

## Apolipoprotein B 100 and 48 Thomas Dayspring MD, FACP

Apolipoprotein B is the main structural surface protein found on all beta-lipoproteins (Chylomicrons, VLDLs, IDLs and LDLs). There is a single molecule of apoB on each of those lipoproteins. It is the only apolipoprotein that is not transferable- i.e. it is with the particle from its birth till its death. Beta-lipoproteins are the lipoproteins capable of trafficking cholesterol into the artery wall and hence if present in increased numbers, they are the cause of atherosclerosis. That is why an apoB level is so predictive of atherosclerosis.

However there are two types of apolipoprotein B. One is produced in the liver and is called apolipoprotein B 100 and the other is produced in the proximal small intestine, which is termed apolipoprotein B 48, because it is a truncated version of apoB which has 48% of the molecular weight of apoB 100. Since the lipoprotein produced in the intestine is the chylomicron, the apoB 48 particles are chylomicrons of intestinal origin. VLDLs containing apoB100 are produced in the liver. After VLDLs are excreted and undergo lipolysis (hydrolysis or removal of TG and phospholipids) they become IDLs and LDLs. Thus there is a single molecule of apoB 100 on each VLDL, IDL and LDL and a single molecule of apoB48 on each chylomicron. Since chylomicrons carry mostly TG, it is intestinal TG levels, not cholesterol levels that drive apoB48 production in the enterocytes.

This has consequences because LDL receptors remove beta-lipoproteins from plasma by recognizing and attaching to the surface charges on certain segments of the apoB 100 molecule. ApoB48 is a truncated apoB and hence has a different conformation (lacks the segment recognized by LDL receptors) present on apoB100 and is therefore apoB48 is not recognized by LDL receptors. Fortunately chylomicrons have a high content of apolipoprotein E and LDL receptors also recognize and internalize apoE-containing lipoproteins. Thus the liver LDL-receptors internalize chylomicrons by attaching to apoE and they internalize VLDLs by attaching to apoB100 or apoE and they internalize LDLs by attaching to apoB100. Any drug that upregulates LDL receptors (statins, ezetimibe) will enhance removal of apoB100 or apoE-containing particles. Thus whether one uses a statin, ezetimibe or a combination, both apoB48 and apoB100 will go down. Of course statins upregulate way more LDL receptors (LDLr) than ezetimibe monotherapy: statin + ezetimibe maximizes LDLr upregulation.

Since 90-95% of the apoB particles that exist in plasma are LDLs, apoB48 is not a meaningful player in most patients as far as atherosclerotic risk related to apoB particle number is concerned (there are trivial numbers of chylos compared to LDLs). Although, chylomicron particle numbers are very low, in patients who cannot metabolize chylomicrons because they lack lipoprotein lipase or apoC-II (required to attached to lipoprotein lipase) or have excess apoC-III, their chylomicrons accumulate as they stay in plasma for long periods (increased plasma residence time) and get very large. Such patients all have significant elevations of fasting and postprandial TG (usually > 1000) and are at risk for pancreatitis. Since the vast majority of atherogenic particles have apoB100, measuring apoB48 provides little if any information that would predict risk or guide treatment it would be useless to measure it even if the test was available.

Having too many TG-rich lipoproteins can be associated with increased cholesteryl ester transfer protein (CETP) activity. This would cause the swapping of TG for cholesterol between the larger TG-rich particles and LDLs and HDLs ---- lading to TG-rich, cholesterol poor LDLs and HDLs and ultimately smaller HDL and LDL species.

Interestingly one might think that since ezetimibe reduces cholesterol absorption it might affect chylomicron (apoB48) synthesis. Keep in mind however that it is TG that drive apoB48 production, not cholesterol. However, here is what is known:

With respect to Ezetimibe on apoB levels (Effect of Ezetimibe on the In Vivo Kinetics of ApoB-48 and ApoB-100 in Men With Primary Hypercholesterolemia (Arterioscler Thromb Vasc Biol. 2006;26:1101-1106): "In conclusion, the present study indicates that the LDL-C lowering effect of ezetimibe is mainly caused by an increase in the catabolism of apoB-100-containing lipoproteins. Our study also shows that ezetimibe has no significant effect on TG-rich lipoprotein apoB-48

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kinetics although variability in apoB-48 measurements could have reduced the power to detect a true effect of ezetimibe. Finally, our results suggest that the ezetimibe-induced reduction in cholesterol delivery to the liver is associated with a compensatory increase in hepatic VLDL apoB-100 production, which may limit the lipid lowering effect of ezetimibe."