

Oxidized LDL May Predict CV Disease Risk

BY MICHELE G. SULLIVAN

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ORLANDO – Low-density lipoproteins that have been modified by oxidative stress and their associated antibodies are strongly associated with increased carotid intima-media thickness in people with type 1 diabetes, and may predict the development of cardiovascular disease years before the symptoms become apparent.

Among a cohort of 479 young people with type 1 diabetes, those with the highest levels of oxidized LDL circulating as immune complexes were seven times more likely than those with lower levels to have high intima-media thickness, Dr. Maria Lopes-Virella reported.

The finding is “really surprising and quite significant,” said Dr. Lopes-Virella of the Medical University of South Carolina, Charleston. “These associations were much stronger than those that we

found to intensively treat everyone, so measurements like this may be able to help us target the people who can get the most benefit,” she said.

Her study population comprised 479 patients from the Diabetes Cohort and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. These patients all had type 1 diabetes, and were enrolled when they were aged 13-39 years (mean age, 28

years). The serum samples she utilized were collected when the patients were enrolled in the study. At that time, the mean duration of type 1 diabetes was 72 months. The mean HbA_{1c} was 9%, and the mean urinary albumin excretion rate was 16 mg/24 hours. The patients underwent an ultrasound measurement of carotid intima-media thickness 8-14 years after they were enrolled in the study, and another measurement 5 years later.

Dr. Lopes-Virella and her colleagues measured the levels of oxidized LDL (Ox-LDL), advanced glycated end product LDL (AGE-LDL), and malondialdehyde-modified LDL (MDA-LDL) in immune complexes that were isolated from the baseline serum samples, and compared those levels with the ultrasound measurements at both time points.

In a recent related article, she explained the importance of these modified

VITALS

Major Finding: Patients with type 1 diabetes who have high levels of oxidized LDL circulating as antigen-antibody (immune) complexes have significantly higher odds of developing increased carotid intima-media thickness and, therefore, cardiovascular events.

Data Source: A cohort of 479 patients aged 13-39 years from the Diabetes Cohort and Complications Trial/Epidemiology of Diabetes Interventions and Complications.

Disclosures: The DCCT/EDIC cohort has been and is being studied by a group of centers around the United States, and is sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases. Dr. Lopes-Virella's study was sponsored by the National Heart, Lung, and Blood Institute and by the NIDDK, as well as by the Juvenile Diabetes Research Foundation. Dr. Lopes-Virella had no financial disclosures with regard to her work.

see with conventional risk factors” for cardiovascular disease. Although the research is still in its early stage, she said in an interview that it could have an important clinical impact.

“In young patients with type 1 diabetes, when their lipid levels are fairly normal and their blood pressure is fine, you may think everything is okay if their blood sugar is also under good control. However, some of these patients can have a heart attack much earlier than people of the same age but without diabetes. If you could measure a biomarker that will indicate that their risk for an early heart attack is very high when they are still young – even children – then you can manage them more intensively and control the other risk factors for cardiovascular disease as tightly as you can. Society can't af-

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lipoproteins in patients with diabetes. “Enhanced oxidative stress and dyslipoproteinemia have been proposed as significant factors contributing to the accelerated development of macrovascular complications in diabetes,” Dr. Lopes-Virella and colleagues wrote (J. Diabetes Complications 2010 June 2 [doi: 10.1016/j.jdiacomp.2010.03.001]).

The unique clinical significance of the levels of Ox-LDL in circulating immune complexes was recently reviewed by Dr. Lopes-Virella (Clin. Immunol. 2010;134:55-65).

Patients with type 1 diabetes are prone to develop immunomodified lipoproteins because of their enhanced forma-

Patients in the upper quartile of the Ox-LDL measurements were 7.72 times more likely to have high vs. normal intima-media thickness than were those in the first quartile.

tion of autoantibodies, she said. “Diabetic patients are also at a higher risk of forming LDL-immune complexes be-

cause LDL glycation favors oxidation and advanced glycation end-product formation. These LDL modifications promote immune complex formation detectable in both serum and atheroma.”

In her current study, Dr. Lopes-Virella found that three different modifications of LDL were associated with increasing carotid intima-media thickness. After adjusting for multiple variables (age, sex, HbA_{1c}, retinopathy, and diabetes duration), patients in the upper quartile of the Ox-LDL measurements were 7.72

times more likely to have high vs. normal intima-media thickness than were those in the first quartile, a difference that was highly significant.

AGE-LDL levels also were significantly associated with an increasing intima-media thickness. Patients in the upper quartile of AGE-LDL were 7.82 times more likely to have high vs. normal intima-media thickness than were those in the lowest quartile; this risk was again highly significant.

In contrast, elevations in conventional biomarkers of cardiovascular disease among this cohort (unmodified LDL, diastolic blood pressure, and HbA_{1c} levels) were much less strongly associated with increased intima-media thickness. “The majority of these associations carry an odds ratio of around a twofold increase in the risk of a heart attack, compared to normal levels. A twofold increase in risk is, in general, considered a strong predictor,” Dr. Lopes-Virella said in the interview.

But even after adjustment for all conventional risk factors, including lipids, blood pressure, and HbA_{1c}, “Ox-LDL and AGE-LDL circulating as immune complexes have been shown to be extremely strong predictors of cardiovascular risk in type 1 diabetes. The tremendous strength of the prediction provided by Ox-LDL and AGE-LDL was quite surprising, but since we studied almost 500 patients, there is very little chance of [its] being just a random association.”

“Whether or not these findings can be applied to predict risk in patients with type 2 diabetes is unclear, since it is possible that the strength of the prediction in type 1 diabetes is related to the fact that type 1 diabetes is an autoimmune disease,” she noted in an interview. “We are doing similar measurements in the serum of patients with type 2 diabetes to see if the levels of Ox-LDL and AGE-LDL circulating as immune complexes are also strongly associated with or predictive of cardiovascular events in type 2 diabetes.”

She would also like to perform similar studies someday on patients without diabetes and in patients with autoimmune disorders other than type 1 diabetes.

The test could be commercialized, Dr. Lopes-Virella added. “Separating the immune complexes by chromatography is relatively simple. You dissociate the two parts of the complex (antigen and antibody moieties), and run an immunoassay against the modified lipoproteins in the antigen moiety.” ■

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