

Beyond LDL-C: Desialylated LDL as a refined marker of coronary atherosclerosis severity

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The core role of low-density lipoprotein cholesterol (LDL-C) in atherosclerosis is well validated. However, the “LDL hypothesis” has evolved over the last 4 decades; apart from the quantity of LDL-C, we now recognise that qualitative modifications of LDL particles are critical in driving the transition from circulating lipoprotein to intimal plaque. Of these modifications—which include oxidation, glycation, and carbamylation—oxidation of LDL is the best described. However, desialylation of LDL is also emerging as an especially potent atherogenic trigger.

The nature and discovery of desialylated LDL. Desialylated LDL (desLDL) is an altered form of LDL, with decreased content of sialic acid residues on the carbohydrate moieties of apolipoprotein B-100 and the lipid components. Sialic acid is a negatively charged sugar that adds to the surface charge and stability of the LDL particle. Its elimination triggers a cascade of physical and chemical modifications, in which the particles become smaller, denser, more electronegative, and more prone to agglomeration.

The discovery of desialylated LDL dates back to the late 1980s and early 1990s, primarily through the pioneering work of Tertov et al.¹ They first identified a “multiply modified” LDL subfraction in the blood of patients with coronary artery disease (CAD) that was uniquely capable of inducing intracellular lipid accumulation in cultured smooth muscle cells and macrophages—a property not shared by native LDL.² Subsequent investigations revealed that the primary and perhaps initiating modification in this subfraction was the loss of sialic acid.³

What we now know about desLDL distinguishes it as a pre-secretory modification. Unlike oxidised LDL, which is thought to be formed primarily within the arterial wall, desLDL can be detected in significant quantities within the systemic circulation. This makes it an ideal candidate for a circulating biomarker:⁴

(1) Enhanced uptake: The loss of negative charge and subsequent particle aggregation facilitate non-specific, scavenger uptake by macrophages, leading to rapid foam cell formation.

(2) Increased retention: Desialylation increases the affinity of LDL for arterial proteoglycans, trapping the particles within the intima.

(3) Pro-inflammatory signalling: DesLDL has been shown to stimulate the secretion of pro-inflammatory cytokines, further exacerbating the local immune response within the vascular wall.

Clinical insight from this study. In the study by Liu et al. published in this issue of *Annals*, the authors provide a contemporary clinical validation of desLDL as a biochemical marker of CAD.⁵ Using liquid chromatography-mass spectrometry—a highly sensitive and specific technique—they quantified plasma desLDL in 162 patients undergoing coronary angiography.

The authors demonstrate that desLDL levels are significantly elevated in patients with CAD compared to those with non-obstructive disease. DesLDL levels correlated strongly with the Gensini score, a measure of the anatomical extent and severity of atherosclerosis. In multivariable models, desLDL remained an independent predictor of CAD severity, even after adjustment for traditional risk factors and standard lipid profiles including LDL-C, apolipoprotein B (apoB) and lipoprotein(a). Notably, the receiver operating characteristic analysis suggests that desLDL offers superior diagnostic performance compared with total cholesterol and LDL-C.

As a single-centre study with 162 participants, the findings require validation in larger, multi-ethnic cohorts to ensure generalisability. The study suggests and quantifies a correlation between desLDL and CAD, but as a cross-sectional study, it does not definitively prove a causal relationship with future major adverse cardiovascular events (MACE).

Future directions. The findings of this study open several promising avenues for future research and clinical application. First, longitudinal prospective trials are needed to determine if baseline desLDL levels can predict the risk of MACE independently of LDL-C, apoB and current risk scoring equations, such as the Framingham Risk Score or Pooled Cohort

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Equations. Integrating desLDL into such equations or even into multi-omic risk profiles—combining lipidomics with genomics and proteomics—may provide a more granular understanding of residual inflammatory risk. Perhaps future characterisation of the various LDL modifications could help clinicians identify the vulnerable patient long before they present with vulnerable plaque.

Second, if the above causal relationship could be proven, therapeutic targeting of desialylation represents an untapped frontier. Research into trans-sialidases and neuraminidases (NEU), particularly NEU1 and NEU3, which are known to be active in the blood and vascular wall, could lead to a new class of “lipid-stabilising” drugs.⁶ Inhibiting these enzymes might prevent the conversion of native LDL into its more atherogenic desialylated form, potentially offering a synergistic effect when combined with statins or proprotein convertase subtilisin/kexin type 9 inhibitors.

The study presented by the authors reinforces the notion that we must look “under the hood” of the LDL particle to truly understand a patient’s cardiovascular risk. Desialylated LDL represents a potentially important bridge between lipid metabolism and chronic inflammation. As cardiovascular care moves towards personalised medicine, markers like desLDL may prove essential in identifying high-risk individuals who may appear low-risk on standard lipid panels, ultimately allowing for more targeted intervention.

Ethics statement

Not applicable, as no study participants were recruited.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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