**Editorial**

**Quality Versus Quantity**

**Making HDL Great Again**

Sylvain Galvani, Timothy Hla

High-density lipoprotein (HDL) particles are characterized by their heterogeneity in composition, structure, and biological properties. In addition to the major structural protein apolipoprotein A1, HDL proteomes and lipidomes show great diversity.¹ ² Such constituents presumably carry out the multitude of HDL functions, for example, reverse cholesterol transport, antioxidant, anti-inflammatory, and anti-infectious properties.³

HDL particles can be further fractionated based on their density, size, and electrophoretic mobility.⁴ ⁵ For instance, sequential ultracentrifugation separates HDL into 2 main subpopulations, namely, lipid-rich large particles named HDL₂ and protein-rich small HDL₁ populations. These 2 subpopulations present variations in their molecular compositions, which are associated with heterogenous antioxidative, anti-inflammatory, and cytoprotective activities.⁴ ⁵ In addition to the structural and functional heterogeneities, HDL particles are dynamically regulated under various physiological and pathological conditions. For example, oxidation of apolipoprotein A1 has been associated with inflammatory processes and impairment of protective HDL functions.⁶

Recently, sphingosine 1-phosphate (S1P), a lipid mediator that acts via G-protein-coupled receptors, has featured prominently in HDL biology. The ability of HDL to protect the endothelium,⁷ myocardial ischemic injury, and vasodilate⁸ depends on the S1P cargo. HDL-bound apolipoprotein M binds, carries, and promotes receptor activation in a physiologically relevant manner.⁹ In addition, HDL-bound S1P seems to be distinct from albumin-bound S1P in the inhibition of endothelial inflammatory processes,¹⁰ barrier function,¹¹ and lymphopoiesis,¹² suggesting that chaperone-bound S1P acts as a biased agonist to evoke specific biological processes. These observations suggest a major function of S1P in the cardiovascular protection mediated by HDL.¹³ Even though HDL-bound S1P was shown to be decreased in acute coronary syndrome¹⁴ and in sepsis,¹⁵ the relevance of this signaling pathway in chronic diseases that promote cardiovascular risk is not well understood.

Type 1 diabetic patients exhibit increased risk of cardiovascular disease, presumably because of hyperglycemia-induced endothelial injury, oxidative stress, vascular dysfunction, and angiopathy of small and large vessels.¹⁶ In this issue of *ATVB*, Frej et al¹⁷ report the role of HDL-bound S1P in type 1 diabetes mellitus. In their study, HDL isolated from healthy controls and patients with type 1 diabetes mellitus did not show apolipoprotein M and S1P alterations. However, a shift of apolipoprotein M and S1P to lipid-rich, light HDL₂ particles was seen in type 1 diabetes mellitus. In functional assays, the light HDL₂ particles show defective anti-inflammatory functions, which could be because of the reduced ability to signal through the endothelial S1P receptor. The authors suggest that increased dysfunctional HDL seen in type 1 diabetes mellitus may contribute to the cardiovascular disease risk (Figure).

Interestingly, Frej et al¹⁷ study further supports the body of work documenting the attenuated HDL-bound S1P level and function in chronic diseases. In type 2 diabetes mellitus, glycation of HDL significantly reduces the S1P content of HDL, leading to impairment of cellular protection from oxidative stress. In that study, HDL function recovered by restoring S1P.¹⁸ In another study focused on patients with metabolic syndrome, reduced HDL-bound S1P resulted in attenuated endothelial nitric oxide synthase activation, which would contribute to vascular dysfunction.¹⁹ In addition, HDL dysfunction observed during coronary arterial disease has been linked to a 5-fold decrease in S1P content, likely because of oxidative modifications. Such HDL can be replenished in vitro using S1P donors like red blood cells to regain their protective functions.²⁰ Therapeutic administration of reconstituted HDL loaded with S1P reduced ischemia–reperfusion injuries in mouse model of myocardial infarction.²¹

These recent findings warrant that S1P-centric function of HDL in health and disease needs detailed and comprehensive interrogation in both basic and translational levels. Molecular basis of decreased HDL-S1P, modifications of apolipoprotein M, and altered S1P-centric signaling properties of HDL₂ versus HDL₁ need to be explored. How such alterations lead to perturbations in S1P receptor signaling is not understood at the mechanistic level. However, based on recent developments in HDL biology and therapeutics,²² these results further echo the concept that HDL quality rather than quantity is a critical factor to reduce cardiovascular risk.
References


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Figure. In normal conditions, high-density lipoprotein (HDL), that chaperones sphingosine-1-phosphate (S1P) interacts with endothelial cell S1P receptor-1 to protect the endothelium. During type 1 diabetes mellitus, lipid-rich/protein-poor HDL$_{ll}$ are more abundant than HDL$_{d}$ particles. These particles are inefficient to inhibit proinflammatory marker expression in endothelial cells. This defect may underlie the increase in cardiovascular risk seen in type 1 diabetes mellitus. ApoM indicates apolipoprotein M.
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Sylvain Galvani and Timothy Hla

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