

Dr. Underberg

From: TDayspring@aol.com
Sent: Sunday, April 03, 2005 11:42 AM
To: TDayspring@aol.com
Subject: Lipid Case # 134 Hypertriglyceridemia: What You Need to Know

Hi Lipidaholics: Today we will discuss a 31 y/o male who presents with a very high Triglyceride level, known since age 21. It is time for another discussion of how the forgotten lipid, Triglycerides are so very important. Of course the biochemists reading this are cringing, because the correct term is triacylglycerol! Three acyl groups (fatty acids) are attached to a glycerol molecule. Triglycerides is an archaic term, that we all keep using.

In an e-mail received from a physician, he writes: Current Height and weight are 5'9" and 170 pounds. BP is 120/65. He does work out 4 days a week and does not smoke. Tries to eat healthy; lots of red meat though...big steak eater...but it always lean cuts of fillet and chicken. His father's first heart attack was age 50 and he passed away after heart transplant at age 64. There is no history of diabetes in the family. Glucose is normal.

The original level of triglyceride was 1440 with a total cholesterol of 220 and an HDL-C of 30. The liver functions were normal. Six months of dietary and lifestyle modifications had no effect on the TG level...he was then put on Lopid (gemfibrozil) 600 mg bid and niacin 500 mg bid.

The TG level went down to 750 after 1 year. The cholesterol went down slightly 180 and HDL-C elevated to 35. The next level 6 months later was 400. The patient (like so many) became noncompliant for 2 years and the TG level shot up to 1840. He was then placed on Pravachol 20 mg/ Lopid 600 mg/ Niaspan 1000 mg. The TG level went down to 1400 again after 6 months. He stopped Pravachol and took Lopid 600 mg bid and Niaspan 2 gm daily for 1 year. The TG levels went to 760 and for some reason after another 6 months of being compliant they went up to 880. The HDL-C was 49.

"That's when I met the good Dr. Thomas Dayspring."....switched to TriCor 160 mg daily and continued the Niaspan 2 gm nightly.... 6 months later lipid panel revealed a TC of 160 and a TG of 340 (the lowest it has ever been). The HDL-C was 39 and calculated LDL-C was 53 (which is the first time it was able to be calculated). LFTs are normal. "Now I'm going to limit alcohol intake and continue with the current medication as directed and see where it takes me next."

DAYSRING DISCUSSION:

Remember last weeks discussion: Triglyceride disorders are classified as:

Moderate Hypertriglyceridemia

- Familial combined hyperlipidemia (FCH)
- Familial Dysbetalipoproteinemia (Fredrickson Type III)
- Familial Hypertriglyceridemia

Very High Triglyceridemia

- Severe chylomicronemia (deficiency of apoCII) Fredrickson Type I
- Familial Lipoprotein Lipase Deficiency

Persons with significant TG abnormalities can have a multitude of genetic perturbations and many but not all have coexisting insulin resistance. This patient's BMI, BP and glucose do not meet the NCEP metabolic syndrome criteria. This patient does not have FCH as the cholesterol level is not high enough. He has a familial hypertriglyceridemia, which could be classified as Fredrickson type III, IV or V. In Type V chylomicrons are present. An easy way to establish that is to let a red top tube with serum stand overnight: if there is a thick dense white band on top then chylomicrons are present and Type V is present. With VLDL induced hypertriglyceridemia the serum would be turbid or milky without the dense band on top. Fredrickson Type III dyslipidemia, associated with the E2 phenotype (available from Berkeley Heart Lab) is usually associated with

higher levels of cholesterol than that seen in this man. 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.

The pharmacologic approach is to use drugs that inhibit TG synthesis, enhance TG catabolism or facilitate TG-rich lipoprotein removal through upregulation of LDL and LRP.

The correct order of use (see NCEP) is:

1) Fibrates and it should definitely be TriCor (fenofibrate) not gemfibrozil for safety reasons. Fibrates increase beta-oxidation of fatty acids (providing less substrate for TG synthesis), inhibit DGAT (the enzyme which catalyzes the addition of FA to glycerol), increase production of LPL and decrease production of apoCIII. Fibrates lower both fasting and postprandial triglyceridemia. Improving the latter has been associated with improved vascular reactivity and endothelial function. In essence fibrates decrease the production of apoB particles and enhance their catabolism

2) Niacin, which should be prescribed as Niaspan titrated up to 2000 mg nightly. Niacin inhibits hormone sensitive lipase which reduces lipolysis in adipocytes (decreasing FA going to the liver). Niacin also inhibits DGAT2 reducing TG synthesis. Thus niacin will reduce apoB particle production (the unrecognized benefit of niacin).

3) Omega-3 2-4 gms daily. These increase the oxidation of FA and also inhibit DGAT2. They also upregulate LDL receptors.

4) Statins (highest dose): Although all are indicated, the only statins one should use with very high TG levels are Crestor and Lipitor. Although Crestor is a far superior lipid improving statin than is Lipitor, they are both very similar on TG lowering. However, Crestor will better lower apoB and raise apoA1 or HDL-C than Lipitor. So why would anyone use Lipitor instead of Crestor?

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 lower TG by upregulating LDL receptors, which can remove TG-rich lipoproteins 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 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 apoCIII. Pravachol has excellent data on CIII inhibition.

The addition of Zetia to a statin has been shown to lessen remnant lipoproteins in insulin resistant patients. So perhaps instead of high dose Lipitor or Crestor, lower doses of Crestor with Zetia or use of low dose Vytorin (Zetia/Zocor combo) is worth a try.

5) 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 triglyceridemia (where all else fails) to reduce the incidence of pancreatitis.

Before you start to treat elevated TG, you need a baseline TSH to r/o hypothyroidism, homocysteine, creatinine, LFTs and CK levels (in anticipation of combination therapy). TriCor can elevate creatinine and both fibrates and especially niacin raise homocysteine. Urine protein (microalbumin) needs to be checked to r/o protein losing nephropathy lipidemia and should be checked before statin use. Microalbumin is also a marker of insulin resistance but can be aggravated by all statins (inhibiting cholesterol synthesis in renal tubules decreases reabsorption of albumin).

This patient using TriCor and Niaspan therapy has the following lipid profile:

TC of 160

TG of 340 (the lowest it has ever been).

The HDL-C = 39

Calculated LDL-C = 53

Is further treatment required? He has had a very nice response, but believe it or not, even though the HDL-C is still low and the TG high, **he is at NCEP goal**. In a person with very serious triglyceridemia (>500 mg/dL), the initial goal of therapy is to get the TG under 500: That has been accomplished. Once that is achieved the goal

of therapy is to normalize the LDL-C and then the Non HDL-C level. The calculated LDL-C is at goal and the Non HDL-C value is $160 - 39 = 121$ (under the goal of 130). Thus, according to NCEP we have reduced the CV risk tremendously and other than continued lifestyle (especially alcohol avoidance) there is nothing more to do. 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 Non HDL-C.**

That being understood, I would not say mission accomplished just yet. With a TG of 340, HDL-C of 39 and a TC of 160, I ask the following: the TC/HDL-C ratio is still high as is the TG/HDL-C ratio. This suggests too many small LDL particles. If the TG/HDL-C ratio is > 4.0 the patient is likely to have very small LDL particles. Yet the excellent levels of LDL-C and Non HDL-C would be against an elevated LDL-P or apoB! I am not going to bet his life on these calculations. I would strongly suggest measuring apoB or better yet the LipoProfile NMR which would quantitate LDL-P and small LDL-P. (PLEASE CHECK OUT THE REFERENCES OF THE WEEK BELOW) If apoB or LDL-P are still abnormal, I would add Crestor 10 mg to the regimen. I would not argue if you wanted to use Vytorin 10 instead. One might also want to add high dose omega-3 FA to combat the TG. One tsp BID of Carlson's Finest Fish Oil Liquid (www.carlsonlabs.com) or the new Omacor 4 gm daily (taken as 4 1000 mg tabs a day).

FOR THE ADVANCED STUDENT:

A quick review of TG-rich lipoproteins: The intestine synthesizes very large TG-rich chylomicrons that enter lymph and then plasma. On their journey to the liver they acquire apoCI, apoCII, apoCIII apoE and other apolipoproteins (from HDL). If there is not too much apoCI and CIII the apoCII attaches to LPL and TG hydrolysis (lipolysis) occurs. The chylomicron shrinks and is termed a remnant chylomicron. This binds to the LDL receptor related protein (LRP) at the liver (LPL and heparan sulfate proteoglycans aid this binding). The liver takes the TG and reassembles it (with cholesteryl ester and apoB) into a VLDL particle. Once secreted into plasma, the VLDL acquires the variable amounts of apoproteins from HDL particles (one of HDL particle's functions is to transport apoproteins needed for lipolysis of T-rich lipoproteins): apoC family and apoE (as well as others) apoproteins. A word about the apolipoproteins that affect TG:

apoCI is an inhibitor of lipoprotein lipase, hepatic lipase, phospholipase A2, CETP, and apoE-mediated uptake of TG-rich lipoproteins by LDL receptor and LRP. CI either masks or displaces apoE from the TG-rich lipoprotein surface, thus delaying catabolism of the particle. In a just published article apoCI is an independent risk factor for atherosclerosis in men. (Jour Amer Col Cardiol 2005;45:1013-7)

apoCII is the main ligand for LPL. It is the physiological activator of LPL which facilitates hydrolysis of TG (lipolysis) into fatty acids

apoCIII 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 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

apoAV acts as a stimulatory modifier of apoC-II induced LPL-mediated TG hydrolysis. Deficiency of apoAV is associated with hypertriglyceridemia

When the intestine and liver overproduce VLDLs and chylomicrons, and especially if their clearance is delayed, the apoB level will 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 small LDL and HDL. 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, and unremarkable LDL-C and elevated levels of Non HDL-C. They get atherosclerosis because the apoB level is high (a measure of atherogenic lipoproteins) and the apoA1 level is low (a measure of the protective HDL particles). **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

LipoProfile on such patients and see how the report lights up!.

Do not be surprised that the lab cannot report an LDL-C level in patients with very high TG. Labs calculate LDL-C by dividing TG by 5. When TG's are much above 150 mg, that calculation becomes increasingly erroneous and at TG > 3-400, it is an absurdity so 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 if TG are high. However because of size disparity neither calculated or direct LDL-C correlates with LDL-P or apoB in patients with elevated TG. Reason: it takes many more small LDL particles to transport a given amount of cholesterol than it takes large particles (volume of spherical particles is a third power of the radius).

REFERENCES OF THE WEEK:

- 1) Plasma Triglycerides and Type III Hyperlipidemia Are Independently Associated With Premature Familial Coronary Artery Disease Paul N. Hopkins, MD, MSPH, Lily L. Wu, PHD, Steven C. Hunt, PHD, Eliot A. Brinton, MD. **CONCLUSIONS** The association between the plasma TG level and premature familial CAD is strong, graded, and independent. Risk of CAD is also strikingly elevated with type III hyperlipidemia. (J Am Coll Cardiol 2005;45:1003–12)
 - 2) Adiposopathy: sick fat causes high blood sugar, high blood pressure and dyslipidemia. Harold Bays MD, FACP, Nicola Abate MD, Manisha Chandalia MD Future Cardiology (2005) 1(1), 39–59. A great review with nice illustrations on this emerging topic. If you can get a copy of this you will really enjoy it.
 - 3) Differences between markers of atherogenic lipoproteins in predicting high cardiovascular risk and subclinical atherosclerosis in asymptomatic men Alain Simon, Gilles Chironi, Jerome Gariepy, Muriel Del Pino, Jaime Levenson: **Conclusions:** ApoB was the best predictor, non-HDL-C the second best predictor, and LDL-C the poorest predictor of high cardiovascular risk and subclinical extra-coronary and coronary atherosclerosis, and triglycerides participated to these differences. Atherosclerosis 179 (2005) 339–344
 - 4) Risk of Cardiovascular Disease by Hysterectomy Status, With and Without Oophorectomy The Women's Health Initiative Observational Study. **Conclusions—**Women with a hysterectomy had a worse risk profile and higher prevalence and incidence of CVD in this cohort. Multivariate models suggest that hysterectomy is not the major determinant of this outcome; rather, CVD risk may be due to the more adverse initial risk profile of women who had undergone hysterectomy. (Circulation. 2005;111:1462-1470.)
- Also see the editorial: Can Hysterectomy Be Considered a Risk Factor for Cardiovascular Disease? Kate M. Brett, PhD Circulation. 2005;111:1456-1458.
- 5) Fenofibrate Reduces Progression to Microalbuminuria Over 3 Years in a Placebo-Controlled Study in Type 2 Diabetes: Results From the Diabetes Atherosclerosis Intervention Study (DAIS) Jean-Claude Ansquer, MD, Christelle Foucher, PhD, Stephanie Rattier, MS, Marja-Riitta Taskinen, MD, and George Steiner, MD, for the DAIS Investigators. **Conclusion:** Improvement in lipid profiles with fenofibrate in patients with type 2 diabetes was associated with reduced progression from normal albumin excretion to microalbuminuria. Am J Kidney Dis 45:485-493. **TD comment:** This is more powerful data on why one uses fibrates before niacin in insulin resistant patients with TG/HDL-C axis disorders (diabetic and metabolic syndrome dyslipidemia)

DAYSRING TRAVELS

Lipid Lectures:

Arlington Heights, Schaumburg and Oak Brook, IL (this week)
 Sarasota and Bradenton, FL
 Evansville (Grand Rounds at St. Mary's) and Bloomington, IN
 Minneapolis, MN
 Nebraska Heart Institute Annual Lipid Symposium April 23 (Lincoln, NE)
 Indianapolis, IN
 Omaha, NE (and surrounding areas): several lectures

I will be doing a series of CME lectures in person and numerous Web Casts on the challenge of treating menopausal symptoms in postmenopausal women with CV risk factors. The lectures get into lipoprotein physiology in women and the effects of estrogens and progestogens. This will be very much appreciated by primary care professionals including gynecologists interested in better understanding CV risk in women.

My upcoming lectures (March through May) are in Baltimore, Washington DC, Dallas, Houston, Tampa, Cincinnati, Columbus (OH), Indianapolis (this week), and Denver. If you are interested in the exact times and dates or in logging into one of the many web casts please contact Genesis Healthcare

Phone 908-231-6083 Fax 908-575-0250 or hagan@genesishhealthcare.com

Reminder: My previous cases of the week discussions can be reviewed and downloaded in PDF form at <http://www.nypcvs.org/pages/1/index.htm>

Remember the National Lipid Association www.lipid.org Join: The new syllabus on Metabolic syndrome is ready for release.

North American Menopause Society www.menopause.org Become a certified menopause practitioner!

WANT MY SLIDES? Two CME CDs are available for free. You get my animated slides, my voice and slide notes. (1) "Understanding the Influence of Triglycerides on Lipid and Lipoprotein Pathobiology" and (2) "Treatment considerations for TG-rich Lipoprotein Pathobiology". The slides are very much worth the price: FREE! Do the Lipoprotein Physiology one first. It is essential to understand the basics before looking at the one dealing with treatments.

If they would like both CDs, **FAX a request to** ACCESS Medical Group Department of Continuing Medical Education at 847-392-2257 Request both CDs. If your fax goes unanswered call you can contact Susan Pazderski at Access Medical, (847) 392-2227.

As always I close by thanking our servicemen and women who allow America to be so special. Last week a Medal of Honor was awarded posthumously to a very brave Marine. In reality all of our guardians overseas serve with great honor to keep us free.

Happy Lipiding,

Tom

Thomas Dayspring, MD, FACP
North Jersey Institute of Menopausal Lipidology
516 Hamburg Turnpike
Wayne, NJ 07470
Tel: 973-790-8604
Fax: 973-790-1488