

# "HDL-Cholesterol Metabolism"

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As the name indicates, Plasma lipoproteins are complexes of lipids and proteins. With the exception of free cholesterol, the lipoprotein lipids are always complex; they include cholesterol esters, triglycerides, and phospholipids. Lipoproteins are classified according to their densities and electrophoretic motilities. In order of decreasing densities, they are HDL, LDL, IDL, VLDL and chylomicrons. The function of lipoproteins is to transport cholesterol and triglycerides in the blood. The first connection between cholesterol and atherosclerosis was made by German scientists in 1910. It wasn't until the mid-1950s that John W. Gofman, MD, a University of California – Berkley biophysicist, observed that elevated levels of high-density lipoprotein (HDL) cholesterol were associated with reduced risk of heart attack. The Framingham Heart Study described the effects of HDL cholesterol in 1977 and subsequently established low HDL-C levels as an independent predictor of coronary risk.

## **HDL assembly**

The assembly of VLDL in the endoplasmic reticulum, and chylomicrons in enterocyte, is clearer than the origin of HDL. Two possible sources of HDL have been identified. The first involves secretion of nascent HDL, which is rapidly converted to mature lipoprotein by plasma enzymes and transfer protein. The other possible synthetic route involves lipolysis of VLDL, and chylomicrons in the plasma compartment (1). The later hypothesis is supported by the observation that HDL-C is increased in individual with low plasma TG, presumably due to very efficient lipolysis. In either instance, an HDL particle that has pre-B mobility and is rich in phospholipids and apolipoprotein A-I, is processed to mature HDL through the activities of lecithin: cholesterol acyl- transferase (LCAT), hepatic lipase (HL) and cholesterol ester transfer protein (CETP). This pre-B-HDL is a preferred acceptor of cholesterol from peripheral tissue.

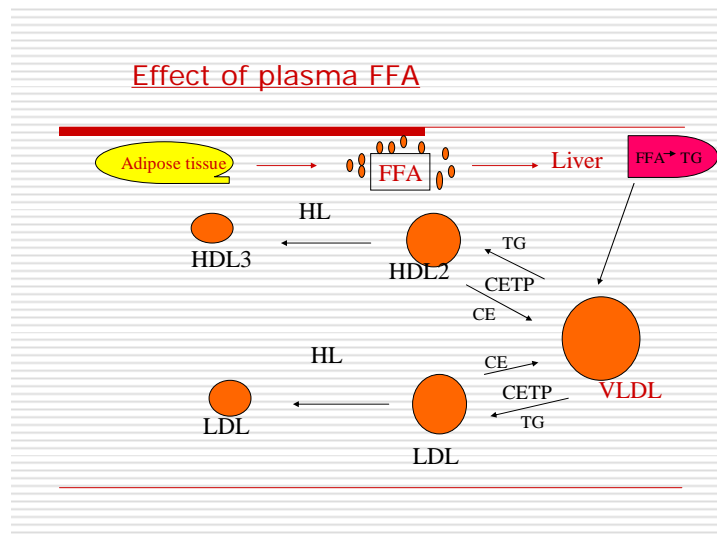
## **Structure of HDL-C**

HDL is the smallest lipoprotein and contains the least amount of lipid. HDL contains a lipid core of cholesteryl esters (CE) and TG surrounded by phospholipids and specialized proteins known as apolipoproteins. Apolipoproteins are a specialized group of proteins that associate with lipids and mediate several biochemical steps associated with plasma lipid metabolism. An early view was that apolipoproteins were simply vehicles for solubilization and transport of lipids in the plasma component. More recent evidence indicates that many of them contain determinants that regulate several activities essential to normal lipid metabolism. Apolipoproteins are required for the structural integrity of lipoproteins and direct their metabolic interactions with enzymes, lipid transport proteins,

and cell-surface receptors (2). ApoA-I, is a major component of all HDL particles and is synthesized in the liver and intestine (3). ApoA-II, the second most abundant apolipoprotein in HDL, is synthesized in the liver (5); its function is unclear.

### Triglycerides and HDL metabolism

The hypertriglyceridemia that frequently accompanies diabetes mellitus and persons with the metabolic syndrome has important metabolic effects on HDL content, particle size and hence affecting its protective function. The increase in visceral fat in case of abdominal obesity leads to increase free fatty acids in the plasma. In the liver, the increased fatty acids, is incorporated into triglycerids and secreted as VLDL particles, which are further remodeled through hydrolysis in the plasma component to free fatty acids that in-turn are incorporated into adipose tissue. Fig.1 demonstrates the metabolic effect of the VLDL particles with high triglyceride content on HDL and LDL particles. As shown in the figure, this triglyceride- loaded VLDL will activate a protein specialized in transfer of cholesterol ester between the different lipoprotein particles. This cholesterol ester transfer protein (CETP), will exchange cholesterol esters in HDL and LDL particles with the triglyceride content of the VLDL particles, a lipid shuttle activity that will end in increasing the triglyceride content of both HDL and LDL particles and decreasing their cholesterol ester content, an effect that is enhanced by the activity of the lipase enzyme. The resultant HDL particles are dysfunctional and less effective in cholesterol removal from the periphery to the liver, with more small LDL particles and progressive atherosclerosis. This metabolic profile with high triglycerides, low HDL and small LDL particles is the atherogenic profile in many cases of diabetes, abdominal obesity and metabolic syndrome.



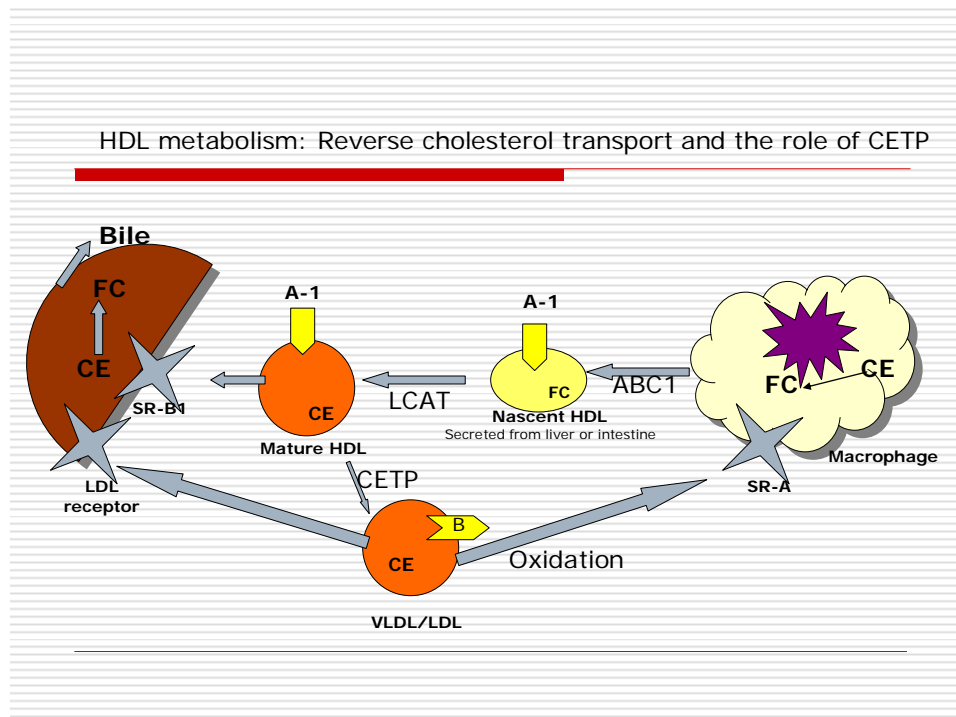
**Fig.1:** FFA: free fatty acids, TG: triglycerides, CETP: cholesterol ester transfer protein, CE: cholesterol ester, HL: hepatic lipase

### Reverse cholesterol transport and the role of CETP

Cholesterol that is synthesized or deposited in peripheral tissues is returned to the liver in a process referred to as *reverse cholesterol transport* in which HDL plays a central role

(6). The nascent HDL-C particles, consisting of phospholipid and apolipoprotein A-I, interacts with peripheral cells, such as macrophages, to facilitate the removal of excess free cholesterol, a process facilitated by the ATP-binding cassette protein 1 (ABC1) gene (Fig.2). HDL is then converted into mature cholesterol ester-rich HDL as a result of the plasma cholesterol-esterifying enzyme lecithin-cholesterol acyltransferase (LCAT), which is activated by apoA-I (2). Cholesterol esters may be removed by several different pathways, including selective uptake by the liver i.e., the removal of lipid without the uptake of HDL proteins. Selective uptake appears to be mediated by the scavenger receptor class-B, type I (SR-BI), which is expressed in the liver and has been shown to be a receptor for HDL (7), cholesterol esters derived from HDL contributes to the hepatic-cholesterol pool used for bile acid synthesis. Cholesterol is eventually excreted from the body either as bile acid or as free cholesterol in the bile.

Fig.2, shows the selective uptake of high-density lipoprotein (HDL) content of cholesteryl ester, together with another important pathway of reverse cholesterol transport involving the action of plasma cholesterol ester-transfer protein (CETP). Cholesterol ester can be transferred from HDL to apolipoprotein B-containing proteins, such as very-low-density lipoproteins (VLDLs) and low-density lipoproteins (LDLs), by CETP (4, 9). Cholesterol esters transferred in this way could be up taken by LDL liver receptors, or oxidized and react with the peripheral tissue via scavenger receptor class-A of the macrophage.



**Fig.2:** CE= cholesterol ester; FC= free cholesterol; A-1= apolipoproteinA-1;  
 ABC1= ATP-binding cassette protein-1;  
 LCAT= Lecithin:cholesterol acyl transferase; CETP= cholesterol ester transfer protein  
 SR-B1=scavenger receptor class B1; SR-A= scavenger receptor class A

The metabolism of HDL is a complex process. Metabolic turnover studies suggest that plasma levels of HDL cholesterol and apolipoprotein A-I (the major structural component

of HDL) are determined by the rate of synthesis versus the rate of catabolism. Genetic defects in HDL metabolism or therapeutic interventions that alter HDL metabolism may affect the development of atherosclerosis. Current research is directed at the genes and proteins that regulate HDL metabolism with the goal of identifying new therapeutic targets for the prevention and treatment of atherosclerosis.

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