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L a b o r a t o r y

News

VOL. 32, NO. 8 - OCTOBER 1, 2009

Changes to Lipid Testing

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Currently, a complex lipid-testing algorithm is used by Marshfield Labs. Samples with total cholesterol and/or triglycerides >300 mg/dL are reflexed to lipoprotein electrophoresis. Additional testing may include direct or β -quantification (ultracentrifugation) for LDL-cholesterol (LDL-C) and Frederickson phenotyping. In today's environment however, few clinicians appear to appreciate this labor-intensive workup and the meaning of the interpretive comments. Even Dr. Donald Frederickson indicated that phenotyping has outlived its utility and is presently only of historical interest[1]. For these reasons, beginning October 1, 2009, we are making the following changes.

When a request is made for a lipid panel, the laboratory will measure total cholesterol, triglycerides (blanked), and HDL-cholesterol (HDL-C). Whether the LDL-cholesterol (LDL-C) is reported will be dictated by the triglycerides concentration.

- If the triglycerides are ≤ 400 mg/dL, the LDL-C will be calculated using the Friedewald formula[§] and all results will be flagged using the NCEP ATP III criteria[2].
- If the triglycerides are > 400 mg/dL, the LDL-C cannot be accurately determined; however, the non-HDL-C will always be calculated^z and added to the report. This simple calculation is a surrogate measure of the atherogenic lipoprotein particles, LDL, VLDL, IDL, and Lp(a); it has no limitations for fasting or triglycerides.

[§] LDL-C = Total Cholesterol – HDL-C – (Triglycerides \div 5)
(Triglycerides \div 5 = VLDL-C)

^z Non-HDL-C = Total Cholesterol – HDL-C

NEW LIPID PANEL:

- Orderable description: Lipoprotein Panel, with LDL
- Specimen: Plasma or Serum
- Minimum volume: 1 mL

When triglycerides are above 400 mg/dL, the sample will be held for 5 days to allow additional testing and the following comment will be added: “Unable to determine LDL-C due to elevated triglycerides. See non-HDL-C and consider ordering apo B, which are both unaffected by fasting status.” The apo B can be ordered online using the electronic U-HAVE system.

Why Apo B?

Numerous studies support the utility of apo B and indicate that it's superior to LDL-C as a cardiovascular disease (CVD) risk marker, as well as a better measure to assist monitoring patients on pharmacotherapy (for on-treatment residual risk)[3].

The following are other factors that make the use of apo B favorable over LDL-C:

- Apo B is a measure of total atherogenic particles
 - LDL particles (large or small) and VLDL particles each have one apo B
 - Apo B = LDL particles (90%) + VLDL particles (10%)
 - LDL particles (not simply LDL-C) play a central role in the atherogenic process
- Apo B is unaffected by the variation in cholesterol content of the lipoproteins
 - Since the assay is not cholesterol-based, it's not biased by variations in LDL size
 - LDL-C can vary widely between people with similar LDL particles
- The patient's fasting status does not affect the result
- The apo B/apo A ratio is superior to cholesterol-based ratios
- The automated method for apo B (immunoassay-based nephelometry) is more standardized and accurate than LDL-C and is inexpensive to perform

Fasting vs. Nonfasting

When the blood sample is drawn, the phlebotomist will ask the patient about their fasting status. If the patient indicates they had not fasted, a comment of “patient not fasting” will be entered into the system. If the comment is not reported, the default “fasting” is implied. It is recommended that a lipoprotein profile involving the measurement of triglycerides and the LDL-C calculation be performed on a specimen after a 9- to 12-hour fast. However, the laboratory will no longer offer credit because of non-fasting, *ex post facto*. Triglycerides have value in both preanalytical situations. If the LDL-C is not calculated either because the patient was not fasting or because the triglycerides were >400 mg/dL, the remaining lipids values still have utility.

In fact, non-HDL-C is a secondary target of therapy when triglycerides are elevated[2].

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Recent studies have suggested that nonfasting triglycerides actually have a greater ability to predict CVD risk in both men and women than fasting levels[4,5]. Even after multivariate analysis, these two studies showed that nonfasting triglycerides were a robust independent predictor of future adverse events. When patients were categorized by triglycerides concentrations (using 5 equally spaced cut-points from 89 mg/dL to >443 mg/dL), the adjusted risk for myocardial infarction increased significantly with each increasing category[4]. Among women, the adjusted relative risk increased from 1.7 to 5.4 (compared to triglycerides below 89 mg/dL). For men, the risk increased from 1.4 to 2.4. Relative risk of ischemic heart disease and overall death also increased with higher triglycerides levels for both men and women. Since individuals spend the majority of their time in a nonfasting state and hypertriglyceridemia correlates with elevations in atherogenic small, dense LDL particles and cholesterol-rich remnant-like lipoproteins, this observation is not surprising.

Non-HDL-C

Numerous studies have also shown that non-HDL-C is equivalent or superior to LDL-C as a marker of atherogenic potential (but not to the same magnitude as apo B)[3,6]. Due to its clinical utility and that it can be calculated at no additional expense, we have been adding the calculated value to lipid panels that include total and HDL cholesterol. Levels respond to lipid lowering therapies in a manner similar to LDL-C, and reference goals have been established for the management of dyslipidemia.

Reference Values

LDL-C (mg/dL)[2]

- <100 if coronary heart disease (CHD), peripheral vascular disease, or diabetes is present
- <130 when no CHD is present, but there are 2 or more risk factors
- <160 when there is no CHD, but there is 0 or 1 risk factor present

Apo B (mg/dL)[3]

- <80 if CHD, peripheral vascular disease, or diabetes is present
- <100 when no CHD is present, but there are 2 or more risk factors
- <120 when there is no CHD, but there is 0 or 1 risk factor present

Non-HDL-C (mg/dL)[2]

- <130 if CHD, peripheral vascular disease, or diabetes is present
- <160 when no CHD is present, but there are 2 or more risk factors
- <190 when there is no CHD, but there is 0 or 1 risk factor present

CHD Risk Factors[2]

- Cigarette smoking
- Hypertension
 - BP \geq 140/90 mm Hg or on antihypertensive medication
- Low HDL-C (<40 mg/dL)
 - Note: HDL-C \geq 60 mg/dL counts as a “negative” risk factor; if present, remove one risk factor from the total count
- Family history of premature CHD
 - CHD in male first degree relative <55 years
 - CHD in female first degree relative <65 years
- Age
 - Men \geq 45 years
 - Women \geq 55 years

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3. Contois JH, McConnell JP, Sethi AA, Csako G, Devaraj S, Hoefner DM, Warnick GR. Apolipoprotein B and cardiovascular disease risk: position statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices. *Clinical Chemistry* 2009;55(3):407-419.
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Direct LDL-C will still be available as a stand-alone orderable test (LDL Cholesterol, Direct). The methodology for “ β -quant” (LDL-C by ultracentrifugation) and lipoprotein electrophoresis will be retained for research purposes, but will no longer be offered for routine clinical testing. 