EDITORIAL (SEE SASONGKO ET AL., P. 474)

Apolipoproteins and Diabetic Retinopathy

In this issue of *Diabetes Care* Sasongko et al. (1) make the intriguing observation that apolipoprotein (apo)B and apoA-I, and particularly the apoB-to-apoA-I ratio, are related to the presence of diabetic retinopathy in a small cohort of type 1 and type 2 diabetic patients. Moreover, this ratio correlated with the retinopathy severity and also was a better predictor of retinopathy than traditional lipid measures such as total cholesterol, LDL or HDL cholesterol, or even the LDL-to-HDL cholesterol ratio.

This study raises many important questions. For example, why are these relationships between retinopathy and lipoproteins seen in this small study, whereas previous studies, some in much larger cohorts, have not shown a consistent relationship? Did measurement of apolipoproteins rather than the lipid components of the lipoproteins make the difference? Lipids and lipoproteins are well-accepted risk factors for macrovascular disease in diabetes via mechanisms that are reasonably well understood. However, do lipids and lipoproteins play a role in microvascular complications such as retinopathy in addition to better known risk factors such as diabetes duration, glycemic control, and hypertension? And if so, by what mechanisms does HDL protect and the apoB-containing lipoproteins increase the risk of retinopathy?

In the current study, stronger relationships were observed between retinopathy and apolipoproteins than with lipid components of the lipoproteins. ApoA-I is the major structural apolipoprotein present in HDL and is reflective of the number of HDL particles. A single molecule of apoB is present in LDL, as well as in VLDL, remnant lipoproteins (often present in the intermediate-density lipoprotein [IDL] density range) and lipoprotein (a) (Lp(a)), another atherogenic lipoprotein. Because each of these lipoproteins contains a single molecule of apoB, apoB concentration is a measure of the total number of these atherogenic particles. If these lipoproteins also have an adverse effect on microvascular complications such as retinopathy, apoB levels might be expected to show a better relationship with retinopathy than individual measurements of LDL, VLDL, IDL, or Lp(a) lipids. Similarly, if HDL has protective properties in the eye as well as in the artery wall, apoA-I levels might be expected to be a better predictor of risk than HDL lipids, since HDL particles are very heterogeneous in composition.

The relationship between lipids and lipoproteins with atherosclerotic cardiovascular disease (CVD) might provide important clues to the relationship between lipoproteins and retinopathy. The earliest observed relationships were between plasma cholesterol and CVD (2–4). Later LDL cholesterol itself was found to be a strong predictor of CVD risk (5,6). Basic studies suggested many potential mechanisms by which LDL might be atherogenic, including the ability to be taken up and be retained in the artery wall, after which they can undergo various forms of modification, including oxidative modification and hydrolysis of components of the lipoprotein by enzymes such as secretory phospholipases and sphinogomyelinase (7–13). Components of modified lipoproteins can damage arterial cells or be atherogenic by other mechanisms. However, the importance of LDL as a risk factor was only firmly established by randomized controlled clinical trials (RCTs) that demonstrated that LDL lowering reduced the risk of CVD (14–16). The role of HDL as an atheroprotective lipoprotein emerged at about the same time. Several mechanisms by which HDL might be atheroprotective (17,18) include its ability to promote reverse cholesterol transport, as well as its anti-inflammatory, antioxidant, and antithrombotic properties (19). However, RCTs have yet to clearly demonstrate a role for HDL in preventing CVD events. Although there is a clear association between triglycerides, which are transported in plasma as VLDL, and CVD (20), RCTs have yet to provide definitive evidence for their causal role in CVD. Because of this type of evidence, guidelines have generally focused on LDL lowering, although more recent guidelines have paid increasing attention to HDL and triglycerides (21).

The role of apolipoproteins in CVD risk is now receiving increasing attention. Correlations of apoB and apoA-I, as well as the ratio of apoB to apoA-I, with CVD risk are well described. Whether apolipoproteins are better CVD risk predictors than traditional lipid measurements remains controversial. In the Apolipoprotein-related Mortality Risk (AMORIS) trial, both apolipoproteins and traditional lipid measurements were predictive, but the apolipoproteins were slightly more significant, particularly in patients with lower LDL levels (22). The INTERHEART study showed that the apoB-to-apoA-I ratio was superior to any traditional cholesterol ratio in estimation of risk for acute myocardial infarction (23). Other studies have not shown apolipoproteins to be better predictors of CVD risk than traditional lipid measurements. For example, the apoB-to-apoA-I ratio was comparable with traditional lipid ratios in predicting CVD risk and did not improve upon the total cholesterol-to-HDL ratio in the Framingham cohort (24). Moreover, case control analysis of healthy participants from the European Prospective Investigation of Cancer (EPIC)-Norfolk study showed that apoB-to-apoA-I ratio was independently associated with CVD risk but did not add to existing measures of lipid analysis (25). Thus, although both traditional lipids and lipoproteins and apolipoprotein ratios are good CVD risk predictors, it remains to be seen whether apolipoprotein measurements will replace traditional risk factors in future CVD guidelines.

What about diabetes, lipoproteins, and CVD risk? Similar relationships appear to exist between lipoproteins and CVD risk as for individuals without diabetes. In the UK Prospective Diabetes Study (UKPDS), LDL cholesterol was the strongest predictor of risk (26). Other studies have shown that triglycerides and low HDL also are important risk predictors in diabetes (27). In the few studies in which apolipoproteins have been assessed in patients with diabetes, apoB-to-apoA-I ratio predicts CVD risk similar to that seen in nondiabetic cohorts. In the Collaborative Atorvastatin Diabetes Study

(CARDS) trial of atorvastatin treatment in type 2 diabetic patients, the apoB-to-apoA-I ratio improved upon the non-HDL-to-HDL ratio for predicting CVD, but it was only a marginal improvement upon the LDL-to-HDL ratio (28). In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study of fenofibrate treatment in type 2 diabetic patients, in contrast with some studies in nondiabetic populations, traditional lipid ratios were as strong as the apoB-to-apoA-I ratio in predicting CVD risk (29). Future studies should help determine whether the apoB-to-apoA-I ratio is more predictive of CVD in nondiabetic versus diabetic subjects.

The mechanisms by which dyslipidemia might increase CVD risk are relatively well understood. However, it is still unclear whether lipoproteins play a role in the pathogenesis of diabetic retinopathy, and if so, how they are involved. Dyslipidemia has been associated with an increased risk of diabetic retinopathy in observational studies (30,31). In the Diabetes Control and Complications Trial (DCCT), the severity of retinopathy was associated with increasing triglyceride levels and inversely correlated with HDL levels (32). Treatment with fenofibrate, a drug that primarily reduces triglycerides and modestly increases HDL cholesterol levels, reduced the need for laser treatment of vision-threatening diabetic retinopathy in FIELD (33). However, this finding was not attributable to changes in lipid levels, which suggests that fenofibrate had pleiotropic effects above and beyond lipid modification. More recently, a decrease in the rate of progression of diabetic retinopathy with fenofibrate treatment was also observed in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (34). Despite these clues, potential mechanisms by which lipoproteins might affect diabetic retinopathy remain unclear. In the present study, low HDL (or apoA-I) levels predicted retinopathy risk more than high LDL (or apoB) levels. It is conceivable that some of the properties of HDL that are atheroprotective might also play a role in preventing retinopathy. Mechanisms by which apoB-containing lipoproteins might exacerbate retinopathy are less clear. They nonetheless open the door for more mechanistic studies to better understand the pathogenesis of diabetic retinopathy.

So should we use apoB-to-apoA-I ratio to predict retinopathy risk? The sample size in this study was small and its provocative findings need to be replicated in larger studies. Moreover, it also will be important to confirm the potential predictive role of apolipoproteins and lipoproteins in longitudinal studies. Even if relationships between dyslipidemia and retinopathy are confirmed, the critical question is whether therapy aimed at altering lipids and lipoproteins will prevent the onset or progression of diabetic retinopathy. Preliminary studies with fibrates are encouraging but may be because of effects of this class of drug distinct from their effect on lipids and lipoproteins. Studies with other drugs that lower apoB-containing lipoproteins and raise HDL need to be performed. Effective therapies are available to lower LDL and apoB. Less effective strategies are currently available to raise HDL and apoA-I levels, although this is an intense area of focus for the pharmaceutical industry. More studies need to show that the relationship between retinopathy and lipoproteins is sufficiently robust to warrant a RCT of lipid-altering therapy. And the relative importance of lipid therapy versus the more traditional approaches of tight glycemic and blood pressure control needs to be evaluated. However, the possibility that lipid and lipoprotein modification might, with time, supplement these other strategies provides light at the end of the tunnel for further reducing this devastating complication of diabetes.

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