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Review Article

ANTI-ATHEROGENIC FUNCTIONS OF HIGH DENSITY LIPOPROTEINS

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HDL has many protective activities against atherosclerosis including its role in reverse cholesterol transport, and its antioxidant, anti-inflammatory, and endothelial cell maintenance functions. Various HDL subclasses vary in quantitative and qualitative content of lipids, apolipoproteins, enzymes, and lipid transfer proteins, resulting in differences in shape, density, size, charge, and antigenicity. After accepting excess cellular cholesterol from arterial macrophages and other peripheral tissues HDL transports the excess cholesterol to the liver for disposal. Although, a routine clinical assay for dysfunctional HDL is not currently available, the development of such an assay would be beneficial for a better understanding of the role that dysfunctional HDL plays as a risk factor for coronary artery disease, and for the determination of how various drug therapies effect HDL functionality. We can conclude that HDL may function as a recipe to longevity and a potential pharmacological target for the therapeutic attenuation of atherosclerosis. Further, reconstituted HDL is a promising candidate for treatment and management of diabetic dyslipidemia, hyperlipidemia, and cardiovascular diseases.

Keywords: HDL, Apolipoproteins, Anti-inflammatory, Dysfunctional HDL

INTRODUCTION

Epidemiological studies have identified low density lipoproteins and high density lipoproteins as independent risk factors that modulate cardiovascular disease (CVD) risk. The role of High density lipoproteins (HDLs) in protecting against the development of coronary heart disease (CHD) has been demonstrated in numerous clinical studies. The studies show an

inverse relationship between the concentration of HDL-C and the development of premature CHD (Gordon and Rifkind, 1989; and Castelli *et al.*, 1992), with a reduction in CHD risk of 2-4% for each 1 mg/dl increase in HDL-C. HDL is a class of heterogeneous lipoproteins containing approximately equal amounts of lipid and protein (Gordon *et al.*, 1989). HDL particles are characterized by high density and small size. The various

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HDL subclasses vary in quantitative and qualitative content of lipids, apolipoproteins, enzymes, and lipid transfer proteins, resulting in differences in shape, density, size, charge, and antigenicity. Apo-A₁ is the predominant HDL protein followed by Apo-A₂. HDL fraction accounts for almost all of the cholesterol quantified as HDL-C. HDL can be further fractionated by density into HDL₂ and HDL₃, by size, or by apolipoprotein composition. The origin of HDL particles is not entirely clear. Several mechanisms have been proposed, including direct secretion in to plasma from hepatocytes or enterocytes; release during the interconversion of various HDL subpopulations by phospholipid transfer protein (PLTP), cholesteryl ester transfer protein (CETP), or hepatic lipase (HL); or direct interaction of free lipoproteins with cell membrane (von Eckardstein *et al.*, 2000). Although our understanding of how HDL protects against CVD is still incomplete, there is evidence that supports at least three major atheroprotective mechanisms of HDL. Scavenger receptor B1 and cholesterol trafficking. The reverse transport of cholesterol from peripheral cells to sites of catabolism, first described by Glomset and Norum in 1973, they has been suggested to be the primary antiatherogenic mechanism of HDLs. Cholesterol efflux from macrophages to HDL can occur by passive diffusion (Yancey *et al.*, 2003), by interaction with the Scavenger receptor-B1 (SR-B1) receptor (Williams *et al.*, 1999), or by binding to the ATP binding cassette-A1 (ABCA1) transporter (Liu *et al.*, 2003; and Oram and Lawn, 2001). The preferred acceptor for the ABCA1 transporter-mediated cholesterol efflux is poorly lipidated apo-A1 (Castro and Fielding, 1988), which is converted to spherical α -HDL after esterification of free cholesterol to cholesteryl esters by lecithin-cholesterol acyltransferase

(LCAT). Both the SR-B1 (Malerod *et al.*, 2002) and ABCA1 transporter (Venkateswaran *et al.*, 2000) pathways are modulated by the cellular content of oxysterols, which regulate the LXR pathway and expression of the SR-B1 and ABCA1 transporter genes. After accepting excess cellular cholesterol from arterial macrophages and other peripheral tissues HDL transports the excess cholesterol to the liver for disposal. HDL is thus an integral component of the atheroprotective reverse cholesterol transport process, functioning as a carrier of excess cellular cholesterol from peripheral tissues to the liver, where it is excreted from the body as bile acids and cholesterol (Glomset, 1968). The second mechanism by which HDL may protect against CVD is the selective decrease of endothelial cell adhesion molecules, which facilitate the binding of mononuclear cells to the vessel wall and promote lesion development (Barter *et al.*, 2002). The HDL-induced increase in NO production may be an important atheroprotective feature of HDL, as diminishing bioavailability of endothelial-derived NO has a key role in the early pathogenesis of hypercholesterolemia-induced vascular disease and atherosclerosis (Cohen, 1995). Apoptosis of endothelial cells has been demonstrated in atherosclerosis. The ability of HDL to inhibit apoptosis has been shown in several studies (Nofer *et al.*, 2001). HDL exerts a protective effect by interfering with the apoptotic stimuli which endothelial cells are exposed. The mechanism is uncertain but this HDL function may contribute to longevity.

HDLS AND ANTIOXIDATIVE MECHANISMS

A third mechanism by which HDL decreases atherosclerosis is to protect LDL from oxidation. Oxidized or modified LDL, unlike normal LDL, is

readily taken up by the scavenger receptor SR-A or CD36 on macrophages, resulting in cholesteryl ester accumulation with foam cell formation. The cholesterol-loaded macrophage produces a number of inflammatory cytokines and stimulates monocyte chemoattractant protein-1 (MCP-1) as well as endothelial cell adhesion molecules. Mechanisms of LDL oxidation *in vivo* involve concerted modification by chemically diverse oxidants, employing that any single low molecular weight antioxidants, such as vitamins E and C, even at physiologically relevant doses, may not provide complete oxidative protection of LDL *in vivo* (Witztum and Steinberg, 2001). Plasma HDLs possess a spectrum of antiatherogenic actions, including potent antioxidant and anti-inflammatory activities (Van Lenten *et al.*, 2001). Although HDLs can themselves undergo oxidative modification (Francis, 2000), several enzymes that may cleave oxidized lipids and thereby inhibit LDL oxidation are associated with HDL particles; these include paraoxonase (PON) in its major isoforms PON1 (Durrington *et al.*, 2001), platelet-activating factor acetylhydrolase (PAF-AH) (Tselepis *et al.*, 2002), LCAT (Goyal *et al.*, 1997), and glutathione selenoperoxidase (Chen *et al.*, 2000). In addition, apo-A₁, a major HDL apolipoprotein can remove oxidized lipids from LDL, suggesting that HDL can function as an acceptor of oxidized lipids (Navab *et al.*, 2000). Apo-A₁ was shown to reduce peroxides of both phospholipids and cholesteryl esters and to remove hydroperoxides, which are products of 12-lipoxygenase, from native LDL (Navab *et al.*, 2000). The diversity of antioxidative actions of HDL particles suggests that HDL provide efficient protection of LDL from oxidation *in vivo*. Plasma LDLs are heterogeneous in their physico-chemical properties and consist of three major particle subclasses, lb-LDL, intermediate LDL, and Sd-LDL; such LDL

subfractions are distinct in their atherogenic and oxidative properties (Kontush *et al.*, 2003). Similarly, circulating HDL particles are heterogeneous in physico-chemical properties, intravascular metabolism, and biological activity (Lamarche *et al.*, 1999). Ultracentrifugally isolated HDL₃ exerts greater inhibition of adhesion protein expression in endothelial cells than HDL₂ (Ashby *et al.*, 1997; 1998). Isopycnic density gradient centrifugation allows reproducible isolation of 5 physicochemically defined, highly purified, major HDL subfractions, HDL2b, 2a, 3a, 3b, and 3c (Goulinet *et al.*, 1997). Indeed, HDL particle phenotypes are qualitatively and quantitatively altered in dyslipidemias associated with premature atherosclerosis, including hyperlipidemias of types IIA, IIB, and IV, and type 2 diabetes (Lamarche *et al.*, 1999). Significant differences between the HDL fractions derived from subjects with type 1 diabetes and those derived from control subjects has been reported (Valabhji *et al.*, 2001). The greater values for HDL esterified cholesterol and phospholipid in the subjects with type 1 diabetes are attributable largely to increased concentrations of esterified cholesterol and phospholipid associated with larger, more buoyant HDL fractions (Valabhji *et al.*, 2001). Paraoxonase catalyzes the breakdown of oxidized phospholipids in LDL. Studies have found that transgenic animals deficient in this enzyme are significantly more susceptible to the development of diet-induced atherosclerosis (Shih *et al.*, 2000). On the other hand, PON transgene in mice produces HDL resistant to oxidation (Oda *et al.*, 2002). Degradation of oxidized phospholipids has also been attributed to PAF-AH. Over expression of human apo-A₁ in apo-E knockout mice increases PAF-AH activity and simultaneously reduces oxidative stress in plasma, decreases intracellular adhesion

molecule (ICAM) and vascular cell adhesion molecule (VCAM) expression, and decreases monocyte recruitment in to the arterial wall (Theilmeyer *et al.*, 2000).

Serum paraoxonase is a calcium-dependent esterase that is known to catalyze hydrolysis of organophosphates, and is widely distributed among tissues such as liver, kidney, intestine, and also serum, where it is associated with HDL (Mackness *et al.*, 1996). PON specificity towards endogenous serum and tissue substrates is not well characterized and therefore synthetic substrates, such as paraoxon and phenyl acetate are used to monitor the enzyme's activity. Serum PON activity was shown to be reduced in patients after myocardial infarction (MI) (Ayub *et al.*, 1999), in patients with familial hypercholesterolemia and in patients with diabetes mellitus (Mackness *et al.*, 1991), diseases that are associated with accelerated atherogenesis. Genetic variations of PON correlated with HDL-cholesterol and apo-A₁, suggesting antiatherogenic properties. Atherosclerosis occurs naturally in humans and rabbits but not in mice. Comparison of PON arylesterase activity revealed that in humans and rabbits, >95 % is HDL associated. In mice, about 30 % of PON activity is lipid poor; in the absence of apo-A₁ in mice, total PON arylesterase activity is reduced and > 60 % is lipid poor. It is striking that the rabbit has so much higher level of plasma PON activity than human and mice, especially in view of the fact that out of these three species, the rabbit is the most susceptible to cholesterol-induced atherosclerosis (Cabana *et al.*, 2003). The PON activity is much more labile to the acute phase reaction in the rabbit than in the mouse, resulting in a substantial decrease in rabbits treated with croton oil (Cabana *et al.*, 2003). Feingold *et al.* have demonstrated that administration of endotoxin lipopolysaccharide in

Syrian hamsters was associated with a decline in serum PON concentration and activity as well as PON mRNA levels in the liver (Feingold *et al.*, 1998). A decrease in PON activity during the acute phase response could therefore be another factor linking the acute phase response with increased atherogenesis (Feingold *et al.*, 1998). Boemi *et al.* (2001) have demonstrated that lower absolute PON concentrations and activities, higher LDL: PON concentration ratios and a lesser capacity to prevent LDL oxidation are consistent with the hypothesis that reduced serum PON in type 1 patients, similar to type 2 diabetics, could contribute to increased risk of vascular disease (Boemi *et al.*, 2001). Although PON can offer protection against the toxicity of some organophosphates, its physiological role is still not clear; however, evidence exists for a protective effect of PON against oxidative damage (Mackness *et al.*, 1996). PON was suggested to contribute to the antioxidant protection conferred by HDL on LDL oxidation (Mackness *et al.*, 1991). The effect of HDL-associated PON or of purified PON on the LDL oxidation process, including its initiation (conjugated diene formation), propagation (peroxides formation), and decomposition (aldehydes formation) phases could be analyzed by using PON inhibitors. The inhibitory effect of HDL on LDL oxidation was suggested to be related to metal ion chelation, or to peroxidase, like activity. Under oxidative stress, not only LDL is susceptible to lipid peroxidation but all other serum-lipids, including those present in HDL, are also prone to oxidation. In fact, HDL has been shown to be the major carrier of lipid hydroperoxides in human serum (Hahn and Subbiah, 1994). In this context it is interesting to mention that HDL-associated cholesteryl ester hydroperoxides are more rapidly reduced to their less reactive hydroxides than are those associated with LDL (Christison *et al.*, 1995).

Oxidative modification of HDL has also been shown to impair the ability of the lipoprotein to promote cholesterol efflux (Morel, 1994). Thus, inhibition of HDL oxidation by PON may preserve the antiatherogenic functions of HDL in reverse cholesterol transport, as well as its protection of LDL from oxidation. Kontush *et al.* (2003) have demonstrated that both serum and plasma-derived small, dense HDL particles possess the most potent capacity among HDL subspecies to protect LDL from both metal-dependent and metal-independent oxidation in normolipidemic subjects (Kontush *et al.*, 2003). The oxidative protection of LDL by ultracentrifugally isolated HDL subfractions (at equal cholesterol or protein concentration or equal particle number) increased in the order HDL2b < HDL2a < HDL3a < HDL3b < HDL3c. HDL subfractions efficiently protected not only total LDL but also intermediate LDL3 (typically the most abundant LDL subfraction in normolipidemic subjects) and small, dense LDL5 (a highly atherogenic LDL subfraction) (Chapman *et al.*, 1998), thereby suggesting that HDL can attenuate oxidation of atherogenic LDL subclass. When HDL subfractions were subjected to nonmetal or copper-induced oxidation in the absence of LDL, their oxidative resistance increased in the order HDL2b < HDL2a < HDL3a < HDL3b < HDL3c, thereby mirroring their antioxidative activity during LDL oxidation. Similarly, PON1 activity with phenyl acetate or paraoxon as substrate increased in the order HDL2b < HDL2a < HDL3a < HDL3b < HDL3c (Kontush *et al.*, 2003). On a particle basis, contents of apo-A₁ and apo-A₂ were elevated in HDL3a and lowest in HDL3c. PAF-AH activity was significantly increased in small, dense HDL3c. LCAT activity was higher in HDL₃ relative to HDL₂ subfractions (Kontush *et al.*, 2003). The present evidence for the differential antioxidative properties

of HDL subfractions may have important consequences for our understanding of the protective antiatherogenic action of HDL *in vivo*. Thus, although small, dense HDL3c typically accounts for <15 % of total HDL, HDL3c may nonetheless play a pivotal role in the protection of LDL against oxidation, significantly exceeding the protection afforded by low molecular weight antioxidants. Indeed, it has been shown that HDL₃, rather than HDL₂, is strongly correlated with the antiatherogenic action of gemfibrozil in the VA-HIT Study (Robins *et al.*, 2001). Considered together these findings identify small, dense HDL as a potential pharmacological target for the therapeutic attenuation of atherosclerosis in subjects had high cardiovascular risk associated with increased oxidative stress, as, for example, in the case of type 2 diabetes and metabolic syndrome.

DYSFUNCTIONAL HDL

HDL is heterogeneous in size and composition, whether all HDL is equally protective against atherosclerosis. There are many ways in which HDL and apoAI can become dysfunctional. For example inflammation changes hepatic gene expression and leads to changes in the protein composition of HDL (also called the HDL proteome). During inflammation or in experimental models where lipopolysaccharide (LPS), a bacterial endotoxin, has been utilized, the levels of apoAI and CETP on HDL are decreased, while the levels of the acute phase reactant proteins serum amyloid A (SAA) and secretory phospholipase A2 (sPLA2) on HDL are markedly increased; and, these changes are associated with decreased cholesterol acceptor activity of HDL (van der Westhuyzen *et al.*, 2007). Enzymes can also modify HDL proteins. Myeloperoxidase

(MPO) is found in neutrophils and monocytes and it plays an important role in killing microorganisms. It performs this activity by using chloride ions and cell generated hydrogen peroxide to create hypochlorous acid, the same chemical that is in household bleach. Myeloperoxidase (MPO) levels were more predictive than C-reactive protein (CRP) levels, with those in the highest CRP quartile having 1.8-fold increased risk compared to those in the lowest CRP quartile (Brennan *et al.*, 2003). Thus, MPO may be a risk factor for CAD, and it can bind to and modify apoAI. The MPO mediated modifications of apoAI include apoAI cross linking that can be observed on SDS denaturing gel electrophoresis, with MPO altering apoAI from a small monomer form to dimer and multimer cross linked forms (Peng *et al.*, 2005). Work by the Hazen and Smith groups in Cleveland, and independently by Heinecke's group in Seattle, have determined that apoAI chlorotyrosine levels are higher in subjects with CAD than in control subjects (Zheng *et al.*, 2004; and Pennathur *et al.*, 2004). Furthermore, both teams have shown that MPO modification of apoAI *in vitro* leads to loss of apoAI cholesterol acceptor activity (Zheng *et al.*, 2004; and Bergt *et al.*, 2004). And, for apoAI isolated from human plasma, there is an inverse correlation between its chlorotyrosine content and cholesterol acceptor activity, such that the apoAI preparations with higher chlorotyrosine contents have less ability to act as cholesterol acceptors from cholesterol loaded macrophages (Zheng *et al.*, 2004). Thus, apoAI becomes dysfunctional in its ability to mediate RCT by either *in vitro* or *in vivo* modification by MPO.

CONCLUSION

HDL is a class of heterogeneous lipoproteins containing approximately equal amount of lipid and protein. It is characterized by high density and small size. Various HDL subclasses vary in qualitative and quantitative contents of lipids, apolipoproteins, enzymes and lipid transfer proteins, resulting in differences in shape, density, size, charge and antigenicity. Although our understanding of how HDL protects against CVD is still incomplete. There is evidence that at least three major atheroprotective mechanism of HDL.

The reverse cholesterol transport from peripheral cells to sites of catabolism has been suggested to be the primary antiatherogenic mechanism of HDLs. The second mechanism by which HDL may protect against CVD is the selective decrease of endothelial cell adhesion molecules, which facilitate the binding of mononuclear cells to the vessel wall and promote lesion development. The HDL induce increase in NO may be an important atheroprotective features of HDL. The third mechanism by which HDL decreases atherosclerosis is to protect LDL as well as self from oxidation. Although HDL can themselves undergo oxidative modification, several enzymes that may cleaves oxidize lipids and thereby inhibit LDL oxidation are associated with HDL particles; these includes PON, in its major isoform PON1, platelet-activating factor acetyl hydrolase (PAF-AH), lecithin cholesterol acyl transferase (LCAT) and glutathione selenoperoxidase.

Consider together these findings suggest HDL as a potential pharmacological target for the therapeutic attenuation of atherosclerosis in subject, had high cardiovascular risk associated with increase oxidative stress, as for example, in

the case of type-2 diabetes and metabolic syndrome. Thus we can conclude that HDL may function as a recipe to longevity.

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