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Obesity Comorbidities

Plasma phospholipid transfer protein (PLTP): review of an emerging cardiometabolic risk factor

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Summary

Plasma phospholipid transfer protein (PLTP) is a lipid transfer glycoprotein that binds to and transfers a number of amphipathic compounds. In earlier studies, the attention of the scientific community focused on the positive role of PLTP in high-density lipoprotein (HDL) metabolism. However, this potentially anti-atherogenic role of PLTP has been challenged recently by another picture: PLTP arose as a pro-atherogenic factor through its ability to increase the production of apolipoprotein B-containing lipoproteins, to decrease their antioxidative protection and to trigger inflammation. In humans, PLTP has mostly been studied in patients with cardiometabolic disorders. Both PLTP and related cholesteryl ester transfer protein (CETP) are secreted proteins, and adipose tissue is an important contributor to the systemic pools of these two proteins. Coincidentally, high levels of PLTP and CETP have been found in the plasma of obese patients. PLTP activity and mass have been reported to be abnormally elevated in type 2 diabetes mellitus (T2DM) and insulin-resistant states, and this elevation is frequently associated with hypertriglyceridemia and obesity. This review article presents the state of knowledge on the implication of PLTP in lipoprotein metabolism, on its atherogenic potential, and the complexity of its implication in obesity, insulin resistance and T2DM.

Keywords: Phospholipid transfer protein, cardiovascular risk factor, obesity, type 2 diabetes mellitus.

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Introduction

Obesity, especially when characterized by the accumulation of visceral fat provides a propitious background for a number of disorders, including insulin resistance, type 2 diabetes mellitus (T2DM), hypertriglyceridemia, hypoalphalipoproteinemia, hypertension and cardiovascular disease (1). Recent studies have highlighted the concept of cardiometabolic risk as a condition of excess visceral adiposity that drives low-grade inflammation and leads to the dys-regulation of adipokines, key players in the development of insulin resistance, T2DM, endothelial dysfunction and atherosclerosis (2). Abnormalities in plasma phospholipid transfer protein (PLTP) levels have been reported in

patients with obesity, T2DM and cardiovascular disease (3). PLTP is expressed at relatively high levels, both in subcutaneous and in visceral adipose tissue (4), and it binds to and transfers a number of amphipathic compounds, including phospholipids, diacylglycerides, unesterified cholesterol, vitamin E and lipopolysaccharides when secreted within the bloodstream. PLTP has longer been studied exclusively for its role in high-density lipoprotein (HDL) metabolism and the knowledge of the impact of PLTP on the metabolism and properties of the potentially atherogenic apolipoprotein (apo)B-containing lipoproteins in high-risk patients is only recent (Fig. 1), suggesting that the role of PLTP as a cardiometabolic risk factor has probably been underestimated so far.

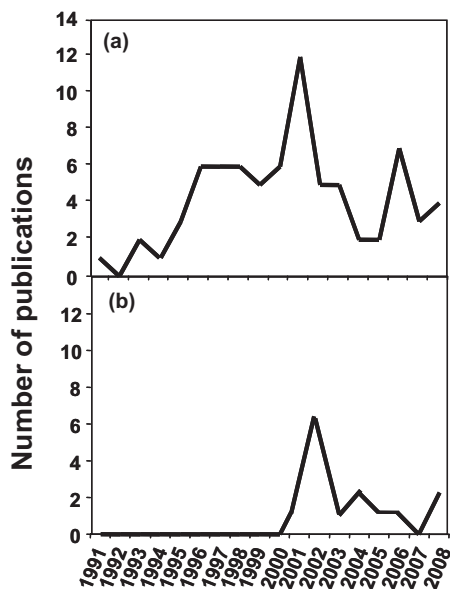


Figure 1 Original publications showing the implication of PLTP in the metabolism of (a) HDL and (b) apoB-containing lipoproteins; Medline analysis from 1991 to 2008. PLTP, plasma phospholipid transfer protein; HDL, high-density lipoprotein.

The role of plasma phospholipid transfer protein in high-density lipoprotein metabolism

Plasma phospholipid transfer protein facilitates the transfer of surface phospholipids from triglyceride-rich lipoproteins to HDL particles during lipoprotein lipase-mediated lipolysis, thus contributing to the formation of new HDL particles in the postprandial state (5). Additionally, and unlike cholesteryl ester transfer protein (CETP), PLTP can promote HDL remodelling through a strictly intra-HDL process. PLTP predominantly favours the appearance of large HDL conversion products, HDL2b and HDL2a, at the expense of small HDL3 with a concomitant release of small lipid-poor pre β -HDL particles, the most efficient cellular cholesterol acceptors (6,7). PLTP is highly responsible for the generation of pre β -HDL, thus supporting its role in the initial step of reverse cholesterol transport (8).

The potential role of PLTP in HDL conversion has been illustrated in experiments with transgenic or adenovirus-injected mouse models, in which human PLTP was expressed at moderate to elevated levels. While modest increments in systemic PLTP activity levels did not always translate into clear changes in HDL metabolism (9,10), pronounced changes in systemic and/or tissue-specific expression of PLTP led to a marked decrease in HDL levels that was due to hypercatabolism (11–15). Another relevant way to determine the effect of PLTP on HDL structure and concentration has been to generate PLTP-knocked-out (PLTP-KO) mice (16). PLTP-KO homozygotes display a marked reduction in plasma levels of α - and pre β -HDL,

while no significant HDL phenotype was observed in PLTP-KO heterozygotes (16).

The role of plasma phospholipid transfer protein in the metabolism of apoB-containing lipoproteins

Although the implication of PLTP in α - and pre β -HDL metabolism may be considered positive in terms of facilitation of the reverse cholesterol transport pathway, recent *in vivo* studies rather support the pro-atherogenic properties of PLTP. The mixed picture was explained by the variety of PLTP functions *in vivo*, and its potentially beneficial effect on HDL metabolism was actually counterbalanced, at least in part, by an independent role in increasing the production of atherogenic apoB-containing lipoproteins by the liver and in reducing their antioxidant protection (14,17,18). In mouse liver, PLTP was found to be involved in the final step of the intracellular pathway that allows lipids to be added to nascent apoB-containing lipoproteins (17). In subsequent studies, livers of PLTP-KO mice were found to contain less vitamin E but more oxidized lipid derivatives than did the livers of wild-type controls. The concomitant increase in the quantity of reactive oxygen species in PLTP-KO livers was found to be responsible for the defect in apoB secretion (18). In addition to liver observations, PLTP was also proven to be involved in the secretion of cholesterol from enterocytes, in this case with alterations in the assembly and secretion of both chylomicrons and intestinal HDL (19).

Pro- and anti-atherogenicity of plasma phospholipid transfer protein: a janus-faced protein in animal models

Genetically engineered mouse models have made an important contribution to the elucidation of the role of PLTP in atherosclerosis, and they suggested that the metabolic context could be a major determinant of the atherogenic potential of PLTP. In a landmark report, Jiang *et al.* (17) bred PLTP-KO mice into various hyperlipidaemic strains with increased atherosclerosis susceptibility. The lack of PLTP clearly resulted in a marked decrease in the extent of aortic lesions in most of the mouse models studied. Decreased atherogenicity of PLTP-deficient animals was consistent with the decrease in the circulating levels of pro-atherogenic apoB-containing lipoproteins and the increase in their antioxidant protection (see previous discussion).

In addition, PLTP could also be pro-atherogenic by influencing inflammatory processes. In mice, PLTP deficiency improves the anti-inflammatory properties of HDL and low-density lipoproteins (LDL) (20), and reduces levels of interleukin-6, an inflammatory cytokine that is increased in atherosclerosis (21). The expression of some pro-

inflammatory genes was also found to be reduced in the PLTP-deficient mouse model (22).

Studies in macrophages provided further clarifications of the pro- vs. anti-atherogenic properties of PLTP (23–25). Selective deficiency of PLTP in hematopoietic cells, including macrophages, was achieved by the transplantation of PLTP-deficient bone marrow cells in the mouse. Unlike systemic PLTP deficiency, the isolated PLTP knockout in macrophages was found to result in higher atherogenicity in transplanted, hyperlipidaemic animals (23,24). In complementary studies on isolated peritoneal macrophages, PLTP was actually found to decrease the accumulation of cholesterol in macrophages through changes in the vitamin E content and antioxidant status of the cells (26). Vikstedt *et al.* (25) reported that PLTP expression in macrophages from female LDL receptor-KO mice is associated with decreased atherosclerosis, but in this case, PLTP expression was not confined to the vicinity of macrophages but extended towards the bloodstream, with a twofold increase in the level of systemic activity.

It can be postulated that the atherogenicity of PLTP might actually be dependent on its site of action. Systemic/plasma PLTP would act as a pro-atherogenic protein by increasing production of apoB-lipoprotein and by depleting it of beneficial vitamin E. In contrast, local production of PLTP within the arterial wall would be anti-atherogenic by increasing macrophage vitamin E content, decreasing oxidative stress and reducing cholesterol accumulation. Additionally, the metabolic context such as levels of triglycerides, apoA-I and pre β -HDL could also modulate the action of PLTP.

Plasma phospholipid transfer protein in human metabolic disease

Puzzling animal observations have generated major interest with regard to understanding the dominant trait associated with elevated PLTP expression in humans, in particular to determine whether high PLTP expression promotes or inhibits atherosclerosis. PLTP activity and HDL levels have

been shown to correlate either positively (27,28) or negatively (29,30) in various patient populations. Schlitt *et al.* (29) suggested that PLTP activity is an independent risk factor for coronary heart disease (CHD) and that the vascular risk in CHD patients with the highest quintile of PLTP activity was 1.9 times that of patients in the lowest quintile. In contrast, it has been suggested that PLTP mass is an independent protective factor for CHD, although there were only a small number of CHD cases in this study (31). Plasma PLTP activity was found to be a positive determinant of carotid intima-media thickness, an established marker of atherosclerosis in T2DM (32). Increased PLTP activity was found in normolipidemic patients with peripheral arterial disease (33). In a very recent study by Schgoer *et al.* (34), PLTP activity, but not PLTP mass, was found to be significantly decreased in peripheral arterial disease and proven to be an independent atheroprotective factor in these patients. Finally, PLTP activity has been reported to correlate positively with C-reactive protein, an inflammatory marker known to be strongly associated with increased risk of atherosclerosis in patients with CHD documented by angiography (35). Immunohistochemistry studies on histological sections of human carotid artery have shown that PLTP is highly expressed by macrophages and smooth muscle cells that are present in atherosclerotic lesions (36,37). Interestingly, local overexpression of PLTP in macrophages has been found to augment cellular uptake of triglyceride-rich lipoprotein-derived phospholipids and to trigger apoptosis in human macrophages and endothelial cells, thus compromising vascular structure and function (38).

Human clinical studies exploring the involvement of PLTP in atherosclerosis are presented in Table 1. Again, and in agreement with mouse studies, they indicate that the PLTP-associated risk should not be related *per se* to expression of the protein, but should rather be evaluated with regard to the pathophysiological state and the efficiency of lipoprotein production and uptake. As far as apoB-containing lipoprotein metabolism is concerned, it is tempting to speculate that PLTP could act as a potentially

Table 1 PLTP levels and atherosclerosis in clinical studies in humans

Study	Population	PLTP levels	Reference
PLTP pro-atherogenic			
CS	1102 CAD, 444 controls	Higher in CAD	Schlitt <i>et al.</i> , 2003 (29)
CS	87 T2DM, 83 controls	Higher in T2DM, correlated with IMT	de Vries <i>et al.</i> , 2006 (32)
CS	18 PAD, 21 controls	Higher in PAD patients	Ruhling <i>et al.</i> , 1999 (33)
PLTP anti-atherogenic			
CS	2567	Inversely correlated with risk of CAD	Yatsuya <i>et al.</i> , 2004 (31)
CS	153 PAD, 208 controls	Lower in PAD	Schgoer <i>et al.</i> , 2008 (34)

CAD, coronary artery disease; CS, cross sectional; IMT, intima-media thickness; PAD, peripheral artery disease; PLTP, plasma phospholipid transfer protein; T2DM, type 2 diabetes mellitus.

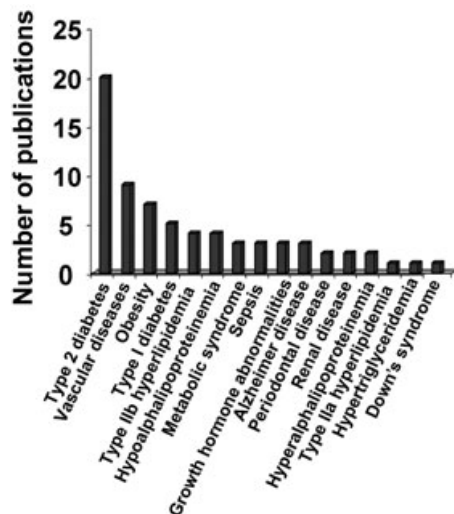


Figure 2 Original publications on the role of plasma phospholipid transfer protein (PLTP) in human pathology; Medline analysis from 1991 to 2008.

beneficial factor under normal physiological conditions that require production of apoB-containing lipoproteins by the liver and efficient tissue uptake of these particles both in the periphery and the liver. However, in case of high circulating levels of potentially atherogenic apoB-containing lipoproteins that tend to accumulate in the bloodstream, PLTP-mediated overproduction of apoB-containing lipoproteins by the liver would unfavourably add to the atherogenicity of the lipoprotein profile.

As detailed in the following discussion, PLTP metabolism has been studied in metabolic diseases with pro-atherogenic potential such as obesity and T2DM, and these studies have given important insights into the pathophysiology of these states (Fig. 2).

Obesity

Adipose tissue is now recognized as an active endocrine organ producing several hormones and other factors known as adipokines (adiponectin, tumour necrosis factor- α , resistin, interleukin-6), most of which account for alterations in insulin resistance, endothelial dysfunction and atherosclerosis (2,39). CETP and PLTP mRNAs are highly expressed in adipose tissue, and these two proteins can thus be considered members of the adipokine family. Adipose tissue contributes substantially to CETP and PLTP plasma levels, at least in obese populations (4,40). Interestingly, average PLTP mRNA levels were found to be similar to leptin mRNA levels in obese subjects, and the body mass index (BMI) of patients correlated positively with PLTP mRNA levels in the subcutaneous, but not in the visceral adipose tissue (4).

Several clinical studies have described elevated plasma PLTP levels in obese subjects, with no gender effect

(27,41,42). Earlier studies showed a positive association between PLTP levels and insulin resistance parameters (27,41). However, more recent studies suggest that increased PLTP in obese patients is a consequence of obesity *per se*, with no evidence that insulin resistance is involved (42–44). In further support of a direct effect of obesity on PLTP levels, PLTP mass and activity have been found to be positively associated with BMI, fat mass and leptin levels (27,45). In an experimental study on human hepatoma cells, both insulin and leptin suppressed the production of PLTP and CETP (46). These surprising findings were interpreted in terms of an adaptive response of the liver that would compensate for the concomitant increased secretion of these lipid transfer proteins in the periphery in obese and insulin-resistant subjects (46). Weight reduction achieved by either dietary intervention (43) or bariatric surgery (47) resulted in substantial decreases in PLTP levels. In the study by Murdoch *et al.* (43), a hypocaloric formula diet was given to obese patients for 3–6 months, leading to simultaneous decreases in mean body weight (–15%), BMI (–15%) and plasma PLTP concentration (–9%). These alterations were associated with changes in subcutaneous fat and plasma levels of free fatty acids (FFA), but not with changes in abdominal fat or insulin resistance (43). Kaser *et al.* (47) measured PLTP activity in morbidly obese subjects who underwent adjustable gastric banding surgery. After 1 year of follow-up, the pronounced BMI reduction of 10 kg m⁻² was associated with a significant decrease in PLTP activity.

In a prospective study, the influence of obesity on plasma CETP and PLTP mass concentration was investigated in 38 obese women, and the effect of short-term weight loss (obtained after administering a moderate hypocaloric well-balanced diet) on these parameters was assessed (44,48). At baseline, both CETP and PLTP correlated significantly with obesity indices, and a positive correlation between CETP and PLTP mass concentration was observed. These data brought new support to the role of adipose tissue as a significant contributor to systemic CETP and PLTP. The positive correlation between plasma CETP and PLTP was lost in the very early phase of weight loss, suggesting that the contribution of adipose tissue to the plasma levels of the two proteins became less prominent (44). Plasma CETP and PLTP concentrations continued to decrease with further decreases in body weight obtained through prolonged dietary intervention, with concomitant changes in obesity indices (48). No associations were observed between the two lipid transfer proteins and nutrients of the diet, energy density or indices of insulin resistance. Clinical studies of obesity that report PLTP levels at baseline and after weight reduction are summarized in Table 2.

It can be concluded from these studies that like CETP, PLTP is increased in obese subjects and may contribute to

Table 2 Levels of PLTP in obesity at baseline and after weight reduction

Study	n	PLTP baseline	PLTP after weight loss	Role AT	Role IR	Effect on HDL	Reference
CS	24	↑	NR	Yes	Yes	NP	Dullart <i>et al.</i> , 1994 (41)
CS	15	→	NR	No	Yes	No	Murdoch <i>et al.</i> , 2000 (27)
CS	190	↑	NR	Yes	No	No	Kaser <i>et al.</i> , 2001 (42)
PR, DI 3–6 months	19	↑	↓	Yes	No	No	Murdoch <i>et al.</i> , 2003 (43)
PR, SI 1 year	16	NR	↓	NR	NR	No	Kaser <i>et al.</i> , 2004 (47)
PR, DI 1 month	38	↑	↓	Yes	No	NP	Tzotzas <i>et al.</i> , 2006 (44)
PR, DI 4 months	24	↑	↓	Yes	No	NP	Tzotzas <i>et al.</i> , 2007 (48)

AT, adipose tissue; CS, cross-sectional; DI, dietary intervention, HDL, high-density lipoprotein; IR, insulin resistance; NR, not reported; NP, not proven; PLTP, plasma phospholipid transfer protein; PR, prospective; SI: surgical intervention; ↑, Increased; ↓, decreased; →, similar to non-obese.

the high atherogenicity that has long been associated with obesity. Today, weight loss is considered an appropriate therapy to decrease both CETP and PLTP in a coordinated way. To the best of our knowledge, the effect of the two currently available anti-obesity drugs (orlistat, sibutramine) on PLTP levels has not yet been investigated.

Although it could be suspected that the PLTP-mediated changes in HDL might contribute to the disturbed HDL phenotype in obesity and to its reversal during weight loss, its influence is probably rather modest. Indeed, recent clinical studies in obese subjects did not show any clear correlations between PLTP levels and HDL subfractions at baseline (27,41), and the same is true for studies involving weight reduction (43,44,47). In the light of recent findings in animal models, further investigation of the role of PLTP in the abnormal metabolism of apoB-containing lipoproteins in obese subjects is warranted in order to establish its contribution to the pro-atherogenic state in this population.

Type 2 diabetes mellitus

Plasma PLTP levels are elevated in patients with T2DM (49,50). PLTP changes were found to be concomitant with obesity, insulin resistance and hypertriglyceridemia (50). No abnormalities in PLTP mass concentration were reported in patients with familial hypercholesterolemia or combined hyperlipidaemia (49), and plasma PLTP activity is not elevated in non-obese patients with T2DM (51) or impaired glucose tolerance (52). In contrast to dyslipidemia and diabetes, obesity *per se* could be considered an important determinant of plasma PLTP activity. Accordingly, PLTP activity and leptin levels were found to be strongly and independently associated in the plasma of T2DM patients (45). However, the involvement of insulin in the regulation of PLTP levels cannot be excluded. Indeed, interventions reducing FFA and triglycerides, which are parameters of insulin resistance, decrease PLTP activity (51,53). In addition, the decrease in plasma PLTP activity after insulin therapy is blunted in T2DM patients, suggesting that high levels of PLTP in insulin-resistant states could be

in part due to decreased insulin response (53). Therefore, insulin resistance could also be the pathophysiological background for the relationships between FFA, triglycerides and PLTP activity, but the molecular basis remains to be established.

In T2DM, triglyceride levels are often elevated and several studies have reported a close relationship between triglycerides and PLTP, and hypertriglyceridemia could alter the early steps of cholesterol efflux in the reverse cholesterol transport process (41,51). This relationship is interesting given the capacity of triglycerides to facilitate the PLTP-mediated HDL conversion process (54). It was recently observed that the relative amount of pre-β1 HDL is increased in hypertriglyceridemic T2DM patients, and the same is true for the *in vivo* conversion of α-HDL into preβ1-HDL (55). In agreement with this observation, de Vries *et al.* (56) found that cholesterol efflux to plasma from hypertriglyceridemic T2DM patients was enhanced in association with increased PLTP activity and cholesterol esterification. However, this mechanism may not apply to all the populations studied, and although PLTP activity was consistently increased in type 2 diabetic patients with or without coronary artery disease, cellular cholesterol efflux activity has been reported to be significantly decreased (57).

Besides triglycerides, plasma apolipoproteins are also involved in the regulation of PLTP activity in diabetic patients (58). According to recent studies, higher apoE and lower apoA-I concentrations in type 2 diabetic subjects may contribute to the increase in PLTP activity seen in these individuals by altering the distribution of high and low active-PLTP forms (58,59). Treatment with atorvastatin in dyslipidemic T2DM patients was able to decrease PLTP activity and this decrease was solely determined by the decrease in apoE in a multivariate model (60). However, it should be emphasized that active PLTP has been reported to be associated with apoA-I but not apoE in non-diabetics (61), and it is therefore difficult to determine the exact contribution of these two apolipoproteins to the transition from the inactive to the active forms of PLTP (58).

Table 3 Levels of PLTP in type 2 diabetes mellitus

Study	n	PLTP levels	Main modulator	Important associations	Reference
CS	50	↑	NR	Glycaemia	Desrumaux <i>et al.</i> , 1999 (49)
PR, INT	8	↑	I, IR (↓)	TG, FFA (-)	Riemens <i>et al.</i> , 1998 (51)
PR, INT	8	NR	Acipimox (↓)	FFA (-)	Riemens <i>et al.</i> , 1999 (53)
CS	240	↑	NR	Small-dense LDL (+)	Tan <i>et al.</i> , 2003 (64)
CS	230	↑	NR	ApoE levels (++)/ApoA ₁ levels (-)	Tan <i>et al.</i> , 2006 (59)
CS	31	↑	NR	Vitamin E (-)	Schneider <i>et al.</i> , 2004 (62)
PR, INT	215	NR	Atorvastatin (↓)	ApoE (+)	Dallinga-Thie <i>et al.</i> , 2006 (60)
CS	83	↑	NR	Leptin, BMI, HOMA, TG (+)	Dullaart <i>et al.</i> , 2008 (66)
CS	84	↑	NR	TG (+)	de Vries <i>et al.</i> , 2008 (56)
CS	59	↑	NR	Cholesterol efflux level (+)	Attia <i>et al.</i> , 2007 (57)

ApoA₁, apolipoprotein A₁; ApoE, apolipoprotein E; BMI, body mass index; CS, cross-sectional; FFA, free fatty acids; HOMA, homeostasis model assessment; I, insulin; INT, interventional; IR, insulin resistance; LDL, low-density lipoproteins; NR, not reported; PLTP, plasma phospholipid transfer protein; PR, prospective; TG, triglycerides; ↑, increased; ↓, reduced; (-), negative; (+), positive.

In diabetic patients, PLTP can decrease the vitamin E content of apoB-containing lipoproteins thus contributing to a greater potential for LDL oxidation (62), a finding that is consistent with previous studies in animals (63).

The contribution of high PLTP activity to accelerated atherosclerosis in type 2 diabetic subjects is supported by the finding that PLTP was a positive determinant of carotid intima-media thickness, a surrogate marker of atherosclerosis (32). An independent association between PLTP and cardiovascular risk factors such as C-reactive protein and small-dense LDL has been demonstrated (64,65).

Clinical studies reporting PLTP levels in patients with T2DM are summarized in Table 3.

Metabolic syndrome

Metabolic syndrome is a cluster of metabolically interrelated risk factors for diabetes mellitus and cardiovascular disease (1). Plasma PLTP activity was found to be associated with metabolic syndrome in recent studies. In a cross-sectional study, PLTP activity was determined by metabolic syndrome *per se*, independently of diabetes, and was significantly correlated with serum hepatic transaminases (66). Although HDL cholesterol is decreased in metabolic syndrome, it has been suggested that higher cholesterol esterification, PLTP activity and apoE levels contribute synergistically to the maintenance of cellular cholesterol efflux (67). The involvement of PLTP and other parameters in HDL metabolism in metabolic syndrome was investigated in a small number of patients with the use of tracer kinetics of apoA-I and apoA-II metabolism. The study of HDL kinetics by Ji *et al.* (68) showed accelerated catabolism of the two major HDL subpopulations, LpA-I and LpA-I:A-II, in subjects with metabolic syndrome. This was associated with the selective overproduction of LpA-I, which maintained a normal plasma concentration of LpA-I. Overall, perturbations of PLTP levels corresponded to the main features of metabolic syndrome, including central obesity,

insulin resistance, and hypertriglyceridemia. However, the association of PLTP with the various features of metabolic syndrome remains to be ascertained.

Conclusions

Although high PLTP expression might contribute to the maintenance of efficient cellular cholesterol efflux in the vicinity of the vascular wall, it is produced in large amounts in the extracellular medium and joins the bloodstream where it can produce adverse effects on apoB-containing lipoproteins at the systemic level. Beyond changes in HDL structure and metabolism, the deleterious impact of PLTP on atherogenic/apoB-containing lipoproteins might well predominate in obese and insulin-resistant patients at high cardiometabolic risk. Accordingly, high levels of plasma PLTP levels have been found in these patients in association with the enlarged adipose tissue and hypertriglyceridemia. Whether PLTP constitutes a relevant target in cardiovascular risk management in high-risk populations deserves further attention and should be analysed in the light of the complexity of PLTP activity at the crossroads of lipoprotein metabolism, oxidative stress and inflammation.

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Conflict of interest statement

No conflict of interest was declared.

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