Metabolic Syndrome and Remnant-like Particle Cholesterol (RLP-C)

BIOCHEMICAL MARKERS OF INSULIN-RESISTANT DYSLIPIDEMIA

In recent years, a clustering of clinical abnormalities, termed "metabolic syndrome," has been identified as conferring markedly elevated cardiovascular risk, including a 3-fold excess of coronary heart disease (1). The metabolic syndrome comprises abdominal obesity, insulin resistance, impaired glucose tolerance, hypertension, and dyslipidemia. Depending on the diagnostic criteria used, more than 20% of adults in the US have metabolic syndrome (2); about 75% of type 2 diabetics meet the criteria (1).

Dyslipidemia associated with type 2 diabetes and metabolic syndrome is highly atherogenic and yet complex and subtle. Total cholesterol levels are either in the normal range or only mildly elevated. Instead, this dyslipidemia is characterized by reduced HDL cholesterol, elevated triglycerides and remnant lipoproteins, and a preponderance of small, dense LDL particles. Moreover, there are disproportionate amounts of large VLDL and small HDL particles, which are a reflection of the dysregulated remnant pathway, and this constellation is considered very atherogenic (3).

Etiology of the characteristic dyslipidemia associated with metabolic syndrome remains incompletely understood. However, insulin resistance results in a failure of insulin to suppress lipolysis, with inappropriate delivery of free fatty acids (FFAs) to the liver, leading to increased synthesis of triglyceride-rich very low density lipoproteins (VLDLs). This in turn leads to elevated blood triglyceride levels as well as enhanced cholesterol ester transfer protein (CETP)-mediated exchange of cholesterol ester between VLDL and HDL, with subsequent lowering of circulating HDL levels (1). Moreover, high triglyceride concentrations and increased activities of CETP and lipoprotein lipase are thought to be responsible for small LDL size (4).

Another characteristic feature of the metabolic syndrome is the presence of low-level systemic and vascular inflammation, which likely accelerates the progression of atherosclerosis. Etiology of the inflammation is unknown, but obesity, diabetes and metabolic syndrome, including acute-phase reactants such as CRP and fibrinogen, cytokines such as IL-6, TNF-α, and sCD40 Ligand, and adhesion molecules such as ICAM-1 (5).

From the above considerations it is evident that diverse biochemical markers are useful in defining the presence and progression of metabolic syndrome, and these markers are therefore valuable clinical surrogates for the development of drugs targeting this syndrome. Dyslipidemia requires more in-depth testing than can be provided by standard lipid panels, and should include LDL and HDL subclass fractionation, and an estimate of triglyceride-rich lipoprotein remnants. Measurement of oxidized LDL should also be considered. In addition, markers of systemic and vascular inflammation should be included, as mentioned above, as well as lipoprotein associated phospholipase A2 (Lp-PLA2), which provides a link between small, oxidized LDL and vascular inflammation.

RLP-C (REMNANT-LIKE PARTICLE CHOLESTEROL)

- Immunoaffinity method for remnant lipoproteins
- Anti-apoB100/A1 MAbs remove HDL, LDL, & VLDL
- Supernatant assayed for cholesterol (RLP-C) & triglyceride (RLP-TG)

Remnant-like particle cholesterol (RLP-C) represents the cholesterol content of remnant lipoproteins, which are recognized to be highly atherogenic. These particles derive from triglyceride-rich lipoproteins (chylomicrons and VLDL), are enriched in apo E and apo CIII, and have a long resistance time in the circulation. Several lines of evidence suggest that elevations of remnant lipoproteins are particularly prominent in the dyslipidemia of diabetes and metabolic syndrome (3, 6-8).
RLP-C is an independent predictor of cardiovascular disease risk (10) and has been shown to correlate with insulin resistance in visceral obesity (11).

Moreover, RLP-C levels have been shown to correlate with carotid artery intima-media thickness in healthy men, underlining the notion that this test is a surrogate marker for atherosclerosis (12).

In a recent study, treatment with Pioglitazone (a PPAR-γ agonist that reduces insulin resistance) for 12 months resulted in significant reductions in RLP-C and triglyceride levels, whereas total cholesterol and HDL cholesterol were not changed (13). Moreover, reduction in RLP-C was observed in the responder group (change of HbA1c > 1%) and was linked to the level of insulin resistance (IR) at baseline, indicating that RLP-C may be a surrogate for IR related dyslipidemia.

RLP-C levels are measured by an immunoaffinity procedure developed and manufactured by Japan Immunoresearch Laboratories and approved by the FDA for the assessment of CHD risk (14, 15). The assay is performed by isolating triglyceride-rich remnants from serum or plasma by incubation with an immunoaffinity gel containing unique monoclonal antibodies to apo B100 and apo A1. The cholesterol in the unbound fraction is measured by an ultra-sensitive cholesterol assay.

REFERENCES