Perspectives

Plasma High Density Lipoproteins

Metabolism and Relationship to Atherogenesis

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Introduction[1]

Plasma HDL are small, dense, spherical lipid–protein complexes. They consist of ~ 50% lipid and 50% protein. The major lipids are phospholipid (PL),[2] cholesterol (C), cholesteryl esters (CE), and triglycerides (TG). The major proteins are apo A-I (M_r 28,000) and apo A-II (M_r 17,000). There are also a variety of minor but metabolically important apoproteins in HDL called apo E and apo C (C-I, C-II, and C-III). HDL are heterogeneous and can be classified into larger, less dense HDL_2 or smaller, denser HDL_3. Although the major proportion of HDL is normally present in HDL_3, individual variability in HDL levels in human populations usually reflects different amounts of HDL_2.

A major known function of HDL is to act as a receptacle for excess PL and C, derived from cells or as by-products of lipolysis. These lipids are normally recycled from HDL to the liver in a process called reverse C transport (Fig. 1). This involves a direct pathway where C is transferred into HDL, then taken up by the liver, and also an indirect pathway, involving transfer of CE from HDL to VLDL, followed by uptake of VLDL in liver, or conversion of VLDL to LDL, and uptake of LDL by the liver. Another important function of HDL is to act as a reservoir for apo E and C proteins. These proteins transfer onto TG-rich lipoproteins (e.g., during alimentary lipemia), providing a signal for the activation of lipolysis (the enzyme lipoprotein lipase [LPL] is activated by apo C-II) or targeting information that allows uptake of lipolyzed remnant lipoproteins by liver receptors (apo E is attracted to chylomicron or VLDL remnants and acts as a ligand for uptake of these particles by liver receptors).

1. There are excellent reviews covering genetic disorders of HDL (1) and HDL epidemiology (2).
2. *Abbreviations used in this paper:* C, cholesterol; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; HL, hepatic lipase; LCAT, lecithin:cholesterol acyltransferase; LPL, lipoprotein lipase; PL, phospholipid; RFLP, restriction fragment length polymorphism; TG, triglyceride.

Overview of HDL metabolism

Secretion, remodeling in plasma, and catabolism. The major apolipoproteins of HDL are synthesized in both the liver and small intestine. These proteins may be secreted with lipid as nascent HDL, and probably also as free apolipoproteins. Newly formed HDL appear as spherical particles containing neutral lipid or as apolipoprotein/PL bilayer discs. Spherical HDL may be seen in the secretory organelles of hepatocytes or enterocytes, indicating intracellular assembly (3). However, discoidal HDL are not seen within cells and are probably formed extracellularly, for example by hydrolysis of newly secreted TG-rich HDL (4). A major portion of the apolipoprotein and phospholipid destined to become HDL is initially secreted on large, TG-transporting VLDL (liver) or chylomicrons (intestine). During lipolysis of these particles surface lipids (PL and C) and proteins (apo A-I, A-II, and Cs) are transferred into HDL (5, 6).

The transfer of lipids between HDL, lipoproteins, and cells is illustrated schematically in Fig. 2. The lipolysis of chylomicrons and VLDL by LPL results in a net transfer of PL into HDL. Free C diffuses into HDL from other lipoproteins, erythrocytes, and endothelial cells. The HDL-associated enzyme lecithin:cholesterol acyltransferase (LCAT) uses PL and C, generating CE and lysophospholipid, and driving the influx of further PL and C into HDL. In humans, a major part of CE formed within HDL is transferred into larger TG-rich lipoproteins, as a result of the action of a plasma CE transfer protein (CETP). This hydrophobic 74,000 M_r glycoprotein facilitates the exchange of neutral lipids and PL between the lipoproteins, and its activity is enhanced by lipolysis (7, 8). The CETP effects a net exchange of HDL CE with the TG of VLDL or chylomicrons. The TG-enriched HDL may then be hydrolyzed by hepatic lipase (HL), resulting in the removal of core lipid. HL also has substantial phospholipase activity resulting in removal of surface lipids from HDL.

Thus, there is a cycle of enlargement of HDL due to influx of lipid and LCAT action (Fig. 3, step *1*), followed by CE-TG exchange (step *2*), and then shrinkage of HDL as a result of TG and PL hydrolysis by HL (step *3*) (9). The conversion of HDL_2 into HDL_3 is also accompanied by loss of apo A-I. The balance of this cycle may be shifted toward larger HDL during alimentary lipemia, or toward smaller HDL during fasting.

The cycle of lipid exchange and lipolysis provides a mechanism for net removal of neutral lipid from HDL and accounts for the fact that the CE of human HDL are turned over 10–40 times more rapidly than its major structural apoproteins. In addition, there may be mechanisms that favor net uptake of HDL C by liver cells, such as the phospholipase activity of HL (10). In vivo studies of the turnover of HDL C suggest that
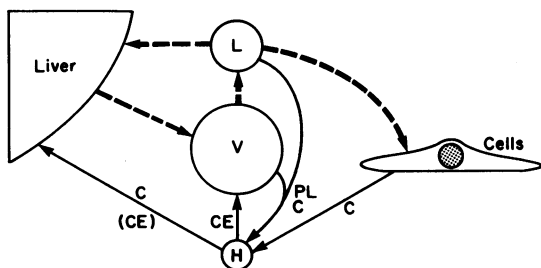
Figure 1. Function of HDL–reverse C transport. *V, L,* and *H* represent VLDL, LDL, and HDL, respectively. The thick broken lines represent particle secretion, interconversion, or catabolism; the thin lines depict net lipid movement.

Figure 3. Interconversion of HDL. See text for explanation.

tissues exchange C primarily with HDL and not with VLDL + LDL; HDL C is also rapidly exchanged with the liver C pool (11). There is net transfer of C from tissues to liver via HDL, of similar magnitude to the net transfer of HDL CE through LDL + VLDL to liver (11). Large, CE-rich HDL₂ containing apo E may also be removed by receptor-mediated endocytosis mediated by liver LDL receptors. The receptor-mediated removal of HDL is probably less important in humans than in species with low CETP activity in plasma, such as rats (8). In rats a further catabolic pathway of HDL involves selective uptake of HDL C esters in liver, adrenal, and ovary, with disproportionate degradation of HDL protein in the kidney (12). The mechanism of selective CE uptake from HDL is poorly understood, but it does not involve receptor-mediated endocytosis (13). Although cellular HDL₃ binding proteins have been described (14), their role in HDL metabolism remains to be determined.

HDL in interstitial fluid. There is a rapid equilibration of plasma HDL with HDL in the extravascular compartment. The latter contains ~ 40% of apo A-I in humans (15). HDL isolated from interstitial lymph appears discoidal and is enriched with apo E relative to plasma HDL (16). HDL particles in interstitial fluid may acquire apo E from peripheral sources (e.g., by synthesis in steroidogenic and nervous tissues), and may play a local role in lipid or hormone metabolism (17). For example, after crush injury of a nerve axon, there is an influx of macrophages that ingest lipid from the degenerating nerve and synthesize increased amounts of apo E
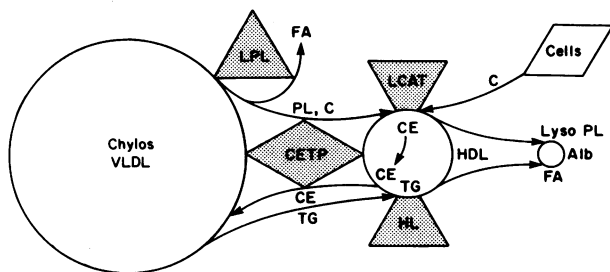
(17). As the nerve regenerates, it expresses increased numbers of LDL receptors, which take up apo E–HDL, formed in conjunction with macrophage secretion of apo E. Thus, the HDL acts as a vehicle to transport lipid from local storage sites to cells with increased C need (17).

Mechanisms of variation of HDL C and apoproteins

HDL levels may be altered by a variety of factors (Table I). Alterations in plasma HDL levels may be effected by changes in the synthesis or catabolism of the major HDL proteins. Variation in HDL C and apo A-I between individuals are correlated with differences in the fractional catabolic rate of apo A-I (18). Hypertriglyceridemic subjects with low HDL C and apo A-I levels have an increased fractional catabolic rate of apo A-I, compared with normolipidemic subjects (19). The decrease in HDL caused by a low fat, high carbohydrate diet was associated with an increase in the fractional catabolism of plasma apo A-I and apo A-II, and, conversely, the increase in HDL associated with nicotinic acid ingestion was due to a decrease in fractional catabolism of apo A-I and apo A-II (15). In contrast, a diet rich in polyunsaturated fat (polyunsaturated/saturated ratio = 4.0) gave rise to a decrease in HDL C and apo A-I, due to a decrease in the production rate of apo A-I, without any change in catabolism (20). Also, subjects with low HDL C and apo A-I, who do not have hypertriglyceridemia, seem to have decreased production rates of apo A-I (19).

Unfortunately, kinetic studies provide no direct information on the molecular mechanisms responsible for the turnover parameters. For example, variations in apo A-I transport (synthesis) rates might be related to changes in synthesis and secretion of apo A-I by liver or small intestine. Alternatively, the appearance of apo A-I in HDL might reflect the efficiency

Figure 2. Enzymatic modification of HDL. The lipolysis of chylomicrons and VLDL by LPL in tissues (adipose, muscle) results in uptake of fatty acids *(FA)* by the tissues and transfer of PL and C into HDL. Plasma LCAT uses PL and C as substrates, forming CE. The plasma CETP facilitates the transfer of PL, CE, and TG as shown. HL hydrolyzes HDL, PL, and TG in the liver. Lysophospholipids *(Lyso PL)* and FA formed by LCAT and HL may be bound to albumin *(alb)*.
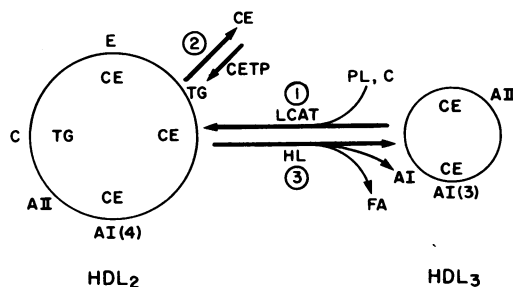
Table I. Some Factors That Alter HDL Levels

Increased HDL
Female sex
Exercise conditioning
Alcohol intake
Nicotinic acid, fibrates, phenytoin
Estrogens
Decreased HDL
Low fat diet
High polyunsaturated fat diet
Obesity, esp. truncal
Probucol, β-blockers, progestins, and androgens
Smoking

of intravascular processing of nascent TG-rich lipoproteins containing apo A-I. Monkey studies indicate that variations in hepatic mRNA levels and secretion rates for apo A-I are an important source of variation in plasma apo A-I levels (21). It seems likely that genetic or nutritional factors affecting human apo A-I gene expression may be a source of variation of plasma apo A-I levels. However, attempts to probe this question by analysis of restriction fragment length polymorphisms near the apo A-I gene locus have produced conflicting and inconclusive results (22).

In contrast to the studies of HDL protein turnover (15–20), some recent evidence suggests that changes in the catabolism of apo A-I can occur secondary to alterations of HDL lipid metabolism. Goldberg et al. (23) have shown that antibody inhibition of LPL in monkeys causes a rise in plasma TG and a fall in HDL CE and apo A-I levels. It seems that the rise in TG or the process of CE-TG exchange within HDL triggers more rapid catabolism of apo A-I, with the uptake of increased amounts of apo A-I by the kidneys (23). Another indication that apo A-I levels may be influenced by lipid exchange events is that humans with genetic absence of CETP show an increase in both HDL CE and apo A-I levels (24).

Overall, the data suggest that apo A-I catabolism is influenced by changes in HDL core lipid composition or HDL size. In the presence of increased levels of TG-rich lipoproteins, there is increased TG-CE interchange. Lipolysis of TG-enriched HDL_2 results in a smaller particle (HDL_3). The smaller CE-enriched HDL_3 may have lower affinity for apo A-I, leading to apo A-I catabolism in the kidney, or transfer of apo A-I to remnants, which are removed by catabolism in liver. A similar process may occur irrespective of the cause of hypertriglyceridemia. The well-known inverse correlation between plasma TG and HDL C or apo A-I may in part be due to accelerated transfer of CE from HDL to TG-rich lipoproteins, with a secondary decrease in apo A-I levels due to enhanced catabolism.

Regulation of plasma HDL by lipases and lipid transfer protein

Several of the major factors known to regulate HDL levels act by altering the activities of enzymes that mediate the intravascular processing of HDL (i.e., LPL, HL, and CETP [Fig. 2]). Genetic absence of each of these enzymes clearly demonstrates their importance in HDL metabolism (1, 24). In human populations the activity of LPL is positively correlated with HDL C measurements (25). LPL is higher in females than males, and is increased in response to several factors known to increase HDL C levels (e.g., insulin, nicotinic acid, and fibrate administration, alcohol, and exercise conditioning [Table I]). In some cases there is good evidence that the increase in LPL activity causes the increase in HDL C. For example, a recent study showed a 10% increase in HDL_2 C across exercise-trained muscle, associated with enhanced lipolysis of VLDL TG (26). The increase in HDL C associated with chronic alcohol intake may be due to enhanced lipolysis of TG-rich lipoproteins, associated with increased LPL activity in adipose tissue (27). These observations point to the importance of LPL activity in skeletal and adipose tissue as factors regulating HDL. Conversely, activity of HL is inversely correlated with HDL levels, is lower in women than men, and is increased by androgen and decreased by estrogen, treatments that decrease and increase HDL, respectively (28–30).

The importance of CETP in human HDL metabolism is illustrated by the recent discovery of subjects with CETP deficiency, due to a CETP gene splicing defect (24). The subjects with homozygous CETP deficiency have markedly increased (four to six times) HDL C levels, including substantial amounts of large apo E–enriched particles (HDLc) (24). Studies of individuals with heterozygous CETP deficiency show that they have CETP mass levels within the lower part of the normal range of CETP values, an increased ratio of HDL_2/HDL_3, and increased HDL C, compared with unaffected family members. These results suggest that the ratio of HDL_2 to HDL_3 and the mass of HDL C may be influenced by physiological variation of CETP levels. Furthermore, the rate of CETP-mediated neutral lipid transfer in plasma is responsive to the total TG level (31). Thus, variations of plasma CE transfer rates, whether due to variation in CETP mass or to plasma TG levels, probably play an important role in the determination of HDL C levels.

Given that LPL, HL, and CETP each has an important influence on HDL metabolism, the next level of understanding will be related to the molecular mechanisms regulating the activities of these enzymes. In tissue culture, there is evidence for regulation of LPL gene expression at the steps of transcription, translation, and posttranslational processing (32, 33). Recent studies of human adipose tissue biopsies indicate that increases in LPL activity mediated by a high carbohydrate meal are associated with constant LPL mRNA and protein levels and seem to involve altered protein processing within or outside the cell (i.e., posttranslational events) (33). A variety of molecular mechanisms that may regulate LPL protein activation have been described, including glycosylation, dimerization, and intracellular degradation (32–35). Though less studied, changes in HL activity have also been correlated with changes both in mRNA levels and in posttranscriptional processing of protein (36). In rabbits increases in plasma CETP caused by an atherogenic diet were associated with an increase in liver CETP mRNA levels (37). These findings indicate that CETP mRNA levels in liver may be influenced by nutritional factors, and may be one factor influencing plasma CETP levels.

Twin studies indicate a strong genetic component in the inheritance of HDL C levels. One study (38) suggests that much of this variation may be mediated by genetically determined variation in HL activity, and not by genetic variations in LPL. The recent elucidation of restriction fragment length polymorphism (RFLP) markers for HL, LPL, and CETP will permit gene haplotype studies in families to determine if there is common variation at the respective gene loci that are linked to changes in HDL levels.

HDL and atherosclerosis

Genetic defects in the synthesis of apo A-I result in very low HDL levels and premature atherosclerosis (1). In contrast, in Tangier disease or in individuals with apo A-I_{Milano}, the synthesis of apo A-I appears to be normal, there are reduced but detectable levels of apo A-I in plasma, and there is no marked increase in atherosclerosis. Abnormalities of HDL, either with or without hypertriglyceridemia, are very common in individuals suffering from coronary artery disease (39). The hypoalphalipoproteinemia is commonly familial (39), but the cause is unknown. Conversely, hyperalphalipoproteinemia also occurs in families and may be associated with longevity. There are

probably several different causes of hyperalphalipoproteine-mia, one of which is genetic CETP deficiency (23). Whereas hyperalphalipoproteinemia due to CETP deficiency may be associated with longevity, hyperalphalipoproteinemia due to HL deficiency seems to be associated with premature athero-sclerosis (1). The difference is probably due to the contrasting effects of these conditions on VLDL and LDL.

An inverse relationship between HDL levels and the inci-dence of atherosclerotic coronary artery disease has been docu-mented in numerous epidemiological studies (2). In contrast to the findings in Western societies (2), a study of 40–59-yr-old males in Moscow and Leningrad recently found no significant association of coronary heart disease mortality and HDL C levels, and a positive association between HDL C level and mortality from all causes (40). The latter was largely due to an excess of deaths from suicides and accidents. In the USSR the HDL C levels were 8–10 mg/dl higher than in North America, were skewed towards higher values, and were correlated with alcohol intake. The differing results in North America and the USSR could suggest that an alcohol-mediated increase in HDL C may not have beneficial consequences for cardiovas-cular disease. However, several earlier studies in Western soci-eties had shown that moderate alcohol intake was associated with protection against cardiovascular disease, and was corre-lated with increased HDL C (41).

Several drugs that are used to treat hyperlipidemia have important effects on HDL. Nicotinic acid typically increases HDL C levels by 20–30%, fibrates (e.g., gemfibrozil) by 10–20% (42), and lovastatin by 5–10%; conversely, probucol lowers HDL C by 15–25%. Subset analysis of various drug intervention trials, which were designed primarily to reduce LDL C levels, suggests that effects on HDL of gemfibrozil (43), cholestyramine (43), and nicotinic acid and lovostatin (44) influence clinical or angiographic coronary artery disease inde-pendent of the effects of these agents on LDL C or TG levels. In the case of gemfibrozil, the major clinical benefit was seen in individuals with hypertriglyceridemia (42). However, changes in TG levels were not independently associated with benefit, whereas the increase in HDL was. Although none of these intervention trials was designed primarily to address ef-fects on HDL, the consistency of the HDL–coronary artery disease relationship suggests that the effects of lipid-lowering agents on HDL C levels is part of their spectrum of action to protect against coronary artery disease. There is a great need to design an intervention trial that would assess the effect of drugs affecting HDL on coronary artery disease, where the primary selection criterion for entering the trial is a low level of HDL C.

Animal studies also show a strong link between HDL and atherosclerosis. Plasma HDL in monkeys is inversely corre-lated with susceptibility to atherosclerosis, comparing individ-uals or different species of monkeys (21). Inbred strains of mice also show large differences in susceptibility to dietary atherosclerosis as well as in HDL metabolism. When chal-lenged with a high fat diet the susceptible strain C57 BL/6 exhibited a pronounced decrease in HDL C and apo A-I, due to an increase in HDL catabolism (45). Inbreeding studies showed that the levels of HDL lipid in mice maintained on a high fat diet cosegregate with susceptibility to diet-induced atherosclerosis (45). These results have suggested the presence of a gene, called Ath-1, that controls HDL levels as well as susceptibility to atherosclerosis (45). The identification of the

Ath-1 gene and a possible human homologue is awaited with great interest.

Why is there an inverse relationship between HDL C and coronary artery disease?

Reverse C transport. This hypothesis states that the level of HDL C is a marker of the efficiency of a system of reverse C transport (Fig. 1). Despite the popularity of this theory, the evidence supporting it is limited. It is clear from animal and human studies that C is removed from atheromata when plasma LDL C levels are lowered and HDL levels are in-creased. It is likely that the regression mechanism involves C removal by HDL. In tissue culture studies HDL can remove C from cells, including CE-loaded macrophage foam cells (46). These cells also secrete apo E and lipid, giving rise to locally formed apo E HDL, which may be subsequently targeted to the liver (46). The infusion of HDL-like particles has been shown to accelerate the regression of atherosclerosis in rabbits (47).

Although HDL is central to the process of reverse C trans-port (48), what remains unclear is whether reverse C transport mediates the protective effect of HDL noted in epidemiologi-cal studies. For example, it has never been shown that varia-tions in HDL C concentration similar to those in plasma mod-ulate C removal from cells of the arterial wall. Furthermore, the original finding of an inverse relationship between HDL C levels and human tissue C stores (as measured by isotopic C turnover studies) was not confirmed in subsequent studies of a larger group of subjects (49). However, these measurements are macroscopic in nature, and no kinetic parameter accu-rately measures the pool of C in arterial wall. A further point of evidence against the reverse C theory might be that genetic deficiency states of LCAT and Tangier disease do not result in markedly increased atherosclerosis. However, in each of these conditions the effects in arterial wall may not be pronounced because of concomitant reduced levels of LDL, and because sufficient HDL is present to mediate C removal.

Atherogenic remnant hypothesis. Zilversmit (50) originally proposed that some chylomicrons bearing dietary C would be hydrolyzed on the arterial wall surface, and that the locally formed chylomicron remnants might enter the artery and con-tribute to atherosclerosis. The atherogenic remnant hypothesis was subsequently modified to say that low HDL levels might be a marker for the accumulation of chylomicron or VLDL remnants in plasma. In addition to bearing dietary C, the remnants would become enriched in CE derived from HDL and LDL as a result of CETP activity. The concentration of chylomicron or VLDL remnants might be increased due to overproduction of VLDL, inefficient lipolytic processing, or defective receptor-mediated clearance. The remnants, enriched with dietary C and endogenous CE, would enter ar-tery wall and be taken up by macrophages, giving rise to ath-eroma foam cells. The low levels of HDL result from both inefficient lipolytic transfer of lipids into HDL (see Fig. 2) and accelerated CE-TG interchange due to the accumulation of TG-rich lipoproteins.

A clear example of the accumulation of atherogenic rem-nants of TG-rich lipoproteins is seen in human dysbetalipo-proteinemia (type III hyperlipidemia), where there is overpro-duction of VLDL, defective hepatic removal of remnants, ac-celerated transfer of CE from HDL into remnants, and

reduced levels of HDL CE (51). Direct evidence for a more general link between the accumulation of chylomicron remnants and HDL levels was obtained by Patsch et al. (52), who showed that the elevation of postprandial TG levels is strongly inversely correlated with fasting HDL2, HDL C, and apo A-I levels. The postprandial triglyceridemia was correlated relatively weakly with fasting TG levels, suggesting that the measurement of postprandial triglyceridemia might be more informative for linkages between HDL levels and TG-rich lipoprotein metabolism than measurements of fasting TG.

Other theories. In cross-sectional population studies there is an inverse correlation between HDL_2 and the levels of smaller LDL and IDL. There is evidence that smaller, apo B–rich LDL and IDL may be atherogenic (53). Thus, low HDL_2 levels could be markers of small LDL or IDL accumulation. Krauss (54) has described a lipoprotein profile characterized by small LDL, increased IDL, high fasting TG, and low HDL C. Family studies suggest that one or more dominant genes may determine this phenotype (54). In a case/control study of survivors of myocardial infarction, the small LDL–low HDL_2 phenotype was found significantly more often in cases than in controls (55). However, multivariate analysis showed that case/control status was most strongly predicted by fasting TG levels and HDL C; levels of IDL, total LDL, or small LDL were not significantly associated with case/control status. These findings suggest that the risk of this distinctive lipoprotein phenotype is more closely tied to TG and HDL C levels than to IDL or LDL subclasses.

In summary, it is likely that HDL C is associated with protection against coronary artery disease (1) because HDL levels indicate the efficiency of reverse C transport in subjects with normal or increased LDL levels, and this process is involved in removal of C from atheromata, and/or (2) because HDL acts as a marker of atherogenic chylomicron and VLDL remnant accumulation. Many, though not all, of the factors that increase HDL will be antiatherogenic, due to the complex interrelationships of HDL and TG-rich lipoprotein metabolism and other metabolic effects (e.g., hypertension associated with alcohol intake). Each intervention affecting HDL will have to be prospectively evaluated on its own merits.

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