Fat Fuels the Flame
Triglyceride-Rich Lipoproteins and Arterial Inflammation
Peter Libby

Recent reviews duly recite the prevailing concept of the mechanisms of atherogenesis. According to this model, a surfeit of low-density lipoproteins (LDL) favors accumulation and retention of these particles in the arterial intima. There, LDL undergoes oxidative modification. Lipid mediators derived from this oxidized LDL stoke the inflammation now widely deemed a critical culprit in the formation and complication of atheroma.6

Does the Prevailing Model Explain Atherogenesis?
This oft repeated schema rests on a firm experimental foundation. Clinical and human pathological observations corroborate this view. Yet, the “oxidized LDL” hypothesis may not explain all aspects of atherogenesis. Most laboratory experiments with oxidized LDL use mixtures of products of incubation of LDL with transition metals. The Fenton chemistry used to generate oxidized LDL in the laboratory may have little to do with the oxidative processes at work in the atherosclerotic arterial wall. Biochemical studies have however begun to identify the structures of components oxidized LDL that do elicit proinflammatory effect on cells involved in atherogenesis.3,4 The lack of clinical benefit of antioxidant vitamin supplements does not alone vitiate a pathogenic role for oxidized LDL.7,8 Antioxidant vitamins may well not distribute to the proper compartments or may be chemically inappropriate agents for the oxidation chemistry that pertains to lipoproteins entwined with the intimal extracellular matrix during atherogenesis. The clinical trials of antioxidant vitamins may have enrolled patients at a stage of their disease too advanced to show a benefit of the antioxidant strategy.

LDL lowering does consistently confer clinical benefit, even in trials in which antioxidants have failed to do so. Yet the most aggressive LDL-lowering regimens still do not prevent the majority of events.9 For these reasons, we need to seek pathways beyond LDL that drive atherogenesis and its associated heightened inflammation.

Lipid Triggers for Atherogenesis Beyond LDL
Manipulation of high-density lipoprotein (HDL) furnishes one attractive strategy. Numerous observational studies support strongly the inverse association of HDL and cardiovascular events. Strong experimental and human genetic studies have revealed molecular pathways by which HDL may protect against atherosclerosis by effects of reverse cholesterol transport or by antiinflammatory actions. Diet, physical activity, and some classes of pharmacological agents can raise HDL levels, but we still lack clinical evidence that therapeutic elevation of HDL confers clinical benefit. The recent finding reported in the lay press of excess mortality in diabetic individuals with one cholesterol ester transfer protein inhibitor that handsomely boosted HDL level could relate to an idiosyncratic effect of that particular molecule or to inefficacy of this approach to HDL elevation. Conclusions in this regard must await at least the analysis and publication of the clinical end point and imaging trials with this agent.

Levels of HDL usually vary inversely with triglyceride concentration. Epidemiologists still fret over whether triglycerides actually comprise a risk factor for cardiovascular events independent of HDL or of glycemic control in diabetic populations. Triglyceride levels depend exquisitely on diet and vary from hour to hour, challenging such analysis in large populations, and rendering HDL the more reliably measured of the two. Partly for this reason, the notion of postprandial lipemia as an atherogenic risk factor, championed by Zilversmit, remains incompletely explored.10 Turning the usual notion on its head, could the traditional dependent variable in such analyses (triglyceride levels) become the independent variable? Could triglyceride-rich lipoproteins directly promote atherogenesis and trigger inflammation? Should triglyceride-rich lipoproteins become a target for intervention?

Proinflammatory Mechanisms of Triglyceride-Rich Lipoproteins?
Dwarfed by the voluminous data regarding proinflammatory effects of LDL and its derivatives, we possess scant information about triglycerides or triglyceride-rich lipoproteins as instigators of inflammation and other atherogenic functions of cells found in plaques. In 1999, Dichtl and colleagues reported that the triglyceride-rich lipoprotein very low-density lipoprotein (VLDL) activates the pivotal transcriptional regulator of inflammation nuclear factor-kappa B (NF-κB).11 As lipoproteins can bind bacterial lipopolysaccharides, ubiquitous laboratory contaminants that can activate inflammatory signaling in vascular cells and leukocytes in minute concentrations, such results bear careful scrutiny and replication. In this issue of Circulation Research Tong et al provide further independent data that support a role for triglyceride-rich lipoproteins in inflammatory activation of vascular cells in vitro.12 They found that triglyceride-rich lipoproteins at postprandial concentrations do not alone elicit

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(Circ Res. 2007;100:299-301.)
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Circulation Research is available at http://circres.ahajournals.org
DOI: 01.RES.0000259393.89870.58

See related article, pages 381–390
an inflammatory response in human aortic endothelial cells. Treatment of the endothelial cells with the triglyceride-rich lipoproteins did substantially raise the expression of leukocyte adhesion molecules and monocyte adherence in response to the proinflammatory cytokine tumor necrosis factor-α (TNF-α). Lipopolysaccharide levels measured in the lipoprotein preparations appeared low. The mechanism of this effect appeared to depend on LDL-receptor related proteins (LRP) and downstream activation of p38 MAP kinase and NF-κB (Figure). The disparity between the Dichtl study that showed direct effects of VLDL on NF-κB activation and the Ting study that demonstrated a potentiation of cytokines but no direct effect of triglyceride-rich lipoproteins alone on inflammatory functions of endothelial cells, will require further study. The specter of endotoxin contamination demands eternal vigilance in such quests. Interestingly, Stollenwerk et al showed that in human monocyte-derived macrophages VLDL potentiated lipopolysaccharide-induced TNF-α expression but by itself did not do so.13 Another proinflammatory mechanism of triglyceride-rich lipoproteins could depend on their content of apolipoprotein CIII. Our recent work has shown that apolipoprotein CIII or VLDL that bear this apolipoprotein can increase monocytoid cell adhesion to endothelial cells in a vascular cell adhesion molecule-1–dependent manner.14,15 Apolipoprotein CIII appears to activate NF-κB through a pertussis-sensitive G protein-protein kinase C–dependent pathway.16 Thus, triglyceride-rich lipoproteins can fan the flame of inflammation during atherogenesis in several ways (Figure).

**Putting Proinflammatory Mechanisms of Triglyceride-Rich Lipoproteins in Clinical Context**

The risk factor profile of the typical patient with atherosclerosis is shifting at the advent of the 21st century. Our armamentarium includes effective and clinically proven interventions to address high levels of LDL, the cardiovascular scourge of the latter half of the 20th century. We now face a burden of obesity and diabetes, and the attendant dyslipidemia noteworthy for elevated triglyceride-rich lipoproteins and low HDL rather than excessive LDL levels. Thus, the pressing current clinical cardiovascular challenges include mastery of triglyceride-rich lipoproteins. The emerging data regarding pathways that link features of dyslipidemia to inflammation and atherogenesis provide new insight into the mechanisms that underlie a burgeoning epidemic of heightened atherosclerotic risk because of dyslipidemia.

**Sources of Funding**

This work is supported by the Donald W. Reynolds Foundation and the National Heart, Lung, and Blood Institute.

**Disclosures**

None.

**References**


KEY WORDS: very low density lipoprotein ■ endothelium ■ apolipoprotein CIII ■ atherosclerosis ■ coronary risk factors
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Circ Res. 2007;100:299-301
doi: 10.1161/01.RES.0000259393.89870.58
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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