Lipid Triad or Atherogenic Lipoprotein Phenotype: A Role in Cardiovascular Prevention?

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The term “lipid triad” or “atherogenic lipoprotein phenotype” has been introduced to describe a common form of dyslipidemia, characterized by three lipid abnormalities: increased plasma triglyceride levels, decreased high-density-lipoprotein (HDL)-cholesterol concentrations and the presence of small, dense LDL particles. It has been suggested that the clinical importance of the atherogenic lipoprotein phenotype probably exceeds that of LDL-cholesterol, because many more patients with coronary artery disease are found to have this trait than hypercholesterolaemia. There is a body of evidence that therapies effective against plasma HDL-cholesterol and triglycerides are associated with a strong reduction of cardiovascular risk; in addition, hypolipidemic treatment is able to increase LDL particle size and this increment correlates with regression of coronary stenosis. Recently, the Coordinating Committee of the National Cholesterol Education Program suggested that very high-risk patients may benefit from stronger lipid-lowering measures, a category of individuals that includes those with the atherogenic lipoprotein phenotype. Since the therapeutical modulation of each of the three components of the lipid triad is associated with a strong reduction in the risk of cardiovascular events, LDL size measurement may be extended as much as possible to patients at high risk of cardiovascular diseases. J Atheroscler Thromb, 2005; 12: 237–239.

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Introduction

The term “lipid triad” has been introduced to describe a common form of dyslipidemia, characterized by three lipid abnormalities: increased plasma triglyceride levels, decreased high-density-lipoprotein (HDL)-cholesterol concentrations and the presence of small, dense low-density-lipoprotein (LDL) particles (1). Since this lipid triad commonly occurs in individuals with cardiovascular diseases, it has been designated the “atherogenic lipoprotein phenotype” (2).

LDL particles in humans show not a normal, but a bimodal, distribution in peak size and can be separated into two phenotypes that differ in size, density, physicochemical composition, metabolic behavior and atherogenicity. These phenotypes have been assigned as pattern A when larger, more buoyant LDLs predominate and pattern B when smaller, more dense LDLs predominate (3, 4).

Small, dense LDLs are associated with the metabolic syndrome and increased risk of developing cardiovascular disease and diabetes mellitus. A reduction in LDL size has been reported in patients with acute myocardial infarction, with angina itself without atherosclerosis, as well as in patients with non-coronary forms of atherosclerosis.

LDL size seems also to be an important predictor of cardiovascular events and progression of coronary ar-
tery disease and a predominance of small dense LDLs has been accepted as an emerging cardiovascular risk factor by the National Cholesterol Education Program Adult Treatment Panel III (1, 3, 4).

Measuring LDL Peak Particle Size

The particle size distribution of plasma LDL subfractions may be measured by different laboratory techniques, including analytical, preparative and nonequilibrium density gradient ultracentrifugation, as well as nuclear magnetic resonance (5–7). However, the most common procedure is 2–16% gradient gel electrophoresis at 10°C using a Tris (0.09 M)- boric acid (0.08 M)- Na2 EDTA (0.003 M) buffer (pH 8.3) (3, 4, 8). The plasma is adjusted to 20% sucrose, and 3 to 10 µL is applied to the gel. Potentials are set at 40 mV (15 minutes), 80 mV (15 minutes), and 125 mV (24 hours). Gels are fixed and stained for lipids in a solution containing oil red O in 60% ethanol at 55°C, and for proteins in a solution containing 0.1% Coomassie brilliant blue R-250, 50% ethanol and 9% acetic acid, and then scanned at 530 nm with a densitometer. Molecular diameters are determined on the basis of distance migrated by comparison with standards of known diameter (3, 4, 8).

The assignment of LDL subclass phenotypes is based on particle diameter of the major plasma LDL peak: LDL pattern A (larger, more buoyant LDL) is defined as an LDL subclass pattern with the major gradient gel peak at a particle diameter of 258 Å or greater, whereas the major peak of LDL pattern B (small, dense LDL) is at a diameter of less than 258 Å (4, 6, 9).

Atherogenic Lipoprotein Phenotype and Hypolipidemic Treatments

Although there is a number of evidence that effective therapies on each of the three components of the lipid triad are associated with a strong reduction of cardiovascular risk (1), probably physicians are well acknowledged that this is true for HDL-cholesterol and triglycerides, but not for LDL size.

Hypolipidemic treatment is able to alter LDL subclass distribution (10). Medications with triglyceride-lowering effects cause a shift from smaller, denser to larger, more buoyant particles and this may be explained by the fact that a reduced availability of triglyceride-rich particles leads to a reduction in the production of small, dense LDLs. This has been shown for both fibrates and niacin: these substances lower levels of preferentially small, dense LDLs, but in many studies the net effect was only moderate (3). Statins potentially lower concentrations of all LDL subclasses, but a number of studies have showed a greater reduction for the atherogenic small, dense LDLs, especially with atorvastatin and simvastatin (3).

Conclusions

The term “lipid triad” or “atherogenic lipoprotein phenotype” has been introduced to describe a common form of dyslipidemia, characterized by three lipid abnormalities: increased plasma triglyceride levels, decreased HDL-cholesterol concentrations and the presence of small, dense LDL particles (1). It has been suggested that the clinical importance of the atherogenic lipoprotein phenotype probably exceeds that of LDL-cholesterol, because many more patients with coronary artery disease are found to have this trait than hypercholesterolaemia (11, 12).

There is a body of evidence that therapies effective on plasma HDL-cholesterol and triglycerides are associated with a strong reduction of cardiovascular risk (1); in addition, hypolipidemic treatment is able to increase LDL particle size and this increment correlates with regression of coronary stenosis (3, 4).

Recently, the Coordinating Committee of the National Cholesterol Education Program suggested that very high-risk patients may benefit from stronger lipid-lowering therapies (13), a category of individuals that includes those with the atherogenic lipoprotein phenotype. Since the therapeutic modulation of each of the three components of the lipid triad is associated with a strong reduction in the risk of cardiovascular events, LDL size measurement may be extended as much as possible to patients at high risk of cardiovascular diseases.

References

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