Hypertriglyceridemia
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Understanding and Treating Triglyceride Disorders
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Triglycerides (TG), the so-called forgotten lipid, are so very important to both human life and unfortunately to atherogenesis. Of course the correct term is triacylglycerol. Three acyl groups (fatty acids) are attached to a glycerol molecule. Triglycerides are an archaic term, which we all keep using. Serum TG refers to all of the TG trafficked within all of the lipoproteins that exist in a deciliter of plasma. A physiologic TG level is 10-70 with a mean of 30 mg/dL. NCEP ATP-III stated that unless pathological conditions are present, the TG should be < 100 mg/dL. With respect to CV risk, they stated borderline risk is > 150 mg/dL, high risk > 200 mg/dL and very high risk > 500 mg/dL when pancreatitis enters the picture. There is no specific NCEP ATP-III TG goal of therapy but it is suggested that non-HDL-C be normalized in patients with high TG or high TG and low HDL-C. Persons with significant TG abnormalities can have a multitude of genetic perturbations and many but not all have coexisting insulin resistance. NCEP ATP-III states that anyone with a TG > 100 mg/dL likely overeats, does not exercise, smokes, has diabetes, renal or other metabolic diseases, is on certain drugs or if the TG is >200 mg/dL has genetic forces at play.

Genetic Triglyceride disorders are classified as:

Moderate Hypertriglyceridemia
    Familial combined hyperlipidemia (FCH – Fredrickson Type IIB, IV or V)
    Familial Dysbetalipoproteinemia (Fredrickson Type III)
    Familial Hypertriglyceridemia (FHTG): usually not associated with CV risk

Very High Hypertriglyceridemia
    Severe chylomicronemia (deficiency of apoCII) (Fredrickson Type I)
       Familial Lipoprotein Lipase Deficiency (Fredrickson Type V)

Persons with FCH often have coexisting elevations of cholesterol level due to high VLDL-C or chylomicron-C. FCH can meet the Fredrickson criteria for Types IIb, IV or V and familial hypertriglyceridemia can be classified as Type IV or V. In Types I and V chylomicrons are present. An easy way to establish that is to let a red top tube with serum stand overnight: if there a thick dense white band floating on top then chylomicrons are present. That is a quick way to distinguish Types I and V from IIb or IV. With VLDL induced hypertriglyceridemia the serum would be turbid or milky without the dense band on top. In Fredrickson Type III dyslipidemia, the elevated triglyceride is usually associated with higher levels of cholesterol. This disorder is due to increases in small VLDLs and IDL particles associated with the E2 phenotype (available from Berkeley Heart Lab). Of course it does not matter whether the person has Type III, IV or V dyslipidemia as the treatment is going to be the same. Other than severe fat restriction and use of dietary supplied medium chain triglycerides (contain fatty acids that can be absorbed directly into plasma without being incorporated into chylomicrons), there is no treatment for Type I. The pharmacologic approach of the other TG disorders is to reduce fatty acid absorption (orlistat), inhibit TG synthesis, enhance TG catabolism (fibrates, high dose N-3 fatty acids and high dose niacin) and to facilitate TG-rich lipoprotein removal through upregulation of LDL receptors (LDLr) (statins, especially high dose atorvastatin or rosuvastatin and ezetimibe). Patients with FHTG simply have very large TG-rich VLDL and/or chylomicron particles but do not have an excess number of such particles. Thus TG can be very high but apoB is not elevated. The particles are too big to enter the arterial wall: pancreatic risk is present but atherosclerosis is not a risk due to the normal apoB.

Triglyceride–rich lipoproteins:

The intestine synthesizes very large TG-rich chylomicrons that enter lymph and then plasma. On

Hypertriglyceridemia
Thomas Dayspring MD, FACP

their journey to the liver (lymphatic and vascular circulation) they acquire apoA-V, apoA-II, apoC-I, apoC-II, apoC-III apoE and other apolipoproteins (from HDL). VLDLs are hepatic synthesized TG-rich lipoproteins, and are basically smaller versions of chylomicrons. ApoA-V attached to proteoglycans in muscular and adipocyte vascular beds where LPL is expressed and apoE binds to VLDL receptors (similarly expressed in muscular and adipocyte capillaries). If there is not too much apoC-I and C-III on their surface, the apoC-II attaches to LPL and TG hydrolysis to fatty acids (lipolysis) occurs (due to many more copies of apoC-II and apoE, chylomicrons are the preferred substrate particle for LPL. The chylomicron or large TG-rich VLDL shrinks and is termed a remnant particle. Using their surface apoE, the remnant particle binds to the LDL receptor related protein (LRP) at the liver (LPL and heparan sulfate proteoglycans aid this binding). The liver takes the TG, hydrolyzes it to fatty acids which can be oxidized or is reassembled (with cholesteryl ester and apoB100) into a VLDL particle. Once secreted into plasma, the VLDL acquires variable amounts of the above apoproteins from HDL particles (one of HDL particle's functions is to transport apoproteins needed for lipolysis of TG-rich lipoproteins): apoA-II, apoA-V, apoC family and apoE (as well as others) apoproteins.

A word about the apolipoproteins that affect TG:

  apoA-II: can delay the catabolism of TG-rich lipoproteins, perhaps by camouflaging or displacing apolipoproteins that mediate lipolysis.

   apoC-I is an inhibitor of lipoprotein lipase, hepatic lipase, phospholipase A-II, CETP, and apoE-mediated uptake of TG-rich lipoproteins by LDLr and LRP. ApoC-I either masks or displaces apoE from the TG-rich lipoprotein surface and inhibits cholesteryl ester transfer proteins (CETP), thus delaying catabolism of the particle. ApoC-I is an independent risk factor for atherosclerosis in men. (Jour Amer Col Cardiol 2005;45:1013–7)

  apoC-II is the main ligand for LPL. It is the physiological activator of LPL which facilitates hydrolysis of TG (lipolysis) in to fatty acids. Total apoC-II absence is very rare and causes massive hypertriglyceridemia (Type I).

  apoC-III is an important regulator of TG levels. The ability of apoC-III to increase plasma TG concentration is believed to be due to its capacity to inhibit TG-rich lipoprotein (TRL) catabolism. Several different mechanisms have been proposed, including; (a) apoC-III inhibition of lipoprotein lipase and/or hepatic lipase (b) apoC-III interference with the interaction of TRL with LPL and/or (c) apoC-III inhibition of TRL binding to hepatic lipoprotein receptors

  apoA-V acts as a stimulatory modifier of apoC-II induced LPL-mediated TG hydrolysis. Its primary function is to attach to endothelial proteoglycans that exists in areas where lipoprotein lipase is expressed (muscle and adipose tissue vasculature). Deficiency of apoA-V is associated with hypertriglyceridemia

A word about the lipases that affect TG:

        1) Intestinal lipases (salivary, gastric, pancreatic): Hydrolyze ingested TG into fatty acids and monoacylglycerols which can incorporated into biliary micelles and then be absorbed.

        2) Lipoprotein Lipase: The main triglyceridase, expressed mostly in muscular and adipocyte vascular beds, but also in hepatic sinusoids.

        3) Hepatic Lipase: A lipase with both triglyceridase and phospholipase activity, used to convert small VLDLs and IDLs to LDLs and to promote lipolysis of large TG-rich HDLs.

        4) Endothelial lipase: mostly a phospholipase used in HDL lipolysis.

Hypertriglyceridemia
Thomas Dayspring MD, FACP

5) Hormone Sensitive Lipase: an adipocyte produced triglyceridase very effective in hydrolyzing TGs to fatty acids.

Plasma Residence Time:

1) Chylomicrons: Upon exposure to LPL they undergo rapid lipolysis on muscular and adipocyte vascular beds and then clearance by the liver: Lipolysis begins within minutes of entering plasma and half-life is 1 to 2 hours.

2) VLDLs: Half-life is typically 2-6 hours. Upon exposure to LPL, they also undergo fairly rapid lipolysis (not quite as rapid as chylomicra) during which they release large chunks of surface phospholipids: most are cleared by hepatic LDLr after the TG content is hydrolyzed: as VLDLs

3) IDLs: Half-life is 1-2 hours

Under conditions of delayed lipolysis, plasma residence time of TG-rich lipoproteins can be significantly extended causing both fasting and postprandial hypertriglyceridemia. TG-tolerance tests in normal humans shows maximal rise in TG at 4 hours with return to normal by 6 hours. A physiologic TG is 10-70 mg/dL with a mean of 30 mg/dL. Four hours after meals or a FA-load,

The TG increases to 70 mg/dL with a one standard deviation being up to170 mg/dL. Any postprandial TG higher than that is abnormal. The most common cause is insulin resistance. Any clinician seeing a TG > 170-200 mg/dL must realize the level is abnormal and repeating the TG fasting serves no purpose (other than to get an accurate calculated LDL-C). However if one uses non-HDL-C then there is no need to know LDL-C, as non-HDL-C is a better surrogate of atherogenic lipoproteins and is the NCEP goal of therapy in patients with TG between 200-500 mg/dL. .

Treatment Issues: The correct order of drug use (see NCEP) is: There are two equal options for the first line medication when TG are > 500 mg/dL

1) Fibrates and it should definitely be fenofibrate or fenofibric acid not gemfibrozil for safety reasons. Fibrates decrease fatty acid synthesis, increase beta-oxidation of fatty acids (providing less substrate for TG synthesis), inhibit diacylglycerol acyltransferase (DGAT2), the enzyme which catalyzes the addition of fatty acids (FA) to diacylglycerol, increase production of lipoprotein lipase (LPL) and apoA-V and decrease production of apoC-III. These benefits cause production of less number of VLDL, the VLDLs are less TG-rich and associated with less CETP activity. Fibrates lower both fasting and postprandial hypertriglyceridemia. Improving the latter has been associated with improved vascular reactivity and endothelial function. In essence fibrates decrease the production and enhance their catabolism of TG-rich apoB particles (VLDL, IDL, remnants).

1) Omega or N-3 fatty acids (eicosapentaenoic or EPA and docosahexanoic or DHA acids) 4 grams daily (available as FDA approved Lovaza). Note 4000 mg or higher must be used to reduce TG. Acting through a variety of nuclear transcription factors, EPA and DHA increase the oxidation of FA, decrease FA synthesis and also inhibit DGAT2. They also increase LPL activity. N-3's are available as food supplements as capsules and liquids under a wide variety of brand names but purity is never as assured as they are not regulated by the FDA.

2) Niacin, which should be prescribed as the FDa-regulated Niaspan (extended-release niacin) titrated up to 2000 mg nightly. Lower doses of niacin are less effective in reducing TG. Niacin, a B vitamin used in pharmacologic doses) has PPAR-gamma activity and inhibits fatty acid synthesis, and increases beta-oxidation of FA. Niacin also inhibits DGAT2 reducing TG synthesis. Thus niacin will reduce TG-rich apoB particle production and TG content within VLDL

(an often unrecognized benefit of niacin). CETP activity is diminished.

   4) Statins (highest dose) to upregulate LDL receptors: Although all are indicated, the only statins one should use with very high TG levels are Crestor (rosuvastatin) and Lipitor (atorvastatin). Although Crestor is a far superior lipid-improving statin than is Lipitor, they are both very similar on TG lowering. However, Crestor will more effectively lower apoB and raise apoA-I more than Lipitor. So I prefer Crestor. One could also add ezetimibe to a statin to further upregulate LDLr and clear more VLDLs, thereby additionally lowering TG. I believe a smarter approach in persons with elevated TG is to prescribe a drug that inhibits TG synthesis (fibrates, high dose niacin or high dose N-3 FA). The addition of Zetia (ezetimibe) to a statin has been shown to lessen remnant lipoproteins in insulin resistant patients.

Diet, exercise, fibrates, niacin and omega-3 FA all shift LDL particle size from small to large, by decreasing TG synthesis. Statins do not shift LDL particle size (per se), they simply upregulate receptors which clear apoB particles.

   Why do statins usually lower TG when levels are very high and have little impact when TG are under 200. Statins upregulate LDL receptors, which can remove TG-rich lipoproteins (and hence lower TG) by attaching to the apoE on such particles. Patients with very high TG, have delayed catabolism (long half life) of TG-rich lipoproteins. This long half life provides plenty of time for the LDL receptors to grab the apoE on the particles. VLDL particles in patients with lower TG levels have shorter half lives (that is why the TG level is not so high) and LDL receptor upregulation plays little role in their removal. Thus, statins do not impact much on TG levels in patients without very high TG. Statins through a PPAR alpha effect also induce LPL and can decrease apoC-III both of which would result in more efficient lipolysis (hydrolysis of TG). Pravachol has excellent data on C-III inhibition.

    5) Orlistat by reducing FA absorption can also when used with a low fat diet significantly reduce TG.

   6) After the above therapies If the TG are still very high, then androgens can be tried. Androgens induce lipases. However, the overall clinical CV benefit of this is totally unknown. It is only tried in people with massive hypertriglyceridemia (where all else fails) to reduce the incidence of pancreatitis.

   7) Emergency treatment of massive hypertriglyceridemia (causing pancreatitis or severely symptomatic eruptive xanthomas) includes insulin in diabetics or IV heparin.

Bile acid sequestrants, especially resins (Questran and Colestid) but not the polymers (WelChol) can elevate TG and are relatively contraindicated for use in patients with TG elevations. Because they decrease the return of bile salts to the liver, there will be downregulation of farnesoid X receptors needed to resynthesize 25-hydroxy sterols (bile salts) from 27-hydroxy sterols (cholesterol). Reduction of FXR action through an effect of the short heterodimer partner (or protein) and liver receptor homolog-1 activates liver X receptors (LXR), upregulates sterol regulatory binding element proteins involved with not only LDL receptor upregulation but also TG synthesis.

Before you start to treat elevated TG, you need a baseline TSH to r/o hypothyroidism, homocysteine, uric acid, creatinine, LFTs and CK levels (in anticipation of combination therapy). Urine protein (microalbumin) needs to be checked to rule out protein loosing nephropathy lipidemia (often associated with very high TG).

Treatment Goals:

The risk associated with elevated TG is due to many factors:

Hypertriglyceridemia
Thomas Dayspring MD, FACP

1) Elevated apoB. Too many TG-rich lipoproteins: remnants and small LDL
2) Decreased apoA-I or HDL-C due to excretion of TG induced small HDL particles. Reduced apoA-I or HDL-P is associated with impaired macrophage reverse cholesterol transport and decreased numbers of functional (antiatherogenic) HDL particles (HDL-P).
3) Increased endothelial dysfunction manifested as increased inflammatory markers and decreased flow mediated dilation of arteries.
4) Hypercoagulability due to increased fibrinogen and PAI-1 levels
5) Insulin resistance

In a person with very serious hypertriglyceridemia (>500 mg/dL), the initial goal of therapy is to get the TG under 500 mg/dL. Once that is achieved the goal of therapy is to first normalize the LDL-C and then the Non HDL-C level. Of course LDL-C and Non HDL-C are simply the NCEP surrogates for apoB. It is amazing how few physicians realize that the **NCEP goal of therapy is when one treats people with TG/HDL-C axis disorders is to normalize not only LDL-C but also Non HDL-C.** That being understood, I would not say mission accomplished just yet. Since non-HDL-C is only moderately concordant with apoB, I prefer to measure apoB or LDL-P to be sure risk has been eliminated.

When the intestine and liver overproduce VLDLs and chylomicrons, and especially if their clearance is delayed, the apoB level will often be high as will CV risk as apoB particles are the atherogenic particles. The VLDL story is complicated. VLDLs exist as a heterogeneous group of particles varying in size and composition (TG - cholesteryl ester content). If the liver produces increased numbers of smaller sized TG-rich, cholesterol-poor VLDL they undergo lipolysis (via LPL and hepatic lipase) and the result is increased numbers of small LDL particles. Under conditions of hypertriglyceridemia, the liver will also produce increased numbers of large TG-rich VLDL which, via CETP exchanges TG for cholesteryl ester in HDL and LDL. This will result (after action of hepatic lipase) in smaller LDL and HDL particles. The VLDL with increased cholesteryl ester content is acted upon by LPL creating smaller VLDL remnants which are highly atherogenic. Thus patients with high TG typically have reduced HDL-C (low apoA-I), and unremarkable LDL-C but elevated VLDL-C and elevated levels of Non HDL-C (increased apoB). They get atherosclerosis because the apoB level is high (a measure of atherogenic lipoproteins) and the apoA-I level is low (a measure of the protective HDL particles). The apoB/apoA-I ratio is elevated (an excellent measure of CV risk).

PEARL: WHENEVER LDL-C IS FINE BUT NON HDL-C IS ELEVATED, THE PATIENT HAS INCREASED NUMBERS OF SMALL LDL AND REMNANT PARTICLES). Just do an NMR (nuclear magnetic resonance spectroscopy) LipoProfile on such patients and see how the report lights up with abnormal particles.

Do not be surprised that a lab cannot report a calculated LDL-C level in patients with very high TG. Labs calculate VLDL-C by dividing TG by 5. When TG's are much above 150 mg, that calculation becomes increasingly erroneous and at TG > 200-400 mg/dL, it is an absurdity. Therefore labs do not report LDL-C when TG are very high. One can request the lab do a direct LDL-C measurement if you want to know the accurate LDL-C in hypertriglyceridemic patients, however these test are very poorly standardized and of little value. Also because of particle size disparity or core TG/cholesterol abnormalities, neither the calculated or direct LDL-C correlates with LDL-P or apoB concentrations in patients with elevated TG. Reason: it takes many more cholesterol depleted particles (small LDL particles or TG-rich, CE-poor LDL particles) to transport a given amount of cholesterol than it takes large cholesterol-rich particles (volume of spherical particles is a third power of the radius) or CE-rich particles.