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Editorial

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Small Dense LDL Tied to Diabetic Retinopathy-Similarity to Atherosclerosis

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Retinopathy is a typical microvascular complication of diabetes and is mainly caused by hyperglycemia. Cardiovascular (CV) diseases, such as coronary artery disease and stroke, are macrovascular complication of diabetes, and dyslipidemia is deeply involved in its etiology. Epidemiological studies have shown that diabetic patients with retinopathy have higher incidence of CV events and death compared to those without retinopathy. Therefore, diabetic retinopathy has a very high risk of CV disease. The intEnsive statin therapy for hyper-cholesteroleMic Patients with diAbetic retinopaTHY (EMPATHY) study was a primary prevention trial investigating the incidence of CV events with intensive or standard statin therapy in patients with hypercholesterolemia and diabetic retinopathy[1]. As a result, there was no significant reduction in CV outcomes with intensive care, probably due to the slight difference in LDL-cholesterol (-C) between the intensive and standard treatment groups. Nonetheless, a sub-analysis of the EMPATHY study provided unexpected results suggesting that dyslipidemia is associated with diabetic retinopathy.

In this issue of the Journal of Atherosclerosis and Thrombosis, Nakayama *et al.*[2] reported that small dense (sd) LDL-C was not only a sensitive marker for predicting CV events but also a marker for predicting the need for laser treatment. Laser treatment is used to prevent the exacerbation of retinopathy, so sdLDL-C can be considered as a predictor of exacerbation of diabetic retinopathy. This study is unique in suggesting that dyslipidemia affects both the microangiopathy and macroangiopathy. SdLDL particles are thought to be more atherogenic than large buoyant LDL particles, because they have a long residence time in the blood circulation, easily penetrate into the arterial wall, and are easily oxidized. These properties facilitate the production of toxic oxidized-LDL in the subendothelial space and promote plaque formation. We established a fully automated assay kit for quantifying sdLDL-C levels[3], and this assay system has been adopted in famous cohort studies, such as the Suita, the ARIC, the Hisayama, and the Framingham Offspring. All studies have consistently proven that sdLDL-C is superior to LDL-C in predicting CV events. The present study demonstrated that triglyceride (TG), TG-rich lipoprotein (TRL) -C, and sdLDL-C can all predict CV events. However, the predictive power of sdLDL-C for CV events was lost in subjects with higher TG levels (>113 mg/dl). It should be noted that unlike other studies, all participants in the EMPATHY study had type 2 diabetes. In addition, the CV events in this study included renal outcomes[1, 2] in which TG metabolism would be significantly impaired. They may enhance the impact of TG and TRL-C on CV events and relatively mask the atherogenicity of sdLDL-C. SdLDL-C correlated more closely with apolipoprotein B than LDL-C, suggesting that the number of LDL particles is a major determinant of sdLDL-C concentration. There is plenty of evidence that LDL particle numbers are superior to LDL-C in predicting CV events.

Few studies have investigated specific changes in plasma lipids in diabetic retinopathy. Diabetic retinopathy often coexists with diabetic nephropathy, and albuminuria and/or renal dysfunction strongly affects plasma lipoprotein metabolism[4]. Therefore, the relationship between diabetic retinopathy and plasma lipids should take into account the presence of diabetic nephropathy. The authors analyzed that serum creatinine and sdLDL-C were independently associated with the need for laser treatment. Therefore, it is possible that sdLDL-C is directly associated with diabetic retinopathy, regardless of nephropathy. As the authors introduced, fenofibrate, a TG-lowering drug,

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suppressed the need for laser treatment in patients with type 2 diabetes (the FIELD study). Another well-known study, the ACCORD eye trial, also found that intensive care of dyslipidemia with fenofibrate and simvastatin slowed the progression of diabetic retinopathy[5]. Plasma TG levels are the most powerful determinant of LDL particle size and highly correlates with sdLDL-C[4]. We reported that fenofibrate and pitavastatin equally reduced sdLDL-C in diabetic patients[6]. Therefore, these lipid-lowering drugs may suppress the progression of retinopathy through a decrease in sdLDL-C.

The authors speculate that sdLDL-C has harmful effects on the vascular structure and function, including retina as shown in Figure 9 of their article[2]. However, it is unclear whether sdLDL particles can penetrate into the arterial wall of the retina in the same way as the coronary arteries. Similar issues are being discussed for diabetic nephropathy (the lipid-nephrotoxicity hypothesis). How can we explain the close relationship between sdLDL-C and diabetic retinopathy when sdLDL particles cannot enter the walls of microvessels? There are some speculations. First, retinopathy may reflect widespread vascular endothelial damage, leading to a decrease in functional lipoprotein lipase (LPL) anchored to the endothelium[7]. LPL is a rate-limiting enzyme for TG lipolysis and a suppressor for sdLDL generation[4]. SdLDL-C may respond sensitively to a decrease in LPL of damaged vascular endothelium. Second, insulin resistance stimulates the production of sdLDL, and conversely, sdLDL-C is a sensitive marker of insulin resistance[8]. The retina expresses amount of insulin receptors equivalent to the liver and brain, and insulin receptor signaling is important for retinal physiology[9]. SdLDL-C may reflect impaired insulin signals, including the retina. Third, dyslipidemia often impairs blood rheology, which can exacerbate diabetic retinopathy. Takiwaki *et al.*[10] reported that sdLDL-C was the most strongly associated with blood viscosity among lipid parameters. These speculations could be explained by TG instead of sdLDL-C. However, sdLDL has a much longer residence time in the blood circulation than TRLs, making sdLDL-C a more stable biomarker than TG for detecting decreased LPL, insulin resistance, and abnormal blood rheology. In the present sub-analysis study, only a relatively small number of patients could investigate eye outcomes. Therefore, it is difficult to compare intensive statins to standard statins for the need for laser treatment. A prospective intervention trail with statins or fibrates will be required to determine if sdLDL-C is causally associated with diabetic retinopathy.

Conflicts of Interest

Tsutomu Hirano receives advisor fee from Denka Co., and lecture fee from Kowa Co.

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