

Understanding Sterols

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What is a sterol? Simply an alcohol with steroid rings with one OH (hydroxy) group; the systematic names contain either the prefix hydroxy- or the suffix -ol, e.g., cholesterol, ergosterol. We eat many exogenous sterols from plants, (sitosterol, campesterol, stigmasterol, etc.) and animal (cholesterol) as well shellfish sources (desmosterol, fucosterol) and yeast sources. Plant sterols and stanols (the latter are saturated or reduced sterols) are similar in structure to cholesterol but have a methyl, an ethyl or other groups in their side chains. These differences minimize their absorption compared to cholesterol. If plant sterols and stanols are esterified (combined with fatty acids) they can be incorporated into margarines. Sterols, other than cholesterol are collectively referred to as noncholesterol sterols. Since sitosterol represents 80% of noncholesterol sterols in the diet it is the most well known of the noncholesterol sterols. Collectively these sterols are often called phytosterols, although some come from non-plant sources.

Terminology: Cholesterol and sitosterol are sterols and cholestanol and sitostanol are stanols. If cholesterol is esterified (with the addition of a fatty acid) via the cellular enzyme acyl-cholesterol acyltransferase (ACAT) or the lipoprotein enzyme lecithin-cholesterol acyltransferase (LCAT) it is called cholesteryl ester (CE). Cholesterol is synthesized in virtually every cell of the body from fatty acids derivatives. One of the intermediary sterols in the synthetic chain is lathosterol and its measurement can be used as a marker of cholesterol synthesis. Noncholesterol sterols or stanols such as campesterol or cholestanol can be measured as markers of sterol absorption.

When fats (triglycerides) enter the intestine (in our food) they are hydrolyzed (changed into mono or diglycerides and fatty acids) by salivary and intestinal lipases and amylases (enteric and pancreatic). Dietary sterols include cholesterol, CE and noncholesterol sterols. Only unesterified sterols can be absorbed. Intestinal esterolases convert some of the CE into cholesterol. The vast majority of the cholesterol in the jejunum is of biliary origin. All of the lipids collectively are organized and emulsified by lecithin (a phospholipid in biliary secretions) and then grouped by amphipathic bile salts into biliary micelles which are collections of cholesterol and non-cholesterol sterols and monoglycerides, phospholipids and fatty acids surrounded by bile acids. The micelles "ferry" the sterols and FA to the intestinal epithelium. Once there, FA are absorbed by passive diffusion or fatty acid transport proteins through the lipid cell membranes.

The sterols in the micelles are internalized into the enterocyte via the Niemann Pick C1 Like 1 (NPC1L1) protein which is a sterol permease (a protein involved with absorption of sterols). NPC1L1 protein works with other proteins to facilitate sterol absorption. It is found in the brush border of the intestinal epithelium. NPC1L1 has absolutely nothing to do with the absorption of fatty acids. Most humans absorb about 50% of the sterols in the gut, but some people are hyperabsorbers (60-80%) and some are hypoabsorbers. Ezetimibe (Zetia) blocks sterol absorption from micelles by interfering (binding to) with the NPC1L1 / AP2-clathrin complex in the intestinal epithelium. Ezetimibe typically reduces sterol absorption by about 50%. Because ezetimibe blocks the absorption of all sterols, it is approved not only to reduce cholesterol levels but also to reduce the very high noncholesterol sterol levels seen in patients with phytosterolemia (sitosterolemia). Since the vast majority of intestinal cholesterol is of biliary origin, ezetimibe in effect has only a minority effect on ingested cholesterol. NPC1L1 is also expressed at the hepatobiliary interface and thus facilitates re-entry of biliary cholesterol back into the liver.

Once at the intestinal epithelial brush border, the fatty acids do not gain entry into the intestinal cells via the NPC1L1 protein, they simply diffuse in or are pulled in by fatty acid transport proteins. Thus ezetimibe cannot block fatty acid absorption. Also note there are no TG in micelles, only fatty acids, monoglycerols, phospholipids and sterols. So again, there is no way ezetimibe interferes with hydrolysis of TG or absorption of FA and thus it is not likely for ezetimibe to cause fatty diarrhea or steatorrhea. Likewise, ezetimibe does not inhibit absorption of fat soluble vitamins. Orlistat inhibits intestinal lipases and the ingested TG cannot be hydrolyzed and thus cannot be absorbed (TG cannot enter micelles). The fatty acids are excreted in the stool and that often causes steatorrhea.

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Cholestyramine (Questran), a bile acid resin or colesevelam (WelChol) a bile acid polymer are termed bile acid sequestrants (BAS). By binding bile acids (the most common of which is glycolic acid), they block their ileal reabsorption. BAS have no major effect on fatty acids or cholesterol absorption. Therefore BAS mechanism of action has absolutely nothing in common with the MOA of ezetimibe and indeed can be considered additive, as each will ultimately cause an upregulation of hepatic LDL receptors. BAS (especially the older resins) can cause a loss of fat soluble vitamins and can also interfere with the absorption of many drugs, which is why most drugs have to be administered 2 hours before or 4 hours after a BAS. Interestingly for years BAS were used to treat patients with sitosterolemia with mild effect. The BAS really do not impair sterol absorption. But until ezetimibe came along, there was really nothing for these patients.

What happens when the sterols (cholesterol and noncholesterol) are absorbed at the intestinal epithelium? First of all, evolution has gone to great lengths to keep noncholesterol sterols out of the human body so almost immediately after absorption some of the cholesterol and virtually all of the noncholesterol sterols are pumped back into the gut via ATP binding cassette transporters, ABCG5/G8. Only about 50-55% of ingested cholesterol makes it into chylomicrons. These ATP binding cassette half-transporters G5 and G8, also called sterolin 1 and 2, are membrane ATP dependent transport units that facilitate transport of sterols out of cells, especially the enterocytes (into the gut lumen) and hepatocytes (into the bile). If one lacks these transporters (homozygote), all sterols are absorbed and none are pumped back out: this is a very rare homozygous condition leading to the disease sitosterolemia or phytosterolemia. It is associated with severe atherosclerosis, as noncholesterol sterols (which cannot be esterified) are more atherogenic than cholesterol. Heterozygotes eliminate some but not all of the undesirable sterols. Polymorphisms of these transporters also exist.

Of course any sterols that are not pumped back into the intestine become part of the contents of the intestinally produced chylomicron particle that transports lipids to the liver. Once cholesterol is absorbed it is esterified (long chain FA attached to it) via the enzyme ACAT and joins with intestinally reassembled TG and apoB to form the chylomicron. Esterified cholesterol is called cholesteryl ester (CE) and 70% of the cholesterol in the body is transported as an ester, not as free cholesterol. Any noncholesterol sterols that were not sent back to the intestine via ABCG5/G8 also become part of the chylomicron and thus gain "systemic" entry. Noncholesterol sterols are not esterified as humans do not have the enzymes necessary for that. Unesterified sterols, should they get into an arterial wall macrophage or foam cell are more atherogenic than cholesterol (an esterified sterol) as in their unesterified state, they are very prone to oxidative forces.

Very interestingly if noncholesterol sterols make it to the hepatocyte in chylomicrons, there are additional ABCG5/G8 transporters in hepatocytes near bile canaliculi. This is the body's second line of defense to pump out such sterols should they make it to the liver. Of course if one has less than perfect function (polymorphisms) of sterolin (G5/G8) some of the noncholesterol sterols will remain in the hepatocyte and become part of the contents of VLDL.

We are now beginning to understand that not everyone has perfect functioning G5/G8 transporters and noncholesterol sterols get into some people: especially those with family history of CHD and postmenopausal women. These sterols may contribute to their atherosclerosis. Such patients have slightly elevated sitosterol and campesterol levels (no where near what the homozygous patients have). Since we as clinicians have no way of knowing which of our patients may be over absorbing sterols (without measuring sitosterol levels), this is a major reason to combine ezetimibe with low dose statins: you can be comfortable knowing you have dramatically reduced all sterol absorption, enhanced the ability of a statin to upregulate hepatic LDL receptors and you have safety with the low dose statin.

We are also now recognizing that there is a relationship to hepatic sterols and the rate at which we intestinally absorb sterols. In some but not all studies, humans, (especially men) with the E4 allele, hyperabsorb cholesterol. Because the liver gets increased delivery of cholesterol it

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downregulates production of HMGCoA reductase and slows cholesterol synthesis (this can be assayed by finding low lathosterol levels). These people respond poorly to statins (which of course are less efficacious with decreased levels of HMGCoA reductase being present. These folks are now called statin hypo-responders: previously this phenomenon was termed statin tachyphylaxis. If one administers ezetimibe to them, cholesterol absorption is reduced and the liver upregulates HMGCoA and the statin works with renewed vigor. This is another reason why ezetimibe so effectively and synergistically makes statins more potent on improving lipoprotein abnormalities.

One also has to be watchful when prescribing statins: as demonstrated in 4S trial with simvastatin (Zocor): when cholesterol synthesis is blocked or reduced by a statin, the intestine begins to hyperabsorb cholesterol and noncholesterol sterols, presumably through NPC1L1 protein upregulation. Increased cholesterol (and noncholesterol sterols if sterolin function is not perfect) goes to the liver in chylomicrons and the liver then slows (downregulates) production of HMGCoA reductase and the statin necessarily becomes less efficacious. Using ezetimibe with statins would eliminate this. In the 4S trial simvastatin had no effect on CV endpoints when administered to hyperabsorbers of cholesterol.