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Lipid Swings Provoke Vascular Inflammation

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Lipid variability, much like glucose variability, has significant implications for vascular health. Numerous studies have investigated this phenomenon, demonstrating its impact on the risk of cardiovascular disease (CVD).

Recent research using a large electronic health record-based cohort has demonstrated that high variability in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) is linked to an increased risk of CVD, independent of traditional risk factors. After adjusting for these factors, individuals with the highest TC variability exhibited a 20% increased risk of CVD (hazard ratio, 1.20; 95% confidence interval, 1.06 to 1.37). Similar findings were noted for variability in LDL-C and HDL-C [1]. Another study reported that variability in hemoglobin A1c and lipids were significant predictors of all-cause mortality in patients with diabetes [2]. A meta-analysis of 11 articles from seven cohorts demonstrated that variability in LDL-C, HDL-C, and TC, but not triglycerides (TG), is associated with increased risks of CVD and all-cause mortality [3]. Furthermore, a decade-long cohort study revealed that among patients with type 2 diabetes, variability in LDL-C, the TC to HDL-C ratio, and TG was linked to a 27%, 31%, and 9% increased risk of composite endpoints of CVD and mortality, respectively [4].

Despite the significant clinical implications, the molecular mechanisms by which lipid variability affects cardiovascular outcomes remain poorly understood. In their study, Rhee et al. [5], the researchers employed an innovative method to simulate lipid variability by alternating the concentrations of palmitic acid between 0 and 100 μM every 8 hours over a 48-hour period in endothelial cells. Their comprehensive analysis encompassed real-time polymerase chain reaction, Western blot, enzyme-linked immunosorbent assays, reactive oxygen species measurements, and functional assays, which evaluated inflammation, oxidative stress, mitochondrial function, and endothelial cell viability. Although clinical lipid variability typically reflects long-term visit-to-visit changes, this research was conducted *in vitro* over a shorter duration. Therefore, further *in vivo* studies are essential to improve our understanding of how lipid variability influences cardiovascular outcomes, as highlighted by the authors.

In response to a cytokine challenge, endothelial cells increase nuclear factor κB expression, which subsequently upregulates vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 [6]. As the authors noted, mitochondrial function severely deteriorates in response to palmitate treatment with withdrawal. Given that endothelial mitochondrial dysfunction is the mediator of endothelial dysfunction and atherosclerosis [7], it is plausible to assume that mitochondrial dysfunction is one of the mechanisms by which lipid variability induces endothelial dysfunction.

This study illuminates the mechanistic pathways by which lipid variability exacerbates cardiovascular risk, demonstrating that fluctuating lipid levels can induce endothelial dysfunction through oxidative stress and inflammation. This highlights the importance of a sustained lipid-lowering strategy to prevent atherosclerotic diseases.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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