LIPID CASE 250 Following Lipids over Time

A provider contacted me and stated: "I had a family friend come in the other day with the following situation: 42 year old white female with a family history of both parents on lipid meds but no known CVD and a brother with T2DM. She herself has had cholesterol and TG abnormalities for, many years (see labs below). Her BMI is 27.2, waist size 34 inches and BP 170/110 mm/hg. No signs on PE of atherosclerosis: no arcus senilis and no xanthomas."

1992 TC = 248 LDL-C = 171 TG = 298 (she was age 24) (all in mg/dL)
1994 TC = 235 LDL-C = 153 TG = 193 (age 26)
2009 TC =356 LDL-C = 260 TG = 233 HDL-C = 49

The provider noted her dietary habits showed no gorging on saturated fat. He says she clearly has the metabolic syndrome and after seeing the latest profile she bluntly asked what the hell happened. (those are the patient's words - No Jersey Boy would ever use the word hell!). Making a diagnosis of familial combined hyperlipidemia but suspecting development of a mutation the clinician asked about testing for LDL receptor mutations, apoB gene mutations and markers of sterol absorption and synthesis as well as inflammatory markers. He started the patient on Vytorin 80 mg and supplemented with Omega-3 fatty acids and aspirin. I was asked for thoughts on the big change in lipid concentrations.

DAYSPRING DISCUSSION:

To answer the patient: Nothing really happened: I believe we are simply dealing with Familial Combined Hyperlipidemia (FCH) and age related worsening insulin resistance (IR). She has at least 3 of the metabolic syndrome criteria, noting the borderline waist size does not qualify, but hypertension and TG/HDL-C axis disorder do (I was not given the glucose): The IR is driving her abnormally inherited lipogenic genes. Keep in mind the most common cause of worsening IR is age - the second is of course poor lifestyle. Let's take a close look at the lipids over time and see is she really much worse off with CV risk now than she was 18 years ago? Let's also do some calculations to more fully examine and better understand the older lipid data. You all likely noted HDL-C was not reported to me on the older profiles. No problem: we can calculate them.

In 1992 at age 24 her
HDL-C is calculated as = TC - [LDL-C + VLDL-C]
HDL-C = 248 - [171 + 60] = 17 (VLDL-C = TG/5)
Her non-HDL-C is then calculated as 231 (extreme elevation)

In 1994 her HDL-C = 235 - [153 + 38] = 43
Her non-HDL-C was 192 No major change since 1992 (still an extreme elevation)

In 2009 her non-HDL-C is 50% worse at 307 (an even worse extreme elevation)

In effect she was a lipid disaster way back in 1992 and 1994. Relatively speaking she is simply a somewhat worse CV risk disaster in 2009.

As mentioned, the diagnosis is familial combined hyperlipidemia or FCH (IR related hyperbetalipoproteinemia, a termed coined by guru Pete Kwiterovich a long time ago). Her real problem is way too many betalipoproteins (LDLs). This condition almost always worsens with age, and lifestyle. The patient is a little young to consider menopause but when that occurs and she becomes estrogen deficient, the IR and lipid panel may worsen further.

Is there an apoB or LDL receptor mutation at play here? I doubt it as these folks usually have hypercholesterolemia (FH). We can only speculate on the following mutation possibilities related to FH:

1) Defective LDL receptors (LDLr): multiple abnormalities from synthesis, translocation to cell membrane, internalization, etc are known. Testing would be expensive and not really change therapeutic approach.

2) Defective apoB: the apolipoprotein B molecule is abnormal and thus not readily recognized by LDLr resulting in delayed clearance of apoB particles.

3) PCSK9 overexpression: Proprotein Convertase Subtilisin Kexin Type 9 gene regulates a protein (peptidase) involved with LDLr degradation. Reduction of LDLr half life would clearly elevate apoB and the lipids those particle traffic. Such patients have increase d CVD risk. Interestingly under-expression results in hypobetalipoproteinemia and longevity.

FCH is a multifactorial disease in which several genes affect the lipid and lipoprotein metabolism: her lipogenic (both fatty acid and cholesterol) genes been working overtime-this has to be age, including the insulin resistance (also age related), ? early estrogen loss related?, or who knows what? Please see the new article in references 1 and 2 below for a nice discussion on the etiology of FCH.

Any 24 year old with an LDL-C of 171 mg/dL has to be considered as having some type of FH or FCH if the TG are also quite high. Elevated apoB would confirm the diagnosis. Measuring sterol synthesis and absorption markers can provide interesting insight as to prognosis and treatment. Patients with elevated noncholesterol sterol levels (sitosterol, campesterol, etc.) are known to have increased CHD risk (PROCAM, Framingham Heart Study and others). Insulin resistant folks also typically have over-absorption of sterols. Elderly folks, especially diabetics have increased mortality. Another reason to document the sterols (order cholesterol balance test at Boston Heart Labs) is that this patient is surely going to need a high dose statin, all of which can worsen or induce over absorption of cholesterol and noncholesterol sterols (potentially more atherogenic). If the apoB is as high as I suspect, I cannot imagine this patient can be controlled without ezetimibe as part of the regimen. One might say - if you are going to use ezetimibe anyway to get to goal, why spend money on sterol testing? I like to know what is happening and if she has full

blown sitosterolemia her therapy will be very different than if she does not. Now that sterol testing is available, I think we are going to find the incidence of phytosterolemia is higher than we ever imagined. Virtually all new patients to my high-risk lipid referral practice get the cholesterol balance test, especially those on high dose statin monotherapy. (Please note: I have no relationship with Boston Heart Lab). Also do not get me wrong: LDL-P or apoB is the #1 test – we need that before or with sterol testing.

Lipoprotein phospholipase A2 (Lp-PLA2) or PLAC test, an atheroma specific inflammatory marker, would be of interest but her CV risk is high and it would not change treatment. Personally I never use simvastatin 80 mg as there are far too many drug-drug interactions and being the most lipophilic statin, it (at that dose) has the worse risk for myopathy of all the statins. This woman is going to need Crestor 20, Zetia 10, and one or more of these three in no particular order: 1) Lovaza 4000 mg (to get a TG effect) or 2) Trilipix or 3) high dose Niaspan. I would also screen her for CHD with coronary calcium imaging and after a stress test get her on a serious aerobic exercise program. If I had a reliable place to do it in NJ, CIMT testing would be helpful.

In retrospect using today's knowledge, this woman probably needed to be on drug therapy many years ago.