplement of vitamin E is lower than in those individuals not taking such a supplement (9, 10). Although the body of evidence supports a role of antioxidant vitamins, particularly vitamin E, in the prevention of cardiovascular disease definitive prospective trials have not been conducted and several questions remain. These include, what is the optimal use of antioxidants to make sure they protect LDL from oxidation in humans? Should these recommendations differ in patients with a higher risk of oxidative stress (e.g. smokers)? Is antioxidant therapy in humans warranted in addition to measures which focus on the control or elimination of conventional cardiovascular risk factors including a reduction in plasma LDL cholesterol concentrations? In the absence of more convincing clinical trial data it seems premature to advocate supplementation with antioxidant vitamins except in selected high risk patients, particularly those with refractory hypercholesterolemia or premature atherosclerosis. Trials currently under way in the United States involving supplemental betacarotene (The Physicians Health Study) or a trial of vitamin E and betacarotene in 40,000 women, together with ongoing trials with probucol in the United States and Sweden should, when completed, provide further insights into the potential role of antioxidants in the prevention of atherosclerosis (17).

REFERENCES

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