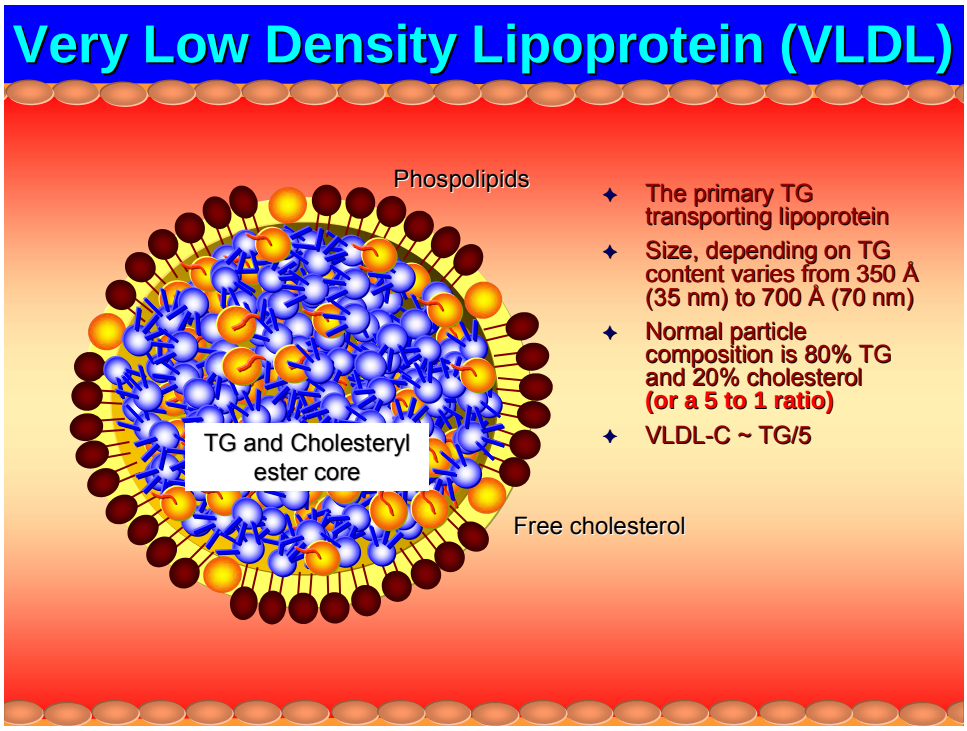
Triglyceride Transport
Thomas Dayspring MD, FACP

Triglyceride (TG) or more accurately triacylglycerol is simply a compound of three acyl groups (fatty acids) attached to a glycerol molecule. They are easily measured in the laboratory and reported as serum TG level: it actually refers to all of the TG that are being trafficked within all of the lipoproteins that exist in a deciliter of plasma. A physiologic fasting TG concentration is on average 30 mg/dL with one standard deviation ranging from 10 to 70 mg/dL. The two major lipoproteins that transport TG are chylomicrons and very low density lipoprotein (VLDL). Since chylomicrons are basically postprandial lipoproteins with very short half life's (and hour or so) most of the TG reported are in VLDLs (4-6 hour half life). The purpose of the triglyceride-rich lipoproteins (TGRLP), VLDL and chylomicrons are to transport energy in the form of fatty acids (FA) trafficked as triglycerides (TG), to the energy-requiring tissues (muscles) or the energy-storing tissues, the adipocytes. If the muscles do not require the fuel, the FA in the TG will then be delivered for storage in adipocytes. Normally the liver (hepatocytes) packages TG, cholesterol and phospholipids with a single, molecule of apolipoprotein B100 (apoB) and the enterocytes package the lipids with a truncated version of apoB; termed apolipoprotein B48 (has 48% of the molecular weight of hepatically produced apoB100). A normally composed VLDL particle has five times more TG than cholesterol (a 5:1 ratio) and since most TG are presumed to be in VLDLs; the VLDL-C is calculated as TG/5. If 150 mg/dL is a normal TG, then a normal VLDL-C is < 30 mg/dL. A high VLDL-C implies a high TG level. In conditions of elevated TG, many of the VLDL will be very large and TG-rich. If hepatic TG levels are not elevated the liver produces fewer as well as smaller VLDL particles (VLDL-C is reduced).



VLDL particles, as they exit the liver rapidly acquire several other apolipoproteins (some in the space of Disse and others transferred from circulating HDL particles). These include apoC-I, apoC-II, apoC-III, apoE, apoA-II, apoA-V and others. These apolipoproteins are integral to the proper trafficking of lipids and efficient catabolism of the VLDL and chylomicron. If any of the aforementioned apolipoproteins are absent or present in abnormal concentrations or defective, the VLDL particle will have altered catabolism. Typically when a VLDL (or chylomicron) enters vascular beds rich in the triglyceridase called lipoprotein lipase (LPL) and VLDL receptors, notably skeletal muscle, adipose tissue, and myocardium, rapid hydrolysis of the TG to

fatty acids occurs (this process is termed lipolysis). The free (unesterified) fatty acids (FFA or NEFA) enter the nearby cell with by simple diffusion or cell membrane fatty acid transport proteins or also attach to circulating albumin and are dispersed in plasma for delivery to other cells. It is VLDL surface apoC-II which is the ligand for LPL. The VLDL or chylomicron docks as follows: surface apoA-V attaches to endothelial proteoglycans in areas rich in LPL and VLDL receptors. The VLDL receptor docks the particle and apoC-II interacts with LPL initiating lipolysis. If one has absent or defective apoC-II, apoA-V or lacks LPL, effective lipolysis will not occur and such patients have variable degrees of hypertriglyceridemia (fasting and especially postprandial). Unlike LDL receptors, VLDL receptors do not endocytose VLDLs or chylomicrons but rather help dock the particle so LPL-mediated lipolysis can occur and then facilitate FA entry into the cell.

Excess ApoC-III has the ability to block the attachment of C-II to LPL thus modulating the rate of VLDL lipolysis. Too much apoC-III (often seen in insulin resistant patients) markedly delays the catabolism of TG-rich lipoproteins like VLDL and chylomicrons. It is also thought that too much apoC-III can displace apoE off of the VLDL or hinder CII/LPL interaction. This is associated with both fasting and especially postprandial hypertriglyceridemia. When you see a Type 2 diabetic or metabolic syndrome patients with TG > 150 mg/dL, you should suspect elevated apoCIII (an independent risk factor for CHD). The apoC-III/apoC-II ratio is an indicator of the rate of VLDL & chylomicron lipolysis: high ratios indicate delayed lipolysis.

ApoA5 or apoA-V is becoming better understood as a regulator of TG. It is thought that apoA-V on the VLDL surface locates or “parks” the lipoprotein by attaching to surface proteoglycans in the vicinity of LPL, where surface apoC-II can interact with the LPL. ApoC-III and apoA-V and likely other apolipoproteins are regulated by PPAR-alpha and hepatic nuclear factor 4-alpha (inhibits CIII and induces A-V) and may be amenable to pharmacologic modulation.

The several molecules of apoE on the TG-rich lipoprotein particle serves (as does apoB) as a ligand for the LDL receptor and the LDL receptor related protein and VLDL receptor. If there is abnormal or absent apoE on VLDL, this will also result in delayed LDL receptor (LDLr) or LDL Receptor Related protein (LRP) associated hepatic clearance of VLDL, VLDL remnants (defined below) and IDL (elevating apoB and TG levels). This is seen in the Type III Fredrickson Hyperlipidemia patients. ApoC-I can also interfere with apoE binding to VLDL and LDL receptors and thereby delay clearance of remnant VLDL particles. ApoC-I is also an inhibitor of cholesterol ester transfer protein (CETP) discussed below.

As the VLDL looses its TG core, it reduces in size, and looses surface phospholipids (which are picked up by phospholipid transfer factor), as well as surface apolipoproteins (which are picked up by HDL). The VLDL gets smaller and smaller (called a remnant) and ultimately becomes an apoB particle termed an intermediate density lipoprotein (IDL). The apoB is a nontransferable apolipoprotein (stays with the particle from birth to death), so the IDL particle still has the same single molecule of apoB with some of the remaining apoE. Most of the VLDL remnants and IDLs and their cholesterol content are rapidly cleared by liver LDL receptors which bind to the surface apoE/apoB: this process is termed indirect reverse cholesterol transport. A few are subjected to further lipolysis and become LDLs.

Depending on their TG content, VLDL particles can vary tremendously in size from 35-40 to several hundred nanometers (nm). Keep in mind that for an apoB particle to enter the wall of the artery it has to be less than 70 nm in diameter. On an NMR LipoProfile, the smaller and medium VLDL particles are identified as V1-V4. The very large VLDLs and chylomicrons (V5 and V6) cannot enter the arterial wall (too large) and are thus do not deliver sterols to plaque. That is why some people with very serious hypertriglyceridemia are not at risk for CHD. They simply have a few large particles carrying lots of TG (the apoB or LDL-P is normal).

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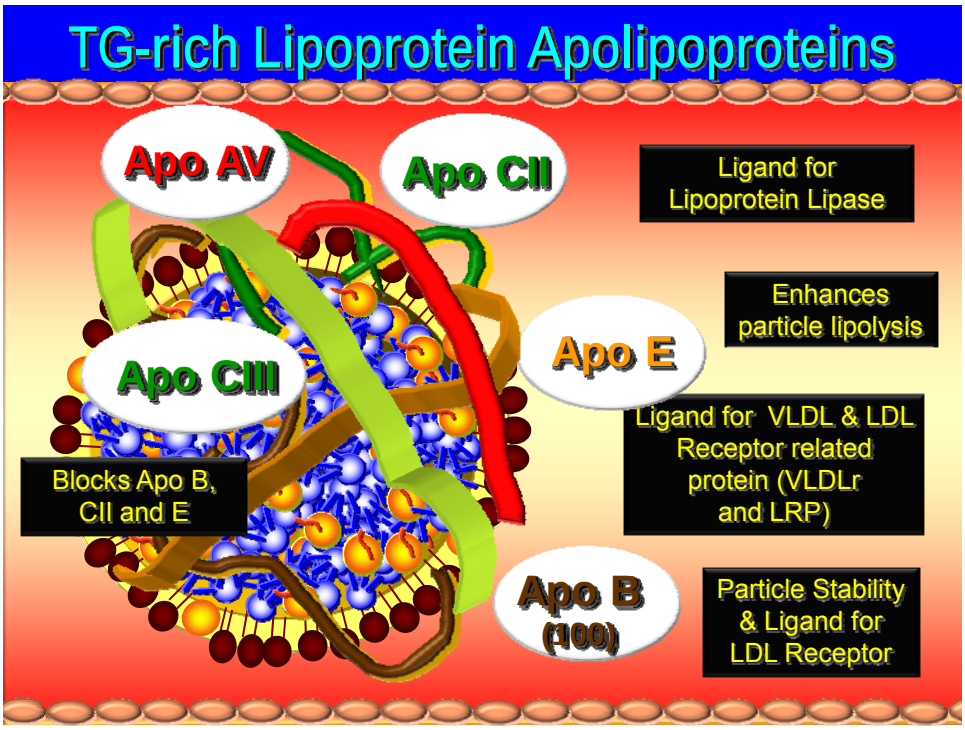
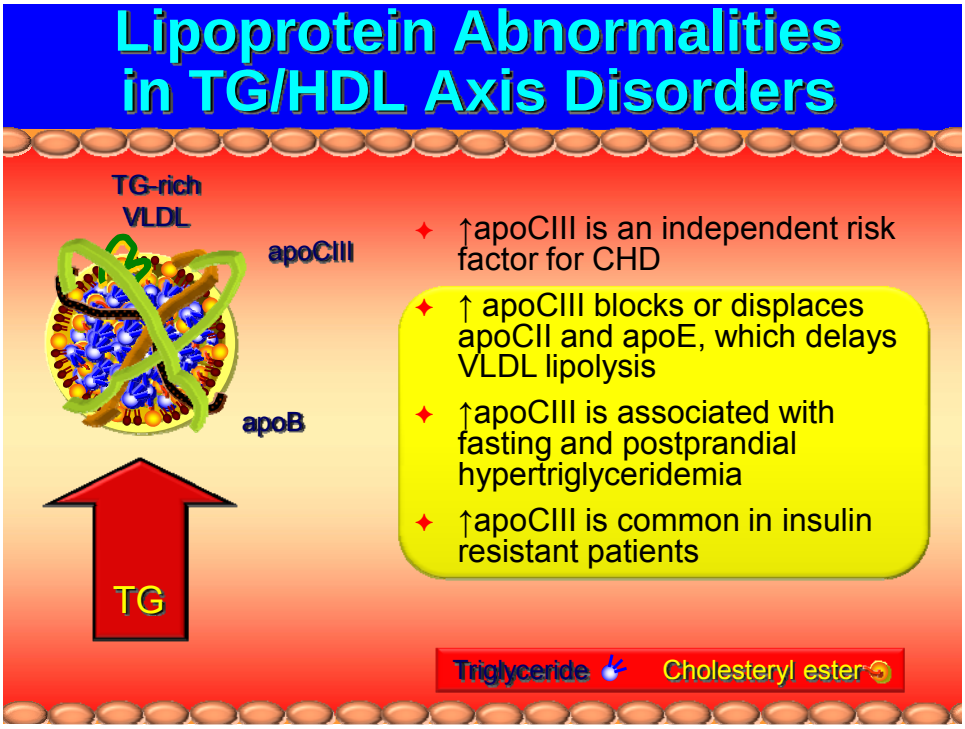


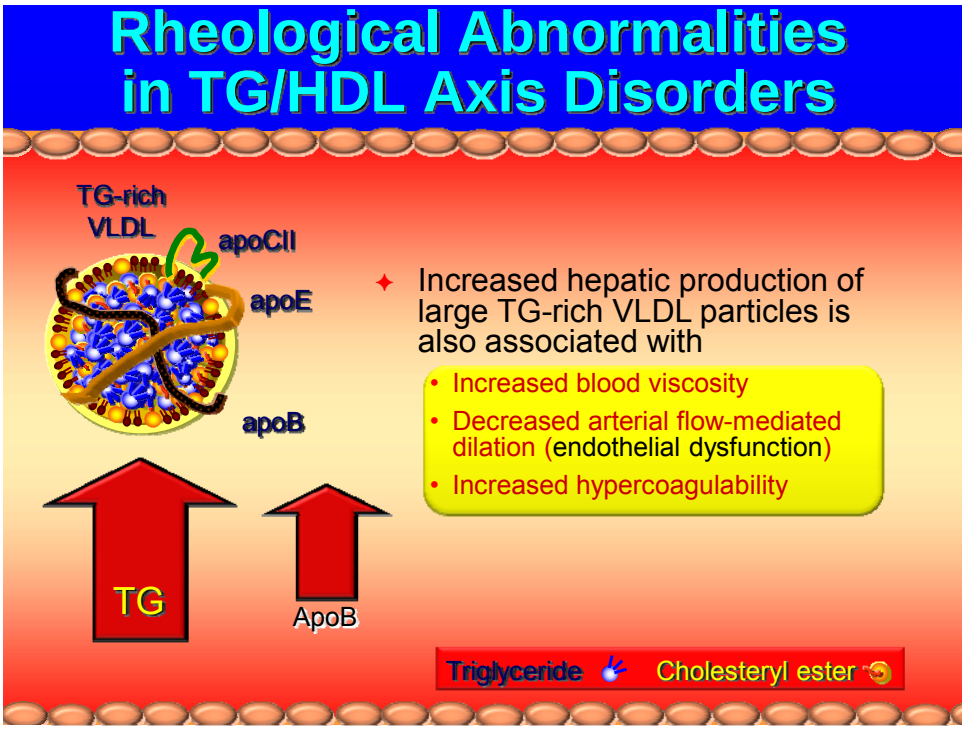


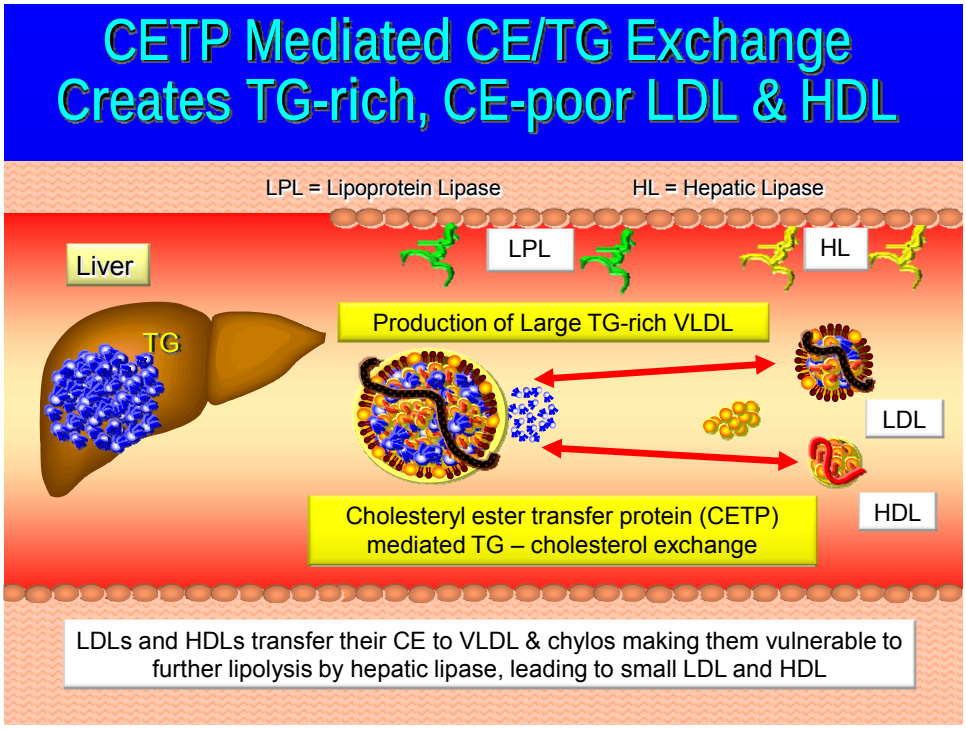
The IDL particle, which may still be trafficking residual TG is a substrate for hepatic lipase (HL) which has both triglyceridase and phospholipase activity. The IDL particle, as it looses TG (lipolysis) shrinks and becomes an LDL. The IDL particle because of its apoE and apoB content can also internalized by hepatic LDL receptors. The physiologic half life of a VLDL becoming an LDL is about 4-6 hours. The half life of an LDL is 2-3 days. LDL particles, if present in physiologic concentrations are ultimately removed by the liver LDL receptors in (indirect reverse cholesterol transport). If present in excess quantities, smaller VLDL, IDL or LDL particles enter the arterial wall resulting in atherogenesis.

If a patient has a physiologic TG of 30 mg/dL (10-70), they make only enough VLDL particles needed to transport the TGs for cellular energy. That is, they have physiologic levels of normally sized VLDL particles. After efficient lipolysis they would have physiologic amounts of LDL particles (an LDL-P well under 1000 nmol/L) and the LDL-C would be 20-40 mg/dL (considered a physiologic LDL-C).

It is not unusual to see low HDL-C levels in patients with high TG. VLDL particles that do not undergo rapid catabolism, linger in the plasma, elevating apoB levels and increasing CV risk. What also happens is the TG and cholesteryl ester (CE) are exchanged between HDL, LDL and VLDL, via CETP. The longer the half-life of VLDL, the more time they have to swap TG for CE from HDL using CETP. The HDL particles become TG-rich and cholesterol-poor, thereby reducing HDL-C levels. Hepatic lipase then hydrolyses the remaining TG and surface phospholipids creating very small, cholesterol deficient, small HDL particles (~7 nm in diameter) which are easily excreted by the glomerulus, lowering apoA-I or HDL-P concentrations. A similar CETP-mediated exchange of TG for cholesteryl ester occurs with LDL particles enhancing the formation of small LDL particles through a similar process. We now call such patients, TG/HDL axis disorders and of course this is most commonly seen in metabolic syndrome patients and Type 2 diabetics. In this scenario the VLDL, which has transferred its TG, becomes CE rich (increased VDL-C). As lipolysis proceeds the VLDLs loose further TG and become smaller. These CE-rich, TG poor VLDLs are called remnants and have been associated with increased CV risk. However, the vastly preponderant particle present in TG/HDL axis disorders is the LDL.

Much of the risk associated with elevated TG is related to its association with increased apoB. Too many VLDLs cause increased levels of IDLs and especially LDLs. ApoB and LDL-P starts to elevate with TG levels >100 mg /dL and by a value of 200 mg/dL 80% of patients will have a high apoB or LDL-P. However when there are increased amounts of large TG-rich VLDLs and/or chylomicrons, the excess fat increases blood viscosity, down regulates NO and causes endothelia dysfunction, increase coagulation markers (PAI-1 and fibrinogen) and induces (probably through increased apoC-III) multiple inflammatory markers.


Rheological Abnormalities in TG/HDL Axis Disorders
TG-rich VLDL
apoCII
apoE
apoB
TG
ApoB
Increased hepatic production of large TG-rich VLDL particles is also associated with
Increased blood viscosity
Decreased arterial flow-mediated dilation (endothelial dysfunction)
Increased hypercoagulability
Triglyceride
Cholesteryl ester


CETP Mediated CE/TG Exchange Creates TG-rich, CE-poor LDL & HDL
LPL = Lipoprotein Lipase
HL = Hepatic Lipase
Liver
LPL
HL
TG
Production of Large TG-rich VLDL
LDL
HDL
Cholesteryl ester transfer protein (CETP) mediated TG – cholesterol exchange
LDLs and HDLs transfer their CE to VLDL & chylos making them vulnerable to further lipolysis by hepatic lipase, leading to small LDL and HDL

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REVIEW OF APOLIPOPROTEINS:

ApoA-II: is transferred to VLDL from HDL. ApoA-II, though not well understood, can interfere with the apoCII/LPL interaction. This would also delay catabolism of TG-rich lipoproteins.

ApoA-IV: involved with intracellular synthesis and trafficking of TG

ApoA-V on the VLDL surface locates the lipoprotein by attaching to surface proteoglycans in the vicinity of LPL, where surface apoC-II can interact with LPL. Decreased apoA-V is associated with hypertriglyceridemia.

ApoB: is the main surface apoprotein of VLDL, IDL and LDL and provides structural stability and solubility of the lipoprotein in aqueous plasma. It also serves as the ligand for LDL receptors (LDLr). It is the only nontransferable apolipoprotein. It exists as hepatic produced (apoB100) and enterocyte produced (apoB48). Interestingly apoB48 cannot bind to the LDL receptor.

ApoE: is a ligand for LDLr, LDL receptor related protein (LRP) and VLDL receptor. It is also found on HDL particles and like apoA-I can serve as a cholesterol acceptor protein.

ApoC-I: displaces apoE or somehow interferes with apoE binding to apoE receptors. This delays catabolism of TG-rich particles. Also inhibits CETP, reducing TG for CR swapping between lipoproteins.

ApoC-II: the ligand for lipoprotein lipase (LPL), the main TG hydrolyzing enzyme in the plasma. Removal of TG from lipoproteins is called lipolysis. A lack of C-II will markedly delay VLDL catabolism. The preferential lipoproteins to which LPL binds are the chylomicrons (the largest TG-rich lipoproteins)

ApoC-III: prevents apoC-II from binding to LPL (delaying lipolysis). ApoC-III can also block or displace apoE. ApoC-III will delay catabolism of TG rich lipoproteins leading to elevated apoB levels. ApoC-III is an independent risk factor for CHD.

REFERENCES:

1] Szapary PO and Rader DJ. The triglyceride–high-density lipoprotein axis: An important target of therapy? *Am Heart J* 2004;148:211–21.

[2] Brewer, HB Jr, Hypertriglyceridemia: Changes in the Plasma Lipoproteins Associated with an Increased Risk of Cardiovascular Disease. *Am J Cardiol* 1999;83:3F–12F.

[3] Henry N. Ginsberg, et al. Review Article Regulation of Plasma Triglycerides in Insulin Resistance and Diabetes Archives of Medical Research 36 (2005) 232–240

[4] Davidson M et al. New Concepts in Dyslipidemia in the Metabolic Syndrome and Diabetes. Metabolic Syndrome and Related Disorders. Volume 4, Winter, 2006 299-314