Review Article

Circulating levels of lipoprotein lipase and glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1: new markers for cardiovascular diseases among noncommunicable diseases: a brief narrative review

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Background and Objective: Despite optimal statin treatment, the risk of cardiovascular disease persists. Higher circulating triglyceride levels are linked to the development of cardiovascular disease. Clinical trials are currently being conducted to determine the efficacy of promoters of lipoprotein lipase (LPL) activity. However, the clinical significance of measuring plasma and serum LPL concentrations is unknown.

Methods: The MEDLINE, EMBASE, PubMed, Web of Science, and Cochrane Central databases were scoured for English publications using the following keywords: triglyceride; lipoprotein lipase (LPL); glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1 (GPIHBP1); chylomicron (CM); very low-density lipoprotein (VLDL); heparin; noncommunicable disease; insulin resistance; diabetes mellitus; pre-diabetes; cardiovascular disease; diagnosis; and prognosis.

Key Content and Findings: LPL activity is highly regulated at the transcriptional, post-transcriptional, translational, and post-translational levels. The circulating levels of LPL show a negative relationship with triglycerides and HbA1c and a positive relationship with high-density lipoprotein (HDL) cholesterol and adiponectin. Circulating LPL levels are significantly reduced in arteriosclerotic diseases such as metabolic syndrome, diabetes, and cardiovascular diseases. The clinical significance of pre-heparin LPL measurement must be determined to assess the efficacy of triglyceride lowing drugs.

Conclusions: Circulating LPL levels are linked to lipid parameters and are reduced in arteriosclerotic diseases; however, the regulatory mechanism of circulating LPL levels is unknown.

Keywords: Lipoprotein lipase (LPL); glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1 (GPIHBP1); heparin; triglyceride

Received: 20 February 2023; Accepted: 25 May 2023; Published online: 25 June 2023.
doi: 10.21037/jlpm-23-12
View this article at: https://dx.doi.org/10.21037/jlpm-23-12

Introduction

Noncommunicable diseases (NCDs) account for roughly three-quarters (74%) of all deaths worldwide. The most common NCDs are cancers, diabetes, chronic lung disease, and heart disease. Metabolic risk factors, such as overweight/obesity, high blood pressure, hyperglycemia, and hyperlipidemia increase the risk of NCDs (1). An increased risk of atherosclerotic cardiovascular events is associated with high levels of triglyceride-rich lipoprotein (TRL) remnants derived from hepatic and intestinal sources (2). Increased levels of circulating TRLs, such as chylomicrons (CMs) and very low-density lipoproteins (VLDLs), exacerbate cardiovascular disease by promoting atherosclerosis (3). Most conventional triglyceride-lowering therapies do not reduce the risk of cardiovascular events in statin-treated patients; however, in patients with varying triglyceride levels and experimental models, new treatment modalities that target catalytic pathways in TRL metabolism decrease TRL concentrations and atherosclerosis (2-4). These studies may lead to the development of new therapies that reduce TRL levels and cardiovascular risk (2). The majority of new therapeutic targets regulate lipoprotein lipase (LPL) activity (2,5,6). LPL is an important player in TRL metabolism (7); however, the actual clinical significance of pre-heparin LPL mass and the relationship between circulating LPL levels and NCDs remains unknown. In this review, we updated the clinical significance of determining LPL concentration in pre-heparin serum. We present this article in accordance with the Narrative Review reporting checklist (available at https://jlpm.amegroups.com/article/view/10.21037/jlpm-23-12/rc).

Methods

We used the following search terms to find articles published in English in the Cochrane Central, EMBASE, MEDLINE, PubMed, and Web of Science databases: triglyceride; lipoprotein lipase (LPL); glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1 (GPIHBP1); chylomicron (CM); very low-density lipoprotein (VLDL); heparin; noncommunicable disease; insulin resistance; diabetes mellitus; pre-diabetes; cardiovascular disease; diagnosis; and prognosis. All authors compiled the final reference list after independently selecting articles and evaluating data quality, presentation, and interpretation in light of the study's central idea (*Table 1*).

LPL

LPL hydrolyzes triglyceride and acts as a ligand

LPL was discovered in 1943 as a heparin-activated clearing factor (8) and renamed LPL in 1955 (9,10). LPL is a 50 kDa protein that hydrolyzes triglycerides in circulating CMs and VLDL on vascular endothelial cell surfaces (11). LPL-catalyzed lipolysis of TRLs by LPL is the rate-limiting step in triglyceride clearance from the blood, making it an important process in lipid metabolism. Natural lipolysis by LPL results in the release of fatty acids for tissue uptake, the production of low-density lipoprotein (LDL), and the elevation of high-density lipoprotein (HDL) (12). LPL is transported to the surfaces of vascular endothelial cell surfaces from its primary sites of production in the heart, adipose tissues, and skeletal muscle (13-15). LPL mass detaches from the vascular endothelial surface and is carried to the liver for elimination as it degrades (16,17). Although LPL mass exists in pre-heparin serum, LPL activity is rare (in the absence of intravascular heparin injection) (16,17). LPL, which is catalytically inactive, mediates lipoprotein metabolism in the liver for lipoprotein receptors and glucosaminoglycans via its ligand function rather than its lipolytic function (18-22). Inactive LPL promotes the uptake of cholesteryl ester and VLDL into cells and organs. This results in decreased VLDL triglycerides (22). However, because serum pre-heparin LPL is catalytically inactive, measuring pre-heparin LPL concentration has not been widely studied as a diagnostic marker (23).

Regulatory mechanism of triglyceride lipolysis by LPL

Recent reviews summarized the regulatory mechanisms of intravascular lipolytic processing of TRLs by LPL along the luminal surface of capillaries (11,24). LPL activity is tightly regulated at the transcriptional, post-transcriptional, translational, and post-translational levels because of its critical role in lipid homeostasis (25,26). Several proteins, including apolipoprotein (apo)C1 (27,28), apoC2 (29), apoC3 (28,30), apoA5 (31), angiopoietin-like protein 3 (ANGPTL3) (32), ANGPTL4 (33,34), and ANGPTL8, regulate LPL (35). LPL is synthesized and secreted as a monomer rather than a homodimer from head-to-tail (36,37). To preserve its native fold, LPL must be chaperoned in all compartments because it is inherently unstable (38). LPL is chaperoned in the endoplasmic reticulum by lipase maturation factor 1 (LMF1) and Sel-1

Table 1 The search strategy summery

Items	Specification
Date of search	December 1 to 31, 2022
Databases and other sources searched	PubMed
Search items used	"Triglyceride"; "LPL"; "GPIHBP1"; "CM"; "VLDL"; "LDL"; "Heparin"; "Noncommunicable Disease"; "Insulin Resistance"; "Diabetes Mellitus"; "Pre-Diabetes"; "Cardiovascular Disease"; "Diagnosis"; "Prognosis"
Timeframe	January 1943 to December 2022
Inclusion criteria	English text; human and animal investigation
Selection process	All authors selected and had consensus

LPL, lipoprotein lipase; GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1; CM, chylomicron; VLDL, very low-density lipoprotein; LDL, low-density lipoprotein.

suppressor of Lin-12-like 1 (Sel1L) during parenchymal cell biosynthesis. LPL is chaperoned by heparan sulfate-modified syndecan-1 (SDC1) as it moves from the trans-Golgi network into the secretory pathway (39). Heparan sulfate proteoglycans (HSPGs) in the extracellular matrix and the glycocalyx of parenchymal cells regulate LPL in the subendothelial space. GPIHBP1 transports LPL from the abluminal endothelial surface to its site of action in the capillary lumen (11,40-42). GPIHBP1, an effective chaperone for LPL, maintains its native and active states (43). The acidic domain increases the rate of GPIHBP1 and LPL association by 2,500-fold, allowing LPL to transition from an HSPG-bound to a GPIHBP1-bound state and then enter the capillary lumen via transcytosis (44). LPL is stabilized by binding to TRLs; however, apoC1 and apoC3 displace LPL from lipid droplets (LDs) (26). Angiopoietin-like protein (ANGPTL)-3, -4, and -8 inhibits LPL activity by converting stable LPL dimers to unstable monomers. By binding directly to LPL monomers, ANGPTL4 catalyzes the irreversible unfolding of LPL's α/β-hydrolase domain (37,38,44,45). GPIHBP1 binding to LPL prevents this inhibition. An ANGPTL3/ANGPTL8 oligomeric complex regulates LPL activity in oxidative tissues (46-51). Therapeutic strategies that improve LPL function, decrease apoC3 and ANGPTL4 function, or increase apoA5 function are expected to have cardioprotective effects (26). Genetic alterations affecting LPL activity are summarized by Shaik *et al.* LPL activity is elevated by loss of function of apoC3, ANGPTL3 and ANGPTL4 and decreased by loss of function of apoA5 (2,3) (*Figure 1*).

LPL activity in the fasted and fed state

Kristensen *et al.* indicated fasting- and fed-state LPL activity (24). During fasting or exercise, TRLs must be directed away from storage in white adipose tissue (WAT) and toward oxidative tissues such as the heart and skeletal muscles. This is accomplished by (I) increasing the expression of ANGPTL4 in WAT, which inhibits LPL secretion and inactivates LPL in the subendothelial space, and (II) downregulation of hepatic ANGPTL8 expression, which significantly reduces the effectiveness of ANGPTL3-mediated LPL inhibition (46,52,53). The TRL flux must quickly switch from oxidative to storage tissues after re-feeding. This transition is mediated by the rapid upregulation of ANGPTL8 expression in the liver and WAT, combined with a decrease in ANGPTL4 expression in WAT (51). The resultant secretion of a hepatic ANGPTL3-ANGPTL8 complex mediates endocrine inhibition of LPL in oxidative tissues. The increased synthesis of ANGPTL8 may attenuate LPL inhibition by ANGPTL4 in an autocrine/paracrine manner that favors TRLs processing in WAT.

LPL as a ligand

LPL improves the binding of CMs, β-VLDL, and apolipoprotein E (apoE)-containing liposomes to LDL receptor-related protein (LRP) (18). The pre-heparin LPL mass aids in the clearance of residual lipoproteins. LPL can act as a ligand for LRP and may mediate remnant uptake (54). Inactive LPL does not promote remnant uptake into Hep G2 according to research on denatured bovine milk LPL (55); LRP is the receptor for activated α2-macroglobulin (19,56,57). Eisenberg suggested that LPL primarily influences the binding of human plasma lipoproteins to heparan sulfate on cell

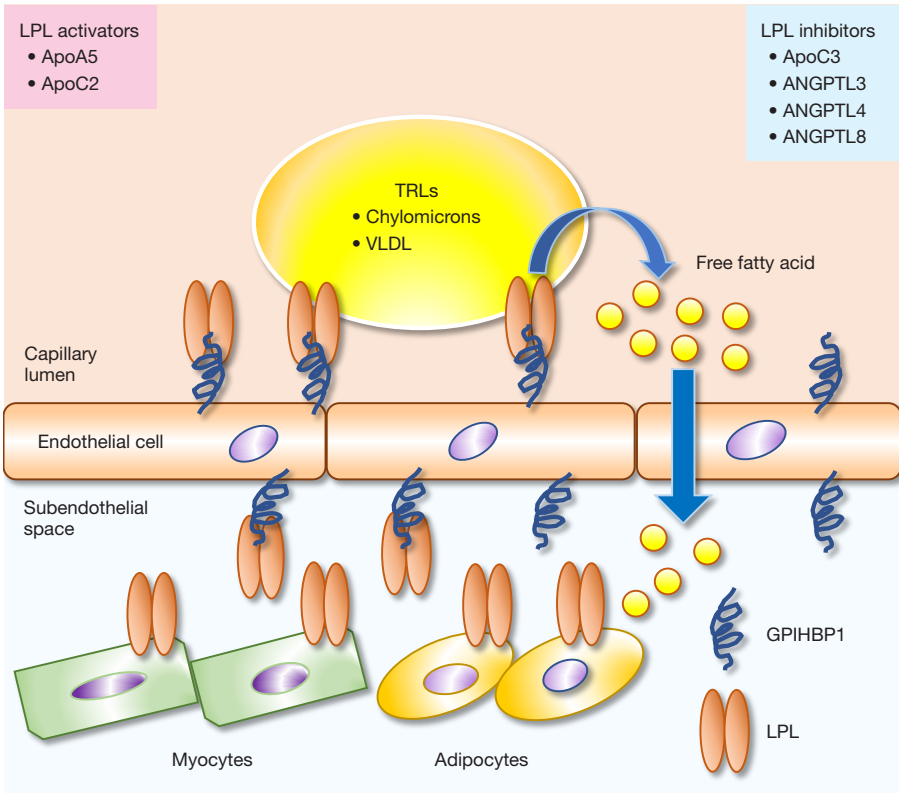

Figure 1 Lipolysis of TRLs by LPL on capillary lumen. LPL is synthesized in adipocytes and myocytes, moves from the subendothelial spaces into capillary lumen by GPIHBP1, and hydrolyzes TG. LPL, lipoprotein lipase; TRLs, triglyceride rich lipoproteins; ApoA5, apolipoprotein A5; ApoC2, apolipoprotein C2; ApoC3, apolipoprotein C3; ANGPTL3, angiopoietin-like protein 3; ANGPTL4, angiopoietin-like protein 4; ANGPTL8, angiopoietin-like protein 8; VLDL, very low-density lipoprotein; GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1; TG, triglyceride.

surfaces and in the extracellular matrix (20). LPL binds to both the α2-macroglobulin receptor (α2MR)/LRP and β-VLDL. Dimeric LPL mediates the binding of β-VLDL to the receptor protein. LPL in combination with β-VLDL improves binding to α2MR/LRP. LPL-mediated binding and uptake of remnant particles induce the physiological remnant removal and pathophysiology of atherosclerosis (21). Catalytically inactive LPL mediates organ uptake of VLDL particles and selective uptake of cholesteryl ester into cells, resulting in lower VLDL triglyceride levels and myopathy (22).

GPIHBP1 (glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1)

GPIHBP1, a capillary endothelial cell GPI-anchored protein (11,25,40), is a dedicated LPL chaperone. GPIHBP1 transports LPL from the subendothelial spaces into the capillary lumen (11,24,41,58). LPL-mediated intravascular triglyceride processing is dependent on GPIHBP1-chaperoned LPL transport across capillaries (11,24,42). GPIHBP1 maintains LPL's structure and catalytic activity (11,24,43,45). The literature suggests that GPIHBP1 chaperones LPL in four ways (11). First, LPL capture from subendothelial spaces is dependent on the GPIHBP1 protein found on the abluminal surface of capillary endothelial cells (41,44). Second, the binding of GPIHBP1 to LPL stabilizes its structure and activity (43-45). Third, GPIHBP1 transports LPL across endothelial cells in the capillary lumen to its site of action (41). Fourth, GPIHBP1-bound LPL is required for lipoprotein regulation in the bloodstream (42), allowing LPL-mediated lipoprotein processing to occur. We recently reported hypertriglyceridemia caused by GPIHBP1 autoantibodies (59). The discovery of inhibitory GPIHBP1 autoantibodies revealed a new etiology of acquired hypertriglyceridemia in some patients with no known mutations in LPL, GPIHBP1,

APOC2, APOA5, or LMF1 (59-61).

Circulating levels of LPL and GPIHBP1

LPL is released into the bloodstream by heparin injection

LPL is released into the bloodstream after being detached from vascular endothelial cells by heparin injection (62). Although pre-heparin plasma contains a significantly large amount of LPL, the activity of TG hydrolysis is very low or non-detectable (23). Therefore, LPL in various lipoprotein disorders has been studied using post-heparin plasma (with intravascular heparin injection) (63-65). However, at room temperature, LPL activity in post-heparin plasma rapidly decreases at room temperature (7), making it unsuitable for routine clinical use. Because of the requirement for heparin injection, LPL determination has not been used in general clinical research. Heparin injection can cause bleeding, which is dangerous for patients with peptic ulcers or proliferative diabetic retinopathy. There are also issues with post-heparin LPL mass determination that prevent it from becoming a widely used test (66). An enzyme-linked immunosorbent assay was developed to detect LPL in human plasma using specific monoclonal antibodies (67,68). LPL concentration and activity measurements in post-heparin plasma have been used in clinical trials to detect LPL deficiency (69) but not to diagnose lipid disorders or the risk of cardiovascular disease. Because heparin injection causes LPL to dissociate from vascular endothelial cells, the measured concentration is not indicative of normal or pathological LPL levels in the bloodstream (70). Therefore, the importance of determining circulating LPL in the absence of heparin treatment, such as pre-heparin serum/plasma, should be considered.

The LPL mass and activity in pre-heparin and post-heparin plasma

The function, turnover, and transport of plasma LPL before and after heparin treatment differ significantly, as evidenced by LPL mass and activity. All of the parameters had a significant but distinct relationship with plasma lipoprotein lipid concentrations (17). The low correlation between pre- and post-heparin LPL may be due to pre-existing LPL (pre-heparin LPL) in post-heparin plasma (68). The percentage of LPL that separates from the entire vascular endothelial cell surface after heparin injection is unknown. It is clear that post-heparin LPL mass contains an artificial factor given that it is affected by variables such as heparin dose, the time elapsed after injection, and circulation (17,68). Pre-heparin LPL mass may indicate whole-body LPL activity because LPL hydrolyzes triglycerides, lowering serum triglyceride levels and increasing HDL-C (68). The serum pre-heparin LPL concentration is high enough to be measured. A comparative analysis reveals that post-heparin plasma LPL activity can replace pre-heparin serum LPL concentration (23). Therefore, using an automated LPL assay to measure the LPL concentration in pre-heparin serum can provide practical clinical applications in TG-rich patients without the need for heparin injection (68).

Pre- and post-heparin plasma LPL in TRLs metabolism

TRL-associated atherogenic dyslipidemia is characterized by elevated fasting triglycerides, remnant lipoproteins (RLPs), LDL-C levels, and small dense LDL cholesterol (sdLDL-C), as well as postprandial accumulation of TRLs (71). Post- and pre-heparin plasma LPL primarily metabolizes RLPs. LPL activity and concentration correlated inversely with RLP particle size as measured by the RLP-TG/RLP-C ratio in both pre-and post-heparin plasma. RLP particle size is consistent with pre-heparin plasma LPL concentration and post-heparin plasma LPL activity (23,72-77) (*Table 2*). Furthermore, both postprandial pre-heparin plasma LPL concentration and post-heparin plasma LPL activity were similarly inversely related to RLP particle size. Fasting post-heparin plasma LPL activity and postprandial pre-heparin plasma LPL concentration had the greatest similarity. Despite the inverse relationship between LPL concentration and RLP particle size (23,72-75,77), an increase in LPL is associated with an increase in RLPs (23,72-75,77). This suggests that insufficient hydrolysis of TG-rich lipoproteins by LPL on the endothelium after a fatty meal may result in RLP with a large particle size. RLPs are sdLDL-C precursors. Plasma sdLDL-C concentration is positively correlated with TG and RLPs but negatively correlated with LPL activity (23,72-74,76). Post-heparin plasma LPL activity and concentration correlated negatively with pre-heparin plasma TG, RLP-C, RLP-TG, and sdLDL-C concentrations (23,72-75,77). LPL concentration in pre-heparin plasma is more physiologically associated with adiponectin than maximum LPL activity or concentration in post-heparin plasma (*Table 2*). Therefore, LPL activity or concentration measured in post-heparin plasma may not accurately reflect the physiological state of TRL metabolism. This implies that pre-heparin plasma

Table 2 Association between pre-heparin lipoprotein lipase and metabolic parameters, arteriosclerotic disease, and therapeutic approach

Items	Association with pre-heparin LPL	Reference number
Metabolic parameters		
Body weight	Inverse association	(78,79)
Fasting plasma glucose	Inverse association	(78,79)
Fasting plasma insulin	Inverse association	(78,79)
HOMA-IR	Inverse association	(78-81)
Triglyceride	Inverse association	(23,72-75,77,78,82,83)
Remnant lipoprotein	Inverse association	(23,72-75,77,78,82,83)
Small dense LDL-C	Inverse association	(23,72-75,77,78,82,83)
HDL-C	Positive association	(72,78)
Adiponectin	Positive association	(72,78)
GPIHBP1	Positive association	(82)
Skeletal muscle	Positive association	(83)
Arteriosclerotic disease		
Type 2 diabetes mellitus	Low pre-heparin LPL mass	(84-94)
Cardiovascular disease	Low pre-heparin LPL mass	(17,82,95-101)
Number of symptoms of metabolic syndrome	The higher the number of symptoms, the lower the pre-heparin LPL	(78,80)
Therapeutic approach		
5-hydroxytrptamine2A receptor antagonist	Increase pre-heparin LPL	(102)
Angiotensin II receptor antagonist	Increase pre-heparin LPL	(103)
Bezafibrate	Increase pre-heparin LPL	(104-106)
Colestimide	Decrease pre-heparin LPL	(107)
Incretin	Increase pre-heparin LPL	(6,108-112)
Insulin	Increase pre-heparin LPL	(84-87,91)
Metformin	Increase pre-heparin LPL	(113)
Pioglitazone/Troglitazone	Increase pre-heparin LPL	(113-118)
Statin	Increase pre-heparin LPL	(119-123)
	No effect	(93,124,125)
	Decrease pre-heparin LPL	(93,126)
LSG	Increase pre-heparin LPL	(127)
Konjac glucomannan	Increase pre-heparin LPL	(128)

HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1; LSG, laparoscopic sleeve gastrectomy; LPL, lipoprotein lipase.

LPL activity may be more useful for diagnosis than measuring post-heparin plasma LPL concentration. The circulating levels of LPL are inversely related to TG, RLP-C, RLP-TG, and sdLDL-C (23,72-75,77) (*Table 2*).

LPL and adiponectin

Adiponectin, a fat-derived adipocytokine, has been linked to insulin resistance (129,130), lipoprotein metabolism, and abdominal fat (129). Insulin regulates LPL expression and production in adipocytes (131,132). Pre-heparin LPL has a strong relationship with plasma adiponectin (72,78) (*Table 2*). Both adiponectin and pre-heparin LPL levels fall as symptoms of metabolic diseases worsen (78,80), and they are inversely related to body weight and TG but positively related to HDL-C (78) (*Table 2*). Low LPL mass in pre-heparin serum indicates rising insulin resistance and adipose tissue accumulation (78) (*Table 2*). Plasma adiponectin and RLPs are inversely related (81,130,133). Reduced adiponectin levels are frequently associated with increased RLP levels in patients with high insulin resistance (129,133). VLDL and RLP hydrolysis is delayed by reduced LPL levels linked with low adiponectin levels (72,81,129,133). The mechanism that increases LPL activity in cardiomyocytes is well characterized (84,134). Adiponectin increases cell-surface expression and LPL activity time-dependently in adult rat cardiomyocytes (84). Adiponectin aids LPL activation by translocating it to the cell surface (84). Adiponectin increases fatty acid uptake in cardiomyocytes (134-137). Diabetic cardiomyopathy is defined by an increased dependence on free fatty acids for energy production in the myocardium and decreased glucose utilization (138). Increased cardiac LPL activity caused by adiponectin may be critical in the progression of heart failure. Decreased adiponectin levels linked to lower cardiac LPL raise plasma triglyceride concentrations. Cardiac-specific deletion of LPL is linked to heart dysfunction (139). Adiponectin increases insulin signaling and restores insulin sensitivity by reducing ectopic lipid storage in the liver and skeletal muscle. Adiponectin mediates these effects by stimulating LPL in increased muscle fat oxidation (140).

LPL and insulin sensitivity

Insulin resistance is closely linked to the development of atherosclerosis. In adipose tissue, insulin regulates LPL production (81,133). The biosynthesis of LPL is activated by an insulin-sensitive element in the LPL gene (133). LPL expression is increased in skeletal muscle and adipose tissue in response to insulin (81,133). Pre-heparin LPL mass reflects the total body LPL production and is linked to insulin resistance (141). Insulin resistance, measured by the homeostasis model assessment of insulin resistance (HOMA-IR) index, is considerably associated with pre-heparin serum LPL but not with post-heparin plasma LPL (81,133) (*Table 2*). Pre-heparin LPL mass correlates negatively with body weight, fasting blood glucose, HbA1c, fasting immunoreactive insulin (IRI), and HOMA-IR (78,79) (*Table 2*). Hypertriglyceridemia, high sdLDL-C, and low HDL-C are linked to insulin resistance (85-88,142) and may cause a decrease in LPL production (142). The degree of insulin resistance in metabolic syndrome may be linked to the pre-heparin LPL mass (which reflects insulin sensitivity) and oxidative stress (78).

LPL and diabetes

Insulin plays a major role in regulating pre-heparin LPL mass. Patients with type 2 diabetes mellitus have significantly lower LPL production and circulating pre-heparin LPL mass than non-diabetic healthy controls (84-94) (*Table 2*). Pre-heparin LPL mass correlates negatively with HbA1c in patients with diabetes (92) (*Table 2*). Post-heparin LPL activity reportedly declines in diabetes (90). Pre-heparin LPL mass and HDL-C levels are significantly increased by insulin injection, followed by a drop in FBS (84-87,91) (*Table 2*). LPL activity in adipose tissue is significantly lowered in diabetic men but not in diabetic women (92). Decreased LPL lipolysis of plasma TG-rich lipoproteins may cause the inferior lipid profile found in men with poorly controlled type 2 diabetes than women (93). LPL activity in adipose tissue is significantly reduced in men with diabetes but not in women (92). In type 2 diabetes mellitus, low adiponectin in plasma is linked to low post-heparin LPL (94). Pre-heparin LPL mass indirectly shows the amount of working LPL activity *in vivo* (89).

LPL and fatty acid metabolism in the diabetic heart

The regulatory mechanism of LPL in the heart was thoroughly evaluated and well-illustrated by Rodrigues and colleagues (143). On the apical side of coronary endothelial cells, GPIHBP1-bound LPL hydrolyzes triglycerides, synthesizes fatty acids, and supplies them to the cardiomyocyte (143,144). In cardiomyocytes, fatty

acids undergo mitochondrial b-oxidation and oxidative phosphorylation to generate ATP or accumulate as lipid metabolites/droplets (143). Accumulated lipid intermediates activate insulin signaling and substrate utilization (143). In the heart, 95% of the generated ATP is acquired from glucose and FAs through mitochondrial metabolism (143). The heart cannot synthesize FAs and obtains them from other sources (143). LPL-mediated lipolysis of lipoproteins is a critical source of FAs in the heart (145). In type 2 diabetes mellitus, glucose utilization efficiency declines due to increased insulin resistance and insufficient insulin action. Following diabetes, the heart shifts its primary energy source from glucose to fatty acids, causing diabetic cardiomyopathy (143-145). In diabetes, increased fatty acid use due to underutilization of glucose is compensated by an increase in vascular LPL or adipose tissue lipolysis. There is a mismatch between the delivery of FAs and their oxidation in the diabetic heart, causing lipid metabolite accumulation and myocyte LD synthesis (143). This mediates lipid-induced insulin resistance, cell death, and, eventually, diabetic cardiomyopathy (67-69,87,88,143-145).

LPL and coronary heart diseases

Pre-heparin LPL levels and LPL activity are decreased in cardiovascular disease, including plaque instability, coronary stenosis, coronary vasospasm, and acute myocardial infarction, as repeatedly highlighted in this review (17,82,95-101) (*Table 2*). Shirai and colleagues reported that pre-heparin LPL mass was the highest risk factor for coronary stenosis than other risk factors such as age, smoking, family history, hypertension, hyperuricemia, diabetes mellitus, total cholesterol, triglyceride, HDL-C, and BMI (95-97,104) (*Table 2*). The hepatic triglyceride lipase (HTGL) concentration demonstrates positive correlations, while GPIHBP1 shows inverse correlations with RLP-C and sdLDL-C. Elevated HTGL is linked to an increased risk of CAD, while increased LPL is associated with a reduced risk of cardiovascular disease (82) (*Table 2*). Low LPL production was found to be associated with atherosclerosis and the overexpression of LPL decreased serum TRL, particularly RLPs, in mice (146). Low pre-heparin LPL, hypertriglyceridemia, and higher sdLDL are independent risk factors for cardiovascular diseases and are considerably related to each other (17,95-100). Furthermore, a prospective study revealed that low pre-and/or post-heparin LPL mass predicts future coronary events (147).

LPL and exercise

Pre-heparin LPL and GPIHBP1 serum concentrations assessed in young Japanese men were shown to be significantly high in skeletal muscle-rich participants and positively correlated with skeletal muscle mass. Increasing skeletal muscle mass increases energy use by boosting TRL hydrolysis through circulating LPL and GPIHBP1 concentrations. In contrast, elevated HTGL serum concentrations are linked to a rise in serum LDL-C synthesis that is independent of skeletal muscle mass (83). Post-heparin plasma LPL activity increases after prolonged exercise (148). Increased post-heparin LPL activity was observed to be significantly correlated with exercise-induced reductions in fasting and postprandial triacylglycerol (TAG) concentrations (149). Skeletal muscle LPL activity is maximized more than 8 h after exercise (150). On the contrary, moderate-intensity cycling performed the day before loading moderate-fat food reduced postprandial serum TAG concentrations in young men without affecting pre-heparin LPL concentrations measured in the fasted and postprandial states the following day (151). Further study is required to determine the effect of exercise on circulating pre-heparin LPL levels. Because there are distinctions between men and women in body composition, such as body fat percentage and muscle mass, gender differences are anticipated in the effect of exercise on circulating pre-heparin LPL levels.

LPL and lipid-lowering therapy

Plasma triglyceride levels are more than just a marker. It is a risk factor for coronary artery disease (152,153) and one of the risks associated with statin therapy (154). In the future, lipid-directed treatment will include treating TRL in specific patient populations and lowering LDL-C levels (6). LPL plays an important role in TRL hydrolysis. The fasting and postprandial blood triglyceride levels are determined by LPL-mediated lipolysis and hepatic uptake of remnant particles (6,155). Reduced plasma LPL mass is associated with an increased risk of coronary artery disease (95,97) (*Table 2*). The administration of drugs such as fibrate, insulin sensitizers, and statins to healthy volunteers or patients with diseases that are likely to progress arteriosclerosis affects the plasma LPL mass concentration. Triglyceride levels were lower after taking bezafibrate, which is thought to be due in part to increased LPL production (156,157). Bezafibrate administration increased LPL mass and activity in pre- and post-heparin plasma (104-106) (*Table 2*).

Insulin sensitizer administration activates PPARγ, such as pioglitazone and troglitazone, and increases LPL mass and activity (113-118) (*Table 2*). Metformin raises pre-heparin LPL levels (113) (*Table 2*). Glucagon-like peptide 1 (GIP), one of the incretins, inhibits CM secretion (6,108,109) and activates LPL (110-112) *(Table 2*). Recently, adding konjac glucomannan (KGM) powder to rice gruel reduced TG while increasing LPL and GPIHBP1 (128) (*Table 2*). It is unknown what mechanism increased LPL in response to KGM supplementation in rice gruel (128). The LPL increase could be explained by incretin induction, which promotes KGM intestinal activity. Statins' effects on LPL mass and activity are contradictory. The effect of statin administration includes: (I) increased LPL mass or activity (112,113,119-123); (II) had no effect (93,124,125); (III) decreased LPL mass or activity (93,126) (*Table 2*). Colestimide, but not ezetimibe, considerably reduced plasma LPL mass (107) (*Table 2*). In addition to these human studies, statins also stimulate LPL synthesis *in vitro* studies. Statin promoted LPL expression in preadipocytes (158) and skeletal muscle cells (159). Studies on the effects of statins revealed no clear relationship between changes in lipase mass and changes in plasma lipid levels (97). Additionally, angiotensin II receptor antagonist (103) and 5-hydroxytryptamine2A receptor antagonist (102) are also known to increase serum LPL mass. LPL activity-related genetic abnormalities mediate cardiovascular risk. Loss-of-function mutations in apoC3, for example, which is an LPL inhibitor, decrease the risk of coronary artery disease (152). In contrast, loss-of-function mutations in apoA5, which is an LPL activator, increase the risk of coronary artery disease (160). Furthermore, a surgical method also attenuated pre-heparin LPL. Pre-heparin LPL levels increased during BW reduction and laparoscopic sleeve gastrectomy (LSG), a bariatric surgical procedure in obese patients (127) (*Table 2*). LSG effectively improves diabetes, hypertension, and dyslipidemia (161,162). Bariatric surgery, including LSG, has amazing therapeutic effects for obesity and obesity-related diseases (160-162). During coronary angiography, LPL increased 15 minutes after heparin administration, and TG and sdLDL decreased, but returned to the basal levels 4 hours later (82). In hemodialysis, administration of heparin transiently increases LPL and decreases TG. After that, LPL and TG return to pre-heparin levels. Repeated administration of heparin in hemodialysis depletes LPL stores, therefore, chronic dialysis patients have decreased LPL activity, dyslipidemia, and an increased risk of CVD (163,164). At present, administration of heparin for the treatment of hypertriglyceridemia due to increased LPL has not been investigated.

Conclusions

Despite optimal statin treatment, the risk of cardiovascular disease persists. Reducing the prevalence of cardiovascular diseases is critical for reducing the number of NCD patients. Epidemiological and genomic research suggests the contribution of TRLs in the development of cardiovascular diseases. According to natural selection studies, novel triglyceride-lowering therapies can reduce cardiovascular risk. Clinical trials are currently underway to determine the efficacy of LPL activity modulators that inhibit apoC3 or ANGPTL3. The clinical significance of pre-heparin LPL measurement must be determined to assess the efficacy of these drugs. LPL activity is highly regulated at the transcriptional, post-transcriptional, translational, and post-translational levels. We have successfully developed assay systems for human LPL and GPIHBP1, as well as mouse assay systems. Using these measurement systems should lead to a better understanding of the clinical significance of pre-heparin LPL and GPIHBP1.

Acknowledgments

We thank Mayumi Nishiyama (Department of Clinical Laboratory Medicine, Gunma University Graduate School of Medicine, Maebashi, Japan) for their technical assistance and helpful discussion.

Funding: This work was supported in part by Grants-in-Aid 20K07841 and 23K08003 (to TK) for scientific re-search from the Ministry of Education, Culture, Sports Science, and Technology of Japan.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Tatsuo Shimosawa) for the series "New Biomarkers in Non-communicable Diseases" published in *Journal of Laboratory and Precision Medicine*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://jlpm.amegroups.com/article/view/10.21037/jlpm-23-12/rc

Peer Review File: Available at https://jlpm.amegroups.com/

article/view/10.21037/jlpm-23-12/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jlpm.amegroups.com/article/view/10.21037/jlpm-23-12/coif). The series "New Biomarkers in Non-communicable Diseases" was commissioned by the editorial office without any funding or sponsorship. TK was supported by Grants-in-Aid 20K07841 and 23K08003 for scientific research from the Ministry of Education, Culture, Sports Science, and Technology of Japan. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/jlpm-23-12
Cite this article as: Kimura T, Tsunekawa K, Nagasawa T, Aoki T, Miyashita K, Yoshida A, Nakajima K, Murakami M. Circulating levels of lipoprotein lipase and glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1: new markers for cardiovascular diseases among noncommunicable diseases: a brief narrative review. J Lab Precis Med 2023;8:18.