

Case Study: Advanced Lipid Testing—Beyond LDL-P and Apo B

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JM, a healthy 45-year-old woman who is on a low-glycemic diet and exercises 150 minutes a week, comes in for an evaluation of abnormal lipids despite her excellent lifestyle efforts. She is resistant to “cholesterol-lowering” medication and is interested in understanding her risk for cardiovascular disease (CVD). There is no family history of premature CVD, but her mother and maternal grandmother both had adult onset Type 2 diabetes.

Pertinent initial labs:

Total cholesterol	250 mg/dL
LDL-C	150 mg/dL
Triglycerides	220 mg/dL
HDL-C	56 mg/dL
Non-HDL-C	194 mg/dL
HsCRP	3
Fasting glucose	98 mg/dL
HbA1C	5.7%
ALT/AST	within normal limits
TSH	1.24 mIU/L
Blood pressure	120/82
Body Mass Index	25

According to the recently published American Heart Association (AHA) guidelines for CVD prevention in women, JM would be characterized as “at risk” based on having a high total cholesterol of

>200mg/dL and diastolic blood pressure of >80mmHg.¹ Her Framingham Risk Score is <5%; it is therefore debatable whether lipid-lowering therapy is indicated. Recent data from the Multi-Ethnic Study of Atherosclerosis (MESA) study² supporting previous research shows CV risk is more directly related to the low-density lipoprotein particle (LDL-P) concentration than to low-density lipoprotein cholesterol (LDL-C), and one could argue that LDL-P or apolipoproteinB (Apo B) would be a better measure to determine her risk for cardiovascular disease. A nuclear magnetic resonance (NMR) analysis was performed, and results are as follows:

LDL-P	2,552 nmol/L (optimal <1000)
Small LDL-P	1,732 nmol/L (optimal <850)
HDL-P	48 umol/L
LP-IR score	65 (optimal <45/100)

Her LDL-P of 2,552 is considered very high risk and places her in the >95th percentile of the population based on both Framingham and MESA data (Table 1). If there were any hesitation to treat her dyslipidemia, one would be more inclined to treat with this additional information and elevated highly sensitive C



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reactive protein (hsCRP). She is currently preventing future childbearing, so a statin would be the first choice of therapy. If she

“Insulin resistance is a common secondary cause of dyslipidemia characterized by high triglycerides and low HDL-C.”

is open to pregnancy, then alternatives to statin could include niacin, fibrates or bile acid sequestrant. A bile acid sequestrant would help lower LDL-P but should not be the first choice, because it has the

potential to raise triglycerides further. Now, let's take a step back before getting out the prescription pad.

It is important to rule out secondary causes of dyslipidemia before initiating lipid-lowering therapy, especially in a patient with no family history of CVD. She is on no medications or supplements, so this is not a secondary cause. She has had a normal thyroid-stimulating hormone (TSH) test, ruling out hypothyroidism as a contributor to dyslipidemia. Her glucose was 98 with optimal being <100 mg/dL. Her glycated hemoglobin (HbA1C) was 5.7. American Diabetes Association (ADA) guidelines published in 2010 now consider HbA1C to be a valid diagnostic tool for diabetes.³ They define an HbA1C of 6.5 and above to be diagnostic of diabetes and an HbA1C of 5.7-6.4 to be in the category of "prediabetes."³ This patient also has predominantly small dense LDL, which encompasses more than 50% of her total LDL-P, suggesting insulin resistance is contributing to high LDL-P.

Insulin resistance is a common secondary cause of dyslipidemia characterized by high triglycerides and low HDL-C. The metabolic changes induced by or accompanying insulin resistance produce even greater and more extensive abnormalities in lipoprotein subclass levels and particle size distributions, which are detected by advanced lipoprotein testing.^{4,5} Specifically, large very-low-density lipoprotein (VLDL) and small LDL subclass particle concentrations are higher and large HDL subclass levels are lower in insulin-resistant individuals. NMR-measured VLDL LDL, and HDL particle sizes also reflect insulin-resistance status. VLDL size tends to be greater and LDL and HDL sizes smaller when a patient is insulin resistant. This unique lipoprotein "window" into insulin resistance gives us an opportunity to identify, by nature of the lipoprotein status, a patient who may be a candidate

for more aggressive lifestyle efforts or pharmacologic therapy. Liposcience's Lipoprotein Insulin Resistance Index (LP-IR) score, ranging from 0 (most insulin sensitive) to 100 (most insulin resistant), helps summarize a patient's insulin resistance status based on the strength of associations with each of the lipoprotein parameters listed here. Other labs also include various measures of insulin resistance in their profiles.

Insulin resistance precedes the beta cell dysfunction that ultimately leads to the development of diabetes. Early identification of insulin resistance may help prevent, not just delay, the onset of diabetes. The world is undergoing a diabetes pandemic and it is estimated that the total number of cases will increase by more than 50% during the next two decades, from 285 million cases worldwide in 2010 to 438 million cases worldwide in 2030.⁶ While these statistics may be depressing, it is empowering to know that diabetes is largely a preventable disease if early intervention and prevention efforts are made. Early intervention may include

more aggressive efforts at making lifestyle changes, and, in those at high risk for cardiovascular disease, metformin may be an appropriate initial therapy. It is important to note that no medications are currently FDA-approved to prevent progression to diabetes. However, ADA guidelines recommend metformin therapy for prevention of Type 2 diabetes in those at the highest risk for developing diabetes, such as those with multiple risk factors, especially if they demonstrate progression of hyperglycemia (e.g., A1C ≥6%) despite lifestyle interventions.⁷ Because metformin does not produce hypoglycemia it is safe to use as monotherapy in patients with insulin resistance and normal glycemic status.

There also are cardiovascular mortality data with metformin. In the United Kingdom Prospective Diabetes Study (UKPDS), overweight patients with newly diagnosed Type 2 diabetes were randomly allocated to control their glucose levels by dietary modification alone (n=411) or by undergoing intensive blood-glucose control with metformin (n=342). At the

Population Equivalent Cutpoints for Alternate LDL Measures					
(LDL-C, MEasured Apo B and NMR LDL-P)					
Biomarker	Population	Percentile Equivalent Concentration			
		< 70	100	130	160
LDL-C (mg/dL)	Framingham ¹	< 70	100	130	160
Measured Apo B (mg/dL)	Framingham ¹	< 60	80	100	120
NMR LDL-P (nmol/L)	Framingham ¹	< 850	1100	1400	1800
	MESA ²	< 700	1000	1300	1600

¹Controls, et al. *Clinical Chemistry* 2009;407-419
²Cromwell WC. *Clinical Challenges in Lipid Disorders*. Oxford: Clinical Publishing, 2008:249-259

Table 1.

end of the sub-study (median treatment duration 10.7 years), the median HbA1C level was 7.4% in the metformin group compared with 8.0% in the conventional-therapy group. Treatment with metformin resulted in risk reductions of 32% for any diabetes-related end point (95% confidence intervals (CI) 13%-47%, $p=0.002$), 42% for diabetes-related death (95% CI 9%-63%, $p=0.017$), and 36% for all-cause mortality (95% CI 9%-55%, $p=0.011$), compared with conventional therapy. The risk of myocardial infarction in the metformin group was reduced by 39% ($p=0.011$), and the risk of all combined macrovascular disease end points (myocardial infarction, sudden death, angina, stroke and peripheral vascular disease) was reduced by 30% ($p=0.02$), compared with the conventional-treatment group.⁸

Ten years of post-trial monitoring to determine whether the improved glucose control of intensively treated patients persisted and whether early intensive treatment had a long-term effect on macrovascular outcomes revealed that the difference in HbA1c levels between intensive therapy and conventional therapy was lost after one year. However, the reduction in diabetes-related endpoints was still evident 10 years after completion of the intervention trial. Among patients in the intensive treatment arms, significant reductions in the risk of myocardial infarction (by 15%, $p=0.01$ and by 33%, $p=0.005$ for the sulfonylurea-insulin and metformin groups, respectively) were observed.

At least two retrospective cohort analyses of sulfonylurea and metformin therapies support the UKPDS findings. In the eight-year Diabetes Audit and Research in Tayside, Scotland (DARTS) study of 5,730 patients, there was a 30% lower risk for all-cause mortality in the metformin group, after adjustment for baseline confounders, and a 41% lower risk for cardiovascular

47 yr old female maximized TLC

	FIRST VISIT Doing 150 minutes exercise/week on low glycemic diet	FOLLOW UP at 2 months Metformin ER 1500	GOALS OF THERAPY
Total cholesterol	250	229	<200 mg/dL
Triglyceride	220	99	<150 mg/dL
HDL-C	56	62	>50 mg/dL
LDL-C	150	147	<100 mg/dL
LDL-P	2552	1440	<1000nmol/L
Small LDL-P	1732	592	<850 nmol/L
Non HDL-C	194	167	<130 mg/dL
IR Score	64	42	<45/100
hsCRP	3	1	

Table 2.

mortality.⁹ In the five-year Saskatchewan Health database study of 2,272 new users of oral antidiabetic agents, the adjusted odds ratio (OR) for all-cause mortality for metformin monotherapy was 0.60 (95% CI 0.49-0.74) compared with sulfonylurea monotherapy and 0.64 (0.49-0.84) for cardiovascular deaths.¹⁰

Today, we diagnose diabetes based on impaired glucose tolerance. At the time of diabetes diagnosis, most patients will have lost 60%–70% of beta cell function, which is largely irreversible (Table 2). We need better ways to diagnosis this disease before it causes loss of beta cell function and microvascular and macrovascular complications. In our patient case, metformin ER 1500 mg was initiated at the first visit because of the abnormal HbA1C, family history of diabetes and lipoprotein parameters suggestive of insulin resistance. After two months of metformin use, her lipoprotein and lipid values improved. LDL-P dropped from 2,552 to 1,440 without a significant change in LDL-C. Metformin, as expected, caused triglycerides to improve, and she had a five-pound weight loss without any further

change in her diet and exercise regimen.

Advanced lipid testing provides information beyond just LDL-P and Apo B. This information may allow us to better diagnose a secondary cause of dyslipidemia, namely insulin resistance. Metformin ER, an effective therapy for insulin resistance, is available as an inexpensive generic medication. Metformin also causes weight loss, improves lipids and is pregnancy category B, a safe option in women of childbearing age. The main contraindications for metformin are renal disease and/or elevated creatinine > 1.4. As monotherapy, there should be minimal risk for hypoglycemia. ■

Disclosure Statement: Dr. Dall has received honoraria related to speaking from Abbott Laboratories, GlaxoSmithKline, HDL Labs, LipoScience Inc., and Santarus Inc.

References are listed on page 39.