

Editorial Comment

Lipoproteins and the Endothelium: Past, Present and Future

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Recent large observational studies suggest that apolipoprotein (Apo) measurement offers a benefit over conventional lipid measurements in the assessment of cardiovascular risk. This editorial accompanies the article by Antoniades et al¹ describing their investigation of the influence of lipids and apolipoproteins on endothelial function in a young healthy cohort. Their observations that low-density lipoprotein (LDL) cholesterol and ApoA-I are independent predictors of endothelial function is supported by advances in our understanding of the vascular biology of apolipoproteins.

In this interesting study the authors examine the relationship between lipid parameters and endothelial function in healthy individuals. As might be expected, higher levels of serum cholesterol were associated with impairment of the endothelium-dependent vasodilatory response. However, recent large studies, such as AMORIS and INTERHEART, have suggested that measurements of lipoproteins are superior to conventional lipid measurements for determining cardiovascular risk.^{2,3} Interestingly, in this study ApoB did not appear to have a better predictive value than LDL cholesterol, while along with LDL ApoA-I was the other independent predictor of endothelial function.

Endothelial dysfunction and dyslipidaemia

Lipids are strongly related to the develop-

ment of atherosclerosis. Dysfunction of the endothelium precedes the development of macroscopic disease, and the earliest event in atherogenesis may be subendothelial retention of lipoprotein particles.⁴ Furthermore, the harmful effect of dyslipidaemia on endothelial function in subjects at risk of but without overt vascular disease has been recognised for many years.⁵ Endothelial dysfunction itself also has value as a prognostic marker in patients with established disease when measured in both coronary and peripheral vessels.^{6,7}

When should we measure ApoB?

ApoB is the main apolipoprotein in atherogenic particles such as LDL and very low density lipoprotein (VLDL) cholesterol. It is present in a ratio of one apoB per lipoprotein particle and thus represents the total number of atherogenic particles.⁸ LDL particles exist in a range of subtypes; small dense LDL (sdLDL) is particularly atherogenic, at least partly because it is avidly retained in the subendothelial space.⁹ Therefore, the value of measuring ApoB is in discriminating between individuals with similar levels of LDL. Individuals with type 2 diabetes mellitus and metabolic syndrome often have "normal" serum levels of LDL cholesterol, but this consists of a high concentration of atherogenic ApoB-containing sdLDL particles.¹⁰ By contrast, in the healthy population without risk factors

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studied by Antoniadou et al, LDL rather than ApoB emerged as the independent predictor of endothelial function. A similar observation has been made in other studies, where if the population studied is relatively young and healthy ApoB has little further value over LDL.¹¹

Broad beneficial effects of ApoA-I

According to data from the Framingham cohort, high density lipoprotein (HDL) cholesterol is a stronger risk factor than LDL.¹² There is also increasing interest in HDL elevation as an anti-atherogenic target.¹³ ApoA-I is the major lipoprotein and probably the principal active component of HDL, and in this study was an independent predictor of endothelial function. An important action of HDL is thought to be reverse cholesterol transport, where lipid-poor ApoA-I plays a key role by accepting cholesterol from the ATP binding cassette proteins, such as ABCA-1, in the vessel wall for eventual delivery to the liver. In addition, there is emerging evidence, mostly from animal models or *in vitro*, that ApoA-I can directly prevent the inflammatory response to arterial injury and oxidation of lipids.^{14,15} While the mechanisms by which ApoA-I influences the endothelium in humans are not yet fully established, Spieker et al reported that a single infusion of ApoA-I could restore endothelial function in hypercholesterolaemic patients.¹⁶

Since initial observations decades ago,¹⁷ the key role of lipids and lipoproteins in the development of endothelial dysfunction and atherosclerosis is now firmly established. As our understanding of lipoprotein biology increases, we can expect further advances, including novel approaches to the diagnosis and treatment of atherosclerotic disease.^{18,19}

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