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Abstract

Lipoprotein lipase (LPL) is a lipolytic enzyme involved in catalyzing hydrolysis of triglycerides (TG) in chylomicrons and very low-density lipoprotein (VLDL) particles. Over the last decade, increasing attention has been paid to the clinical significance of measuring serum LPL protein mass without heparin injection to the study subjects. In earlier studies, this marker was utilized to classify LPL deficient subjects, which is an extremely rare metabolic disorder with a frequency of one in one million. Later, researchers paid more attention to the clinical significance of measuring this parameter in more common metabolic disorders. Studies have shown that pre-heparin plasma or serum LPL mass has significant relationships with serum lipids and lipoproteins, visceral fat area, insulin resistance, and even the development of coronary atherosclerosis in cross-sectional studies, although this might be a metabolic surrogate marker with almost no catalytic activities, which does not appear to be involved in catalyzing hydrolysis of TG in TG-rich lipoproteins. Recently, a prospective study has demonstrated that low serum LPL concentration predicts future coronary events.

Taken together, we suggest that pre-heparin LPL mass in plasma or sera provide us with useful and important information on the development of metabolic disorders leading to atherosclerotic disease.

1.**Introduction**

Lipoprotein lipase (LPL) plays a central role in lipoprotein metabolism by catalyzing hydrolysis of triglycerides (TG) in chylomicrons and very low-density lipoprotein (VLDL) particles [1-3]. Since a decade ago, it has been noted that besides its function of catalytic enzyme, LPL functions as a mediator facilitating binding and/or incorporation of series of lipoproteins through either lipoprotein receptors or heparan sulfate proteoglycans [4-8] into several lines of cells. LPL is synthesized and secreted in adipocytes, muscle cells, cardiomyocytes and macrophages [3], which is transferred to heparan-sulfate on the luminal surface of the endothelial cells in vessels through unknown mechanism [9-11].

In clinical studies, post-heparin plasma (PHP) is usually used as a material for the measurement of LPL mass and activity. From the last decade, however, several groups of researchers [12-19] have shown the clinical significance of measuring LPL protein mass in plasma or sera by an enzyme-linked immunosorbent assay (ELISA) without heparin injection (simply put as serum or plasma LPL mass). In earlier studies, researchers applied the measurement of plasma or serum LPL mass to detailed analysis and characterization of type 1 hyperlipidemia (HLP) [16,17]. In 1989, Auwerx et al. [16] proposed that type 1 HLP be classified into three subtypes according to the amount of LPL mass in pre- and post-heparin plasma. In 1990, Kern et al. [17] conducted detailed analysis of LPL protein in pre- and post-heparin plasma from both normal subjects and type 1 HLP. In recent years, the measurement of plasma or serum LPL mass has been conducted to clarify the pathophysiology of more common metabolic

disorders. Tornvall et al. [13,15] have studied the correlation between lipoproteins and plasma LPL mass from men before the age of 45 years with coronary heart disease and from age-matched controls, and found that there was a strong positive correlation between plasma LPL mass and HDL-C levels as well as weak negative relations to VLDL-TG in the patients. The study by Watanabe et al. [14] has shown that serum LPL mass is lower in conditions in which TG catabolism is disturbed, such as hypertriglyceridemia and individuals with increased remnant lipoproteins.

In this review, we focus on recent advances in the research on clinical significance of measuring plasma or serum LPL mass without heparin-injection into study subjects, based on several clinical findings reported in the last decade.

2. Biochemical Properties of Pre-Heparin LPL

It has been shown that LPL activity in plasma increased about as high as 170-fold, whereas LPL mass increased only about 9-fold after heparin injection [13]. Most of the LPL protein in plasma elutes as an early peak from heparin-Sepharose, corresponding to the position for inactive monomeric LPL and is demonstrated to be full-length LPL, which is bound to plasma lipoproteins [12]. Thus, it is unlikely that the measured plasma LPL mass directly contributes to catalyzing hydrolysis of triglycerides in TG-rich lipoproteins in the plasma. Several researchers have shown that this inactive protein may act as a ligand targeting lipoproteins for binding to cell surfaces and receptors [18].

3. Correlation of Serum LPL to Post-Heparin Plasma (PHP) LPL Mass

It has been reported that serum LPL mass had a positive relation with PHP-

LPL mass [14,19,20], although the degree of the relation appeared to differ among the reports. It should be noted that Hirano et al. [20] have shown that the delta LPL concentration was strongly related to the PHP-LPL concentration (r =.965, P </=.0001), but not to the serum LPL mass, suggesting that the weak correlation between serum LPL and PHP-LPL levels was attributable to contamination of PHP by pre-existing LPL.

4. Relationship Between Plasma LPL Mass and Intra-Abdominal Visceral Fat

It is generally recognized that individuals with obesity have high prevalence of complications, such as impaired glucose tolerance, hyperlipidemia, and hypertension However, it is also true that the degree of obesity does not necessarily account for the severity of these disorders [21]. Studies have suggested that fat distribution and abdominal fat accumulation are good predictors of the development of coronary heart disease [22-24]. Moreover, intra-abdominal visceral fat accumulation is shown to be associated with insulin resistance [25]. Several clinical studies were conducted for analyzing the relationship of LPL mass, either in pre-heparin plasma (or serum) or PHP, to visceral fat accumulation. We and other groups have reported that intra-abdominal visceral fat area assessed by CT at umbilical level had an inverse relationship to LPL mass and activity in PHP [26-28]. Similar results were obtained on the association between intra-abdominal visceral fat and pre-heparin LPL mass [19] by recruiting a total of 58 subjects comprising 50 hyperlipidemic and 8 normolipidemic subjects. In that study, plasma LPL mass had an inverse relationship to intra-abdominal visceral fat area, but did not show any statistically significant correlation to subcutaneous fat

area. Multiple regression analysis performed with plasma LPL mass as a dependent variable, and visceral fat area and BMI as independent variables revealed that the visceral fat area had an inverse relation to plasma LPL mass, independent of BMI. We have conducted the receiver operator characteristic (ROC) analysis for LPL concentration to predict the presence of intra-abdominal visceral fat area>100cm^2 (Fig.1). This finding suggests that the optimal cut off point of serum LPL mass for predicting visceral fat accumulation could be around 40 ng/ml. Furthermore, we also subdivided the whole subjects into each gender and found that the optimalcut off point of LPL mass for men might be 35 ng/ml rather than 40 ng/ml (Fig.2).

5. Relationship of serum LPL concentration with lipoproteins and apolipoproteins

We have shown that plasma LPL mass correlated positively with serum HDL-C level and inversely with serum TG level, but did not significantly correlate with low-density lipoprotein (LDL)-C [19]. Other group in Japan has reported similar results for 377 Japanese individuals who underwent annual health examinations [14].

The study by Tornvall et al. [13] has shown this association existed in 61 men who had suffered myocardial infarction before the age of 45 years. For the association with serum apolipoproteins, plasma LPL mass had a positive correlation with serum apolipoprotein (apo) A-I, but not apo B or E. Furthermore, it has been shown that serum LPL correlated inversely with TG, remnants, and insulin resistance and positively with HDL cholesterol and LDL size in164 Japanese hyperlipidemic subjects [20]. This finding has been confirmed by the recent report [29] showing a strong positive correlation between serum LPL concentration vs. LDL and HDL sizes measured by

nuclear magnetic resonance. These observations support the association of a high serum LPL concentration with a beneficial lipid profile.

6. Serum LPL Mass in Type 2 Diabetes Mellitus

A study has shown that serum LPL concentration was considerably lower in type 2 diabetic patients (n=40) than in non-diabetic healthy controls, and had an inverse relation to HbA1c in diabetic individuals [30]. For 15 subjects among them, they investigated the effect of insulin treatment on serum LPL mass and plasma glucose levels, and found that serum LPL mass increased significantly at week 4 on insulin treatment, with concomitant reduction in fasting blood glucose level. We analyzed gender difference in plasma LPL mass and other metabolic parameters from Japanese type 2 diabetic subjects after adjusting for age, BMI, and HbA1c [31]. The men group showed a higher serum TG and lower HDL-C levels along with lower plasma LPL mass than did women. Troglitazone, an insulin sensitizer and now out of market in Japan, was reported to cause an increase in pre-heparin LPL mass [32], which is consistent with our study showing this agents increased LPL mass in PHP [33].

7. Serum LPL mass in acute inflammation

We had a diabetic woman with severe foot gangrene, who had a markedly low HDL-C and serum LPL mass [34]. Serum LPL mass and serum HDL-C returned to almost normal level during treatment of her diabetes and gangrene with insulin and anti-biotics. Serum C-reactive protein levels had an inverse relationship to serum LPL mass, suggesting that in acute inflammation, the production of LPL in adipocytes or muscle tissue is highly inhibited. Serum C-reactive protein levels also showed an

inverse relation to plasma glucose levels, although to a lesser degree.

8. Serum LPL concentration and insulin resistance

The recent report by Hanyu et al. [35] has indicated that serum LPL mass correlated significantly with insulin sensitivity analyzed by minimal model, which is applied to all of the subjects they studied regardless of whether the subjects had normal glucose tolerance, impaired glucose tolerance, and diabetes. Also, serum LPL mass correlated negatively with HOMA-R and fasting IRI.

9. Serum LPL concentration and serum adiponectin levels

Recently, it has been shown that LPL activities in post-heparin plasma were positively associated with serum adiponectin levels [36-38]. More recently, Saiki et al [39] have reported that in 362 Japanese subjects with metabolic syndrome, the correlation coefficient between serum LPL mass and plasma adiponectin was high (r=0.562). They also have shown that both serum LPL mass and adiponectin correlated positively with HDL-C and inversely with body weight and TG. Also, serum LPL mass and plasma adiponectin decreased with an increase in severity of the metabolic syndrome with/without obesity and with/without diabetes.

10. The Association of Pre-Heparin LPL Mass and the Incidence of Coronary artery disease (CAD)

Hitsumoto et al. [40,41] compared pre-heparin LPL mass in men with angiographically determined coronary atherosclerosis versus that in men with normal coronary or healthy men. They found that men with coronary atherosclerosis had significantly lower pre-heparin LPL mass than did men without coronary atherosclerosis or healthy men.

They suggest that serum LPL mass is an independent determinant of incidence[40] or severity[41] of coronary artery disease even after adjustments of a number of metabolic parameters, including serum triglycerides and HDL-C.

11. Prospective associations between serum LPL concentration and risk for future CAD

To demonstrate whether or not low LPL mass is the result or the cause of coronary heart disease, it is essential to conduct a prospective study on the association of these two markers. Recently, Rip et al. [29] determined serum LPL concentrations from men and women in the EPIC-Norfork population cohort who developed fatal or nonfatal CAD during 7 years of follow-up. Subjects with highest LPL concentration quartile had a 34% lower risk for future CAD compared with those in the lowest quartile. This effect remained significant after adjustment for blood pressure , diabetes, smoking, body mass index, and LDL-C but not significant after additional adjustment for TG or HDL-C. Their results suggest that high LPL concentrations may be athero-protective through associations with decreased TG levels and increased HDL-C levels. In this regard, their study did not appear to be consistent with the above-mentioned cross-sectional study by Japanese investigators suggesting that serum LPL mass could be risk factor for CAD, independent of TG and HDL-C. In addition to the relation of serum LPL mass to the incidence of coronary heart disease, we have recently found that in Japanese hyperlipidemic subjects, serum LPL mass showed an inverse association with average intima-media thickness of right and left common carotid arteries assessed with ultrasonography following previously reported method [42],

independent of age,gender, body mass index, LDL-C,HDL-C and TG in a multiple regression analysis, (Table 1). This finding suggests that serum LPL mass predict the development of atherosclerosis in carotid artery as well as in coronary artery.

12. Effects of Several Lipid-Lowering Agents on serum LPL Mass

It has been shown that bezafibrate, a lipid lowering compound known to cause a reduction in serum TG level with increase in HDL-C levels [43], has produced a considerable increase in serum LPL mass in hypertriglyceridemic patients [44]. This observation has been in line with the previous reports on the effects of this compound on LPL activity in PHP [45,46]. Recently, it has been reported that series of statins, such as pravastatins, atorvastatins and pitavastatins may produce a significant increase in serum LPL mass after the treatment [47,48]. An in vitro study has shown that that pitavastatins increase the expression of LPL mRNA from cultured 3T3 L1 cells [47]. Their study appeared to be somehow incompatible with our study showing atorvastatin did not produce an increase in pre-heparin LPL mass in hyperlipidemic subjects, despite causing a substantial reduction in serum TG level [49]. This might be partly associated with the different clinical profile of the study subjects with their study subjects being type 2 diabetes having lower serum HDL-C levels at baseline compared with ours.
We have suggested that the main mechanisms by which atorvastatins produced considerable TG reductions may be due to their inhibition of the production and secretion of VLDL from the liver.

13. Concluding remarks

According to considerable number of evidence above mentioned, measuring pre-heparin

LPL mass in plasma or sera provides us with useful information on understanding the pathophysiology of several metabolic disorders, such as visceral fat accumulation, diabetes mellitus and insulin resistance, which are highly associated with the incidence of coronary heart disease, despite its simplicity from a practical point of view in daily clinical practice.

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Figure legends

Figure 1 The receiver operator characteristic (ROC) analysis for serum lipoprotein lipase mass to predict the presence of intra-abdominal visceral fat area $\geqq 100$ cm^2

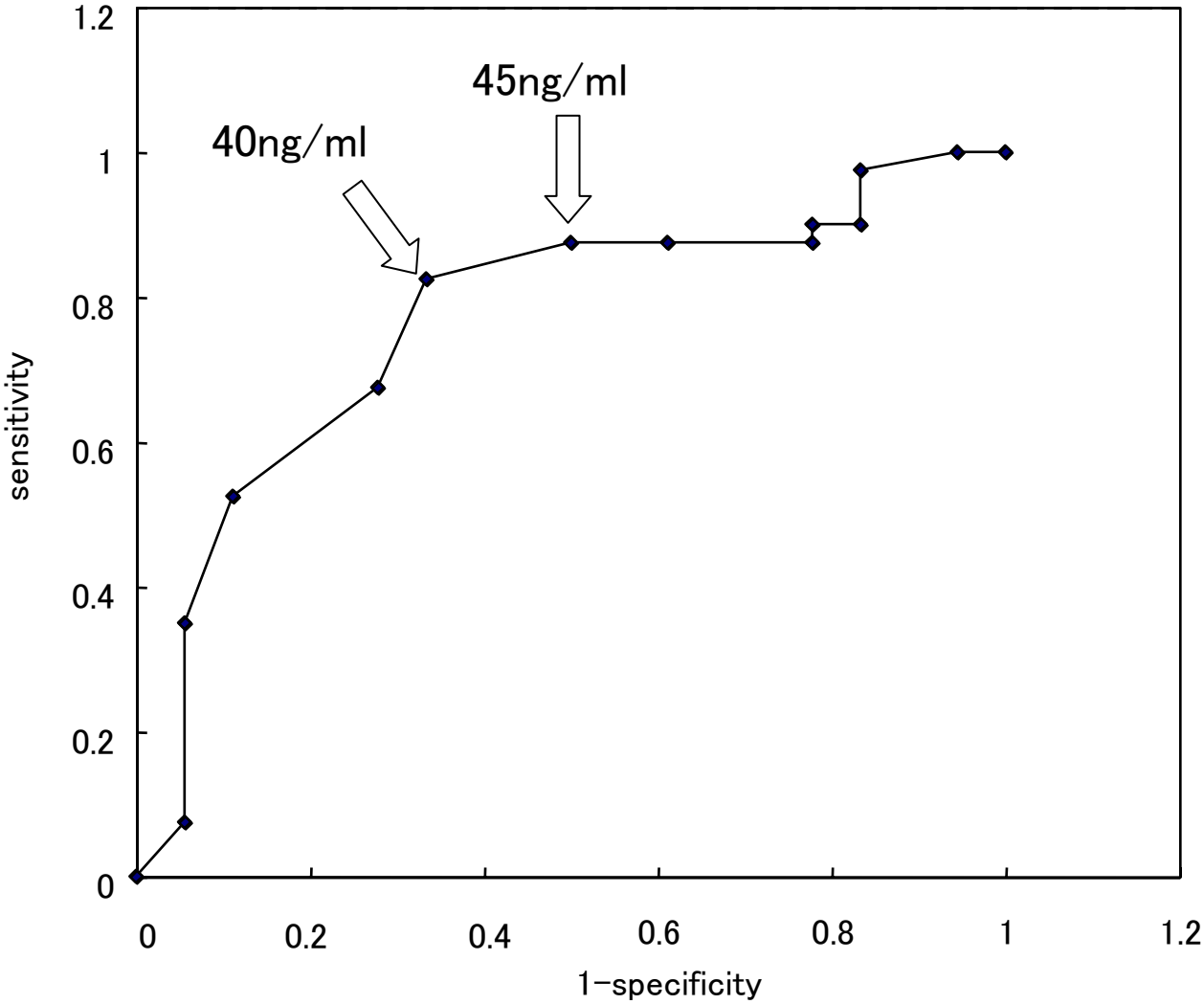
Figure 2 The receiver operator characteristic (ROC) analysis for serum lipoprotein lipase mass to predict the presence of intra-abdominal visceral fat area $\geqq 100$ cm^2 in men (n=33) and women (n=25), separately.

Table 1 A multiple regression analysis with intima-media thickness of common carotid artery assessed with ultrasonography, with age, gender, body mass index, LDL-C, HDL-C and TG as independent variables

	S.E	β	t	p
Ln LPL	.142	-.461	-2.209	.0352
age	.004	.409	2.467	.0198
gender	.092	.093	.519	.6079
Body mass index	.020	-.091	-.497	.6228
LDL-C	.001	.296	1.608	.1187
HDL-C	.003	.046	.224	.8245
TG	$3.765E^{-4}$	.215	.896	.3776

The measurement of intima-media thickness in the common carotid artey was made along a 10 mm long section just proximal to the carotid bulb. The means of three separately analyzed images was used and average IMT was calculated from right and left intima-media thickness of common carotid arteries.

Figure 1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sensitivity
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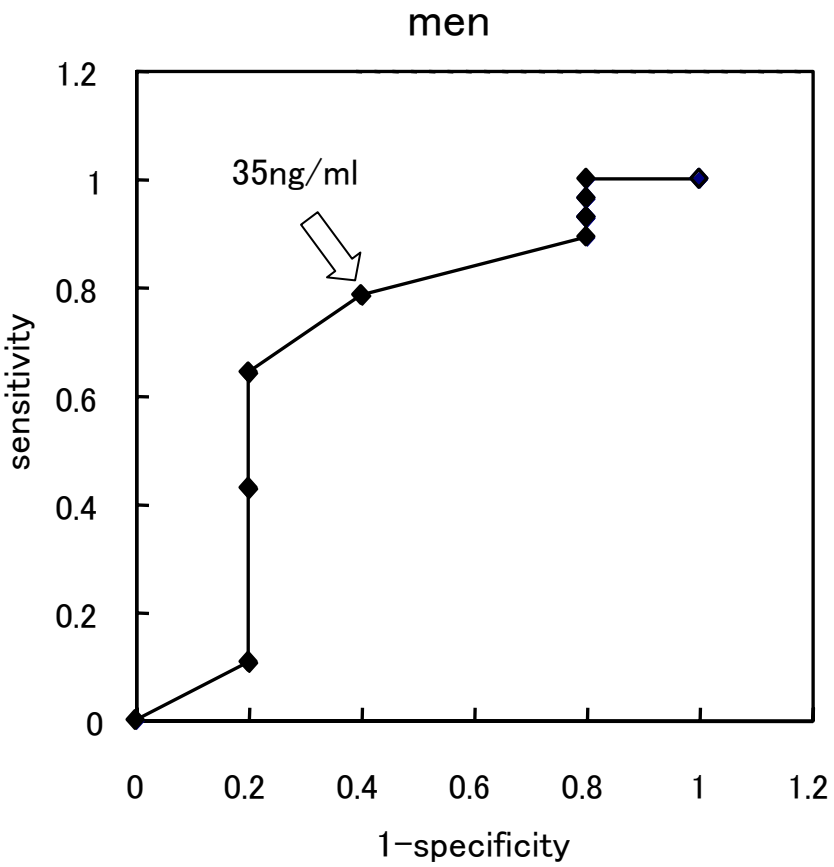
Figure 2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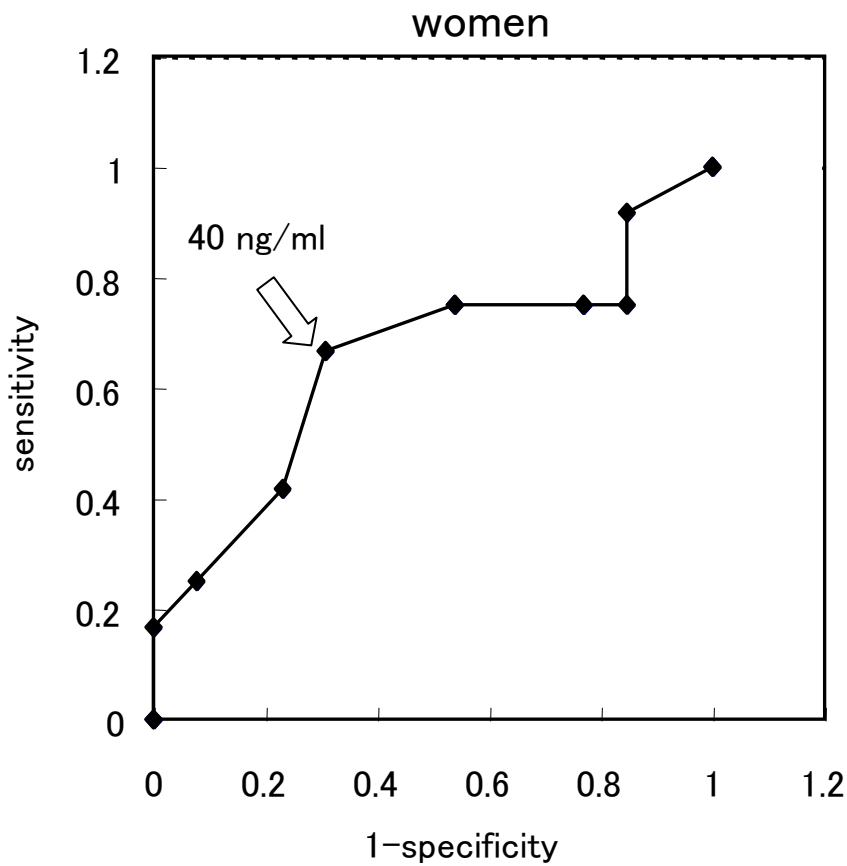
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