

# Which is the Best Predictor for the Development of Atherosclerosis Among Circulating Lipoprotein Lipase, Hepatic Lipase, and Endothelial Lipase?

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The triglyceride lipase gene subfamily plays a central role in lipid and lipoprotein metabolism. There are three members of this subfamily: lipoprotein lipase (LPL), hepatic lipase (HL), and endothelial lipase (EL).

LPL, in general, is considered to be inversely associated with atherosclerosis; however, in several *in vitro* analysis using cultured cells, this enzyme has been found to increase monocyte adhesion to aortic endothelial cells, function as a monocyte adhesion protein<sup>1</sup>, and promote foam cell formation<sup>2</sup>.

In experiments using animal models, mice overexpression of human LPL<sup>3</sup> or rabbit expressing human LPL<sup>4</sup> caused reductions in aortic atherosclerotic lesions.

In a clinical point of view, LPL deficiency might be the best model for predicting the relation of LPL to the development of cardiovascular disease. But the atherogenicity of this rare genetic disease is still controversial<sup>5</sup>. In a cross-sectional study, Japanese investigators have reported that males with coronary atherosclerosis had significantly lower serum LPL mass than those without coronary atherosclerosis or who are healthy<sup>6</sup>. In the EPIC-Norfolk population cohort who developed fatal or nonfatal CAD during 7 years of follow-up, reduced levels of serum LPL were associated with an increased risk of future coronary artery disease<sup>7</sup>.

The contribution of HL to the development of atherosclerosis is less clear than LPL. In a study with animal model, Mezdour *et al.*, in their study using mice lacking both HL and apoE, have suggested that HL deficiency may be associated with increases in plasma cholesterol but reduced susceptibility to atherosclerosis<sup>8</sup>.

In humans, HL deficiency might be a good model for understanding how this enzyme affects the devel-

opment of atherosclerosis, but the prevalence of this disease in the general population might be even lesser than that of LPL deficiency. The available message from the reported HL deficiency is that unlike LPL deficiency, most of the reported HL deficiency is pro-atherogenic<sup>9</sup>. This suggests that HL is an anti-atherogenic molecule. However, there is no prospective study investigating whether this lipolytic enzyme is atherogenic. Recently we established a new ELISA method for measuring serum human HL proteins<sup>10</sup>, which would enable us to measure HL protein mass in large number of samples.

EL was identified by Hirata *et al* in 1999<sup>11</sup>, mainly contributing to HDL catabolism. Since then, numerous investigators have studied on the association of this lipase with the development of atherosclerosis. A number of studies have suggested that EL can predict the development of atherosclerotic disease in humans<sup>12-15</sup>, whereas a prospective case-control study nested in the EPIC-Norfolk cohort (1138 CAD cases, 2237 matched controls) has denied the association between common genetic variants in LIPG and CAD risk<sup>16</sup>.

To the best of our knowledge, there are no previous reports directly comparing the atherogenicity of these three enzymes. In this issue of JAT, Yu *et al.*<sup>17</sup> have compared the atherogenicity of these three enzymes in 86 patients with CAD and 65 healthy controls and found that serum EL and HL concentrations were significantly increased in patients with CAD or in-stent restenosis, whereas serum LPL concentration was significantly reduced in patients with CAD. Their multivariate logistic regression analysis indicated that the three lipases were simultaneous independent risk factors for CAD but only serum EL concentration was considered an independent risk factor for in-stent restenosis. In our univariate analysis on the associations of carotid artery intima-media thickness (IMT) with the

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three triglyceride lipases in Japanese subjects with heterozygous familial hypercholesterolemia ( $n=16$ ; mean age, 63 years)<sup>18)</sup>, we found that among the three lipases, only serum EL concentrations had a statistically significant association with right carotid artery IMT (EL,  $r=0.59$   $p=0.017$ ; HL,  $r=0.074$   $p=0.79$ ; LPL,  $r=0.32$   $p=0.22$ ) and left carotid artery IMT (EL,  $r=0.51$   $p=0.044$ ; HL,  $r=0.25$   $p=0.35$ ; LPL,  $r=0.29$   $p=0.28$ ). This observation combined with the above mentioned finding by Yu *et al.*<sup>17)</sup> showed that EL may be the strongest determinant of atherogenicity among the three triglyceride lipases. Additional studies, with much larger sample size for long term follow-up, are needed to confirm the current findings on the effects of these three triglyceride lipases on the development of atherosclerotic disease.

### Conflict of Interest (COI)

I have no COI to declare regarding this manuscript.

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