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Cholesterol Metabolism and Therapeutic Targets: Rationale for Targeting Multiple Metabolic Pathways

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Summary: The liver is the major regulator of the plasma low density lipoprotein cholesterol (LDL-C) concentration because it is not only the site of formation of very low density lipoproteins (VLDL), the precursors of most LDL in the circulation, but it is also the organ where the bulk of receptor-mediated clearance of LDL takes place. The liver also initially clears all the cholesterol that is absorbed from the small intestine. The absorption of excess cholesterol can potentially increase the amount of cholesterol stored in the liver. This, in turn, can result in increased VLDL secretion, and hence LDL formation, and also downregulation of hepatic LDL receptor activity. Such events will potentially increase plasma LDL-C levels. The converse situation occurs when cholesterol absorption is inhibited. Cholesterol enters the lumen of the small intestine principally from bile and diet. The major steps involved in the absorption process have been characterized. On average, about half of all cholesterol entering the intestine is absorbed, but the fractional absorption rate varies greatly among individuals. While the basis for this variability is not understood, it may partly explain why some patients respond poorly or not at all to statins and other classes of lipid-lowering drugs. There are few data relating to racial differences in cholesterol absorption. One study reported a significantly higher rate in African Americans compared with non-African Americans. Multiple lipid-lowering drugs that target pathways involving the absorption, synthesis, transport, storage, catabolism, and excretion of cholesterol are available. Ezetimibe selectively blocks cholesterol absorption and lowers plasma LDL-C levels by an average of 18%. When ezetimibe is coadministered with lower doses of statins, there is an additive reduction in LDL-C level, which equals the reduction achieved with maximal doses of statins alone. Dual inhibition of cholesterol synthesis and absorption is an effective new strategy for treating hypercholesterolemia.

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Role of the Liver in Regulation of Whole Body Cholesterol Balance and Plasma Low Density Lipoprotein Cholesterol Concentration

The adult human body contains approximately 140 g of sterol, essentially all of which is cholesterol.[1] Remarkably, this content normally remains constant throughout life, even though there is a daily net entry of around 1 to 1.5 g of cholesterol into the body from diet and from synthesis by the tissues.[2, 3] The input of cholesterol from these two sources is balanced by the excretion of cholesterol in various forms from the body. The liver plays a central role in articulating this balance process.[4] Thus, it is not only the organ that receives most of the sterol that is absorbed from the intestine, but it is also the site for the degradation and excretion of cholesterol through the bile.

The liver also plays a major role in regulating plasma low density lipoprotein cholesterol (LDL-C) concentrations.[5] This occurs because the liver is the principal site for the production of LDL, as well as the receptor-mediated clearance of LDL from the circulation. Cholesterol entering the liver through the uptake of chylomicron remnants and other lipoproteins is believed to mix with locally synthesized cholesterol in a common pool of sterol. Presumably, the cholesterol in this putative pool is used for different functions, including the formation of very low density lipoproteins, which are the precursors of most of the LDL in the circulation. Although nearly all organs utilize LDL-C, the bulk of the receptor-mediated clearance of LDL occurs in the liver. Thus, circulating LDL-C levels can be modulated over a broad range by changes in the rate of LDL production and/or clearance by the liver.

As depicted by the schema in Figure 1, the plasma LDL-C concentration can be altered by effecting changes in the amount of cholesterol that is synthesized or excreted by the body. Treatment with statins, which partially inhibit cholesterol synthesis by the body,[2] results in upregulation of LDL receptor

activity and reduction in LDL formation.[6] Similar responses can potentially occur when the rate of conversion of cholesterol to bile acids in the liver is driven by treatment with bile acid sequestrants, or by cholesterol absorption inhibitors, which diminish the delivery of chylomicron cholesterol to the liver.

Atherogenic Potential of Chylomicron Remnants

Chylomicrons are secreted from enterocytes into the intestinal lymph and enter the blood stream via the thoracic duct. In the peripheral circulation, much of the triglyceride in chylomicrons undergoes hydrolysis by lipoprotein lipase in the surface of capillary endothelial cells.[7] This results in the formation of cholesterol-rich remnant particles that normally are rapidly cleared from the circulation by the liver. The clearance of these particles can be delayed in patients with diabetes or disorders of lipid metabolism.[8] The question of the atherogenic potential of chylomicrons and their remnants, as well as of triglyceride-rich lipoproteins, has been reviewed and continues to be investigated.[9, 10] Studies with animal models show that chylomicron remnants can potentially penetrate the endothelial lining of blood vessels and thus contribute to plaque formation.[11] Hence, blocking cholesterol absorption might reduce the risk of atherosclerosis, not only by a lowering of plasma LDL-C concentrations, but also by decreasing the level of chylomicron remnant particles and triglyceride-rich lipoproteins in the circulation.

Intestinal Cholesterol Absorption and Its Regulation

This subject has been reviewed recently.[12] The absorption of cholesterol is essentially a triphasic process which, in the average human consuming a typical Western diet, is responsible for delivering hundreds of milligrams of cholesterol to the liver every day. The cholesterol that is absorbed comes primarily from the bile and to a lesser extent from the diet. The first, or intraluminal, phase of sterol absorption involves the digestion and hydrolysis of dietary lipids and the micellar solubilization of cholesterol and other noncholesterol sterols. In the second phase, the sterols are released from the micelles at the surface of the brush border membrane of the enterocytes and are then taken into cells by a mechanism largely involving a protein called Niemann-Pick C1 like1 (NPC1L1).[13] This newly discovered function of NPC1L1 represents a critical breakthrough in our efforts to understand fully, at a molecular level, every step in the sterol absorption process. In the third, or intracellular, phase of absorption, cholesterol that is taken into the enterocyte is largely re-esterified and incorporated into nascent chylomicrons, which are secreted into the lymph. In contrast, most of the phytosterols and other noncholesterol sterols, and potentially some of the cholesterol entering the enterocyte, are rapidly effluxed into the lumen by the action of the two half-transporters, adenosine triphosphate-binding cassette (ABC) G5 and G8 (ABCG5/8). Mutations in either of these two proteins result in sitosterolemia.[14, 15] Although it is well documented that the amount of cholesterol reaching the circulation from the lumen of the small bowel can be modulated by targeting events within either the intraluminal or intracellular phases of the absorption process, the newly discovered role of NPC1L1 in facilitating the uptake of sterols provides another target for regulating the enterohepatic movement of cholesterol.

Interpatient Variability in Cholesterol Absorption

Cholesterol absorption is most frequently measured as a fractional or percentage value, which is taken to represent the

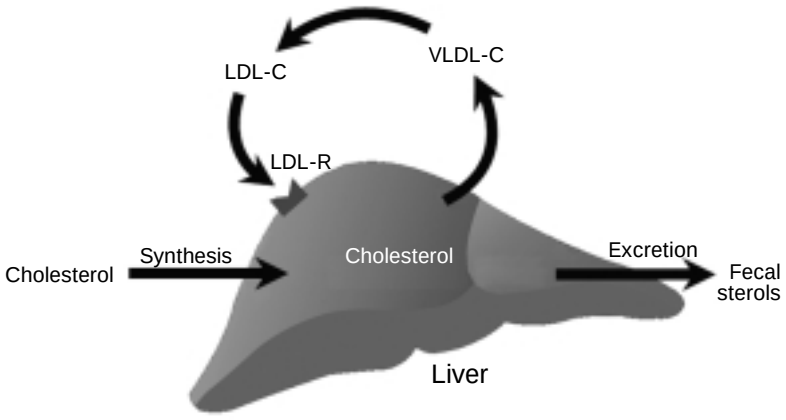

FIG. 1 The liver is a major regulator of plasma LDL-cholesterol (LDL-C) concentrations because it is not only the site of formation of very low density lipoproteins (VLDL), the precursors of most LDL in the circulation, but it is also the organ where the bulk of receptor-mediated clearance of LDL occurs. Treatment with statins (inhibitors of cholesterol synthesis) or with agents that promote cholesterol loss from the liver and ultimately the body (either by increasing the conversion of cholesterol to bile acids or by inhibiting the absorption and delivery of cholesterol from the small intestine) reduces the cholesterol content of liver cells. This can, in turn, lead to an upregulation of LDL-receptor (LDL-R) activity and/or a reduction in the rate of hepatic VLDL secretion, and thus LDL formation.

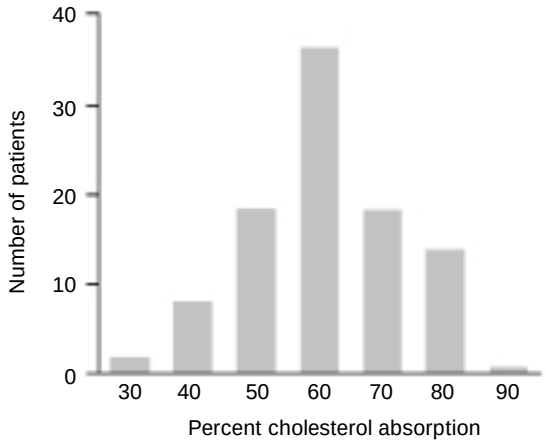

FIG. 2 Cholesterol absorption levels vary widely among individuals. The fraction of all cholesterol entering the intestine from the bile and diet that ultimately gets absorbed and delivered to the liver varies greatly from one individual to another. This has been documented in numerous studies. Data presented here are from Ref. No. 25 (copyright 1999 by American Society for Biochemistry and Molecular Biology) and reproduced with permission.

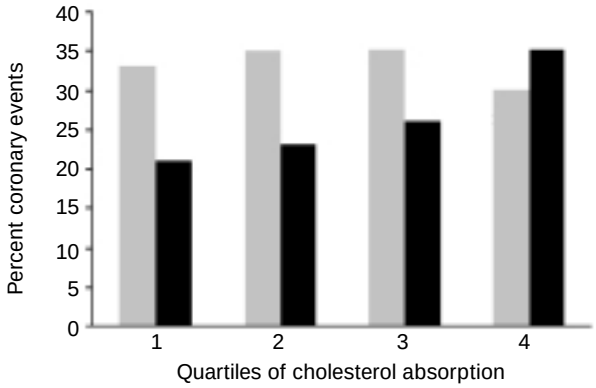

FIG. 3 The level of cholesterol absorption may be a factor in determining how well patients respond to various classes of lipid-lowering drugs, including statins. Data from the Finnish cohort of the Scandinavian Simvastatin Survival Study (Ref. No. 31) suggest that the efficacy of simvastatin in reducing coronary events was lower in patients who absorbed cholesterol more efficiently, based on the serum levels of certain sterols that are established markers for intestinal sterol absorption levels. □ Placebo (n = 434), ■ simvastatin 20–40 mg (n = 434).

proportion or fraction of all cholesterol entering the intestinal lumen that is subsequently absorbed across the intestinal wall and delivered into the circulation via the lymphatic system. Over about the past four decades, fractional cholesterol absorption values have been measured in many different types of patient groups as well as in healthy subjects.[3, 16–27] Although the methodology used to make such measurements has not been standardized, most studies have found marked individual variation in fractional absorption values. Perhaps the study that best illustrates this point is one reported by Bosner *et al.*[25] In this study, fractional cholesterol absorption was measured in 94 subjects (79 Caucasians, 12 African Americans, 3 Asians) who consumed a generally low-cholesterol diet; the absorption data are reproduced in Figure 2. Although the average fractional absorption rate for all subjects was 56%, rates ranged from 29 to 80%. Similar ranges have been reported by other investigators.[3, 24] These types of data clearly show that, while in a normal human population the average individual absorbs about half of all the cholesterol entering their small intestine, there are clearly subsets of individuals who hypoabsorb or hyperabsorb cholesterol. This phenomenon is not peculiar to humans. It has been documented in numerous other species, including various nonhuman primate models and mice.[28, 29] Although the basis for wide individual differences in sterol absorption is not well understood, genetic factors are apparently involved.[30]

It is important that the underlying cause(s) of the high individual variability in cholesterol absorption be determined, because it may explain why some patients respond poorly, or not at all, to statins and other lipid-lowering drugs. In individuals who hyperabsorb cholesterol, the efficacy of some hypolipidemic drugs might conceivably be diminished simply because of the continual delivery of excessive amounts of chylomicron cholesterol to the liver. Evidence for this thesis comes partly from an analysis of data from the Finnish cohort of the Scandinavian Simvastatin Survival Study,[31] some of which are presented in Figure 3. Miettinen *et al.*[31] found that the individuals who showed least benefit from simvastatin treatment in terms of coronary events were the most efficient absorbers of cholesterol, as determined by levels of specific sterols in the plasma that are markers for the level of cholesterol absorption.

Effect of Gender and Race on Cholesterol Absorption

As previously noted, cholesterol absorption measurements have been performed in diverse population groups. However, little attention has been given to the question of whether fractional absorption values vary significantly as a function of either gender or race. The most definitive data on this point come from a study of Bosner *et al.*[25] Although these investigators found no difference in fractional cholesterol absorption between men and women, they did find that the 12 African-Americans in their study manifested a marginal but statistically significant higher level of absorption compared with all the other subjects. This difference, which is illustrated in Figure 4, suggests that further measurement of cholesterol absorption and related parameters of sterol metabolism are warranted in much larger numbers of African Americans versus non-African Americans.

Low Density Lipoprotein Cholesterol-Lowering Agents That Work Primarily in the Small Intestine

Several classes of lipid-lowering agents that act primarily at the level of the small intestine are available. The two dominant

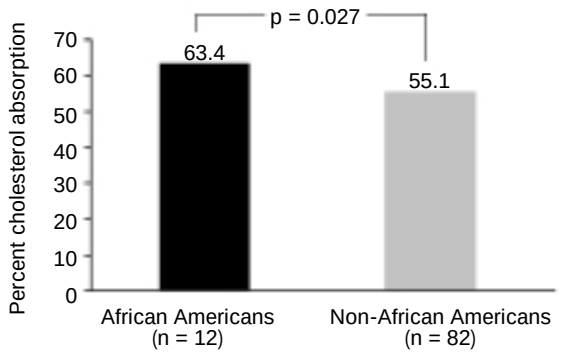

FIG. 4 There are few data relating to racial differences in cholesterol absorption. One study found a marginal, but statistically significant higher level of absorption in African Americans versus non-African Americans. Data from Ref. No. 25.

groups of drugs in this category are bile acid sequestrants and cholesterol absorption inhibitors. The sequestrants, which include cholestyramine, colestipol, and colesevalam, act by binding bile acids in the lumen, thereby preventing their reabsorption in the terminal small bowel through the ileal bile acid transporter (IBAT).[32–34] The diminished return of bile acids to the liver results in an accelerated conversion of cholesterol to bile acids, with a portion of this cholesterol coming from LDL. As an alternative to sequestrants, other drugs are being developed that directly inhibit IBAT activity.[34]

Cholesterol absorption inhibitors do not affect the reabsorption of bile acids, but rather disrupt one of the steps involved in the movement of cholesterol from the lumen to the lymph. Currently there are two types of therapies in use that inhibit cholesterol absorption. Plant sterols or their saturated derivatives, stanols, when taken in gram quantities, appear to disrupt the micellar solubulization of cholesterol within the lumen. This results in lower levels of cholesterol absorption and in an increase in fecal cholesterol loss. Plant sterols and stanols are usually added to various margarine products and are considered a useful adjunct to other lipid-lowering therapies.[35] Within the last 2 years, ezetimibe, a novel, specific, selective, and potent cholesterol absorption inhibitor, has become available. The mechanism of action and efficacy of this drug are described below.

Other agents such as orlistat, neomycin, and olestra, while not marketed as inhibitors of cholesterol absorption, nevertheless act primarily in the small intestine and do effect a reduction in plasma LDL-C concentrations. Orlistat, a lipase inhibitor, and olestra, a dietary fat substitute, both partially inhibit cholesterol absorption, presumably because both agents cause the formation of an intraluminal oil phase that may trap cholesterol, thereby preventing its movement into the enterocytes.[26, 36] The mechanism by which neomycin, an antibiotic, inhibits cholesterol absorption has not been clearly established but may be an effect of changes in the composition of the intestinal pool of bile acids caused by this drug.[37]

Ezetimibe, a Novel, Potent, and Specific Cholesterol Absorption Inhibitor

At a single daily dose of just 10 mg, ezetimibe inhibits cholesterol absorption by about 50% and lowers LDL-C concentrations by an average of 18% when used as monotherapy.[38] In addition, when used alone, it effects both a modest reduction in plasma triglyceride levels and a marginal increase in the high-density lipoprotein cholesterol concentrations.[38] The finding that ezetimibe lowers LDL-C levels in subjects with homozygous familial hypercholesterolemia indicates that the rate of production of LDL may fall in response to the reduction in cholesterol absorption.[39] The extent to which the LDL-C-lowering effect of ezetimibe may also reflect upregulation of hepatic LDL receptor activity has not been determined. Ezetimibe blocks the absorption of cholesterol and plant sterols, but does not affect the absorption of bile acids, fatty acids, fat soluble vitamins, or triglycerides.[40, 41] Newly published studies show that ezetimibe reduces cholesterol absorption by inhibiting a pathway in the brush border membrane of the enterocytes that is dependent on the activity of NPC1L1.[13]

Other Classes of Lipid-Lowering Agents

In addition to statins, bile acid sequestrants, and cholesterol absorption inhibitors, there are numerous other types of lipid-lowering agents that effectively change plasma lipoprotein composition, thereby either preventing or halting the progression of atherosclerosis. These agents, which include fibrates and various forms of niacin, target one or more pathways involving cholesterol and/or triglyceride metabolism. Several recent comprehensive reviews discuss the mechanisms of action and efficacy of these drugs.[6, 34, 42, 43] Other articles focus on using combinations of these drugs to treat patients with a constellation of disorders such as those seen in the metabolic syndrome.[44]

Rationale for Combining Cholesterol Absorption Inhibitors with Statins

Although the contribution of the liver to whole body cholesterol synthesis in normal human subjects is not known, studies with animal models suggest that it may vary inversely with the inherent level of cholesterol absorption in each individual.[28, 45] Higher levels of cholesterol absorption generally result in a suppression of cholesterol synthesis by the liver and an accumulation of cholesterol in the hepatocytes.[4] When a major pharmacologic block of cholesterol absorption is imposed, the diminished delivery of chylomicron cholesterol to the liver results in a partial compensatory upregulation of hepatic cholesterol synthesis. To the extent that this occurs, the LDL-C-lowering benefit of blocking cholesterol absorption may potentially be blunted. Thus, while cholesterol absorption inhibitors can be used effectively as monotherapy for treating hypercholesterolemia, a more effective outcome will

generally be achieved if the inhibitor is coadministered with a statin; this will dampen the compensatory increase in hepatic cholesterol synthesis that ensues when cholesterol absorption is blocked.

Efficacy of Combination Therapy Using Ezetimibe with a Statin

There is now a large volume of published data describing the additional cholesterol lowering that is achieved when ezetimibe is either coadministered with a statin or given to patients receiving ongoing statin therapy.[40, 46, 47] Together, these data clearly demonstrate that the dual inhibition of both cholesterol synthesis and absorption is an attractive new strategy for the treatment of primary hypercholesterolemia.

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