Increased ApoB in Small Dense LDL Particles Predicts Premature Coronary Artery Disease

John D. Brunzell

The relation between plasma lipoproteins and atherosclerosis has evolved over the past fifty years. Serum cholesterol levels were shown to be associated with coronary artery disease (CAD) in familial hypercholesterolemia in the early 20th century (see Frederickson1). This cholesterol was determined to be in a particular lipoprotein class2 now termed low-density lipoprotein (LDL) cholesterol.3 LDL cholesterol has been shown to predict premature CAD in many studies,4 and a reduction in LDL cholesterol with statin therapy has been shown to decrease CAD events by up to 50% in primary5 and in secondary6 intervention trials. The National Cholesterol Education Program Adult Treatment Panel7 initially based recommendations for therapy to prevent CAD on LDL cholesterol levels. Later the measurement of HDL cholesterol was added to estimate risk.8

Because treatment for LDL cholesterol levels only decreases the risk for premature CAD by about half, other lipoprotein factors have been sought to explain the additional risk. Plasma triglyceride levels are associated with CAD, independently of LDL and HDL cholesterol levels.9 Hypertriglyceridemia also has been associated with small dense LDL particles.1–10

Studies of the heterogeneity of LDL particles and their number have suggested that small dense LDL and increased number of LDL particles, as reflected by increased apoB, are specific components of LDL important in the risk for premature CAD. Several studies noted heterogeneity of LDL particles with apoB enrichment of LDL in hypertriglyceridemic individuals.11–13 Total apoB levels were then noted to be elevated in individuals with atherosclerosis.14,15 Hyperapobetahlipoproteinemia, an elevated LDL apoB with small cholesterol-poor LDL particles, was also reported in individuals with CAD.16,17 A number of prospective studies18–20 demonstrated that small LDL particles predicted CAD. The Interheart Study of 15,000 individuals in 52 countries found that the apoB/Apo AI ratio was a major predictor of CAD in men and women in all parts of the world.21

In the 13-year follow-up of the Quebec Cardiovascular Study (in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology), the Laval University group report that small LDL are a strong and independent predictor of CAD, particularly in the first 7 years of follow-up.22 They report that big LDL particles at baseline were not predictors of future CAD events. This implies that much of the association of LDL cholesterol with premature CAD is due to the small dense LDL component. These were studies of 2072 men 46 to 75 years of age chosen to represent the male population in Quebec City. No women were involved with the study, and individuals with high levels of big buoyant LDL particles with familial hypercholesterolemia would be uncommon. In the Quebec Cardiovascular Study they found that particle number, as determined by plasma apoB levels, was an important codeterminate of risk. It cannot be said that large buoyant LDL are never a risk for CAD, eg, when present in excess numbers of particles. Individuals with familial hypercholesterolemia have increased numbers of LDL particles of large size, which together account for the very high levels of LDL cholesterol seen with an early onset of CAD.

Who are these individuals with increased numbers (elevated apoB) of small dense LDL particles23,24? These individuals tend to be centrally obese, to have hypertriglyceridemia with low HDL cholesterol, and occur in familial clusters. NCEP-ATP III25 has attempted to include these individuals in a risk stratification plan by incorporating the metabolic syndrome into the guidelines with LDL and HDL cholesterol. It is clear that individuals with the metabolic syndrome who have type 2 diabetes27 and those with familial combined hyperlipidemia28,29 are at increased risk for premature CAD. However, the risk for those individuals with the metabolic syndrome with normal fasting apoB and glucose levels is unknown at this time.24 Because the metabolic syndrome encompasses such a large proportion of adults, this is a question that needs to be addressed.

Perhaps it is time to add the measurement of plasma apoB levels to the standard lipid profile to find those individuals with the metabolic syndrome at high CAD risk. An apoB/AI ratio could be measured as in the Interheart Study,21 or apoB levels and determination of LDL size (or density) could be measured as in the Quebec Cardiovascular Study. If one has a standard lipid profile, the LDL cholesterol level in the context of the plasma apoB level can be used to determine the presence or absence of small dense LDL particles. It is expected that the apoB level would help to assess the risk of CAD due to small dense LDL particles in those who have borderline levels of LDL cholesterol in a primary prevention program. A nomogram for apoB levels by age and sex has been generated from the NHANES III data set.24

© 2005 American Heart Association, Inc.

Arterioscler Thromb Vasc Biol is available at http://www.atvbaha.org
DOI: 10.1161/01.ATV.0000156537.78366.1d

From the Division of Metabolism, Endocrinology, and Nutrition, Department of Medicine, University of Washington, Seattle.

Correspondence to John D. Brunzell, University of Washington, Division of Metabolism, Endocrinology, and Nutrition, Seattle, WA 98195-6426. E-mail brunzell@u.washington.edu


© 2005 American Heart Association, Inc.
References


29. Ayyobi A, McGladdery SH, McNeely MJ, Austin MA, Motulsky AG, Brunzell JD. Increased ApoB and Small Dense LDL.
Increased ApoB in Small Dense LDL Particles Predicts Premature Coronary Artery Disease
John D. Brunzell

*Arterioscler Thromb Vasc Biol.* 2005;25:474-475
doi: 10.1161/01.ATV.0000156537.78366.1d
*Arteriosclerosis, Thrombosis, and Vascular Biology* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/25/3/474

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Arteriosclerosis, Thrombosis, and Vascular Biology* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Arteriosclerosis, Thrombosis, and Vascular Biology* is online at:
http://atvb.ahajournals.org//subscriptions/