

The Triglyceride / HDL-C Ratio Thomas Dayspring MD, FACP

Examine the following lipid panel:

TC 207 LDL-C 129 HDL-C 45 Trig 242
Non-HDL-C = 162
TG/HDL-C = 5.3
TC/HDL-C = 4.6

My guess is she has way too many LDL particles and that the LDL predominant size is small or her LDLs are large but they are TG-rich (and thus cholesterol-poor). She will lack normal numbers of large HDL and will have increased large VLDL. I've made that conclusion (guess) by looking at the TG/HDL-C ratio and the increased TC/HDL-C and Non HDL-C value in the face of an unremarkable LDL-C.

Studies have demonstrated that **the elevated TG/HDL-C (>3.8) ratio would suggest the predominant LDL particle size is small in 80% of the patients.** If you understand why this is so you are an advanced lipid student. Think about the physiology and pathophysiology aspects of the statement and the reason is obvious. The question implies these patients have elevated TG levels and reduced HDL-C levels.

If there are increased serum TG levels present is a patient where would you find those TGs? They have to be inside lipoproteins. Which lipoproteins transport TG under normal circumstances? The answer is chylomicrons (very transiently) and mostly VLDLs. If a patient has increased TG levels, those lipoproteins likely contain more TG and may also have increased plasma residence time.

The TG-rich VLDL and chylomicrons then transfer the TG (using cholesteryl ester transfer protein or CETP) to the TG-poor lipoproteins in exchange for cholesteryl ester (CE). Thus VLDL sends TG to LDL and HDL in exchange for their CE. The LDL and HDL become cholesterol poor and TG-rich and the VLDL-C becomes more CE enriched. The TG-rich, and CE-poor particles are susceptible to lipolysis (hydrolysis or removal of TG) by hepatic and other lipases. When the TG (and lipoprotein surface phospholipids) are removed from such CE-poor particles, the particle itself collapses and becomes smaller as it is now transporting only the reduced amount of cholesterol: the TG are now reduced in concentration or gone. Thus even subtle increases in TG will both deplete the particles of cholesterol and often shift HDL and LDL size from large to small.

Here is the NMR (nuclear magnetic resonance) measured lipoprotein data on the above patient and just as predicted the LDL size is small:

LDL Particle Concentration 1775 (ideal <1000 high risk > 1600)
LDL Particle Size 19.8 (small dense) (normal > 20.5 nm)

How many of you would have guessed the LDL-P would be in the high risk category? Her LDL-C is 129 and her LDL particles are very, very small. Because the volume of a circular particle is a third power of the radius. It will take an awful lot of small LDL particles to transport any level of cholesterol compared to how many large particles would be required. Of course CV risk is most directly related to the number of apoB particles not how much cholesterol is within the particles. Entry of the apoB-containing LDL particles into the vascular wall is concentration driven.

Return to the lipid profile: when you see unremarkable LDL-C but elevated TC/HDL-C or non HDL-C levels, especially in a patient with a TG greater than 100-130, you should suspect there are increased numbers of apoB particles (LDL, because of its long half-life of course is the predominant apoB particle in most patients). An important caveat is the TG/HDL-C ratio predicts LDL size but not necessarily LDL-P (particle concentration or apoB). However as a general rule most patients with small LDLs have increased numbers of LDLs. DIABETES CARE 2005;28;1798-1800.

The Triglyceride / HDL-C Ratio Thomas Dayspring MD, FACP

Thus a lipid profile with an elevated TG/HDL-C ratio will likely be indicative that the patient has a predominance of small LDL and a lack of large HDL particles. The non-HDL-C and/or TC/HDL-C ratio predicts increased numbers of LDL particles. The treatment is to reduce the increased numbers of atherogenic apoB (LDL) particles, not per se to raise the HDL-C.

The clinician must upregulate LDL receptors (LDLr) to remove the apoB particles from plasma. The most efficacious way of doing just that is to prescribe a statin or statin/ezetimibe or bile acid sequestrant (BAS) combo. The increased numbers of LDL particles would be lessened thereby reducing CHD risk. However, it is easier for LDLr to attach to and endocytose large LDL than small, as LDLr more readily recognize the electrostatic charges on the apoB conformation present on large LDL. The apoB conformation and surface charge will be very different on a small LDL, making it less recognizable to the LDLr. Using an analogy where a baseball glove is an LDL receptor, it is far easier to catch baseballs than golf balls or marbles!

Thus using combination therapy with a fibrate or niacin or perhaps omega or N-3 FA supplement or TZD, all of which increase LDL size would enhance the LDL particle removal by the statin or statin/ezetimibe/BAS upregulated numbers of LDL receptors. These patients are virtually all insulin resistant and that makes the fibrate the preferable therapy to niacin to add to the statin or statin/ezetimibe: of course when talking fibrates and statins we are talking fenofibrate or fenofibric acid for safety reasons!

When one increases the removal of cholesterol containing apoB particles (like LDL) by removal through LDLr, one is increasing "Indirect Reverse Cholesterol Treatment." Which statin lowers apoB the most or which statin upregulates the most LDLr? In head to head studies the answer is Crestor. Which combo therapy upregulates the most LDL-r (statin-ezetimibe or statin-bile acid sequestrant). Thus I suggest using Crestor (5-10)/Zetia 10 or Vytorin 20/10. If the non-HDL-C remains high add fenofibrate or Niaspan.

Studies have revealed that: At a TG/HDL-C > 3.5, 80 percent of such patients would have a predominance of small LDL. References: (Am J Cardiol 2004;94:219–222). Any exceptions? Unfortunately yes: It has always been a paradox that less African-Americans meet the criteria for metabolic syndrome than do Caucasians, despite the fact that more of the former are insulin resistant. The paradox is explained because we use lipids (specifically elevated TG and low HDL-C) to diagnose the metabolic syndrome. But African-Americans have lower TG levels than do Caucasians and that would make them less likely to be diagnosed as metabolic syndrome patients. Why lower TG if African-Americans?

Let me quote from a nice study (reference in next paragraph) which showed the TG/HDL-C ratio is not predictive of insulin resistance in this population. "Racial differences in lipoprotein lipase (LPL) activity may be responsible for racial differences in TG. Lipoprotein lipase is the enzyme responsible for clearing TG-containing lipoproteins from the circulation. The LPL levels are higher in African Americans than in Caucasians. This is the reason most often cited as to why African Americans have lower TG levels than Caucasians. In Caucasians, insulin resistance leads to an impairment of LPL levels and high TG levels. There is some evidence that insulin resistance may not lead to an impairment of LPL activity in African Americans. If that is the case, then TG-containing lipid particles are cleared from the circulation even in the presence of insulin resistance and plasma TG levels do not rise. This could account in part for a weak association between TG levels and insulin resistance in African Americans. **Conclusion:** In African Americans, TG levels and TG–HDL-C ratio are not reliable markers of insulin resistance." (Fasting Triglyceride and the Triglyceride–HDL Cholesterol Ratio Are Not Markers of Insulin Resistance in African Americans Anne E. Sumner, et al. Arch Intern Med. 2005;165:1395-1400