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Commentary

Lipid Metabolism Alterations in Cardiovascular Diseases

Chen Wei*

Department of Biochemistry, Peking University Health Center, Beijing, China.

ABOVE THE STUDY

Lipid metabolism alterations are central to the development and progression of Cardiovascular Diseases (CVDs), and in my opinion, they represent one of the most clinically actionable yet mechanistically complex aspects of cardiovascular pathology. While traditionally viewed through the lens of cholesterol levels alone, lipid metabolism is now understood as a dynamic and tightly regulated network involving lipid transport, storage, oxidation, and signaling. Disruptions in these interconnected processes contribute not only to atherosclerosis but also to broader vascular dysfunction, inflammation, and cardiac remodeling.

At the core of lipid metabolism lies the balance between lipid uptake, synthesis, and clearance. Low-Density Lipoprotein (LDL) particles transport cholesterol to peripheral tissues, while High-Density Lipoprotein (HDL) mediates reverse cholesterol transport back to the liver. In cardiovascular disease, this balance is disrupted, leading to excessive accumulation of LDL-derived cholesterol in arterial walls. Oxidized LDL plays a particularly harmful role by triggering endothelial dysfunction and initiating inflammatory cascades that promote plaque formation. In my view, the transformation of LDL from a transport molecule into a pro-inflammatory agent is a critical step in atherogenesis.

Atherosclerosis itself can be understood as a chronic inflammatory lipid-driven disease. Once LDL particles infiltrate the vascular endothelium, they undergo oxidative modification and are taken up by macrophages via scavenger receptors, forming foam cells. These foam cells accumulate within arterial walls, forming fatty streaks that evolve into complex atherosclerotic plaques. Importantly, lipid accumulation is not a passive process but is actively regulated by signaling pathways that govern macrophage activation, endothelial permeability, and smooth muscle cell proliferation.

Another important aspect of lipid metabolism in cardiovascular disease is dyslipidemia, characterized by elevated triglycerides, increased LDL cholesterol, and reduced HDL cholesterol. These changes are often associated with metabolic syndrome, insulin resistance, and obesity. In my opinion, the close relationship between metabolic disorders and cardiovascular disease underscores the systemic nature of lipid dysregulation rather than an isolated cardiac phenomenon.

At the molecular level, several key regulatory pathways control lipid metabolism. Sterol Regulatory Element-Binding Proteins (SREBPs) regulate cholesterol and fatty acid synthesis, while Peroxisome Proliferator-Activated Receptors (PPARs) modulate lipid oxidation and storage. Dysregulation of these transcription factors can lead to excessive lipid accumulation in vascular and cardiac tissues. Additionally, Liver X Receptors (LXRs) play a crucial role in cholesterol efflux and reverse transport, and their impaired activity contributes to foam cell formation and plaque progression.

Mitochondrial lipid oxidation is another critical factor in cardiovascular health. In cardiomyocytes, fatty acid oxidation is a major source of energy. However, in diseased states such as heart failure, there is a metabolic shift away from fatty acid oxidation toward glucose utilization. This metabolic remodeling reflects impaired mitochondrial function and altered lipid handling, which can contribute to energy deficiency and cardiac dysfunction. In my view, this energetic imbalance is a key driver of progressive heart failure.

Inflammation is tightly linked to lipid metabolism in cardiovascular disease. Lipid accumulation activates inflammatory signaling pathways such as NF-κB, leading to the production of cytokines that further exacerbate vascular damage. Conversely, inflammatory mediators can alter lipid metabolism by affecting enzyme activity and lipoprotein processing. This bidirectional relationship creates a self-perpetuating cycle of lipid accumulation and inflammation that drives disease progression.

Emerging evidence also highlights the role of lipid-derived signaling molecules, such as eicosanoids and sphingolipids, in cardiovascular pathology. These bioactive lipids regulate vascular tone, platelet aggregation, and immune responses. Dysregulation of these signaling lipids can contribute to thrombosis, hypertension, and endothelial dysfunction. In my opinion, these lipid mediators represent an underexplored but highly important dimension of cardiovascular disease biology.

Correspondence to Chen Wei. Department of Biochemistry, Peking University Health Center, Beijing, China. E-mail: chen.wei@pkuhc.edu.cn

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From a therapeutic perspective, targeting lipid metabolism has been one of the most successful strategies in cardiovascular medicine. Statins, which inhibit cholesterol synthesis by targeting HMG-CoA reductase, have significantly reduced cardiovascular mortality worldwide. However, residual cardiovascular risk remains even in statin-treated patients, suggesting that lipid metabolism is only partially addressed by current therapies. Newer approaches, including PCSK9 inhibitors and therapies targeting triglyceride-rich lipoproteins, aim to further refine lipid control.

Despite these advances, challenges remain in fully understanding lipid metabolism in cardiovascular disease. Lipid networks are highly complex and influenced by genetic, dietary, and environmental factors. In my opinion, future progress will depend on integrating lipidomics with genomics and metabolomics to better capture this complexity. Such systems-level approaches may enable more precise risk stratification and individualized treatment strategies.

In conclusion, lipid metabolism alterations are central to the pathogenesis of cardiovascular diseases, influencing inflammation, energy balance, and vascular function. In my view, a deeper understanding of lipid regulatory networks will be essential for developing next-generation therapies that go beyond cholesterol lowering to address the full complexity of cardiovascular metabolic dysfunction.