TREATMENT OF HYPERCHOLESTEROLEMIA AND OTHER LIPID DISORDERS WITH STATIN DRUGS HAS MADE A MAJOR CONTRIBUTION TOWARD REDUCING CARDIOVASCULAR MORBIDITY AND MORTALITY IN THE UNITED STATES.1 HOWEVER, HEART DISEASE REMAINS THE MAJOR CAUSE OF DEATH IN THE UNITED STATES, EMphasizing THE NEED FOR ADDITIONAL PROGRESS IN THE MANAGEMENT OF LIPIDS. A LOWER LOW-DENSITY LIPOPROTEIN (LDL) TARGETS OFFER 1 POTENTIAL MEANS TO ACHIEVE MORE PROGRESS IN THE BATTLE AGAINST HEART DISEASE. ALTHOUGH STATINS ARE THE MOST POTENT AGENTS CURRENTLY AVAILABLE FOR LOWERING OF LDL, STATINS ALONE ARE UNLIKELY TO ACHIEVE MORE STRINGENT LDL TARGETS VERY OFTEN. CLEARLY, A NEED EXISTS FOR A NEW CLASS OF DRUGS, PRESUMABLY WORKING THROUGH A DIFFERENT MECHANISM, THAT COULD AUGMENT THE EFFECTS OF STATINS AND ACHIEVE SIGNIFICANTLY LOWER PLASMA LEVELS OF CHOLESTEROL THAN CAN CURRENTLY BE ACHIEVED WITH STATINS ALONE. CHOLESTEROL ABSORPTION INHIBITORS OFFER THE POTENTIAL FOR MORE DRAMATIC REDUCTIONS IN CHOLESTEROL LEVELS WHEN COMBINED WITH STATINS, AND EZETIMIBE, THE FIRST AGENT IN THIS NEW CLASS OF LIPID-LOWERING DRUGS, RECENTLY BECAME AVAILABLE.

OVERVIEW OF CHOLESTEROL TRANSPORT

Recognition of the potential of combination lipid-lowering therapy begins with an understanding of the mechanisms of cholesterol transport. The liver is the key in controlling the concentration of cholesterol in the plasma. This organ is responsible for taking up cholesterol that is absorbed from the intestinal tract or is synthesized in the extrahepatic tissues and for the excretion of sterol into the bile either as cholesterol itself or as bile acid.
Peripheral tissues constitute 95% of the body's total weight and are continuously synthesizing cholesterol. Every cell membrane requires the continuous input of sterol to maintain microdomains involved in many cellular transport and signaling processes. Cholesterol does not accumulate in the cells, however, and has to be removed from the membrane at a rate that equals the amount of cholesterol synthesized, a delicate balance maintained by the removal of sterol from the membrane by high-density lipoprotein. Ultimately, all of this cholesterol is carried to the liver.

In the intestine, small amounts of dietary cholesterol mix with larger quantities of endogenously synthesized cholesterol, and this sterol is only partially absorbed. The remainder is excreted into the feces as neutral sterols.

The liver has mechanisms designed to manage cholesterol influx and prevent the accumulation of cholesterol anywhere in the body, including itself. When cholesterol output and input are equal, no expansion of cholesterol pools occurs in the liver or elsewhere in the body. A portion of the pool of cholesterol in the liver is converted into bile acids, and both cholesterol itself and these bile acids are secreted into the bile. This process of sterol excretion is regulated by the ABC transporters ABC-B4, ABC-B11, and ABC-G5/8. This process results in the net excretion of cholesterol, phospholipids, and bile acids into the intestinal lumen and is the major pathway for the excretion of cholesterol from the body (Figure).

Within the context of typical Western dietary habits of excess caloric and fat intake, the hepatic cholesterol pool expands and 4 regulatory mechanisms are stimulated.

1) Expansion of the pool of unesterified cholesterol in the liver suppresses hepatic sterol synthesis. This mechanism has minimal effect because baseline synthesis is normally low.
2) As the pool of unesterified sterol expands, the esterifying enzyme acyl CoA:cholesterol acyltransferase (ACAT) rapidly generates cholesteryl esters in proportion to the excess amount of cholesterol that is present in the endoplasmic reticulum. Expansion of this cholesteryl ester pool is a primary determinant of the rate of LDL cholesterol production.
3) Mediators of LDL receptor synthesis are also partially suppressed. The net effect is expansion of the plasma cholesterol pool coupled with a reduced capacity to remove lipoprotein cholesterol from the blood.
4) Finally, expansion of the unesterified cholesterol pool in the nucleus of the liver cell increases the level of the ABC transporter G5/8 and enhances secretion of cholesterol into the bile. The B11 bile acid transporter and the B4 phospholipid transporter do not change. The net effect is an increase in the level of cholesterol in the bile and an increase in the predisposition for the development of cholesterol gallstones.

**STRATEGIES TO MAINTAIN THE CHOLESTEROL BALANCE**

Most Americans consume relatively little cholesterol. If a person's daily intake is 300 to 400 mg, dietary restriction is unlikely to have a major impact on plasma cholesterol levels. On the other hand, endogenous synthesis generates 1000 to 1200 mg daily, and interfering with reabsorption of this amount of cholesterol in the gut could represent a highly effective means to maintain cholesterol balance.

![Figure. Overview of Cholesterol Transport and Metabolism](image-url)
Reducing the net sterol balance across the liver is a well-recognized and effective way to lower LDL cholesterol levels. This is the mechanism by which statins achieve LDL cholesterol reductions. In the liver, statins marginally reduce the cellular content of cholesterol and suppress cholesterol synthesis. The liver interprets this effect as a shortage of cholesterol and so reduces the rate of LDL cholesterol production while increasing LDL receptor activity. These changes commonly lead to a 30% to 40% reduction in the plasma cholesterol concentration.

Though statins are the most potent drugs available for reducing LDL levels, their capacity to lower the LDL cholesterol level is limited by cellular responses to the partial inhibition of the rate-limiting protein in cholesterol biosynthesis, HMG-CoA reductase. In the presence of a statin, cells increase the synthesis of this enzyme in an attempt to normalize cholesterol synthesis. As a result, increasingly higher doses of a statin have less effect on LDL levels. Doubling the dose of a statin, for example, will lower the plasma LDL cholesterol level by an additional 6% or so over what was achieved with the prior dose.

Another common means of reducing cholesterol levels involves removal of cholesterol from the liver by interfering with enterohepatic absorption of either bile acid or cholesterol itself. Using cholestyramine, for example, to partially block the absorption of sterol from the intestine causes the liver to sense an imbalance resulting from lower tissue cholesterol levels. This is associated with an increase in LDL receptor activity and a small decrease in the circulating plasma LDL cholesterol level. However, the liver also increases its rate of cholesterol synthesis so that the net reduction in plasma cholesterol concentrations is modest in comparison with the effect of a statin. In some animal models, the liver’s adaptive mechanisms work so well that no net change in LDL cholesterol occurs, again emphasizing the limitations of currently available therapy.

Given the limitations of therapy described above, a logical approach to LDL cholesterol reduction would be to combine a drug that effectively removes sterol from the liver with a statin that partially suppresses the adaptive response that leads to increased cholesterol synthesis. Such a combination should result in a much greater increase in LDL receptor activity, a greater reduction in LDL cholesterol production, and a significantly greater reduction circulating plasma LDL cholesterol concentrations.

**Blocking Intestinal Cholesterol Uptake**

Until recently, the mechanisms involved in the regulation of cholesterol absorption were poorly understood. What is now clear is that cholesterol absorption is an inefficient process. Most humans can absorb 100 or 200 g of triacylglycerol with no difficulty. By comparison, most humans can absorb only a few hundred milligrams of cholesterol. Moreover, enormous variation exists from one individual to another with respect to the capacity to absorb cholesterol.

A second key issue relates to the specificity of the uptake process. The body lacks the ability to degrade plant sterols, such that influx of large quantities would pose a major health problem. However, the specificity of the absorptive process is such that 40% to 50% of a cholesterol load might be absorbed, as compared with no more than 5% to 10% of a load of plant sterols, for example.

A major factor in the specificity of cholesterol absorption is the recently described ABC-G5/8 complex, which operates in the liver to facilitate the secretion of free cholesterol. In the intestinal brush border, this complex sorts out the different sterols that are mixed together in the gut and partially excretes them back into the lumen. As a result of this process, net absorption of cholesterol is reduced by about 50%, but the net uptake of plant sterols is reduced by nearly 90%. Clearly, this is a protective mechanism that saves humans from the potentially deleterious effects that might follow the absorption of excessive amounts of both animal (cholesterol) and plant sterols.

Cholesterol is processed within the intestinal epithelial cell, which packages the sterol into a chylomicron that eventually is delivered to the liver. This entire process affords opportunities to interfere with cholesterol absorption at any of the multiple involved steps, and over the last 30 years or so, a variety of strategies have been evaluated. These include dietary cholesterol restrictions; administration of large quantities of plant stanols to interfere with the assembly of mixed micelles, which contain fatty acids, beta monoglycerides, bile acids, and small amounts of plant and animal sterols; and intake of
large amounts of soluble fiber to block diffusion of micelles to the intestinal brush border. All of these strategies achieve modest reductions in cholesterol absorption and plant cholesterol levels.

A more specific approach would be to attack cholesterol absorption within the intestinal epithelial cell. Cholesterol enters these cells through the brush border by means of an as-yet unidentified permease. Once inside cells, the cholesterol and plant sterols are sorted. Approximately half of the cholesterol and virtually all of the plant sterols are expelled back into the lumen. Unesterified cholesterol and fatty acids that have been absorbed are then esterified to cholesteryl esters and triglyceride, respectively. This cholesteryl ester and triacylglycerol, along with apolipoprotein B, is then assembled into a chylomicron, a process influenced by microsomal triglyceride transfer protein.

Logically, this absorptive process could be attacked with pharmacologic agents that intervene at different steps in the assembly process. Microsomal triglyceride transfer protein inhibitors, for example, have been developed, and they clearly block cholesterol absorption. Unfortunately, they also block absorption of triacylglycerol. Inhibition of ACAT prevents formation of cholesteryl esters and triglyceride, respectively. This cholesteryl ester and triacylglycerol, along with apolipoprotein B, is then assembled into a chylomicron, a process influenced by microsomal triglyceride transfer protein.

A New Cholesterol Absorption Inhibitor

While evaluating potential ACAT inhibitors, investigators came across a new molecule that appears to interact with a permease in the brush border to block uptake of cholesterol and plant sterols. The molecule, now known as the drug ezetimibe, turned out to be highly effective at blocking sterol absorption.

In animals, ezetimibe is active in microgram quantities and will inhibit cholesterol uptake by as much as 95%. In humans, doses as low as 10 mg lead to significant inhibition of cholesterol absorption throughout the day. This agent represents an entirely new class of drugs that lowers plasma cholesterol through mechanisms that are quite different from those of statins or other cholesterol-lowering drugs.

If ezetimibe blocks cholesterol uptake in the intestine and reduces the flow of cholesterol to the liver, the liver should produce less cholesteryl ester and incorporate less cholesterol into each LDL particle. This appears to be the case as the drug has shown to lower LDL levels even in individuals who lack LDL receptors. Because ezetimibe blocks uptake of both plant and animal sterols, the drug should be effective for treating the disease sitosterolemia. This has also been shown to be the case in human trials.

Most importantly, in normal individuals, inhibition of sterol influx to the liver should reduce LDL formation and simultaneously increase LDL receptor activity. This, in turn, should lead to significant reductions in circulating LDL cholesterol concentrations. Ezetimibe, in fact, does just that. Perhaps most importantly, the addition of ezetimibe to a statin holds great promise for achieving greater reductions in LDL cholesterol levels. Ezetimibe blocks the input of sterol into the liver and reduces the sterol burden. An HMG-CoA reductase inhibitor further reduces the inflow of sterol into the liver and partially inhibits sterol synthesis in this organ. Thus, acting together but by different mechanisms, ezetimibe and a statin significantly reduce cholesterol input into the liver, enhance LDL receptor activity, and reduce the LDL cholesterol concentration to a significantly greater degree than can be achieved with either drug alone.

Summary

Statin lipid-lowering drugs have made major contributions toward reducing the overall burden of cardiovascular disease. However, the drugs have notable limitations in their ability to reduce total cholesterol and LDL, as do other currently available therapies. Cholesterol metabolism is a complicated process that inhibits the development of new pharmacologic strategies. Nonetheless, the multistep process of cholesterol absorption affords multiple opportunities for intervention. Ezetimibe is the first of a new class of therapeutic agents that prevent cholesterol absorption and lowers plasma cholesterol.
levels by mechanisms that are totally different from conventional lipid-lowering drugs. Ezetimibe can achieve substantial, long-lasting lipid-lowering effects at low doses. Combining ezetimibe with a statin offers the potential to achieve a degree of LDL reduction that surpasses what can be attained with either drug alone.

REFERENCES

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