

## Dr. Underberg

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**From:** TDayspring@aol.com  
**Sent:** Friday, July 29, 2005 3:00 PM  
**To:** TDayspring@aol.com  
**Subject:** Lipidaholics Weekly: Lipid Case # 143 Ignore an elevated LDL-C?

Hi Lipidaholics: I am writing this as I leave the enjoyable but very hot Old Dominion (~100 degrees). One can only imagine the horrors of civil war battles fought in this type of climate. Well we continue to fight present day lipid battles and this weeks case will draw some debate.

I received a problem case from a nurse practitioner. The patient is a 47 year old female physician who is concerned about her lipid profile. Her family history includes a father with PAD, CAD and CVA. Her mother and one sister have no known CAD. She does not smoke and has a normal weight and glucose and participates in regular exercise.

Lipid profile: TC = 284 LDL-C = 151 HDL-C = 118 TG = 79  
 TC/HDL-C ratio = 2. Non HDL-C = 166

LipoScience NMR LipoProfile  
 LDL-P = 1011 nmol/L (perfect < 1000)  
 LDL size 22.6 (fairly large)  
 Large HDL = 53 mg/dL (desirable in a drug naive patient > 30)  
 Large VLDL = 10 mg/dL (perfect < 7.0)

The patient has an Ultrafast CT which revealed no plaque.

My recommendations for cholesterol treatment were requested.

### **DAYSFRING ADVICE:**

As I try to find better and better ways of making it easy to understand atherogenesis I have stumbled onto the current explanation. Human life depends on the transportation of hydrophobic lipids (cholesterol and triglycerides) in aqueous plasma to tissues that require them. In some people, the lipid transportation system goes awry and the cholesterol (and sometimes other sterols) wind up in the vascular wall (intima) and atherogenesis begins. In essence atherogenesis is a result of abnormal lipid transportation. If we are smart enough to fully understand all of the nuances of lipid transportation, and how it becomes faulty then we will have a pretty good idea of how to restore normal lipid transportation with lifestyle and pharmacologic advice.

Of course evolution solved the lipid transportation system by wrapping the lipids (sterols, TG and phospholipids) with proteins (apolipoproteins) thereby creating water soluble "fat-balls" (lipid transportation vehicles) called lipoproteins. This transportation system has two main types of lipoproteins differentiated by their surface apolipoproteins. Those particles wrapped with apolipoprotein B (apoB), the beta-lipoproteins are the chylomicrons, Very low density (VLDL), Intermediate density (IDL) and Low Density (LDL) lipoproteins and the particles wrapped with apolipoprotein A1 (apoA1).

Think of all of the above particles are part of the same lipid transportation company. Their mission is to deliver lipids to tissues that require lipids and return any unused or excess lipid to the liver for re-handling (excretion or recirculation). In brief the function of the individual particles are:

Chylomicrons: Very large apoB containing lipoproteins, synthesized in the intestinal epithelial cells to gather intestinally absorbed lipids (primarily TG but also some sterols) and transport them to the liver (lymphatics to right side of circulation to left side of circulation to portal system to liver). Along the way some TG are hydrolyzed by lipoprotein lipase (lipolysis) to fatty acids making for a smaller particle called a chylomicron remnant. If one has defective lipolysis one will have an impairment of lipid transportation resulting in rather marked hypertriglyceridemia. In those patients with marked impairment of chylomicron transportation there may

be eruptive xanthomas, lipemia retinalis and pancreatitis. Plasma left standing overnight will reveal a thick white layer on top (chylomicron band).

VLDL: Large apoB particles produced by the liver to transport triglycerides, "the energy of life" to those tissues (muscles) requiring them for energy. If muscles do not need the energy the TG will be stored in adipocytes for use in times of famine. If one is ingesting a proper diet and exercising prudently and has a full complement of functional lipolytic enzymes the TG level will range between 10 and 70 with a mean concentration of 30 mg/dL. Postprandially the TG level will rise to between 60 and 170 (never > 200 in normal people). VLDLs carry many other apolipoproteins including E, CI, CII, CIII, A2 and others.

The VLDLs produced in the liver (fully loaded with TG and some sterols) will be large and as lipolysis occurs (lipoprotein lipase mediated) the size the VLDL particle lessens. If one over-produces VLDL or if one is slow to catabolize VLDL an abnormality of the lipid transportation system will occur and the patient will have elevated TG and apoB levels (as each VLDL as a single apoB on its surface).

IDL: The end result of VLDL lipolysis is an in-between sized apoB particle named IDL. It transports the remaining TG that was in the VLDL and the original and acquired cholesterol that was in VLDL. There is a known abnormality of lipid transportation marked by a large excess of IDL particles (due to defective apoE, the particles cannot be cleared and accumulate). Such patients have marked elevations of TG and LDL-C: this is the Type III Fredrickson Hyperlipidemia. Patients many have flexor surface and palmar Xanthomas. Note: When labs calculate LDL-C using the Friedewald formula, the cholesterol that is in IDL particles is incorporated: ie LDL-C is in reality IDL-C plus LDL-C. IDLs carry only apoB and apoE.

LDL: the smallest apoB transportation vehicle is in effect the son of VLDL or the end product of complete VLDL lipolysis. Normal VLDL particles have only apoB on their surface. LDL-C is the cholesterol content of all of the LDL particles in a deciliter of plasma. LDL-P is the number of LDL particles in a liter of plasma. Depending on their lipid content the LDL practices range from large to very small. Because small particles have more protein than lipid they are "dense" on ultracentrifugation: hence the term small, dense LDL. There are several know disorders of transportation related to either LDL over-production or delayed LDL clearance (defective LDL-receptors or defective apoB). Such transportation disorders are characterized by variable elevations of LDL-C, and marked elevations of apoB or LDL-P. Patients with severe, familial elevations of LDL-C have tendon xanthomas and arcus senilis.

HDL: small apoA1, wrapped lipoproteins that exist in varying sizes and containing numerous apolipoproteins, lipid transfer proteins and a variety of other proteins possessing anti-inflammatory antioxidant, anticoagulant and profibrinolytic properties. HDLs are significantly involved in lipid transportation. They are produced as lipid free apoA1 in liver and intestinal cells and rapidly lipidated by ABCA1 transporters (cholesterol efflux proteins expressed in many tissues, especially the liver). Although most of the cholesterol being transported in HDL originates in the liver, some is picked up from other peripheral tissues. In a process now termed "Macrophage Reverse Cholesterol Transport" sterols are delipidated from arterial wall macrophages. Although this is important in stabilizing plaque, the cholesterol removed from macrophages does not contribute significantly to the plasma HDL-C level. The HDL transports the cholesterol to the steroid producing endocrine glands, where the particles are delipidated (made small and ready for relipidation or renal excretion). HDL that is not delipidated at the endocrine glands can transfer cholesterol to apoB particles (VLDL, IDL and LDL) in a "lipid swap process" mediated by cholesteryl ester transfer protein (CETP) or can return to the liver for hepatic delipidation via SRB1 receptors (creating more small HDL) or endocytosis by hepatic "Holoparticle" receptors (destroying the HDL).

If you understand the above, it is obvious that there can be several HDL transportation disorders: Failure to produce apoA1, Failure to lipidate apoA1 (Tangiers Disease), failure to mature HDL (LCAT deficiency), CETP deficiency, etc. Likewise drugs can induce synthesis and lipidation or inhibit delipidation.

Case at hand: Is it possible to have an LDL-C of 150 and not have a lipid transportation abnormality? This patient has normal numbers of LDL particles which are large (Pattern A) and normal numbers of VLDL particles. There is little risk of atherogenesis if LDL-P is normal as particle concentration is the driving force to make particles enter the arterial intima. So, there is no need to worry about this patient.

What explains the high HDL-C? Remember most of the cholesterol in our HDL particles originates in the liver. This patient is probably is producing lots of apoA1 which is being rapidly lipidated by hepatic cholesterol efflux protein, ABCA1. The resultant particle is a prebeta HDL. The LCAT present on apoA1 esterifies the free

cholesterol. The cholesteryl ester is very hydrophobic, driving it to the center of the prebeta HDL creating a larger, more spherical alpha HDL particle (HDL3 or on NMR HI, H2).

Thus in this woman, her liver has extra cholesterol and it is exporting it by using the lipid transportation system, namely creation of HDL and VLDL particles. Where is the liver getting all of the cholesterol to lipidate the HDL and VLDL? She is either overproducing it or is a hyperabsorber of cholesterol. The liver in most such patients exports most of the cholesterol in apoB particles: either VLDL or hepatic synthesis of smaller apoB particles such as IDL or even LDL and there is typically increased LDL-P along with increased LDL-C. She lacks large VLDL and small LDL as she has physiologic(very normal) TG levels. She obviously has no genetic or environmental (overeating) source of TG. She has no insulin resistance. Without elevations of TG you usually do not see large VLDL or small LDL particles. If this lady had IR or elevated TG her LDL particles would be small and her LDL-P would be extremely high, as it would takes lots of small particles to transport her LDL-C of 151.

However in most persons with a TC of 284 and a perfect TG we would expect increased numbers of large LDL particles. For whatever genetic reason, this patient's liver has over expressed ABCA1 and production of apoA1 and thereby chosen to export a lot of the hepatic cholesterol into HDL and not the apoB particles. If the liver exports lots of cholesterol in HDL, it will not have to create so many LDL particles.

I doubt that she has a CETP deficiency which will keep cholesteryl ester in the HDL creating very large particles. She would have what is termed polydisperse LDL (multiple sizes). Although technically a disorder of lipid transportation most CETP patients do not get atherosclerosis. If apoB (LDL-P and VLDL-P) are normal, there are no atherogenic particles present, so again, the risk is not there in this patient.

If the patient demanded her LDL-C be lowered despite the above analysis: To reduce cholesterol absorption plant stanols (Benecol) would be the best (least likely to cause side effects) solution. However ezetimibe or Zetia would also be a solution. I do not think there is an indication for a statin with normal LDL-P in a patient with no CHD.

Is there any way by looking at the lipid profile to have predicted the NMR LipoProfile of normal LDL-P in a patient with and LDL-C of 151? Not really. This is a case where the NMR will spare a patient unnecessary treatment.

- 1) The TC/HDL-C ratio is perfect yet the LDL-C is elevated: that suggest large particles but not an accurate predictor of LDL-P
- 2) The LDL-C / Non HDL-C ratio is almost 1. That strongly suggests large LDL particles
- 3) The TG/HDL-C ratio is less than 1 (rarely seen). This almost certainly means large LDL and HDL particles.

So it would be easy to know the particles are large but almost impossible to know how many particles exist. Most of us would have predicted an increased LDL-P from the lipid concentrations.

#### REFERENCES OF THE WEEK:

- 1) Increased Subclinical Atherosclerosis in Young Adults With Metabolic Syndrome  
The Bogalusa Heart Study. In young adults, MetS is associated with increased atherosclerotic burden, and therefore, increased cardiovascular risk. These results support the importance of screening and early intervention in this population. (J Am Coll Cardiol 2005;46:457– 63)
- 2) Remnant lipoproteinemia is a risk factor for endothelial vasomotor dysfunction and coronary artery disease in metabolic syndrome Atherosclerosis 181 (2005) 321–327. changes in levels of triglyceride, hsCRP, and IL-6, and HOMA index. Thus, elevated levels of RLP-C are a risk factor for CAD and endothelial vasomotor dysfunction, a predictor of coronary events, in metabolic syndrome. Measurement of RLP-C is useful for assessment of CAD risk and therapeutic effects in metabolic syndrome.
- 3) Adipose tissue triglyceride fatty acids and atherosclerosis in Alaska Natives and non-Natives  
Atherosclerosis 181 (2005) 353–362. Findings indicate that Alaska Natives had less advanced atherosclerosis in coronary arteries, along with higher proportions of omega-3 and lower proportions of omega-6 PUFA in adipose tissue, than did non-Natives. We conclude that high dietary intake of omega-3 PUFA may account for the lower extent of coronary artery atherosclerosis, contributing to the

reported lower heart disease mortality among Alaska Natives.

#### 4) Therapeutic Roles of Peroxisome Proliferator–Activated Receptor Agonists

Bart Staels and Jean-Charles Fruchart Very nice review articles by the Gods of PPARs. Diabetes 54:2460–2470, 2005

#### **DAYSPRING TRAVELS (next few months)**

Houston, TX  
 West Nyack, NY  
 Calhoun, GA  
 Pikesville, MD  
 Newark, DE  
 Westchester OH  
 Torrence and Pico Rivera, CA  
 West Chester, PA  
 Birmingham, AL  
 Chattanooga, Knoxville, Nashville, TN  
 Albany, NY  
 Kiawah Isle and Columbia, SC  
 Finally a return to Charleston and Beckley WV

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>

I contributed to a nice discussion on interpreting the NMR LipoProfile at <http://www.sjhg.org/> Click on Hear beat icon and download May 2005.

North American Menopause Society [www.menopause.org](http://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 form 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 you 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 you should contact Susan Pazderski at Access Medical, (847) 392-2227.

If you are having a nice day and things are going well in your life, you owe big thanks to the men and women of the United States Armed Forces. Thumbs up when you see them.

Happy lipiding and may the particles be with you,

Tom

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