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Is it time to reconcile HDL with cardiovascular diseases and beyond?

An update on a paradigm shift

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According to numerous epidemiological studies, low plasma levels of high-density lipoprotein cholesterol (HDL-C) are independently associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD). For instance, in patients with acute coronary syndrome (ACS), low HDL-C levels are associated with an increase in the number of recurrent cardiovascular events [1]. In addition, low plasma HDL-C levels also correlate with an increased risk of developing type 2 diabetes mellitus (T2DM), liver diseases, and dementia [2,3*,4]. However, although elevated HDL-C levels could be expected to be beneficial for health, randomized controlled trials of agents that increase HDL-C levels, such as cholesteryl ester transfer protein inhibitors (CETPI) and reconstituted HDL (rHDL), have failed to reveal a beneficial effect on cardiovascular disease outcomes [5,6*,7]. Moreover, Mendelian randomization analyses have reported that some genetic variants associated with elevated HDL-C levels are not associated with a lower risk of ASCVD, T2DM, or Alzheimer's disease [8,9,10,11,12]. However, the conclusions of these studies regarding the absence of a causal link between HDL-C levels and disease risk are questionable because the analyses did not take into account *i)* changes in HDL composition and functions in disease, *ii)* the complexity of HDL metabolism, as they excluded important genes from their analyses that regulate the levels of lipoproteins other than HDL-C [13].

These discordant results have led to the notion that beneficial functions of HDL particles are not determined solely by the cholesterol moiety in HDL (i.e., HDL-C). This paradigm shift has led to renewed interest in HDL research, particularly in terms of the identification of biomarkers that reflect causal structure-function-disease relationships of HDL, with the ultimate goal of developing novel therapeutic approaches based on restoration/activation of HDL functions rather than increasing HDL-C levels.

HDL particles exert pleiotropic atheroprotective activities, including cholesterol efflux from peripheral tissues to the liver for excretion by reverse cholesterol transport (RCT), in addition to exerting anti-infectious, antioxidative, anti-inflammatory, antithrombotic, anti-apoptotic, vasodilatory, and antidiabetic properties [14]. These pleiotropic beneficial activities rely on the fact that the plasma HDL fraction consists of heterogeneous and highly dynamic particles that contain hundreds of different quantitatively minor proteins and lipid species, most of which are thought to be biologically active [6*,15].

Recently, analyses of data from large epidemiological population studies have revealed that the relationship between HDL-C levels and disease risks is nonlinear, with both extremely low and extremely high HDL-C levels associated with increased risks of ASCVD and infectious diseases [6*,16,17,18]. This observation could account for the negative results of trials of entities that enhance HDL-C levels. Further studies of this parabolic relationship have revealed that extremely

high HDL-C levels (> 100 mg/dL) are associated with endothelial dysfunction [19,20*], impaired glucose metabolism [21] and an impaired capacity of HDL to acquire free cholesterol from triglyceride-rich lipoprotein lipolysis [22]. Alternatively, extremely high HDL-C levels may be attributed to particular lifestyles such as excessive alcohol consumption, or genomic factors such as loss-of-function mutations in key HDL metabolism-regulating genes [23]. Thus, the identification of reliable markers for HDL functions requires in-depth knowledge of HDL complexity.

Under pathological conditions, quantitative and qualitative changes in the composition of HDL particles can compromise their beneficial properties for health [24**]. Interestingly, the distinct profile in the changes in HDL structure and lipid and protein compositions between coronary heart disease (CHD) and T2DM patients has led to the identification of three independent functional HDL components, namely the polyunsaturated sphingomyelin SM 42:3 and glycosylphosphatidylinositol-phospholipase D1 (GPLD1), which inhibit endothelial cell apoptosis, and apolipoprotein F (apoF), which promotes maximal respiration of brown adipocytes [24**]. In terms of hepatic and cognitive diseases, apoA-I levels are negatively associated with the risks of chronic liver failure and dementia [3*,4]. Moreover, HDL particles that contain apoE but not apoJ may predict cognitive decline, independently of the presence of the apoE ϵ 4 allele [25]. Among the other emerging HDL-related biomarkers, ATPase inhibitory factor 1 (IF1) has been proposed to reflect hepatic HDL uptake (one of the last steps of RCT). IF1 has been reported to be independently and negatively associated with the long-term prognosis in CHD patients [26,27]. Importantly, a rapid and inexpensive high-throughput spectrometry-based assay that is amenable to clinical practice and that allows multiplexing in the quantification of circulating apolipoproteins and IF1 was recently developed and could serve to further validate a panel of these emerging HDL-related biomarkers [28,29*].

Studies of HDL-related biomarkers often comprise assessment of the Cholesterol Efflux Capacity (CEC) [30**]. A meta-analysis recently concluded that the CEC is negatively associated with cardiovascular morbidity and mortality [31]. However, as measuring CEC is time-consuming and it has not yet been standardized, there will need to be substantial technical progress before this biomarker will be used in routine clinical practice. A novel score was recently developed, called the HDL apolipoproteomic score (pCAD). This score, which correlates well with the CEC, is based on mass spectrometry quantification of specific HDL-associated apolipoproteins [32**]. Although the pCAD score warrants further clinical evaluation, it has been reported to be independently associated with cardiovascular mortality in CHD patients. Another clinically advanced HDL-related biomarker is based on measurement of the HDL particle number (HDL-P) by nuclear magnetic resonance spectroscopy. HDL-P has been shown to have a greater prognostic value than HDL-C and apoA-I in coronary patients [33], and it may be a surrogate marker of HDL anti-oxidative activity [30**].

Although further studies are needed to validate these biomarkers as proxies of the many protective properties of HDL, their use, either alone or as part of a panel, should permit a biological- and clinical-based reassessment of the optimal therapeutic strategy for targeting HDL. Thus, the use of HDL as therapeutics is contingent on further research, as indicated by the very limited number of current active clinical trials evaluating HDL-based therapies. For instance, of the three formulations of rHDL that have been developed for intravenous infusion, only a randomized controlled trial of the compound CSL-112 is still ongoing (expected completion in 2022), while the two other entities (MDCO-216 and CER-001) did not result in a reduction of atherosclerotic plaque in patients with acute coronary syndrome compared to placebo [30**]. rHDL formulations, which have exhibited disappointing outcomes to date, are mainly composed of poorly lipidated apoA-I and they are expected to exert a beneficial effect by increasing the CEC. However, it should be kept in mind that oxidative stress and inflammatory conditions, which occur in many chronic diseases, may convert HDL into dysfunctional particles. In particular, myeloperoxidase is enriched in atherosclerotic lesions and it promotes oxidative modification of apoA-I at residue Trp72, which is essential for the cholesterol efflux activity of apoA-I [34]. The control of the oxidative stress and inflammation status of patients should thus be evaluated to ensure that injected rHDL remain sufficiently functional to exert their intended beneficial effects. Alternatively, myeloperoxidase inhibitors could be used simultaneously to prevent lipoprotein oxidation [35]. Additionally, a short apoA-I-derived peptide was recently shown to improve glucose metabolism, promote cholesterol efflux, and reduce atherosclerosis in pre-clinical models, thus positioning this peptide as a promising drug candidate to reduce the risk of CVD in individuals with insulin resistance [36].

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