LIPID CASE 255 Female Diabetic with rising LDL-C but Normal LDL-P

Hi Lipidaholics: It goes without saying but to really master lipidology one sooner or later has to master biochemistry (of all the things I have studied in college and med school, I loved organic and biochemistry the most). A new feature of the Lipidaholic newsletter will be a simple and short discussion of the basics of organic and biochemistry (located just before references of the week). Before we get to this case at hand, a reminder that my blog on ACCORD can be read at www.lipidcenter.com On the opening page scroll down and you will see it. While there, pick up our Lipid/Lipoprotein Disorders PocketGuide if you have not already done so. Lastly, I can also be followed on Twitter at http://twitter.com/Drlipid and on the NLA web site community bulletin board under the Lipidaholic and lipid geek groups

Announcement: For those of you ordering your NMR LipoProfiles using Labcorp, the full report that was once only available directly from LipoScience will now be reported by Labcorp. Your will finally get total HDL-P counts (a crucial parameter) which is not available with the Vertical Auto Profile (VAP) or Berkeley (do not confuse apoA-I with HDL-P). If you like the Lipoprotein Insulin Resistance Score (used as a predictor of IR or risk of developing diabetes), that will also be reported.

I hope many are enjoying HBO's "Pacific" but do not forget what was happening in Europe. A lipidaholic sent me the following and I suggest you take a peek:

http://blogs.denverpost.com/captured/2009/06/05/the-65th-anniversary-of-d-day-on-the-normandy-beaches

Now onto this issues case:
I was asked about the following paradox-- The provider states: "I have a diabetic patient who has been intentionally losing weight and improving her insulin resistance. However, despite her much better therapeutic lifestyle over a one-year period her LDL-P has fallen better than her LDL-C which lately is actually rising. What's going on?" Here's the basic data:

44 year old female with type 2 diabetes

11/08 -- weight 230 lbs	LDL-P 2100	LDL-C 167 & 190	(baseline)
1/09 -- weight 215 lbs	LDL-P 837	LDL-C 30	(Zetia/Welchol/Crestor 20)
3/09 -- weight 205 lbs	LDL-P 1300	LDL-C 43	(Zetia/Crestor 40)
11/09 -- weight 180 lbs	LDL-P 424	LDL-C 69	(Zetia/Crestor 40)

"She would like to eliminate the Zetia for cost reasons. I presume that's fine as long as her LDL-P doesn't go back up over 1000. Of course her LDL-C will go over 70, but I also presume that's fine.

DAYSPRING DISCUSSION:

My mantra has long been that atherogenesis, a disease very prevalent in T2DM patients is simply an illegal dump job of sterols (both cholesterol and non-cholesterol sterols) into the intimal layer of the artery. The only way hydrophobic lipids like cholesterol (C), noncholesterol sterols, cholesteryl ester (CE), phospholipids (PL) and triacylglycerols (TG) exist in aqueous plasma is as passengers inside of protein-enwrapped vehicles termed lipoproteins. The only way the sterols generate plaque is if a lipoprotein trafficking sterols, enters the arterial wall, gets oxidized and then ingested by a monocyte turned macrophage which creates sterol-laden macrophages termed "foam cells" which are the histological marker of the fatty streak. The only rational conclusion is that **ATHEROGENESIS IS A LIPOPROTEIN MEDIATED DISEASE** and both the acute and ultimately chronic maladaptive inflammatory response that follows can be minimized or eliminated with aggressive reduction of the "illegal dumpers." For any doubters out there: MANDATORY READING: ***Subendothelial Lipoprotein Retention as the Initiating Process in Atherosclerosis by*** **Ira Tabas** where he shows: "The key initiating process in atherogenesis is the subendothelial retention of apolipoprotein B–containing lipoproteins. Local biological responses to these retained lipoproteins, including a chronic and maladaptive macrophage and T-cell– dominated inflammatory response, promote subsequent lesion development." (Circulation. 2007;116:1832-1844.)

Thank goodness, for all intents and purposes, there are only 5 lipoproteins to be found in human plasma. The intestinally, intracellularly created chylomicrons, the hepatic intracellularly created very low density lipoproteins (VLDL) and its lipolysis induced progeny called intermediate density lipoproteins (IDL) and of course low density lipoproteins (LDL) belong to the apolipoprotein B (apoB) family (Chylomicrons have a shortened or truncated apoB molecule referred to apoB48 as it has 48% of the molecular weight of the hepatic produced apoB100). Early on these lipoproteins got their names because of their buoyancy (density) in the ultracentrifuge.

Historically, particles could also be separated by serum protein electrophoretic techniques: remember there are two types of proteins - albumin and globulins (which have alpha, beta and gamma families). Depending on their surface charges lipoproteins also migrate: the LDLs which migrated with beta-proteins were called beta-lipoproteins. Historically measuring LDLs was called beta-quantification). The slower migrating VLDL and IDL particles were termed prebeta lipoproteins. Although technically beta-lipoproteins strictly refers to LDL particles and prebeta lipoproteins to VLDLs and IDLs, over time many authors use the term beta-lipoproteins to collectively refer to chylos, VLDLs, IDLs and LDLs. The major function of the prebeta and beta-lipoproteins is to traffic energy in the form of TG from the intestine and liver to muscles or adipocytes. A secondary function, once TG are lost in the lipolytic process, is to deliver the remaining cholesterol to any cell that might need it (a minor function since most cells manufacture all of the cholesterol they require) and ultimately to return their cholesterol and CE load back to the liver (a process termed indirect reverse cholesterol transport).

After excluding the beta-lipoproteins, all that is left are the high density lipoproteins (HDL) which migrate with alpha proteins and have the name alpha-lipoproteins. Unlike

their apoB cousins, HDLs are not assembled in the serum but in plasma. Helical shaped molecules of apoA-I are secreted by the hepatocytes and enterocytes and rapidly acquire phospholipids and some unesterified cholesterol from the transmembrane lipid transporter called ATP Binding Cassette Transporter A1 (ABCA1).

Back to the "Dayspring Illegal Dumper Hypothesis," the only lipoproteins that crash the endothelial barrier, get oxidized and serve as fodder for, macrophages are the beta-lipoproteins, 90% of which are LDLs (because of their half life measured in days compared to that of chylos, VLDLs and IDLs which are measured in hours). The major characteristic that determines if a beta-lipoprotein will crash the artery is particle number. It is true that extremely large (>70 nm) particles like chylomicrons and some VLDLs are too large to enter the artery, but their much smaller remnants (a chylo or VLDL that has lost much of its TG) can. Thus apoB or LDL-P levels are out current best method of quantifying lipoproteins and ascertaining lipoprotein mediated risk.

Two things have little to do with LDL particle entry into the artery: particle size (patients with FH have a lot of very large LDLs and sure get a lot of plaque) and particle cholesterol content (LDL-C). In effect this renders lipid concentrations, LDL size, and LDL subfraction cholesterol assays obsolete as predictors of risk or goals of therapy compared to apoB or LDL-P. Those measurements (LDL size and LDL-C) tell you nothing as far as predicting CV risk that the apoB or LDL-P does not already tell you with a significantly higher degree of accuracy.

What variables influence apoB or LDL-P? Very simple:

1) VLDL particle production which depends on hepatic apoB production and its lipidation with the substrates cholesterol and TG. In IR patients hepatic TG drives VLDL-P and VLDL size.

2) LDL Particle size: Because the volume of a sphere is a third power of the radius it takes many more smaller low density lipoproteins compared to large to carry a given cholesterol concentration. Thus contrary to common belief, the real danger of the small LDL is not its size per se, but rather drug-naive patients who have small LDL size almost always have large elevations of LDL-P (and apoB).

3) LDL Particle Core Composition: typically a normally composed LDL has about 80% CE and 20% TG in its core. LDLs are meant to be CE-rich: basically LDLs are VLDLs and IDLs that have lost most of their TG content. AT any given LDL size, the more TG that are in the core of the LDL, the less CE will be present. In other words, TG deplete the CE content of LDL particles. This is one reason that as TG rise, LDL-C often falls and drugs like fibrates and omega-3 fatty acids that significantly reduce TG synthesis often increase LDL-C but not LDL-P. Please remember as TG levels increase the liver over manufactures TG-rich, large VLDL particles that have increased plasma residence time and cholesterol ester transfer protein (CETP) swaps VLDL-TG for CE from LDLs and HDLs. Thus those two particles have drastic alterations in their core composition and in effect become CE-poor and TG-rich.

I often refer to the Ludwigshafen Study which I really implore all (especially lipidologists) to read thoroughly: "Conclusions—Alterations of LDL metabolism characterized by high LDL-TG are related to CAD, systemic low-grade inflammation, and vascular damage. High LDL-TGs are indicative of CE-depleted LDL, elevated IDL, and dense LDL. **LDL-TG may better reflect the atherogenic potential of LDL than LDL-C**." (Circulation. 2004;110:3068-3074).

In clinical practice in a very insulin resistant America: LDL-P is usually elevated in IR patients with small LDL particles, TG-rich, VCE-poor large or small LDL particles, many of whom have minimally elevated, normal or even perfect (desirable) and LDL-C levels.

So let's closely evaluate the case above: at baseline there was an extreme LDL-P elevation (>99th population percentile). The LDL-C ~ 80th percentile. Of course 2100 nmol/L is a very high risk LDL-P in a patient who is a coronary heart disease equivalent (T2DM). The provider in an attempt to get to goal ultimately used both lifestyle (which the patient followed quite well) and triple therapy with Crestor 20 mg, Zetia and Welchol (which would also help control HgbA1c). There was a fantastic response and both LDL-P and LDL-C and both are < than the 5th percentile.

Welchol was stopped (I do not have the reason - perhaps the patient did not want to swallow all of the tabs (we now have a powder to be mixed with water formulation that makes Welchol use much easier and once daily). Despite continued weight loss, off Welchol the LDL-P jumped way up to 1300. The LDL-C went up a tad but was still superb at 43. Why the LDL-P increase? With Welchol cessation, there would be less upregulation of LDL receptors and less efficient clearing of LDL particles. The Crestor was then increased to 40 mg and the Zetia continued.

Next profile again revealed a spectacular reduction in atherogenic LDL-P, but LDL-C continued to rise which perplexed the provider: Almost certainly because of the 50 pound weight loss, TG excess has been eliminated and the LDLs are now larger and back to having a normal composition of CE/TG. The particles which were TG-rich, CE-poor now have just the opposite: little TG and lots more CE. The only thing that matters is the LDL-P is perfect. No particles are entering the arterial wall and setting off inflammatory forces anymore!