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EDITORIAL

Colesevelam, Atherosclerosis, and Reverse Cholesterol Transport

Atherosclerosis is a widely prevalent disease with a complex etiology. Risk factors for atherosclerotic disease are well characterized. Atherogenesis is dependent upon derangements in lipoprotein and glucose metabolism, hypertension, as well as a large array of inflammatory, oxidative, and immune phenomena that injure and adversely remodel focal areas of blood vessel walls. As atheromatous plaque matures, such clinical sequelae as myocardial infarction, stroke, claudication, and sudden death can result. The aggressive identification and treatment of atherosclerotic disease in all of its clinical manifestations is a high public health priority throughout the world.

Among patients at risk, reducing the burden of atherogenic lipoproteins in serum with lipid-lowering medication and lifestyle modification has been shown to reduce the risk for acute cardiovascular events in both the primary and secondary prevention settings. However, even with very aggressive reductions in low-density lipoproteins (LDL), the maximal attainable risk reduction generally approaches 35% to 40%. A large gap in residual risk remains to be closed. A considerable body of recent work suggests that at least a part of this gap may be narrowed further with therapies that augment reverse cholesterol transport.

Reverse cholesterol transport (RCT) is the process by which high-density lipoproteins (HDL) are able to extract excess cholesterol from blood vessel walls and deliver it back to the liver and gastrointestinal tract for disposal (Figure). Unlike atherogenic lipoproteins which deposit cholesterol in vessel walls, HDLs are atheroprotective. In addition to driving RCT, HDL exerts a number of antithrombotic, anti-inflammatory, antioxidative, and other vasculoprotective functions.[1,2] In epidemiologic studies performed around the world, a low HDL is an independent risk factor for coronary heart disease (CHD).[3] A number of expert groups have recommended that therapeutic effort be made to raise low levels of HDL in patients at risk for CHD.

In this issue of *The Journal of Applied Research*, Davidson and coworkers evaluate the effects of a bile acid binding resin, colesevelam, on serum cholesterol, aortic atherosclerotic plaque, and the molecular apparatus of RCT. As expected, colesevelam reduced serum levels of cholesterol quite substantially. Bile acid binding resins are well known to reduce serum cholesterol by reducing

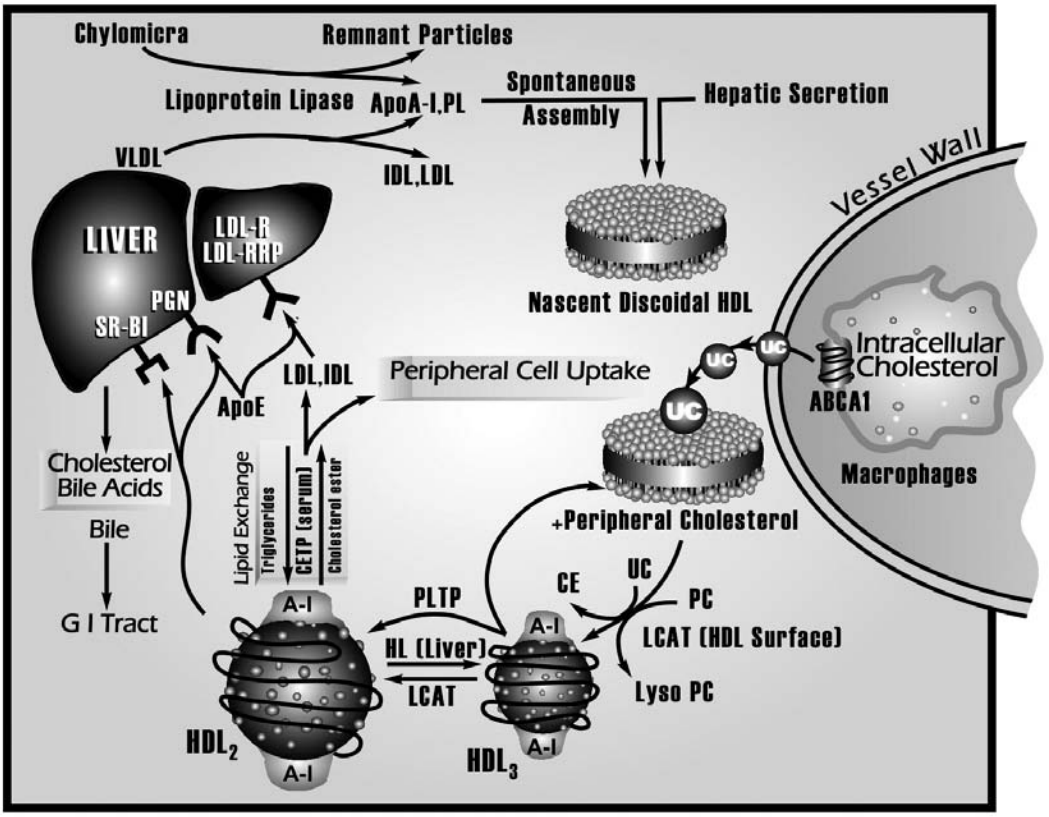

Figure 1. Molecular/enzymatic pathway for reverse cholesterol transport. In order to deliver peripheral cholesterol back to the liver, apo A-I interacts with cells such as macrophages in the subendothelial space of blood vessel walls. The HDL undergoes a series of cell receptor- and serum enzyme-dependent maturation reactions (ie, "HDL speciation"). HDL can interact directly with a variety of hepatic cell receptors, the most important of which is SR-BI. The cholesterol ester in HDL can also be delivered back to the liver via a more indirect pathway for RCT which is dependent upon CETP and the LDL and LDL-RRP receptors. ABCA=ATP-binding membrane cassette transporter A1; Apo A-I=apoprotein A-I; ApoE=apoprotein E; CE=cholesteryl ester; CETP=cholesterol ester transfer protein; HL=hepatic lipase; IDL=intermediate-density lipoprotein; LCAT=lecithin:cholesterol acyltransferase; LDL=low-density lipoprotein; LDL-R=low-density lipoprotein receptor; LDL-RRP=low-density lipoprotein receptor-related protein; lysoPC=lysophosphatidylcholine; PC=phosphatidylcholine; PGN=proteoglycans; PL=phospholipid; PLTP=phospholipid transfer protein; SR-BI=scavenger receptor BI; Trigly=triglyceride; UC=unesterified cholesterol; VLDL=very low-density lipoprotein. *(Reprinted from Toth, PP. High-density lipoprotein as a therapeutic target: clinical evidence and treatment strategies.* Am J Cardiol. *2005;96(suppl);50K-58K, with permission from Excerpta Medica, Inc.)*

the enterohepatic recirculation of bile acids, upregulating the LDL receptor, and stimulating the increased conversion of cholesterol to the bile acids, cholate and chenodeoxycholate, by upregulating the expression of 7 α-hydroxylase. Measured aortic plaque area also decreased 81%. What is somewhat unexpected from colesevelam treatment is the finding that a number of genes involved in RCT, including apoprotein AI (apoAI), lecithin:cholesterol acyltransferase (LCAT), cholesterol ester transfer protein (CETP), and scavenger receptor BI (SRBI) are upregulated in coordinated fashion secondary to the activation of the liver X receptor, a ligand activated nuclear transcription factor. In order to promote RCT, activation of all of these gene products would be

important. ApoAI induces the externalization of intracellular cholesterol from macrophages; LCAT esterifies externalized cholesterol, which is then partitioned into the hydrophobic core of the HDL particle; CETP catalyzes the equimolar exchange of cholesterol ester for triglyceride in VLDL and LDL in a process referred to as "indirect reverse cholesterol transport'; and SRBI mediates the selective uptake of cholesterol esters from HDL and allows the delipidated HDL to dislodge, reenter the circulation, and reinitiate another cycle of RCT.

Two findings are of considerable interest. The first is that fecal cholesterol elimination increased two-fold in response to colesevelam therapy. This is consistent with increased throughput within the RCT system. Second, net cholesterol elimination doubled and atheromatous plaque burden was greatly reduced despite a lower circulating level of HDL. The latter finding is consistent with a growing body of data which suggests it is not the absolute elevation in HDL that a drug induces which determines risk reduction, but rather its net effect on rates of RCT

This paper sheds important new light on the potential of colesevelam therapy. Many new drugs are in development in an effort to promote RCT. Specific LXR agonists, synthetic HDLs, HDL function boosting agents (D4F), CETP inhibitors, and novel PPAR agonists are in clinical trials. This study suggests that it would be worthwhile to reevaluate colesevelam, an established drug with proven safety, in human trials and test its efficacy as a drug that potentiates RCT. When used in combination with a statin it may emerge as a valuable adjunctive therapy that extends well beyond its characterized capacity to simply reduce LDL. The current dosing regimen for this drug may have to be reevaluated as well.

REFERENCES

1. Toth PP. High-density lipoprotein and cardiovascular risk. *Circulation*. 2004;109: 1809–1812.
2. Toth PP. Reverse cholesterol transport: high-density lipoprotein's magnificent mile. *Curr Atheroscler Rep.* 2003;5:386-393.
3. Toth PP. High-density lipoprotein: epidemiology, metabolism, and antiatherogenic effects. *Dis Mon*. 2001;47:369–416.