LIPID CASE 259 Assessing CV risk when HDL-C is quite low

The case is a 20 year old white male, who has a BMI 28. He appears muscular but has a girth of 35-36 inches. He exercises regularly and uses little to no alcohol. There is a positive family history of lipid abnormalities but no premature CAD and no diabetes.

BP is 122/62. Examination was normal without evidence of xanthomas, corneal opacities or orange tonsils, etc. Laboratory evaluation is as follows:

Glucose 87 BUN 13 Cr 0.9 TSH 1.07 No proteinuria

Standard Lipids TC = 101 TG = 100 HDL-C = 20 LDL-C calc = 61 non-HDL-C = 81

Apo B measured directly = 84 with recheck Apo B = 71

Lp(a) = 3.5 mg/dl measured directly

Apo A-I = 117 mg/dl Ratio apoB/A1 = 0.6

NMR from LipoScience

Total LDL-P = 1048 nmol/L with Small LDL-P = 625
Total HDL-P 15.7 (extremely low)
LDL size 20.4 (Pattern B) Small defined as < 20.6 nm
Large VLDL-P nmol/L 2.0 (just under 50th percentile)
Large HDL-P umol/L 1.8 (low)
VLDL size 44.4 (50th [percentile)
HDL size 8.5 (small)
LP-IR score 62 (> 50 suggests insulin resistance)

The clinician states:" I am obviously concerned with insulin resistance and dyslipidemia in a young adult and I suggested 20 # weight loss and have explained to him the importance of maintaining normal body weight. Heaven forbid if he balloons and becomes a big fat person. From a lipid point of view, I am sure that he is excreting HDL particles via the kidney. I also told him that he probably needs lifelong lipid therapy. Thus I elected to touch him with Simcor 500/20 mg daily to see how well he tolerates it and to see what it does to improve particle number and size. I am not "treating his HDL-C."

DAYSPRING DISCUSSION

As always, before we offer treatment recommendations, we must do an accurate risk assessment. Looking at the above data, risk is suggested by increased waist size (I am not sure if the borderline BMI is muscular or fat), small LDL and HDL size, the slightly elevated NMR derived Lp-IR score (although that score should be used to predict diabetes onset and not CV risk per se), the markedly reduced HDL-C, apoA-I and HDL-P and of course the elevated apoB/AI ratio which was a potent risk factor in the INTERHEART Study (Lancet 2008; 372: 224–33) -- indeed the INTERHEART authors stated "*the ratio was superior to any of the cholesterol ratios for estimation of the risk of acute myocardial infarction in all ethnic groups, in both sexes, and at all ages, and it should be introduced into worldwide clinical practice*." The same findings with respect to apoB and the apoB/A-I ratio were noted in the primary prevention trial AFCAPS-TexCAPS ((Circulation 2000;101:477-484.) Contrast those apo conclusions to those in reference 7 below. Against increased risk in this man is age, BP, no smoking, no family history, exercise status, normal (*at goal) LDL-C and non-HDL-C and most importantly an apoB and LDL-P at the 20th percentile population cutpoint (very desirable). For a young man to qualify for drug therapy he has to be high or very high risk. So have all of you decided in your own mind how much risk this man

has? With respect to the low HDL parameters do all agree the explanation is this young man is excreting his HDL particles? Well I am far from convinced this man has any CV risk. There are genetic hypoalphalipoproteinemia conditions that do not seem to be associated with atherosclerosis and of course other such low HDL states are.

1) ApoA-I (the primary HDL structural protein) is initially lipidated at cell membranes (primarily hepatic and jejunal) by the ATP binding cassette transporters (ABCA1). As unesterified cholesterol associates with apoA-I (along with some phospholipids) the free cholesterol is esterified by the enzyme lecithin cholesterol acyl transferase (LCAT) which transfers a fatty acid from the phospholipid (lecithin) to the 3 position of cholesterol, creating the hydrophobic molecule cholesteryl ester. If one lacks total expression of ABCA1, HDL particles cannot acquire cholesterol and the apoA-I can be eliminated via the kidneys. By the way kidneys cannot excrete intact HDL particles, but as the HDL breaks down and releases apoA-I, that can be excreted or reabsorbed through a pathway utilizing the tubular cubilin-megalin complex (for some very new and amazing information on how GFR influences HDL see reference 2 below). The homozygous absence of ABCA1 is called Tangiers Disease. It is quite rare and the HDL-C is near zero. The patients also have elevated TG (thought to be due to delayed catabolism of VLDL, possibly due to apoA-II on VLDL slowing lipolysis: see reference 3 below). Although Tangier patients get ASHD, disease severity is very dependent on the apoB level. If one has a heterozygous deficiency of ABCA1, HDL-C can be in the 20 mg/dL range and again whether ASHD occurs is in large part apoB related. Heterozygosity for an ABCA1 mutation (K776N) conferred two- to three-fold risk of IHD in 37 participants in the Copenhagen City Heart study. (J Am Coll Cardiol 2005;46:1516–20). In another analysis of the same study lower plasma levels of HDL-C due to heterozygosity for loss of-function mutations in ABCA1 were not associated with an increased risk of CHD v(JAMA. 2008;299:2524-2532). In these cases there is reduced lipidation of HDL particles: HDL-C can be reduced by 50 % and these patients with low HDL-C do not get CHD unless TGs (likely a refection of apoB) are high. Could this man have an ABCA1 loss of function mutation and not be at risk for CHD. You Betcha!

2) A deficiency of LCAT prevents esterification of cholesterol within HDLs and apoB particles. Without esterification the HDL particles cannot mature (enlarge) and they are vulnerable to increased catabolism and renal excretion of apoA-I (the HDL-C is usually well under 20). NMR analysis will often pick up lipoprotein X in these cases and that was not seen in this man. For a discussion of Lp(X) go to my web site www.lipidcenter.com (file is attached under lipid and lipoprotein study materials). Heterozygous LCAT patients (Fish Eye Disease) often have corneal opacities and palmar xanthomas. Likely this man does not have LCAT deficiency.

3) Hypoalphalipoproteinemia due to markedly decreased production of apoA-I. Usually associated with significant CHD risk.

4) Secondary causes of severe acquired hypoalphalipoproteinemia: Paraproteinemias, very high TG, certain drugs (man must be questioned about anabolic steroid use): for a discussion of acquired low HDL-C, see Journal of Clinical Lipidology (2007) 1, 41–56).

Of course the most commonly seen cause of low HDL-C that is associated with CHD risk is insulin resistance, metabolic syndrome or T2DM. What suggests IR in the above patient? Waist size and the somewhat elevated NMR Lp-IR score (lipoprotein associated insulin resistance score). The reason his score is > 50 (with 100 being the highest score and 0 the lowest) is he has small LDL phenotype, has small HDL size and has a low concentration of large HDL-P. Of course in real IR, those parameters are usually TG induced: large TG-rich VLDLs transfer their TG to LDLs and HDLs using CETP, creating TG-rich, CE-poor LDLs and HDLs which upon exposure to hepatic lipase reduce in size (hence small HDL, lack of large HDL and small LDL). HDL mapping (see next paragraph) would show high levels of the small preβ-1 and α-3 HDL particles which are markers of high risk (see reference 5 below). Although the NMR technique cannot measure prebeta HDL particles, in the past they did report small HDL-P (not to be confused with prebeta HDL), but alas have stopped doing that. What IR patients usually have (explaining much of their

risk) and this man does not have is increased total LDL-P, increased small LDL-P and increased large VLDL size. I believe in this case the Lp-IR is a false positive. His small HDL size and lack of large HDL-P may simply be due to his HDL disorder and not IR.

So the only real way to get to the bottom of this patient's diagnosis is to send a blood specimen to Boston Heart Lab for their sophisticated HDL Mapping: www.bostonheartlab.com It will be well worth your time to check out: http://www.bostonheartlab.com/HealthCareP_Science_Animation.html The Niaspan and statin should be stopped in this case before sending the blood to Boston HL. Niaspan affects HDL remodeling and would affect the results.

Now to respond to other comments the clinician raised: He stated he is not treating his "HDL" My reply is if not why is he using a drug in this man with normal LDL-C, non-HDL-C or more importantly apoB and LDL-P? The patient may as I discussed above have zero CV risk. The work up at this stage is incomplete (needs a correct HDL diagnosis only obtainable at Boston Heart Lab). The clinician is assuming but does not know if the patient is excreting apoA-I or not (my colleagues at Health Diagnostic Labs in Richmond, VA (*www.**hdlab**inc.com*) advise me apoA-I can be assayed in the urine but that is not a currently available test to clinicians). Maybe the patient is not making apoA-I or maybe he has a benign ABCA1 loss of function mutation (resulting in incomplete lipidation of his HDLs). Since there are hypoalphalipoproteinemias that are not associated with CHD one may not need specific Rx if apoB and LDL-P are normal. Let's presume despite the normal TG, glucose, BP, that this man is IR. Since LDL-P, apoB, LDL-C and non-HDL-C are at goal, lifestyle and not prescription Rx is all that is needed! In this case the apoB of 80 and LDL-P of 1000 are 100% concordant (in agreement) and are perfect. The ADA/ACC consensus statement on patients with cardiometabolic risk, state that the evidenced-based way to reduce CV risk in IR patients with low HDL-C is to normalize apoB (mission already accomplished with no therapy). Reducing the LDL-P or apoB be further would overkill in this man (who is not in a very high risk category).

Lastly LDL size or HDL size per se never needs treatment: no guideline advocates that. Elevated ApoB and LDL-P or their lipid surrogates are what need treatment. So I am not sure why the clinician mentions he wants to see what Simcor does to particle sizes (the niacin will enlarge LDLs and HDLs but niacins benefit is more related to reducing apoB (LDL-P) and raising HDL-P and helping HDL functionality. Many would suggest doing a CIMT study (in capable hands). He is too young for coronary calcium testing and a zero score would not tell much. If the CIMT is abnormal one might conjecture that despite the normal apoB (LDL-P) it might be wise to raise HDL-P, but surely that is speculative and not needed if there is no CV risk. Depending on what is the cause of his reduced HDL parameters, it may be refractory to any pharmacologic Rx.

REFERENCES OF THE WEEK:

1) Clinical Predictors of Plaque Progression Despite Very Low Levels of Low-Density Lipoprotein Cholesterol. Ozgur Bayturan et al. Conclusion: Residual risk factors are associated with the likelihood of disease progression in patients who achieve very low LDL-C levels. In addition, the association between apolipoprotein B and atheroma progression highlights the potential **importance of LDL particle concentration in patients with optimal LDL-C control.** This finding highlights the need for intensive modification of global risk in patients with coronary artery disease. (J Am Coll Cardiol 2010;55:2736–42)

2) Lower HDL-C and apolipoprotein A-I are related to higher glomerular filtration rate in subjects without kidney disease. Jan A. Krikken et al. In conclusion, HDL-C and apoA-I are inversely related to e-GFR and creatinine clearance in subjects without severely compromised kidney function, which fits the concept that the kidney contributes to apoA-I regulation in humans. High glomerular filtration rate may be an independent determinant of a pro-atherogenic lipoprotein profile.

3) Human Apolipoprotein A-II Determines Plasma Triglycerides by Regulating Lipoprotein Lipase Activity and High-Density Lipoprotein Proteome Josep Julve et al. ApoA-II plays a crucial role in triglyceride catabolism by regulating LPL activity, at least in part, through HDL proteome modulation. (Arterioscler Thromb Vasc Biol. 2010;30:232-238.)

4) Colesevelam Added to Combination Therapy With a Statin and Ezetimibe in Patients With Familial Hypercholesterolemia: A 12-Week, Multicenter, Randomized, Double-Blind, Controlled Trial Roeland Huijgen et al. Clinical Therapeutics/Volume 32, Number 4, 2010 p 615-

5) Plasma triglyceride levels and body mass index values are the most important determinants of prebeta-1 HDL concentrations in patients with various types of primary dyslipidemia Vasilis Tsimihodimos et al. All dyslipidemic patients exhibit increased pre-1 HDL concentrations as compared to normolipidemic individuals. Whether this increase represents a defensive mechanism against atherosclerosis or it is indicative of impaired maturation of HDL particles and thus of a defective reverse cholesterol transport mechanism remains to be established. Atherosclerosis 208 (2010) 506–511

6) Beyond Hemoglobin A1c—Need for Additional Markers of Risk for Diabetic Microvascular Complications. Very interesting commentary by Irl B. Hirsch and Michael Brownlee. JAMA, June 9, 2010—Vol 303, No. 22 2291

7) Ability of traditional lipid ratios and apolipoprotein ratios to predict cardiovascular risk in people with type 2 diabetes M.-R. Taskinen et al. Conclusions/interpretation In patients with type 2 diabetes in the FIELD study, traditional lipid ratios were as strong as the ApoB:ApoA-I ratio in predicting CVD risk. The data provide little evidence for replacement of traditional lipids and their ratios with measures of ApoB, ApoA-I and their ratio. Diabetologia DOI 10.1007/s00125-010-1806-9 **DAYSPRING ANALYSIS** Remember, FIELD enrolled low risk T2DM of short duration with basically normal TG and HDL-C levels. Many did not have atherogenic dyslipoproteinemia. In post hoc analysis of FIELD, the only patients fenofibrate worked in were those with metabolic syndrome and TG > 200 mg/dL with reduced HDL-C. I suspect in those patients there would have been a robust relationship with risk and apoB/ApoA-I compared to lipids.