Atherosclerosis 228 (2013) 38–41

Contents lists available at SciVerse ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Invited commentary

Phospholipid transfer protein, an emerging cardiometabolic risk marker: Is it time to intervene?

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ARTICLE INFO

Article history:
Received 28 January 2013
Accepted 28 January 2013
Available online 8 February 2013

Keywords:
PLTP
CVD risk

The global epidemic of cardiometabolic disorders provides a convincing rationale for our continuous drive to explore novel biomarkers and therapeutic targets in order to better classify those subjects at increased risk of cardiovascular disease (CVD), and to preserve their vascular health. It is well appreciated that various abnormalities in lipid metabolism are causally implicated in the development of atherosclerotic vascular disease. Human plasma contains two lipid transfer proteins, cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP), which play pivotal but distinct roles in lipoprotein metabolism [1,2]. The extent to which plasma CETP mass or activity predict CVD in humans independent from conventional lipid and non-lipid risk factors is still disputed [3,4]. Of further interest, effects of pharmacological CETP inhibition on cardiovascular outcome have been disappointing so far [3], although the results of several large-scale clinical end-point studies have to be awaited. As yet, the relevance of plasma PLTP for predicting cardiometabolic disorders is only recently being explored.

PLTP is a 476 amino acid lipid transfer protein which is abundant in the circulation of humans and many other species, where it resides on HDL [1,5–8]. PLTP associates with a variety of proteins; lipids account for only a small fraction of PLTP-containing complexes in plasma [8]. Due to extensive glycosylation the apparent molecular weight of PLTP is about 81 kDa, much higher than its predicted protein weight of 53 kDa [1,8]. PLTP is secreted by a variety of cell types and tissues, including liver, adipose tissue and macrophages. Together with cholesteryl ester transfer protein (CETP), lipopolysaccharide (LPS) binding protein (LBP) and bactericidal permeability increasing protein (BPI), PLTP belongs to a family of LPS binding/lipid transfer proteins [8]. The *PLTP* gene is located on chromosome 20 (20q12-q13.1) in close proximity of *LBP* and *BPI* [1,8]. The transcription of *PLTP* is regulated by liver X receptor, farnesoid X-activated receptor- and peroxisome proliferator-activated receptor-dependent mechanisms [1,8].

It is widely appreciated that PLTP has multiple and complex functions in lipoprotein metabolism [1,2,5–8]. It facilitates the transfer of phospholipids and free cholesterol from triglyceride-rich lipoproteins to HDL particles during intravascular lipolysis [1,2,8]. PLTP activity results in the conversion of mature α-HDL in large HDL_2 and small pre-β HDL particles by a mechanism of particle fusion [1,2,8]. Such lipid-poor or lipid-free pre-β HDL particles are regarded as initial acceptors of cell-derived cholesterol, and thus appear to be critical for ATP-binding cassette A1 (ABCA1)-mediated reverse cholesterol transport. Of considerable interest, novel studies imply an important role for PLTP in hepatic lipoprotein secretion. In rodent models, *Pltp* deficiency impairs hepatic VLDL secretion [9], whereas liver-specific *Pltp* expression increases hepatic VLDL lipidation and secretion [10]. Thus, ample evidence has accumulated that PLTP is important for both the metabolism of HDL and of apolipolipoprotein B (apoB)-containing triglyceride-rich lipoproteins. Additionally, PLTP is able to transfer α-tocopherol and LPS between lipoproteins, and is associated with

DOI of original article: http://dx.doi.org/10.1016/j.atherosclerosis.2013.01.046.
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http://dx.doi.org/10.1016/j.atherosclerosis.2013.01.043

pro-inflammatory proteins in human plasma, in agreement with its contribution to anti-oxidant defense, inflammatory processes and innate immunity [7,8]. Interestingly in rodents, *Pltp* deficiency may protect against oxidative modification of plasma lipids and reduce thrombotic responses [11].

Given the multifaceted functionality of PLTP even beyond effects on lipoprotein metabolism, it is not surprising that the role of PLTP in the development of atherosclerosis is not straightforward. Most studies in mouse and rabbit models show a positive relationship between *Pltp* overexpression and increased atherosclerosis [1,5,7,8,12,13]. However, robust anti- or pro-atherogenic effects of PLTP impacted via HDL remain unclear, since HDL cholesterol is either increased or decreased in response to *Pltp* overexpression, while HDL cholesterol is decreased consequent to *Pltp* deficiency [1,5,7,8]. During the past few years the concept is emerging in support of the hypothesis that effects of PLTP on accelerated development of atherosclerosis may be dependent on the background of the plasma lipoprotein profile with a pro-atherogenic effect in the context of high levels of apoB-containing lipoproteins [8]. It is also possible that specific cell types such as macrophages play a distinct role in the atherogenesis modifying effects PLTP [14–16].

Since it is obvious that many questions about the overall impact of PLTP on the development of human CVD are still unresolved, there is a clear need for studies focusing on the extent to which plasma PLTP independently predicts cardiovascular disease. For a proper interpretation of such reports it is important to realize that plasma PLTP levels are elevated in obesity, as well as in type 1 and type 2 diabetes mellitus even independent of common genetic variation in *PLTP* [17–22]. This necessitates taking account of the degree of obesity and/or insulin resistance when assessing the cardiovascular risk attributable to the plasma level of PLTP. Furthermore, plasma PLTP is in part inactive [8], making that assaying PLTP activity is likely to be advantageous compared to PLTP mass measurement. In fact, there is a poor correlation between PLTP mass and activity in human plasma [23,24]. One approach to circumvent problems inherent to precise and high throughput measurement of plasma PLTP in large-scale clinical studies is to use genetic variation in *PLTP* as a proxy of (circulating) PLTP, independent of environmental factors which affect its plasma activity. Using a *PLTP* gene score, constructed by a combination of two *PLTP* tagging single nucleotide polymorphisms reproducibly associated with plasma PLTP activity and mass in two independent study populations (rs378114 and rs6065904) we demonstrated that *PLTP* gene variation, which confers lower hepatic PLTP transcription and plasma PLTP activity, leads to decreased risk of cardiovascular events among 5 cohorts comprising a total of 4658 cases and 11,459 controls [25]. This study also demonstrated that a higher *PLTP* gene score, reflecting lower plasma PLTP levels, relates to an increased number of HDL particles and a smaller average HDL particle size [23]. In another report, *PLTP* tagging single nucleotide polymorphisms were suggested to be associated with carotid artery disease [26].

In this issue, Robins et al. report that higher plasma PLTP activity, measured with a commercially available exogenous substrate assay obtained from Roar Biomedical (New York, NY, USA; reported inter-

Table 1
Reported relationships of cardiovascular disease with plasma phospholipid transfer protein (PLTP) by different research groups.

Research group	Subjects	Study design	Outcome measure	PLTP assay	Main results
Robins S et al. [27]	187 new CVD cases out of 2679 subjects without CVD at baseline	Prospective case-cohort; mean follow-up of 10.4 years	CAD and stroke combined	Activity; commercial assay	Higher PLTP activity in male cases after adjustment for lipid and non-lipid risk factors and CETP activity; no effect of PLTP activity in women
Schlitt et al. [28]	1102 cases; 444 controls	Cross-sectional; case–control	Cardiac	Activity; commercial assay	Higher PLTP activity in cases after adjustment for lipid and non-lipid risk factors
de Vries et al. [29]	87 T2DM subjects; 83 controls	Cross-sectional	IMT	Activity; in house assay	Positive association of IMT with PLTP activity independent of lipid and non-lipid factors in T2DM only
Schlitt et al. [30]	156 new CAD cases (47 on statin treatment at baseline) out of 1085 subjects with preexistent CAD	Prospective case-cohort; median follow-up of 5.1 years	Cardiac	Activity; commercial assay	Higher PLTP activity in cases who were on statin treatment after adjustment for lipid and non-lipid risk factors; no effect of PLTP activity in non-statin users
Colhoun et al. [22]	195 subjects with and 194 subjects without T1DM	Cross-sectional	CAC	Activity; in house assay	Trend for positive association of CAC with PLTP activity in combined subjects ($P = 0.09$)
Chen et al. [31]	407 subjects with and 215 subjects without CAD, determined by coronary angiography	Cross-sectional; case-control	CAD, defined as $> 50\%$ coronary artery stenosis)	Activity; commercial assay	No difference in PLTP activity between subjects with and without CAD
Yatsuya et al. [32]	10 CAD cases; 7 stroke cases out of 2567 subjects	Prospective case-cohort; mean follow-up 3.1 year	Cardiac	Mass; in house ELISA	Lower PLTP mass in CAD cases after adjustment for some lipid and non-lipid risk factors; no effect of PLTP mass on stroke
Rühling et al. [33]	18 subjects with PAD; 21 controls	Cross-sectional; case-control	Peripheral arteries	Activity; in house assay	Trend for higher PLTP activity in cases ($P = 0.052$); no adjustment for confounders
Schgoer et al. [34]	153 subjects with PAD; 208 controls	Cross-sectional; case-control	Peripheral arteries	Activity & mass; in house assays	Lower PLTP activity in cases after adjustment for hypertension lipids, CRP and glucose and PLTP mass; no effect of PLTP mass on PAD

CAC: coronary artery calcification; CAD: coronary heart disease; CETP: cholesteryl ester transfer protein; CVD: cardiovascular disease; ELISA: enzyme-linked immunosorbent assay; IMT: intima media thickness; PAD: peripheral artery disease; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus.

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