Oxidized LDL and abdominal obesity: a key to understanding the metabolic syndrome\textsuperscript{1,2}

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The pathophysiologic interactions of abdominal obesity, insulin resistance, dyslipidemia, hyperglycemia, and hypertension were first described by Reaven\textsuperscript{(1)} in 1988. Although understood by workers in the field of metabolic diseases and nutrition, the condition was not definitively defined and named “the metabolic syndrome” until the National Cholesterol Education Program Adult Treatment Panel (ATP) III guidelines were published in 2001\textsuperscript{(2)}. Since then, the importance and awareness of the condition have grown rapidly. With subsequent publications, it became apparent that not only obesity was epidemic in the American population, but the metabolic syndrome was as well. The association of the metabolic syndrome with coronary artery disease was underscored by the ATP Advisory of 2004, which placed the metabolic syndrome among the 4 very high-risk conditions for arteriosclerotic vascular disease that were worthy of the option of a most aggressive lowering of LDL to <70 mg/dL, or lower than the fifth percentile, in the LDL distribution of middle-aged populations of men and women\textsuperscript{(3)}.

Much less well understood is the basis for the cardiovascular toxicity of the metabolic syndrome. Is there a common mediator of vascular disease risk that occurs before the onset of the clinical features that make up the metabolic syndrome\textsuperscript{(2)}? A possible candidate is a common inflammatory stress condition, which is expressed as an increase in C-reactive protein and other inflammatory cytokines, such as interleukin 6\textsuperscript{(4)}. Another marker that is popular among practitioners is small dense LDL, which is more susceptible to oxidative stress than is large buoyant LDL, appears to be proportional to the degree of hypertriglyceridemia, and is an important mediator of cardiovascular disease risk and indicator of response to drug therapy\textsuperscript{(5)}.

Proximate to the development of each of these abnormalities is the enhancement of underlying oxidative stress, which is related to increased substrate oxidation and mitochondrial leak of superoxide and is postulated to be a common mediator of the microvascular and macrovascular complications of diabetes\textsuperscript{(6)}. Evidence that oxidative stress is enhanced in the metabolic syndrome is indirect. Reduced plasma concentrations of antioxidant vitamins, beyond the reductions expected from a reduced dietary intake\textsuperscript{(7)}, are reported in the third National Health and Nutrition Examination Survey (NHANES III). We have confirmed this observation in our own cohort of insulin-resistant and obese insulin-resistant subjects\textsuperscript{(8)}. Hansel et al\textsuperscript{(9)} reported a plasma isoprostane concentration (an index of overall oxidative stress) in insulin-resistant and obese insulin-resistant subjects that was 3.7-fold that in nonobese normolipidemic control subjects and a 41% lower antioxidant activity of HDL in the former group. This evidence supports the postulate of Ford et al\textsuperscript{(7)} that the reduced concentrations of antioxidants in the NHANES III cohort were due to enhanced antioxidant consumption as a consequence of enhanced oxidative stress.

An increase in immunologically detected epitopes of lipid peroxides in the LDLs of persons with abdominal obesity, reported in this issue of the Journal by Weinbrenner et al\textsuperscript{(10)}, extends the evidence of enhanced oxidative stress in association with abdominal obesity and, by extension, with the metabolic syndrome. This observation is important for several reasons. First, it indicates that enhanced oxidative stress is associated with the earliest pathophysiologic manifestation of the metabolic syndrome—abdominal obesity. Second, it extends the evidence for enhanced oxidative stress to LDL, which in its small dense form is associated with a greater susceptibility to oxidative stress and is a standard component of the dyslipidemia associated with the metabolic syndrome. Third, the level of proof obtained with the use of an antibody to oxidized LDL is higher than that obtained with earlier approaches to measuring LDL oxidation. The antibody measures oxidized phospholipids in the LDL particle, which are capable of propagating oxidative reactions in their own right.

Given this new evidence—that enhanced oxidative damage to circulating lipoproteins in plasma is related only to abdominal obesity—it is not surprising that there is evidence of enhanced inflammatory stress, as indicated by the increase in CRP reported by many observers. It is also not surprising that numerous other consequences of enhanced oxidative stress would be found in obesity and the metabolic syndrome, including diminished brachial artery reactivity to flow-mediated dilation\textsuperscript{(11)} and to atherosclerosis itself\textsuperscript{(12)}. What to do about this problem is unclear, but it may involve competing dietary approaches to weight loss and dietary interventions to alter redox status, as suggested by the results of the study by Weinbrenner et al. This is a major research challenge for the future.

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