LIPID CASE 269 He said - she said??

I want to have some fun with this issue's case discussion. It was sent to me by a respected lipidologist who shared a case first seen by his nurse practitioner. They have somewhat different takes on the case and so it is up to me to play referee. My comments are in red fonts and italics.

The patient is a 35 year old white male who transferred his care to the new provider after his previous internist changed his practice to concierge medicine. The patient has dyslipidemia, Type 2 DM, sleep apnea, and morbid obesity. His last internist had him on pravastatin 20 mg daily, fenofibrate 160 daily, and lisinopril 5 daily for renal protection. He sees his endocrinologist who treats his DM with metformin 1000 twice a day, Glucotrol 5 daily and Byetta twice a day. The patient is adopted, so no family history is known. He smokes less than 1 pack per day for the last 18 years and has social use of alcohol. He claims that he walks on a treadmill 3 times a week for 20 min.

BP: 106/64; P: 76; Ht: 5'10"; Wt: 310 lbs; BMI: 45; Ideal Body Weight: 183 lbs.
Physical Exam: Normal except for morbid obesity.
EKG: Normal, no old EKG to compare.
Urinalysis: 1.020, pH 5.0, Dip Negative.

Lab Results: (NOTE: no pre-treatment data is available for review, and it is not known how long he has been on the medication for these conditions. the Fasting Glucose is 178 mg/dL with a Hgb A1C of 6.6. All hepatic enzymes are normal. The TSH is1.09 with a Free T4 of 1.3. The rest of the chemistry profile and CBC were all normal. The lipid concentrations (all in mg/dL) are as follows:

TC =96; HDL-C = 21; Non-HDL-C = 75; LDL-C: less than 10 TG: 357; VLDL-C = 71; TG/HDL-C: 17 TC/HDL-C = 4.5

Total LDL-P =695 nmol/L (well under the 5th percentile population cutpoint)
Small LDL-P = 681 nmol/L
LDL size 19.3 nm (quite small)
Large VLDL-P = 14.2 nmol/L (high)
VLDL size 54.2 nm (rather large)
Total HDL-P 24.8 umol/L (bottom 25th percentile)
Large HDL-P < 0.7 umol/L (virtually non-existent)
HDL size 8.4 nm (very small)
LP-IR score 81 (range is 0 to 100 with values > 50 suggesting insulin resistance)

The **lipidologist** states: the Goal for LDL-P should be <1000 due to his DM (CHD Risk Equivalent). He goes on to say: "My well trained Nurse Practitioner reviewed these results before I did, and she brought me her analysis where she concluded the following:"

Nurse: "His TC, LDL-C, and LDL-P are very low on his current meds. In fact, his LDL-P of 695 is under the 5th percentile population cutpoint. Since LDL-P is the carrier that puts the lipoproteins into the artery wall and his LDL-P is well below the goal of therapy,

he is being well managed and there is no need for any medication changes, additions, or adjustments. Therapeutic Lifestyle Changes (TLC) to achieve weight loss are needed. Weight loss will reduce TG and improve DM control. Continue current meds and monitor weight loss. Follow up with endocrinologist for continued DM care."

TD comment: Low density lipoprotein (*LDL) is not the carrier that puts lipoproteins into the arterial wall, but is rather the most prevalent protein (apoB) enwrapped carrier that traffics (puts)* ***lipids*** *into the artery wall. If the LDL and its surface apoB binds to arterial wall proteoglycans it will be subject to oxidation and internalization by monocytes turned into macrophages. Of course other apoB particles (chylomicron and VLDL remnants and IDLs, although usually present in much lower numbers than LDLs, can do the same thing). Never forget every lipoprotein is a oil droplet or collection of core TG and cholesterol ester (CE) with a single molecule surface layer of phospholipids and free or unesterified cholesterol.*

The lipidologist goes on to comment: After reviewing the data, I have to disagree with the nurse practitioner! The above conclusions ignore the persistent very high TG of 357, the very low HDL-C of only 21, and the massively abnormal TG/ HDL ratio of 17. Although the LDL-C is <10, it is a falsely low calculated value that is skewed by the very high TG and very low TC. This patient is a diabetic and has 4 out of 5 characteristics of the Metabolic Syndrome. Only HTN is missing. He is 122 lbs over his ideal weight. The very high TG results in underreporting the calculated LDL-C. There is much more LDL burden than there appears.

TD comment: *I agree that the high TG are contributing to residual risk, but in relating TG to CV risk, much of the TG-related risk is related to causing high apoB or LDL-P and thanks to the medication the LDL-P is superb in this man: therefore a lot of the TG-mitigated risk is well treated. However the TG are no doubt increasing, via CETP activity, catabolism of the HDL particles, explaining and the low HDL-C (due to the near total lack of large HDL-P) and HDL-P. By this I mean CETP exchanges TG for CE between all lipoproteins including VLDLs and HDLs and LDLs. The LDLs and HDLs become TG enriched as well as CE-poor and after exposure (in the liver) to hepatic lipase with the hydrolysis of their core TG and surface phospholipids they become smaller.*

Apart from the above, large TG-rich lipoproteins also increase blood viscosity, and are associated with coagulation and inflammatory factors. The lipidologist seems to put a lot of emphasis on the TG/HDL ratio. However, the TG/HDL-C ratio, like most ratios have no proven meaning in a patient on medication. All of the predictive risk data from those ratios come from epidemiological studies of drug naive patients. The TG/HDL-C ratio in drug naive patients is meant can be used as a marker of LDL size, not LDL-P. A ratio of > 3.5 is indicative of an 80% chance of small LDLs being the predominant LDL species. So in this patient with an on-treatment extremely high TG/HDL ratio does it really matter that the LDLs are small if his total LDL-P is 695? I do not think so.

The **lipidologist** states: "But what about the excellent LDL-P of only 695? Doesn't this tell us that the patient has a low CHD risk since this is so low and under the goal of

<1000? This is where the additional testing by LipoScience gives us the rest of the story. LipoScience measures and reports VLDL particles and size, HDL particles and size, and LDL particles and size. Also, they compute an Insulin Resistance Score.

TD comment: For those readers new to lipoprotein testing, LipoScience uses nuclear magnetic resonance spectroscopy to evaluate lipoprotein sizes and concentrations. By examining the characteristics of some the lipoproteins LipoScience also reports an insulin resistance (IR) score or LP-IR (lipoprotein related insulin resistance score). Lipoproteins typically seen in IR patients are large VLDL, Large VLDL-P, small LDL-P, LDL size, lack of large HDL-P HDL size which are very much a consequence of elevated TG, high CETP activity and hepatic, secretory and endothelial lipase activity. However this score is only validated in drug naive patients (meaning that evidence based speaking, you the LP-IR is not validated as a predictor of IR). It certainly is not an indication that a therapy is reducing IR. Thus, I am not sure it has much meaning in this person who we all sort of know is IR. In the only statin to have shown in a study (WOSCOPS) an association with reduced diabetes onset is pravastatin at 40 mg.

Back to the **lipidologist**: The large VLDL-P is very high at 14.2 (90th percentile) and the VLDL size is huge at 54.2 nm (about the 80th percentile), When these VLDL-P's are too large, they are not processed correctly by LPL. Thus, VLDL-P's do not convert to IDL's, which do not convert to LDL-P's. This accounts for the low number of LDL-P measured.

TD comment: *Well the large VLDLs as previously mentioned do contribute to plasma viscosity and are associated with coagulation and inflammatory abnormalities (PAI-1 and fibrinogen). There is certainly a problem with VLDL catabolism for the following reasons: with very high TG you can bet there are also way too many huge chylomicrons which compete with VLDLs for LPL and because of their much larger size, more apoC-II (the ligand for LPL) chylomicrons are the preferred substrate for LPL - thus delaying VLDL catabolism and increasing its plasma residence time. In addition IR patients usually have apoC-III abnormalities (which prevents apoC-II on TG-rich lipoproteins from binding to LPL), thus further delaying VLDL & chylomicron catabolism and worsening postprandial TG levels. But realize that delayed catabolism does not mean no catabolism - so in drug-naive patients delayed catabolism of increased numbers of VLDL does not reduce LDL-P, but ultimately increases LDL-P. Therefore the comment above as to why the LDL-P is low is not correct.*

***However** although I do not think it is in play here, there is one condition where very high VLDL-P is associated with low LDL-P and that would be the Fredrickson Type III hyperlipoproteinemia - a disorder characterized by marked elevation of VLDL remnants and IDLs, due to apoE and hepatic lipase and other abnormalities. In those patients there is little conversion of the remnants to LDL. However untreated Type III patients in addition to very high TG levels also have very high LDL-C even though they do not have increased LDLs. That is because in reality LDL-C = IDL-C + LDL-C and Type III patients have very high IDL-P and IDL-C. So LDL-C is high driven by the high IDL-C, not LDL-C. But the proper treatment for Type III is a statin and a fibrate, so could this patient be a partially treated Type III? I doubt it, but one could ask LipoScience to report concentrations of small VLDL-P and IDL-P and also use other*

labs to do apoE genotyping to look for the apoE2/E2 genotype (although E2/E2 is not a 100% requirement for Type III). An apoB level would enable one to use the Sniderman formula for diagnosing Type III (Journal of Clinical Lipidology (2007) 1, 256–263). Sniderman noted all cases of type III had a TC/ApoB ratio >6.2 and a TG/ApoB ratio of <10.0. Using LDL-P as a surrogate of apoB, those ratios would not seem to be the case in this patient.

Could this patient have partially treated Familial Hypertriglyceridemia? Such patients, when drug naive have very high TG levels (>1000 mg/dL) but have normal apoB (LDL-P and thus are not at much CV risk. The high TG levels are explained by the presence of vary large VLDLs, but there are not vastly increased numbers of VLDLs. Because of his adopted status, we cannot inquire about a family history of very high TG or pancreatitis.

Lipidologist: Also, these huge VLDL particles are overstuffed with TG at a ratio of greater than 5:1 TG:CE. These huge VLDL-P's are using CETP to exchange TG from the VLDL-P for CE from LDL-P and HDL-P. The LDL-P's and HDL-P's get overstuffed with TG, and this distorts the 4:1 CE:TG ratio for the LDL-P and HDL-P. LPL and HL remove the excess TG from the LDL-P and the LDL-P shrinks to a small size particle. In fact, in this patient with total LDL-P of 695, 681 are the smallest size at 19.3 nm, which is 98% small LDL-P.

***TD comment**: Not much to disagree with those statements except the 4:1 CE/TG ratio is 4:1 for a normally composed LDL. However, the CE/TG ratio for an HDL is not 4:1 but more like 9:1. One should also be aware the various HDL species also use CETP to exchanges lipids between themselves. The exchange does not have to be solely between apoB and apoA-I particles. Also please note LDLs and HDLs are not substrates for lipoprotein lipase. Finally, it is total LDL-P, not small LDL-P per se that relates to atherogenesis. In general untreated patients with small LDL have increased LDL-P: the particle concentration not the particle size is what relates to the atherogenesis.*

Lipidologist: The HDL-P's with excess TG also are acted on by LPL and HL, lose the excess TG, and form a very small size HDL-P. Total HDL-P is only 24.8 (<25th percentile), very small size at 8.4 nm (smallest measured), and large HDL-P is <0.7 (least measured). These tiny HDL-P's are lost in the urine.

***TD comment**: HDLs are acted upon (undergo lipolysis, which is the hydrolysis of TG and surface phospholipids by hepatic lipase and endothelial lipase and some secretory phospholipases but not LPL. Also as small HDLs undergo lipolysis they may break apart and shed apoA-I which can pass through the glomerulus. The kidneys do not excrete intact HDL particles.*

Lipidologist: His LP-IR Score (Insulin Resistance) is 81, making him very high insulin resistance. His DM is being treated by his endocrinologist. Unless he has better DM treatment, his TG will not improve. The patient is 122 lbs over his ideal weight. Unless he loses weight, his DM cannot be improved.

***TD comment:** I have already commented on the on-treatment Lp-IR score. His Hgb A1c is 6.6 which the ADA would consider as adequately treated diabetes - so I am not so*

sure that the residual high TG is due to glycemic issues. There are so many abnormalities, beyond glycemia, in IR patients that can explain high TG: such as lipase activity, C-III, C-I, CETP activity, etc.

Lipidologist: This patient is a nightmare of risk, not "at goal" as his very low LDL-P might suggest. He needs aggressive lipid management and changes to his care.

TD comment: *Well nightmare may be a Dayspring CV risk term, it is not an official NCEP, risk category. Let's call this patient very high risk. However the LDL-P is at goal and the only treatable lipoprotein abnormalities left are the high VLDL-P (and ? IDLs) and very low HDL-P. Of course there are no recognized goals for VLDL or HDL particles or lipid content.*

Lipidologist: I suggest several changes to his lipid treatment:

- Stop pravastatin 20 mg. This is not even at the recommended starting dose, and will be too weak for this patient's needs. Begin a powerful statin like Crestor 20mg daily.

TD comment: *Unless a type III is present which I do not think is the case, this dose of pravastatin is doing an excellent job of controlling LDL-P. However if one wants to better control TG a more potent statin like Crestor or Lipitor could be considered: upregulating additional LDL receptors with those statins might help clear additional VLDL particles and further lower TG. Because of a powerful effect on lipoprotein lipase perhaps pitavastatin (Livalo) could be considered. Pitavastatin is also effective in increasing apoA-I production and upregulating ABCA1, the cell membrane cholesterol transporter that lapidates prebeta HDL.*

- Change fenofibrate 160 to Trilipix 135. FDA approved for combo with Crestor 20. This may be better at lowering the TG.

TD comment: *The main reason to do that switch would be to officially stay on label. Although we know fenofibrate is extremely safe with statins (see FIELD and ACCORD trials) only fenofibric acid has FDA approval to combine with low and moderate dose statin. I know of no head to head data that would suggest the fibric acid fenofibric acid would lower TG and more than its prodrug fibrate (fenofibrate).*

- Begin Lovaza 1 gram, 4 daily to lower TG. With a TG of 357, we have to be concerned about pancreatitis. As the TG goes down, the LDL-C and LDL-P will go up. This is not a bad effect. The very large VLDL-P's will begin to be processed resulting in more LDL-P's being formed that are of the proper size to be cleared by the liver LDL-R. The stronger statin Crestor will upregulate the LDL-R to improve LDL-P clearance.

TD comment: *I do not thing there is any risk of pancreatitis with a TG of 357. As mentioned I do believe the high TG are contributing to other risk factors and the*

increased lipolysis of HDLs leading to the reduction in HDL particles. So adding Lovaza would help with further VLDL and TG lowering, but another option would be to consider Niaspan titrated up to maximal dose to further improve the TG and raise HDL-P. His HgbA1c can be watched. Also the statement that as TG go down, LDL-C and LDL-P will go up is not true. LDL-C may go down, stay the same or even rise, depending on many factors. LDL-P will stay the same or go down a bit (TG lowering will reduce CETP activity and newly formed LDLs will be larger and more amenable to LDL receptor endocytosis and removal from plasma. Again I really do not see the need for Crestor with an LDL-P < 700 nmol/L.

- **Lipidologist:** Therapeutic Lifestyle Changes (TLC): this patient MUST make his commitment to weight loss. If he does not do his part, then nothing that we do medically will be fully effective. He needs a reduced calorie, low fat, low carbohydrate, no alcohol diet. Weight loss will improve insulin resistance, improve DM treatment and help lower TG.

TD comment: *This patient is probably not going to commit to lifestyle. My guess is this patient should be evaluated for bariatric surgery. If he is suddenly going to be compliant with lifestyle the smoking and alcohol will have to go and orlistat can be considered.*

- **Lipidologist:** Implement changes listed above, repeat the LipoProfile in 3 months, goal for patient to lose 10 lbs before next lab. Further adjustments based on his response.

TD comment: *With the LDL-P being excellent, the only thing I'd be looking for in 3 months with respect to lipoproteins is an increase in HDL-P, and a reduction in TG-rich lipoproteins.*

Lipidologist: This case illustrates that even a low LDL-P can be misleading if you do not know how to incorporate the rest of the data.

Final TD comment: So the nurse was off to a good start, but I think the lipidologist was correct in recognizing additional risk and I do think the patient will require Lovaza and Niaspan.