

REVIEW

High-density lipoprotein (HDL) functionality and its relevance to atherosclerotic cardiovascular disease

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Abstract

Several prospective epidemiological studies have shown that there is a clear inverse relationship between serum high-density lipoprotein-cholesterol (HDL-C) concentrations and risk for coronary heart disease (CHD), even at low-density lipoprotein-cholesterol (LDL-C) levels below 70 mg/dL. However, more recent evidence from genetic studies and clinical research has come to challenge the long-standing notion that higher HDL-C levels are always beneficial, while lower HDL-C levels are always detrimental. Thus, it becomes apparent that HDL functionality plays a much more important role in atheroprotection than circulating HDL-C levels. HDL cholesterol efflux capacity (CEC) from macrophages is a key metric of HDL functionality and exhibits a strong inverse association with both carotid intima-media thickness and the likelihood of angiographic coronary artery disease (CAD), independent of the HDL-C level. Thus, extensive research is being conducted to identify new agents with a favorable side effect profile, which would be able to enhance CEC, improve HDL functionality and potentially decrease cardiovascular risk.

This review aims to present and discuss the current clinical and scientific evidence pertaining to the significance of HDL functionality over the actual HDL-C concentration in mediating the favorable effects on the cardiovascular system. Thus, we conducted a PubMed search until December 2017 through the English literature using the search terms 'HDL function/functionality', 'HDL properties', 'cardiovascular risk' and 'cholesterol efflux capacity'. We also included references from the articles identified and publications available in the authors' libraries.

Keywords: ApoA-I Milano, cardiovascular disease (CVD), cholesterol efflux capacity (CEC), HDL-cholesterol (HDL-C), HDL functionality.

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Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, being responsible for approximately 30% of the annual global mortality [1]. In the United States the disease is highly prevalent and over one-third of the population has CVD [2]. Several prospective epidemiological studies have shown that there is a clear inverse relationship between serum high-density lipoprotein-cholesterol (HDL-C) concentrations and risk for coronary heart disease (CHD), even at low-density lipoprotein-cholesterol (LDL-C) levels below 70 mg/dL [3,4]. Furthermore, it has been estimated that for each increment of 1 mg/dL in HDL-C, the CHD risk is reduced by 3% in women and by 2% in men [5].

However, more recent evidence from genetic studies and clinical research has come to challenge the long-standing notion that higher HDL-C levels are invariably beneficial, while lower HDL-C levels are always detrimental [6].

In a genetic study, three functional variants of hepatic lipase associated with a modest rise in levels of HDL-C did not improve cardiovascular risk [7]. On the other hand, functional mutations in ATP-binding cassette transporter A1 (ABCA1) leading to a 29.3% reduction in HDL-C levels, did not adversely affect cardiovascular risk [8]. Furthermore, it was shown that carriers of a single nucleotide polymorphism in the endothelial lipase gene leading to an increase of HDL-C levels by 5.4 mg/dL, but with similar levels of other lipid and nonlipid cardiovascular

risk factors, did not enjoy a reduced risk of myocardial infarction, as compared with noncarriers [9]. In a review, which discussed the latest insights for HDL-C-associated genes, as well as evidence from large-scale genome-wide association studies, it was concluded that the current data do not support a direct causal relation between molecularly defined HDL disorders and atherosclerosis per se [6,10]. In a large clinical study, higher preoperative HDL-C levels were not associated with reduced risk of vascular events in patients with coronary artery disease (CAD) undergoing coronary artery bypass grafting (CABG) [11]. More importantly, it has been shown that very high LDL-C levels and/or very large HDL particle size are associated with increased risk for CAD [12]. This observation, along with the detrimental, neutral or at most slightly positive effects on CVD risk conferred by the cholesteryl ester transfer protein (CETP) inhibitors, despite a large increase in HDL-C levels (from 31% and up to 133.2%) [13–16], significantly weaken the notion that high HDL-C levels are always protective [6].

This review aims to present and discuss the current clinical and scientific evidence pertaining to the significance of HDL functionality over the actual HDL-C concentration for determining cardiovascular risk. Thus, we conducted a PubMed search until December 2017 through the English literature using the search terms 'HDL function/functionality', 'HDL properties', 'cardiovascular risk' and 'cholesterol efflux capacity'. We also included references from the articles identified and publications available in the authors' libraries.

Composition and biological functionality of HDL

HDL constitutes a heterogeneous group of particles differing in density, size, electrophoretic mobility, and apolipoprotein content [17]. The major HDL apolipoproteins are ApoA-I and ApoA-II, and both are required for normal HDL biosynthesis. ApoA-I is synthesized in both the intestine and the liver, constitutes approximately 70% of HDL protein, and is present on virtually all HDL particles. ApoA-II is synthesized only in the liver, constitutes approximately 20% of HDL protein, and is present on about two-thirds of HDL particles in humans [18].

Mass spectrometry studies have revealed that the HDL particles carry a multiplicity of proteins, which not only affect lipid metabolism but are also involved in complement regulation, acute-phase response and proteinase inhibition [19]. Lipidomic approaches have identified more than 200 molecular lipid species in normolipidemic HDL, including phospholipids, sphingolipids, steroids, cholesteryl esters, triglycerides, diacylglycerides, monoacylglycerides and free fatty acids [20]. Furthermore, it has to be emphasized that HDL consists of a group of particles with marked structural, physicochemical, compositional and functional heterogeneity and with significant differences in their biological activities [6,20,21]. Thus, it becomes evident that, given this vast heterogeneity of

biological functions, HDL functionality cannot be inferred from the plain measurement of plasma HDL-C levels [22].

HDL plays a major role in reverse cholesterol transport (RCT), by which excess cholesterol is removed from the peripheral vessels and is transported back to the liver for disposal [23]. However, HDL has several other beneficial biological properties, which enhance its protective effect against CVD. These include antioxidative, anti-inflammatory endothelial/vasodilatory, antithrombotic and cytoprotective functions [24–27]. More specifically, HDL may provide potent protection of LDL in vivo from oxidative damage, induced by free radicals in the arterial intima, with consequent inhibition of the generation of proinflammatory oxidized lipids, mainly lipid hydroperoxides but also short-chain oxidized phospholipids [24]. HDL also inhibits the expression of adhesion molecules in endothelial cells and thus it decreases the recruitment of blood monocytes into the arterial wall [25]. HDL also increases the production of the atheroprotective signaling molecule nitric oxide (NO) via upregulation of the expression of endothelial NO synthase (eNOS), as well as by maintaining the lipid environment in caveolae, where eNOS is co-localized with partner signaling molecules. In addition, HDL stimulates eNOS as a result of kinase cascade activation by the high-affinity HDL receptor, scavenger receptor class B type I (SR-BI) [26]. The antithrombotic function of HDL may be exerted through the activation of prostacyclin synthesis, as well as through the attenuation of the expression of tissue factor and selectins, with consequent downregulation of thrombin generation via the protein C pathway and direct and indirect blunting of platelet activation [26]. The direct cytoprotective effect of HDL on endothelial cells may be exerted through prevention of the suicide pathway leading to apoptosis of endothelial cells by decreasing the cysteine protease P32 (CPP32)-like protease activity. Thus, HDL plays a protective role against 'injury', as this is described in the 'response-to-injury' hypothesis of atherogenesis [27].

The ApoA-I Milano mutation: low levels of a highly functional HDL offering protection from CVD

The ApoA-I Milano (AI-M) mutation was first described in 1980 in a family originating from Limone sul Garda, a small town outside Milan in northern Italy. In this genetic mutation, the ApoA-I variant shows a single amino acid substitution of arginine to cysteine at the position 173 in the primary sequence of ApoA-I. This substitution leads to the formation of homodimers (AI-M/AI-M) and heterodimers with apolipoprotein AII (AI-M/AII). The carriers of the ApoA-I Milano mutation share a lipid profile characterized by very low HDL-C levels and moderate hypertriglyceridemia but without evidence of premature CAD or preclinical coronary or carotid atherosclerosis [28,29].

Weekly infusions of recombinant ApoA-I Milano, as compared with placebo, caused a significant regression of coronary atherosclerosis in patients with acute coronary syndrome (ACS) after 5 only treatments [30]. Furthermore, in an animal study, recombinant ApoA-1 Milano was shown to exert greater anti-inflammatory, antioxidant and plaque-stabilizing effects, as compared with wild-type HDL [31].

These cardiovascular protective effects of ApoA-I Milano provided the initial clinical support for the concept that the functionality of HDL plays a more important role to reduce atherosclerosis than the circulating level of HDL-C [32].

HDL particle subpopulations and HDL functionality

As it was alluded before, plasma HDL constitutes a heterogeneous group of particles with diverse structure and biological activity, mainly due to differences in their lipid and apolipoprotein content [6]. Earlier studies have indicated that the larger HDL particles are more protective [33–36]. However, more recent evidence has come to challenge this concept.

CETP inhibitors failed to provide any meaningful reduction in cardiovascular risk despite a substantial increase in circulating HDL-C levels [13–16]. Similarly, niacin (added to statin therapy) also failed to decrease cardiovascular risk despite a significant increase in HDL-C levels [37,38]. Both CETP inhibitors and niacin preferentially increase the levels of the large HDL particles, whereas their effects on the total number of HDL particles are weaker [39]. There is evidence from experimental studies that cholesterol-overloaded HDL particles may be functionally abnormal with impaired anti-atherogenic potential; they may have a negative impact on the efflux potential of cholesterol from extrahepatic cells and may reduce hepatic selective uptake of cholesterol mediated by scavenger receptor SR-BI [40,41]. This evidence is also supported by a *post hoc* analysis of two large prospective studies, the IDEAL (Incremental Decrease in End Points through Aggressive Lipid Lowering) trial and the EPIC (European Prospective Investigation into Cancer and Nutrition)-Norfolk case-control study, which showed that very high plasma HDL-C levels (≥ 70 mg/dL) and very large HDL particles (> 9.53 nm) were associated with higher risk for CVD. In contrast, ApoA-I remained protective across the major part of its distribution in both studies, thus proving that high plasma ApoA-I more uniformly represents lower risk [12]. Furthermore, in another community-based cohort study, it was clearly shown that cholesterol-overloaded HDL particles were independently associated with progression of carotid atherosclerosis in a CVD-free population. More specifically, participants with the highest estimated number of cholesterol molecules per HDL particle (≥ 53.0) had 1.56-fold (95% confidence interval: 1.14 to 2.13; $p=0.006$) increased progression, as compared with those with the lowest estimated number of cholesterol molecules per HDL particle (< 41.0) [41].

On the other hand, there is evidence showing that small-dense HDL particles may be more 'functional' in many protective mechanisms. More specifically, small-dense HDL particles promote more effectively cholesterol efflux from lipid-loaded macrophages and exhibit more potent antioxidative, anti-inflammatory, cytoprotective, antithrombotic and anti-infectious activity, as compared with larger HDL particles [6,22,42].

The apparent discordancy concerning the atheroprotective potential of the different subfractions of the HDL particles may well be elucidated by more recent data showing that the presence of large HDL particles is linked to a lower number of circulating LDL particles, and primarily of the highly atherogenic small-dense LDL particles [43]. Therefore, it becomes apparent that the cardiovascular protection may not be related to the large size of HDL particles but may be actually due to the associated reduced number of LDL particles [6].

In a large multiethnic study of patients without baseline CHD, which was designed to evaluate the independent associations of HDL-C and HDL particle (HDL-P) concentrations with carotid intima-media thickness (CIMT) and incident CHD, it was clearly shown that, after adjusting for each other and LDL particle (LDL-P) concentration, the concentration of HDL-C was no longer associated with CIMT or CHD, whereas HDL-P remained independently associated with both CIMT and CHD [44]. These data again clearly support the concept that the anti-atherogenic potential of HDL may be related to the total HDL-P concentration but cannot be inferred from the plain measurement of plasma HDL-C.

Factors altering HDL functionality

As mentioned above, HDL plays a major role in RCT, but also exhibits antioxidative, anti-inflammatory endothelial/vasodilatory, antithrombotic and cytoprotective functions. On the other hand, the major proteins of HDL are ApoA-I and ApoA-II but HDL particles also carry a multiplicity of less abundant proteins, which not only affect lipid metabolism but are also involved in complement regulation, acute-phase response and proteinase inhibition. These include ApoC-I, ApoC-II, apoC-III, apoE, apoJ, apoL, lecithin:cholesterol acyl-transferase (LCAT), serum paraoxonase-1 (PON1), and platelet-activating factor acetylhydrolase (PAF-AH) [45]. Modification of the protein components of HDL, brought about by the oxidative environment of the acute-phase response (a systemic response to infection, surgery, myocardial infarction, and chronic inflammation), can convert HDL from an anti-inflammatory to a proinflammatory particle [45,46]. Indeed, during acute-phase response, a new set of proteins, including serum amyloid A (SAA) and ceruloplasmin, bind to HDL and may render HDL pro-inflammatory and pro-atherogenic by limiting its ability to promote RCT and to prevent LDL modification [45]. In a study using human aortic endothelial and smooth muscle cells, it was shown that while

HDL obtained before cardiac surgery completely inhibited the LDL-induced increase in monocyte transmigration, in contrast, acute-phase HDL, obtained from the same patients 2–3 days after surgery, not only did not inhibit the LDL-induced increase in monocyte transmigration but also amplified it by up to 1.8-fold ($p < 0.01$). Thus, anti-inflammatory HDL actually became pro-inflammatory during the acute-phase response [47].

Furthermore, recent studies have shown that HDL and ApoA-I recovered from human atheroma are dysfunctional and are extensively oxidized by myeloperoxidase (MPO). More specifically, ApoA-I containing a 2-OH-Trp72 group (oxTrp72-apoA1) is in low abundance within the circulation but accounts for 20% of the apoA1 in atherosclerosis-laden arteries. Moreover, increased levels of oxTrp72-apoA1 in subjects presenting to a cardiology clinic were associated with increased risk for CVD. Thus, it was suggested that circulating levels of oxTrp72-apoA1 may serve as a marker of the pro-atherogenic process in the arterial wall [48]. In accordance with this study, there is evidence indicating that dysfunctional HDLs have impaired anti-inflammatory potential and their presence in patients with CAD may actually help discriminate between patients with ACS and patients with stable CAD [49].

In addition, it has been shown that glycation may also impair HDL function and this could be a contributing factor to the accelerated atherosclerosis observed in Type II diabetes mellitus [50]. Furthermore, there is evidence that in metabolic syndrome the small-dense HDL particles become dysfunctional displaying impaired antioxidative activity [51]. Moreover, protein carbamylation may also render HDL dysfunctional, which raises the possibility that HDL carbamylation contributes to foam cell formation in atherosclerotic lesions [52]. Additionally, MPO-mediated oxidation of ApoA-I has also been found to impair HDL function in regard to its RCT, antioxidant and anti-inflammatory activities [53].

Ethnicity has also been shown to be associated with HDL functionality. In this regard, there is evidence that black South African women, in comparison to white women, display improved HDL antioxidant functionality and are relatively protected against CHD despite greater prevalence of obesity and lower circulating HDL-C levels than white women [54]. There is also evidence that obesity may impair HDL functionality [54,55], whereas bariatric surgery may actually exert a significant improvement in HDL structure and functionality [56].

Dietary habits may also play a significant role in the functionality of HDL. Consumption of saturated fat has been shown to reduce the anti-inflammatory potential of HDL and impair arterial endothelial function. In contrast, consumption of polyunsaturated fat is associated with an improvement of the anti-inflammatory activity of HDL. These findings highlight novel mechanisms by which different dietary fatty acids may affect atherogenicity [57].

HDL cholesterol efflux capacity: a key metric of HDL functionality

Cholesterol efflux from macrophages to HDL occurs via several mechanisms involving the ABCA1 and ABCG1 transporters, as well as the scavenger receptor SR-BI [58]. Although cholesterol efflux from macrophages accounts only for a very small fraction of the total efflux of cholesterol from peripheral tissues via the RCT pathway, it appears to be the most relevant component in regard to atheroprotection and therefore it may provide an excellent surrogate for HDL functionality [6,59]. Actually, in a cross-sectional study, it was demonstrated that the cholesterol efflux capacity (CEC) from macrophages has a potent inverse association with both CIMT and the likelihood of angiographic CAD, independent of the HDL-C level [60]. The results of this study were confirmed in another recent study, which followed 2,924 adults free from cardiovascular disease who were participants in the Dallas Heart Study over a median follow-up period of 9.4 years. HDL-C level, HDL-P concentration and CEC were measured at baseline. There was a statistically significant 67% reduction in cardiovascular risk in the highest quartile of CEC compared with the lowest quartile. Adding CEC to traditional risk factors was associated with improvement in discrimination and reclassification indexes [61].

In addition, there is evidence that CEC is impaired in patients with chronic kidney disease, metabolic syndrome, diabetes mellitus and autoimmune disorders [62]. On the other hand, CEC is actually enhanced in patients with the metabolic syndrome and low HDL-C levels who were treated with pioglitazone, but not in patients with hypercholesterolemia who were treated with statins [60]. It has also been shown that male sex and current smoking are associated with decreased CEC [60].

Thus, quantification of CEC may be instrumental in the assessment of new therapies targeting HDL metabolism and RCT, as agents that enhance CEC may lead to improvement of HDL functionality and potentially reduction of cardiovascular risk.

Future therapeutic directions

As it was mentioned earlier in this review, infusions of recombinant ApoA-I Milano caused a significant regression of coronary atherosclerosis in patients with ACS [30]. However, subsequent clinical development was delayed by several years due to manufacturing difficulties and contamination from host-derived proteins [32]. More recently, a clean manufacturing process was developed to produce the recombinant ApoA-I Milano without contamination by host-derived proteins and this new product was called MDCO-216 [32]. However, in a pilot trial, MDCO-216 did not produce a significant beneficial effect on CAD progression measured by Intravascular Ultrasound (IVUS) [63] and the sponsor company abandoned its further development.

It is known that plasma-selective delipidation converts α HDL to pre β -like HDL, the most effective form of HDL for lipid

removal from arterial plaques [64]. Autologous delipidated HDL plasma infusions in patients with ACS were proven to be clinically feasible and well tolerated. Furthermore, the IVUS data demonstrated a numeric trend toward regression in the total atheroma volume in the delipidated group compared with an increase of total atheroma volume in the control group, although the results did not reach statistical significance [64]. Further studies will be needed to determine the ability of this therapy to reduce clinical cardiovascular events.

In a randomized, double-blind, placebo-controlled, dose-ranging phase 2b trial, which was designed to assess the safety and tolerability of CSL112 (a reconstituted, infusible, plasma-derived ApoA-I) after acute myocardial infarction (AEGIS-I trial), it was shown that 4 weekly infusions of CSL112 were feasible, well tolerated, and not associated with any significant impairment in liver or kidney function or other safety concerns. The ability of CSL112 to acutely enhance CEC was also confirmed [65]. A phase 3 trial to assess the potential benefit of CSL112 to reduce major adverse cardiovascular events has already been planned and will begin recruiting patients in early 2018.

Although infusions of recombinant ApoA-I Milano or ApoA-I wild type may be potentially safe and effective for clinical application, this therapy is limited for clinical use due to the high cost of large-scale production of ApoA-I and need for

repeated intravenous administration. Thus, gene therapy could represent an alternative approach for its possible long-term effect. Although preclinical studies have provided some evidence of benefit using this approach, further studies are needed for its definitive clinical validation [32]. Recent progress in recombinant adeno-associated virus (AAV) technology appears promising in this regard [32,66].

Conclusions

From the above review of the scientific, epidemiological and clinical data, it becomes apparent that HDL functionality plays a much more important role in atheroprotection than circulating HDL-C levels. Plasma HDL constitutes a heterogeneous group of particles with diverse structure and biological activity, and very high HDL-C levels are not invariably protective but rather, under certain conditions, may actually become pro-inflammatory. HDL functionality is dependent upon genetic, environmental, and lifestyle factors and may be modified in several disease states. HDL CEC from macrophages is a key metric of HDL functionality and exhibits a strong inverse association with both CIMT and the likelihood of angiographic CAD, independent of the HDL-C level. Thus, extensive research is being conducted to identify new agents with a favorable side-effect profile, which would be able to enhance CEC, improve HDL functionality and potentially decrease cardiovascular risk.

Disclosure and potential conflicts of interest: Constantine E Kosmas is a member of the Dyslipidemia Speaker Bureau of Amgen, Inc. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors are available for download at: <http://www.drugsincontext.com/wp-content/uploads/2018/03/dic.212525-COI.pdf>

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