EDITORIAL COMMENT

Oxidized or Native Low-Density Lipoprotein Cholesterol

Which Is More Important in Atherogenesis?

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Atherosclerosis and related disorders are the major causes of morbidity and mortality in the Western world. Atherosclerosis-related diseases are also becoming common in the developing world. The Framingham study and other epidemiologic studies have amply shown that certain conditions are associated with atherogenesis and are appropriately called risk factors. These include age, gender, dyslipidemias (such as high low-density lipoprotein [LDL]-cholesterol, low high-density lipoprotein [HDL]-cholesterol, high triglycerides, and various permutations of lipid abnormalities), cigarette smoking, hypertension, and diabetes. On the basis of the strong association of these risk factors with atherosclerosis-related events, prevention as well as therapeutic strategies have been directed at modification of these conditions. Implementation of these strategies has led to major health benefits, in terms of reduction in death from stroke and myocardial infarction (MI) over the last 2 decades in the U.S. (1).

Various other conditions or risk states have also been proposed as markers of atherosclerosis and related events (2–4). These include hyperhomocysteinemia, prothrombotic state, infections (such as C. pneumonia, H. pylori, and herpes virus), endothelial dysfunction, state of inflammation, and oxidative stress. Attempts are being made to develop new specific biomarkers that will facilitate identification of individuals at risk, therapeutic targets, response to therapy, and prognosis (2,3).

Of these novel risk states, inflammation and oxidative stress have attracted most attention. Inflammation is invariably present in all atherosclerotic regions, with preponderance in regions that are likely to rupture and predispose the patient to develop an acute event. Furthermore, many studies (5–8) have shown a predictive value of a host of inflammatory markers, such as cytokines (tumor necrosis factor, interleukin-6, and interleukin-18), serum amyloid A, C-reactive protein (CRP), myeloperoxidase, and white blood cell count. However, the predictive value of these markers has varied markedly. Whether inflammation represents a primary pathogenic stimulus in atherogenesis or a mere response to vascular injury caused by hypertension, dyslipidemia, and hyperglycemia continues to be debated (9).

Recently, there has also been much interest in the pro-oxidant state in atherosclerosis-related vascular disease states and aging (10). An oxidant state implies that the body’s endogenous antioxidants are not sufficient to neutralize the oxidant species. The concept of a pathogenic role of oxidants is particularly attractive, because oxidant species injure endothelial cells, denature the vasodilator species nitric oxide, induce inflammation and thrombosis, and oxidize LDL cholesterol, all of which accompany atherogenesis. Furthermore, a number of studies in animal and cell model systems have shown protective effects of a variety of antioxidants, including tocochromers and ascorbic acid (11–13). Melov et al. (14) showed a marked prolongation in the life-span of C. elegans with administration of a superoxide dimutase/catalase mimetic. However, clinical trials of common antioxidants have by and large shown no benefit (15).

This implies that either the oxidant/antioxidant imbalance is not pivotal in atherogenesis or appropriate antioxidant formulations have not been used.

A number of studies suggest that the oxidized low-density lipoprotein (ox-LDL) is a more potent pro-atherosclerotic stimulus than the native unmodified LDL. Endothelium exposed to ox-LDL develops early signs of injury, such as apoptosis (16). The ox-LDL decreases the gene expression of endothelial nitric oxide synthase (eNOS) and enhances generation of reactive oxygen species (17). The ox-LDL itself activates inflammatory cells and facilitates release of growth factors from monocytes/macrophages (18,19). Platelet eNOS activity is diminished in the presence of ox-LDL, and these cells demonstrate intense activation in response to small amounts of thrombin (20). The ox-LDL also increases formation of metalloproteinases, thus setting the stage for rupture of a soft plaque. Recent studies have shown that ox-LDL stimulates expression of CD40/CD40L in endothelial cells and release cytokines (21). Other studies have shown that ox-LDL upregulates the expression of various components of the renin-angiotensin system, such as angiotensin-converting enzyme and angiotensin II type 1 receptors in endothelial and vascular smooth muscle cells (22,23). Most importantly, pathologic studies have shown accumulation of ox-LDL in the rupture-prone atherosclerotic plaque (24).

Given the obvious pathophysiologic significance, there has been intense interest in the measurement of ox-LDL or antibodies to ox-LDL as predictor of coronary heart disease (CHD) events (25–29). In a nested case-control study in individuals with and without elevated LDL cholesterol levels, ox-LDL levels were found to be increased in patients who subsequently developed MI (25). In another study,
patients with angiographic coronary artery disease had higher levels of ox-LDL and higher global risk assessment scores than the age-matched control subjects (26). In a larger cohort of individuals, the odds ratio for CHD risk was 2.79 in the top compared with the lower quintile after adjusting for age, gender, race, LDL cholesterol, smoking status, and CRP (27). In keeping with this information, a recent study showed higher plasma levels of circulating lectin–like oxidized LDL (LOX-1), a specific ox-LDL receptor on endothelial cells, in patients with acute coronary syndromes (28). Importantly, LOX-1 levels in plasma had higher predictive value than did the CRP levels.

In this regard, the study by Wu et al. (29) in this issue of the Journal is particularly important. They identified 266 men and 235 women from the Health Professionals Follow-up Study and the Nurses’ Health Study. These individuals had incident MI or fatal CHD, and each index patient was matched with two control subjects by age and smoking status. Plasma ox-LDL levels in these individuals were significantly related to the risk of coronary artery disease in multivariate analysis. However, when ox-LDL, LDL cholesterol, HDL cholesterol, and triglyceride levels were mutually adjusted, ox-LDL levels were no longer predictive. Importantly, apolipoprotein B, total/HDL cholesterol, and other conventional lipid markers, including LDL cholesterol, HDL cholesterol, and triglycerides, remained powerful differentiating factors.

There are many limitations of this study, including use of a single blood draw; ill-defined nature of the antibody against an isotope in the ox-LDL moiety in the ox-LDL kit used in this study; lack of information on patients’ therapy, especially use of antioxidants; and most importantly, the retrospective nature of the study. As recognized by the authors, prospective studies need to be performed, especially in individuals not receiving antioxidants, to determine the value of ox-LDL measurements in predicting CHD events. Further studies will need to be performed to document that ox-LDL measurements are reproducible in the same subject over time; are reliable when frozen and stored samples are used; and, very critically, provide value above and beyond what is available from global assessment algorithms. In this regard, it is noteworthy that the INTERHEART study on risk factors associated with MI in 52 countries identified smoking, high apolipoprotein (Apo)B/ApoA1 ratio, history of hypertension, diabetes, abdominal obesity, psychosocial factors, low daily consumption of fruits and vegetables, alcohol consumption, and lack of physical activity as 9 major risk factors that define population attributable risk in 90% of men and 94% of women (30). In essence, it is quite clear that oxidative stress is present in various stages of CHD. Whether the biomarker will turn out to be ox-LDL, LOX-1, or some other related moiety needs to be determined. Naturally, one would expect any new biomarker to provide significant additional value for mass screening of populations at a low cost.

The author’s opinion about the role of various risk factors for atherosclerosis, including inflammation and oxidative stress, is shown in Figure 1. Needless to say, genetic predisposition to the development of disease might be a critical yet undefined factor.

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