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Commentary

Is lipoprotein-associated phospholipase A_2 correlated with cardiovascular risk in European women?

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is an enzyme expressed in atherosclerotic plaques by inflammatory cells; thus, its measurement could contribute to the identification of patients with rupture-prone plaques[1]. Lp-PLA_2 is carried in the blood stream by low density lipoprotein (LDL) particles, where it is bound to small cholesterol-deplete LDL particles rather than to large cholesterol-enriched LDL particles. As the Lp-PLA_2-LDL complex enters the vessel wall, the reduced phospholipid content of smaller LDL particles increases the oxidative susceptibility of those particles[1].

Among the serum markers of inflammation, the Lp-PLA_2 is correlated with the progression, extension, and severity of cardiovascular disease (CVD) as well as to a greater mortality risk after coronary heart attack[2]. In fact, Lp-PLA_2 has been recommended as an inflammatory marker for CVD risk assessment in patients with moderate or high risk based on Framingham criteria[3]. However, in a large study of individuals without known CVD, the addition of Lp-PLA_2information to the risk scores containing total cholesterol and HDL-C led to only slight improvement in CVD prediction[4].

In this issue, Pop *et al*[5] provide further results of the correlations of Lp-PLA_2 and CVD risk factors. They raised the question of whether to consider this enzyme as an inflammation serum marker and a possible predictor of CVD risk in women. A large review[6] explored the associations between Lp-PLA_2 activity and cardiovascular events with data from 32 prospective studies that included just over 79 000 participants. Risk ratios for coronary heart disease and ischaemic strokes increased progressively for every increase of 1 SD in Lp-PLA_2 activity adjusted for confounding variables. The 2010 ACCF/AHA Guidelines for Assessment of Cardiovascular Risk in Asymptomatic Adults recommend Lp-PLA_2 as a reasonable inflammation serum marker for CVD risk assessment in intermediate-risk asymptomatic adults[7]. CVD is the leading cause of death in women in Europe[5]; almost 55 per cent of female mortality is caused by CVD[5]. The authors compared three groups of patients: group 1 with 37 women with metabolic syndrome; group 2 with 27 men with metabolic syndrome; and group 3 with 26 women without metabolic syndrome. They found no significant differences in Lp-PLA_2 values between the three groups of patients. Female patients without metabolic syndrome displayed a significant inverse correlation between Lp-PLA_2 and HDL-C, whereas men with metabolic syndrome displayed a direct correlation with HOMA-IR. However, in general, they did not find significant correlations between the Lp-PLA_2 levels and the studied risk factors. Further, there was a weak direct correlation between Lp-PLA_2 levels and hsCRP in all the three groups studied[5].

What implications does this study contribute regarding Lp-PLA_2?

Results on LP- PLA_2 are controversial. A recent study showed that after extensive adjustment for covariates, the relationship between Lp-PLA_2 mass and incident CVD was inverse for highest versus lowest tertile (relative risk: 0.55; 95% CI 0.39-0.79), whereas this association was direct for LpPLA_2 activity for highest versus lowest tertile (relative risk: 1.65; 1.12-2.42)[8]. A systemic review showed that there were no clear associations of Lp-PLA_2 mass or activity with insulin-resistance[9]. Even though Lp-PLA_2 promotes vascular inflammation, it also has a cardioprotective role because it is implicated in the degradation of the platelet-activating factor, a potent mediator of inflammation (which is why Lp-PLA_2 is also known as platelet-activating factor acetylhydrolase). This dual role raises the question of which role, proatherogenic or antiatherogenic, is more prominent and under

which conditions[10]. Pop *et al*[5] found that there were no significant correlations between the Lp-PLA$_2$ levels and the CVD risk factors studied. Consistent with this study, a previous study in adult women showed that Lp-PLA$_2$ was positively associated with incident CVD, but after adjustments for CVD risk factors this association lost significance[11]. Another report demonstrated that Lp-PLA$_2$ in children[12] was not significantly associated with obesity whereas other inflammatory markers such as C reactive protein were associated. A recent review of individuals without known CVD showed that Lp-PLA$_2$ improved only to some extent CVD prediction compared to traditional markers[4]. Findings regarding the association of Lp-PLA$_2$ with incident CVD have been inconsistent, and its role in risk prediction is uncertain. This study also showed that even though there was a significant direct correlation between sPLA$_2$ levels and hsCRP in all the three groups studied, the correlation was weak. These results could be due to the small size of the sample studied or to the fact that Lp-PLA$_2$ could have a cardioprotective role in this group of women.

The strength of this study was the inclusion of women with and without metabolic syndrome. However, the study was underpowered. The R^2 in the regression line (sPLA$_2$ vs hsCRP in women with metabolic syndrome) was only 0.02, which means that only 2 per cent of the variation of the dependent variable (Lp-PLA$_2$) was explained by the independent variable (hsCRP). The major limitation of this study was the small size of the sample.

The authors[5] could not accurately conclude that Lp-PLA$_2$was an inflammatory marker for cardiovascular disease risk. Furthermore, we now have more evidence that Lp-PLA$_2$ could have a dual role proatherogenic or antiatherogenic, and it is not clear as to which role is more prominent and under which conditions. The challenge to all researchers now is to investigate under which conditions Lp-PLA$_2$ could have a proatherogenic or antiatherogenic role. Further longitudinal studies in different ethnic and age groups should be performed to confirm these findings.

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