

Hello friends: I received the following case from a clinician who writes: I have a 36 yr old female with a history of PCOS, obesity (wt 235 ht 67 3/4 ") with no reported familial history of CVD.

She had lipids in '94 revealing a TG of 229 then again in '95 with a total cholesterol of 198 and trig 309. At that time going through infertility treatment with Clomid. Was on metformin 1998 on and off through 003 with no change weight (maybe even an increase so it was stopped) .

On OC's lipids in 2/03 (on metformin)

TC = 212; TG = 237; VLDL-C = 47; LDL-C = 110, HDL-C = 55

Non HDL-C = 177 (perfect under 130)

Glucose = 92 Insulin = 16 (elevated)

Off OC's this year (no change weight)

TC =168, TG =101, HDL-C = 42; LDL-C = 106, VLDL-C = 20

CRP 6.6! (quite elevated)

I do think I need to worry about her. Obviously the OC's increase her TGs. She is back on them again due to irregular menses. I don't think I have enough to justify other med use? (except that CRP). Would appreciate your thoughts.

DAYSRING ADVICE: (limited to lipids not management of other aspects of PCOS)

I agree very much that the clinician does have to worry about her. This is one of the cases that drive good docs (who like to prevent CVD) nuts in planning therapeutic options. She qualifies for the diagnosis of metabolic syndrome (ICD code 277.7) and is insulin resistant (with an elevated insulin). Her hs-CRP is elevated and this puts her in the highest CV and diabetes risk quartile of the metabolic syndrome patients. Elevated CRP significantly worsens the prognosis of patients with the metabolic syndrome. We are not given any BP information.

You are correct in saying drug therapy would not be justified using the NCEP guidelines. Her Framingham risk score severely underestimates her risk. Framingham does not take into account weight, TG, or insulin resistance. However, they are simply guidelines written in 2001 when we were less knowledgeable on insulin resistance and hs-CRP. Good docs use guidelines as a map pointing us in the right direction, but we have to be ready to deviate when "blocks in the road" appear.

If we evaluate this case using the new (just published) AHA Guidelines for Women

1) Off OCs: Her HDL-C is below the goal of 50 and her LDL-C is above the goal of 100 and her non HDL-C is just under the desired 130.

2) On OCs last year: the TG, HDL-C, LDL-C and Non HDL-C are all abnormal.

Since you have restarted the OCs, we can expect deterioration in her lipids (TG) and her CRP. At her age if she is not going to be very aggressive with a major change in lifestyle (to include exercise) I would use medication to lower her CV risk. I believe the increased non HDL-C with the very elevated CRP mandates it.

ADVANCED DISCUSSION

If we had to guess what advanced lipoprotein testing might reveal, it would be:

Increased TG and low HDL-C are surrogates for large VLDL (precursors of small LDL), remnant lipoproteins (chylomicrons and VLDL), small LDLs (more atherogenic than large) and a lack of large HDL particles. All of the boxes on the NMR LipoProfile report form will be highlighted with a checkmark. We might be very astonished, as in this type of patient I have often found tremendously increased LDL particle concentrations (>1800 nmol/L). The LDL-C value is unremarkable because the particles are so very small. We often forget that the volume of a sphere is a cube of the radius. So even very

minor decreases in LDL particle diameter change (lessen) the internal lipid concentration (cholesterol) dramatically. Yet the actual particle concentration is very elevated. Since most clinicians focus solely on LDL-C, much lipoprotein pathology is missed.

Remember from previous discussions patients with elevated TG have TG-rich LDLs and HDLs (when those particles usually carry cholesterol and very little TG). LDL and HDL particles carrying excess TG, carry less cholesterol: hence the LDL-C and HDL-C levels will be reduced in the face of hypertriglyceridemia. The TG-rich LDL and HDL become substrates for hepatic lipase.

Hepatic lipase (HL) is an interesting member of the lipase family. It has equal properties of being a TG lipase and a phospholipid lipase (unlike lipoprotein lipases which pretty much hydrolyzes only TG). Hence, HL will not only remove TGs from the core of LDL and VLDL particles but will also hydrolyze surface phospholipids which also reduces the size of the lipoprotein.

Drugs like estrogen and niacin inhibit hepatic lipase. Patients on those drugs will have large HDL particles and when one prescribes those drugs, we usually see increases in HDL-C levels. If you check NMR LipoProfiles the concentration of large HDL particles increase. There is evidence that large HDL particles that have not been subjected to modification by HL, cannot be delipidated at hepatic SRB1 (HDL receptors) thus rendering such particles ineffective in direct delivery of cholesterol to hepatocytes. However, using cholesteryl ester transfer protein (CETP) the large HDL particles can transfer cholesterol to LDL and VLDL particles which then be removed by hepatic receptors.

Fibrates do not inhibit HL and increase hepatic SRB1 (which rapidly delipidate and make small) large HDL particles. So when prescribing a fibrate one will not see an increase in large HDL-C. HDL-C levels usually goes up on fibrates because of significant PPAR alpha induction of apoA synthesis (causing a lot of small HDL particles).

TREATMENT:

I would use pharmacologic approach in this patient. We can always stop it if lifestyle therapeutics is successful.

If we assume her lipids will return to the previous set on OCs, you can make the case (USING LIPID VALUES) for initial pharmacologic therapy with TriCor 160 mg daily or a statin like Pravachol 40 mg (the only statin with data that it can lower insulin levels and delay the on set of impaired fasting glucose and diabetes). There was very interesting trial data presented at ACC revealing that Zetia can also contribute significant to reductions in remnants and Non HDL-C in insulin resistant patients.

If we had NMR particle data and if it did reveal a LDL particle concentration > 1400 nmol/L I would use the Pravachol 40/Zetia 10 mg regimen as initial therapy. It would be very likely that TriCor 160 mg would ultimately have to be added to the regimen (that would be off-label use with Zetia). We always must remember that 40% of the benefit fibrates bring to the management of insulin resistant patients is pleiotropic (not related to lipoprotein benefits).

Metformin at a dose of 2000 mg should also be in the regimen if she is not going to loose weight. As usual baby ASA and omega-3s make good sense.

REFERENCES OF THE WEEK

Effect of an inhibitor of CETP on HDL-C New Eng J Med 2004;350:1505-1515
Even more important is the perspective written by Bryan Brewer (Mr. HDL)

New Eng J Med 2004;350:1491-94 This is a superb state of the art discussion of reverse cholesterol transport with beautiful illustrations

Scavenger receptor type BI potentiates reverse cholesterol transport system by removing cholesterol ester from HDL. *Atherosclerosis* 173 (2004) 197–202. Nice study which helps explain what happens to HDL particles at the liver.

Commonly Used Types of Postmenopausal Estrogen for Treatment of Hot Flashes
Scientific Review *JAMA*. 2004;291:1610-1620 Lots of options

DAYSRING VENUES

Will be doing a series of CME National Teleconferences on Management of Dyslipidemia associated with Diabetes and the Metabolic Syndrome. Call 1-800552-5487 for dates and details

Nebraska Heart Institute Annual Lipid Conference (Lincoln, NE) Next weekend
Indianapolis and Fort Wayne, IN (Menopausal not lipid lectures)
Houston TX and Los Angeles, CA (CME Dyslipidemia Conf)
MidAtlantic Nurse Practitioner Meeting College Park, MD
Bethlehem, PA
Chicago, IL (Menopausal not lipid lectures)
Scarsdale, NY
New Brunswick, NJ
St. Louis, MO
Atlanta, GA
Chattanooga, TN

On this Easter weekend, I hope all take a moment to pause and reflect and have special thoughts about the men and women protecting our way of life at home and especially abroad. What very special people they and their families are!

Happy Lipiding,

Tom

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