The Role of the Laboratory in the Diagnosis of the Metabolic Syndrome

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The metabolic syndrome is now an accepted disorder and has a code in the International Classification of Diseases, Ninth Revision (277.7). It afflicts approximately 1 in 4 American adults. The features of the metabolic syndrome include abdominal obesity and atherogenic dyslipidemia manifesting as elevated levels of triglycerides, low levels of high-density lipoprotein cholesterol (HDL-C), and a preponderance of small, dense low-density lipoprotein (LDL) particles.1-3 Other features include increased blood pressure, insulin resistance and/or glucose tolerance, and prothrombotic and proinflammatory diathesis.

The laboratory has a critical role in the diagnosis of the metabolic syndrome because of the 5 features; 3 are laboratory-based, including triglyceride levels of 150 mg/dL (1.7 mmol/L) or more; HDL-C levels less than 40 mg/dL (1.0 mmol/L) and 50 mg/dL (1.3 mmol/L) in men and women, respectively; and fasting plasma glucose levels of 100 mg/dL (5.6 mmol/L) or more.

The importance of the metabolic syndrome is that it confers at least a 2-fold risk of cardiovascular disease and at least a 5-fold increased risk for subsequent diabetes.1-3 In addition, it is not uncommon for patients with metabolic syndrome to have nonalcoholic steatohepatitis, generally diagnosed by increased transaminase levels with an alanine aminotransferase/aspartate aminotransferase ratio of more than 1 and sonographic evidence of fat accumulation in the liver (best confirmed by nuclear magnetic resonance spectroscopy). Also, patients with the metabolic syndrome can have hyperuricemia and microalbuminuria.

With regard to atherogenic dyslipidemia, because the laboratory reports the results for triglycerides, HDL-C, and LDL cholesterol (LDL-C) in a standardized manner, it is also incumbent on the clinical laboratory to report the non–HDL-C value, which embraces all of the atherogenic apolipoprotein B (ApoB)-carrying particles. It is simply obtained by subtracting the HDL-C value from the total cholesterol value. The non–HDL-C value is especially important in patients with triglyceride levels of 200 mg/dL (2.3 mmol/L) or more, and the goal for non–HDL-C is the LDL-C goal plus 30 mg/dL (0.78 mmol/L). Thus, in a patient with diabetes and metabolic syndrome, the LDL-C goal would be less than 100 mg/dL (2.6 mmol/L) and the non–HDL-C goal would be less than 130 mg/dL (3.4 mmol/L).

Other abnormalities that have been reported in the metabolic syndrome include elevated levels of remnant and remnant-like particles. However, this assay, although approved by the US Food and Drug Administration for cardiovascular risk assessment, is not standardized, and remnant-like particle levels are not generally measured in the clinical setting. By the same token, until there is better standardization, the measurement of lipoprotein subclasses, such as small, dense LDL, is not recommended.

Patients with the metabolic syndrome have elevated levels of ApoB. ApoB gives a measure of particle number, can be measured on a nonfasting sample, and is a better predictor of outcomes in statin trials than is LDL-C. ApoB could easily become a target for treatment in the new Adult Treatment Panel guidelines.4,5 The ApoB assay displays good precision, is standardized, and is generally offered on most platforms. If the ApoB levels are going to be used as a target for treatment, in patients with an LDL-C target of less than 100 mg/dL (2.6 mmol/L), the ApoB target level will most likely be less than 90 mg/dL (0.9 g/L).4,5

Microalbuminuria is also relatively easily measured in the clinical laboratory and, indeed, can be done on a spot urine sample, with the result expressed as an albumin/creatinine
ratio. Microalbuminuria defined as between 30 and 300 μg/mg of creatinine would also encourage clinicians to better manage patients, especially with regard to hypertension and abnormal glucose tolerance.

C-reactive protein (CRP) levels have been shown to predict cardiovascular events when measured by a high-sensitivity (hs) assay and, in fact, are elevated in patients with the metabolic syndrome and appear to confer greater risk for cardiovascular disease. An hsCRP level in patients with the metabolic syndrome between 3 and 10 mg/L (28.6-95.2 nmol/L) could inform clinicians to better target the prothrombotic/proinflammatory status of the patient with therapeutic lifestyle changes and pharmacotherapy.

Another very important adipokine that has great relevance to the metabolic syndrome is adiponectin, which is an adipocyte complement-related protein of 30 kDa. Levels are decreased in the metabolic syndrome, obesity, type 2 diabetes, and coronary artery disease. Adiponectin appears to be an important anti-inflammatory adipokine. However, plasma levels of adiponectin exist in various forms, including trimers, hexamers, and multimers. There is no uniform acceptance of which is the preferred form to be measured. A recent study failed to show the superiority of the ratio of the different adiponectin forms to CRP with regard to predicting the metabolic syndrome by using receiver operating characteristic curves.

While some measure of insulin sensitivity can be obtained by using the homeostasis model of assessment (HOMA), insulin assays are not standardized, and, thus, any recommendation for reporting HOMA or QUICKI (quantitative insulin-sensitivity check index) measures of insulin resistance requires better standardization of the insulin assay for clinical diagnosis.

In addition to offering measurement of triglycerides, LDL-C, and HDL-C to help with the diagnosis of the metabolic syndrome and its management, it is incumbent on the laboratory to report the non–high-density lipoprotein cholesterol value, which involves a simple calculation. Furthermore, the laboratory should gear up in the future to also report ApoB levels, which could easily emerge as a target for treatment. While much is needed with regard to standardization of an adiponectin assay, there are also other circulating biomarkers such as interleukin 6, monocyte chemotactic protein-1, leptin, plasminogen activator inhibitor-1, and retinol binding protein-4 that might be relevant to the pathogenesis of the metabolic syndrome but presently belong in the research arena. In the future in the clinical laboratory, we might be measuring, in addition to hsCRP, other biomarkers such that we will have a panel that will better help us diagnose and manage this global epidemic.

### Table I

**Accepted and Evolving Biomarkers in the Metabolic Syndrome**

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<tr>
<th>Accepted</th>
<th>Lipid profile including non–high-density lipoprotein cholesterol</th>
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<td>Plasma glucose</td>
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<td>High-sensitivity C-reactive protein</td>
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<td>Urinary microalbuminuria</td>
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<td>Apolipoprotein B</td>
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<td>Plasminogen activator inhibitor-1</td>
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<td>Other biomarkers of inflammation</td>
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**References**