Lipoprotein Lipase: A General Review

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Abstract

Carbohydrates (e.g., glucose) and lipids (e.g., free fatty acids or FFAs) are the most important sources of energy for most organisms, including humans. Lipoprotein lipase (LPL) is an extracellular enzyme (EC 3.1.1.34) that is essential in lipoprotein metabolism. LPL is a glycoprotein that is synthesized and secreted in several tissues (e.g., adipose tissue, skeletal muscle, cardiac muscle, and macrophages). At the luminal surface of the vascular endothelium (site of the enzyme action), LPL hydrolyzes triglyceride-rich lipoproteins (e.g., chylomicrons, very low-density lipoproteins), providing FFAs and glycerol for tissue use. Therefore, LPL plays a key metabolic role in providing substrates for lipogenesis and lipid storage, and in supplying immediate energy for different tissues. Knowledge about this enzyme has greatly increased over the past decade. A detailed understanding of the fascinating, although complex, apparatus by which LPL exerts its catalytic activity in the turbulent bloodstream is just one of the examples. Additionally, interest in LPL activity has been reinforced by its pathophysiological relevance in chronic degenerative diseases such as dyslipidemia, obesity, type 2 diabetes mellitus, and Alzheimer's disease, and in other contexts of disordered lipid metabolism such as severe hypertriglyceridemia and the (potentially) associated acute pancreatitis as well as in non-alcoholic fatty liver disease. This work aimed at critically reviewing the current knowledge of historical, terminological, biochemical, pathophysiological, and therapeutic aspects of human LPL activity.

Keywords: Diabetes mellitus; Lipid-lowering drugs; Lipogenesis; Lipoprotein lipase (LPL); Obesity; Polyphenols; Starvation
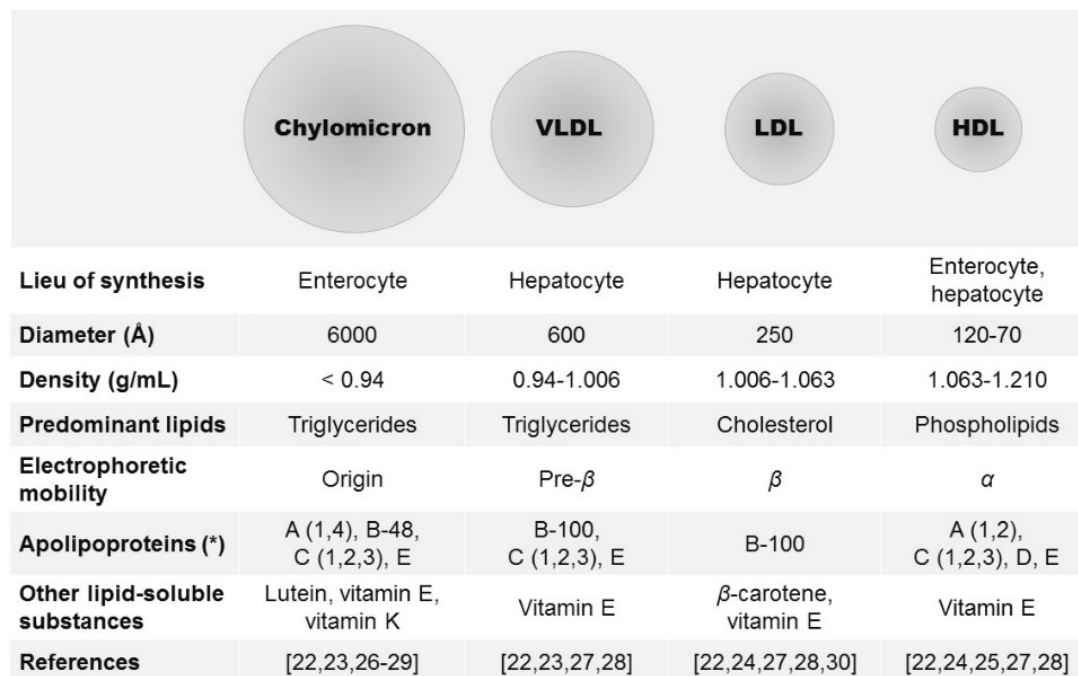
Lipoprotein Lipase: Historical Hallmarks, Enzymatic Activity, Characterization, and Present Relevance in Human Pathophysiology and Therapeutics

Macheboeuf, in 1929, first described chemical procedures for the isolation of a plasma protein fraction that was very rich in lipids but readily soluble in water, such as a lipoprotein [1]. In 1943, Hahn reported, the clearing of severe alimentary lipemia in dogs after transfusion of heparin-containing blood [1-3]. Korn, in 1955, isolated an enzyme from normal rat heart and considered it to be a clearing factor because it effectively hydrolyzed chylomicron triacylglycerol or triglyceride (TG), and he named it lipoprotein lipase (LPL) [3-5]. The first cases of LPL deficiency were described in 1960 by Havel and Gordon [6,7]. LPL deficiency is a rare inherited disease that is characterized by severe hypertriglyceridemia, chylomicronemia, and the risk of recurrent pancreatitis, among other potential complications [8]. Another important step towards understanding LPL activity came with the discovery, in 1970, of apoprotein C2, an obligatory cofactor of the enzyme [5,9]. An apoprotein (APO) is the protein moiety of a conjugated protein, or a protein complex (this term is synonym for apolipoprotein, which was originally coined by John Oncley in 1963) [10,11]. In 1970, human LPL was also purified [12].

According to the Enzyme Commission (EC) number, LPL is a hydrolase (EC 3) that acts on ester bonds (EC 3.1), and it is characterized as a carboxylic ester hydrolase (EC 3.1.1) of its own (EC 3.1.1.34). Besides chylomicron TG (preferential substrate), LPL (EC 3.1.1.34) also hydrolyses other triglyceride-rich lipoproteins (TRLs) in plasma such as very low-density lipoproteins (VLDLs), providing free fatty acids (FFAs) and glycerol for tissue use; experimentally, this was demonstrated by inhibition of the enzyme with antisera that leads to the accumulation of TG in the plasma [13-16]. LPL affects the maturation of several classes of lipoprotein particles [17]. Besides releasing energy-rich lipids such as fatty acids (9 kcal/g) for uptake by tissues, the lipolytic processing also

produces atherogenic remnant lipoproteins (e.g., low-density lipoproteins or LDLs) and provides lipid conjugates (i.e., apolipoproteins, phospholipids) for the biogenesis of high-density lipoproteins (HDLs) [14,18,19]. In 1978, Breckenridge et al. reported the first case of apolipoprotein C_2 deficiency [20]. In 1990, Austin coined the term atherogenic lipoprotein profile, which describes the syndrome of small, dense LDL, elevated VLDL, and low HDL **(Figure 1)** [21].

	Chylomicron	VLDL	LDL	HDL
Lieu of synthesis	Enterocyte	Hepatocyte	Hepatocyte	Enterocyte, hepatocyte
Diameter (Å)	6000	600	250	120-70
Density (g/mL)	< 0.94	0.94-1.006	1.006-1.063	1.063-1.210
Predominant lipids	Triglycerides	Triglycerides	Cholesterol	Phospholipids
Electrophoretic mobility	Origin	Pre-β	β	α
Apolipoproteins (*)	A (1,4), B-48, C (1,2,3), E	B-100, C (1,2,3), E	B-100	A (1,2), C (1,2,3), D, E
Other lipid-soluble substances	Lutein, vitamin E, vitamin K	Vitamin E	β-carotene, vitamin E	Vitamin E
References	[22,23,26-29]	[22,23,27,28]	[22,24,27,28,30]	[22,24,25,27,28]

Figure 1 Characteristics of the major lipid carriers in human plasma. (*) The functions of minor apolipoproteins (e.g., A5, F, H, J, L, and M) are less well-defined [22]. In human plasma, albumin is a universal carrier of many lipophilic substances (e.g., bilirubin, steroid and thyroid hormones), including fatty acids [31]. Vitamin E is the term used for eight naturally occurring fat-soluble nutrients called tocopherols, among which α-tocopherol has the highest biological activity (e.g., antioxidant activity) and predominates in humans and many other species [28]. Carotenoids (e.g., β-carotene) and fat-soluble vitamins (e.g., vitamin E) may confer antioxidant protection for their carrier lipoproteins [28,30]. Relevantly, lipoprotein (a), or LP (a), is a unique lipoprotein particle with a composition similar to that of LDL (including APOB-100) and is bound to APO (a), a glycoprotein, by a disulfide bridge [32,33]. LP (a) is synthetized and secreted by the liver [32]. The physiological function of LP (a) is unclear, but it is considered to be a contributor to atherothrombosis based on its LDL-like properties and its competitive homology to plasminogen (i.e., the precursor of plasmin (EC 3.4.21.7), an enzyme that hydrolyzes fibrin, leading to the dissolution of blood clots) [32-34]. Note: VLDL, very low-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; <, less than.

Human LPL was sequenced in 1987 from a complementary deoxyribonucleic acid (cDNA) clone coding for a mature protein of 448 amino acids with a calculated molecular weight of 50,394 [17,35]. Analysis of the sequence indicated that human LPL, hepatic lipase, and pancreatic lipase are members of a gene family [17,36]. The human gene that encodes LPL is located on the short arm of chromosome 8, residing in the p22 region of the same chromosome and containing nine introns and ten exons (or coding regions) [36-38]. LPL is a glycoprotein synthesized and secreted into the interstitial space in several tissues (e.g., adipose tissue, skeletal muscle, cardiac muscle, and macrophages) [36,38-40]. The tissue-specific regulation of LPL is discussed ahead. The enzyme is then bound by glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1 (GPIHBP1), which transports LPL to the capillary lumen, which is the site of the enzyme's action [39,40]. LPL contains heparin-binding domains that interact with heparan sulfate proteoglycans (HSPGs) and contains lipid-binding sequences that bind TRLs, which bridges capillary HSPGs and circulating TRLs (in a stable multimolecular structure) along the capillary endothelium through the margination process [39]. Unlike heparin, which is only found in mast cells, heparan sulfate is ubiquitously expressed on the cell surface and in the extracellular matrix of all animal cells [41]. However, like heparin, heparan sulphate is a linear polysaccharide consisting of alternating uronic acid and α-(1–4)-D-glucosamine residues, with the difference of exhibiting a reduced degree of sulphation; nevertheless, heparan sulphate's high density of negative charges attracts positively charged LPL molecules and holds them by electrostatic and sequence-specific interactions with highly sulfated domains [42,43]. As further discussed in this review, the endothelial location of LPL is strategically important in lipid metabolism **(Figure 2)**.
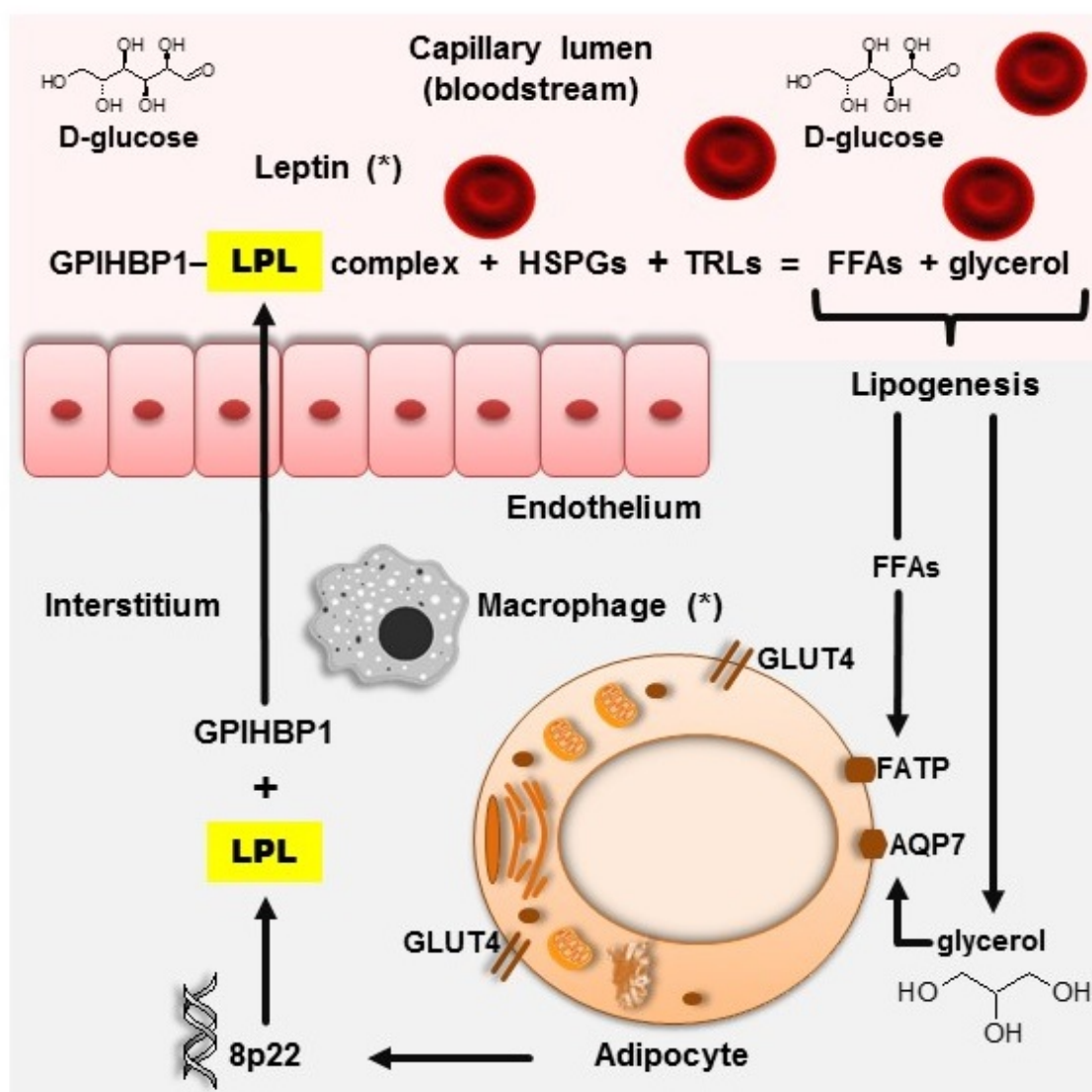
Figure 2 The complex apparatus for LPL activity at the luminal surface of the endothelium. FATP is an evolutionarily conserved membrane-bound protein found in the plasma membrane and intracellular organelles that has fatty acyl-CoA ligase (EC 6.2.1.3) activity and is an important molecule in fatty acid uptake [44,45]. AQP7 is a pore-forming transmembrane protein that facilitates the transport of glycerol across cell membranes [46]. Glycerol is used both in carbohydrate and lipid metabolism, being primarily stored in white adipose tissue as part of the TG molecule [46]. Monocytes are actively recruited into inflammatory sites where they differentiate into macrophages [47,48]. Macrophages phagocytize LDL particles to become lipid-laden foam cells [48,49]. Foam cells are fundamental to the formation, growth, and stability of atherosclerotic plaques [48,50]. (*) Leptin is a 167-amino-acid peptide that is mainly produced and released by adipocytes at concentrations similar to those found in the plasma of diabetic patients, leptin stimulates the in vitro release of increased amounts of active macrophage LPL [9,51,52]. Thus, establishing whether the in vivo effect of leptin on macrophages favors atherogenesis in humans is of clinical interest, especially in diabetic patients who have elevated plasma leptin levels and demonstrate enhanced proatherogenic cytokines secretion by macrophages (e.g., tumor necrosis factor-α; TNF-α) [52]. TNF-α induces appetite suppression and reduced synthesis of LPL, which result in wasting of muscle and adipose tissue (cachexia) [47]. Lastly, heparanase (EC 3.2.1.166) is an endo-β-d-glucuronidase that splits the oligosaccharide chains on HSPGs and promotes the release of LPL from cardiomyocytes for interaction with GPIHBP1 and transport to tsthe endothelium [53,54]. Note: GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1; LPL, lipoprotein lipase; HSPGs, heparan sulfate proteoglycans; TRLs, triglyceride-rich lipoproteins; FFAs, free fatty acids; GLUT4, glucose transporter 4; FATP, fatty acid transport protein; AQP7, aquaglyceroporin 7.

The incidence (i.e., new cases) of cardiovascular diseases has increased significantly over the past decade, seriously affecting human health and quality of life [55]. This is largely a result of the detrimental impact of risk factors such as dyslipidemia, obesity, and type 2 diabetes mellitus. LPL is an integral part of lipoprotein metabolism and its clinical importance derives chiefly from the role of this metabolic sector in atherogenesis (typically described as the formation of atheromatous lesions in the arterial intima) [9,10]. However, endothelial dysfunction is the primum movens (i.e., the starting point) in the pathogenesis of atherosclerosis because it appears long before clinical symptoms arise, and it is eligible to be a surrogate endpoint for the risk of cardiovascular disease [56]. Additionally, interest in LPL has been reinforced over the past decade by its great pathophysiological relevance in the abovementioned diseases and in other contexts of disordered lipid metabolism such as severe hypertriglyceridemia and the potentially associated acute pancreatitis, as well as in non-alcoholic fatty liver disease (NAFLD) [9]. There has been a renewed interest in the possible role of TG as a marker for the risk of cardiovascular disease [57]. Currently, numerous patients with such chronic degenerative diseases may benefit from effective long-term pharmacological treatments. However, only those drugs that modulate LPL activity (e.g., fibrates, nicotinic acid) were revised here. New non-pharmacologic therapeutic options have been developed, especially in the field of phytomedicine (e.g., phytochemicals such as polyphenols). These and other pertinent aspects (e.g., physiological regulation of LPL activity) have been developed and discussed in this review article.

Metabolic Overview of The Major Lipids in Human Beings and Other Important Aspects of Lipoprotein Lipase Activity

Phospholipids, cholesterol, and triglycerides (TGs) are the major lipids circulating in human blood [58,59]. Phospholipids are fundamental biological building blocks that maintain the proper functioning of plasma and other cellular membranes and are crucial for the survivability of cells and the existence of multicellular life [59]. Phospholipids may be synthesized de novo via the Kennedy pathway (which was named after Eugene Patrick Kennedy (1919–2011) who discovered it more than 50 years ago), and salvaged and recycled in a pathway requiring the mitochondria-associated endoplasmic reticulum membrane [60-62]. As mentioned in **Figure 1**, the lipid content of HDL is predominantly composed of phospholipids, accounting for 35–50% of the HDL lipids, with phosphatidylcholine as the major species [25].

Cholesterol has no energy value, but it serves as a building block for many important compounds (e.g., steroid hormones, vitamin D, bile acids) and is a component of the outer membranes of all body cells [63]. The amphipathic (or amphiphilic) surface of lipoproteins is composed of unesterified cholesterol, phospholipids, and apolipoproteins

while the hydrophobic core of these plasma lipid transport vehicles are composed of TGs and cholesterol esters [28]. Of pathophysiological importance, circulating cholesterol is a major component of atherosclerotic plaques [64]. The liver synthesizes more than 80% of the body's cholesterol and less than 20% of it comes from food sources (e.g., egg yolk, meat, seafood, butter) [65-67]. The 3-hydroxy-3-methylglutaryl coenzyme A reductase (EC 3.1.3.47; HMG-CoA reductase), is the key enzyme in the mevalonate pathway for cholesterol biosynthesis [68]. This is important because all statins inhibit HMG-CoA reductase by binding to the active site of the enzyme [69]. HMG-CoA reductase inhibitors (or statins) are a group of medications currently used to treat hypercholesterolemia and other dyslipidemias [70,71].

TGs are chemically characterized as esters of three fatty acids and one glycerol molecule [72]. Although in humans most fatty acids come from the diet rather than from de novo synthesis, preferential oxidation of carbohydrates rather than lipids would leave fatty acids available for TG synthesis [73]. Thus, lipogenesis is a broad term that may be defined as the fatty acid synthesis, including the de novo synthesis, and the subsequent conversion of fatty acids to TGs in the liver and adipose tissue, as partially illustrated in **Figure 2** [74]. It should be emphasized that the term de novo lipogenesis is reserved for the biochemical process of converting non-lipid precursors (e.g., glucose, fructose, leucine, and isoleucine) into fatty acids for storage as energy [75-78]. Additionally, lipogenesis occurs preferentially in adipose tissue, but it also happens in the liver [79]. Conversely, lipolysis is defined as the hydrolytic cleavage of ester bonds in TGs, resulting in generation of FFAs and glycerol [80]. As discussed previously **(Figure 2)**, LPL requires a complex apparatus to perform TRL hydrolysis in the turbulent bloodstream. In this respect, LPL may be appropriately defined as an extracellular enzyme because its catalytic activity takes place outside the secreting cells [81]. APOA5 is associated with TRLs and enhances TG hydrolysis and remnant lipoprotein clearance [82,83]. However, APOC3 inhibits LPL activity [54,83]. Luminal (or endothelial) LPL is referred to as the functional LPL pool, as it represents the portion of tissue LPL that is actively involved in plasma TG hydrolysis [83]. After LPL hydrolyzes TRLs, sortilin, a member of the vacuolar protein sorting 10 (or VPS10) family, facilitates the uptake of secreted LPL and transfers it to endosomes in parenchymal cells, and LPL ends up in lysosomes for degradation [50,84].

Glycerol is a sugar alcohol that exists naturally in foods and living tissues, and it is constantly being produced by the breakdown of lipids in the gastrointestinal tract and absorbed by the mucosa [85]. When oxidized as an energy substrate, glycerol is converted to carbon dioxide and water, with the concomitant release of 4.32 kcal/g of usable energy [85]. Glyceroneogenesis is defined as de novo synthesis of glycerol-3-phosphate from pyruvate, lactate, and certain amino acids [86]. It is correctly considered an abbreviated version of gluconeogenesis (i.e., glucose synthesis from non-glycosidic substrates) [87]. Glycerol metabolism is closely associated with that of carbohydrates [81,85,87].

Physiological Factors Regulating Lipoprotein Lipase Activity

Regulation of LPL activity has so many different features that the adjective multidimensional would be perhaps more appropriate to qualify it [88]. LPL activity is finely regulated by a multitude of factors at the transcriptional, translational, and posttranslational levels [83,89-91]. These are the basic concepts in the central dogma of genetics that was proposed by Francis Crick in 1957 [91,92]. Genes encoded by deoxyribonucleic acid (DNA) are transcribed in the cellular nucleus to produce messenger ribonucleic acid (mRNA), which in turn is translated at the endoplasmic reticulum into functional proteins such as LPL [91,92]. Regulation of DNA transcription is responsible for the upregulation of LPL gene expression and activity during cardiomyogenesis and adipogenesis [83]. Chaperons are proteins with the function of assisting the folding and assembly of other proteins [93]. LPL is synthesized as an inactive monomer in parenchymal cells and, with the support of specific endoplasmic reticulum chaperones (i.e., lipase maturation factor 1 and Sel-1 suppressor of lin-12-like protein), a noncovalent, active LPL dimer is formed, although both active and inactive forms of LPL are secreted [54]. Most of the physiological variation in LPL activity (e.g., during exercise and fasting) appears to be driven via post-translational mechanisms by extracellular proteins [83]. The **Figure 3** is a schematic summary of some physiological factors that regulate LPL activity.

Besides the multiple factors listed below, LPL activity is also regulated by daily circumstances, such as exercise, fed and fasting states, and starvation and cold, in a very intricate manner, with many pertinent aspects that are yet to be elucidated.
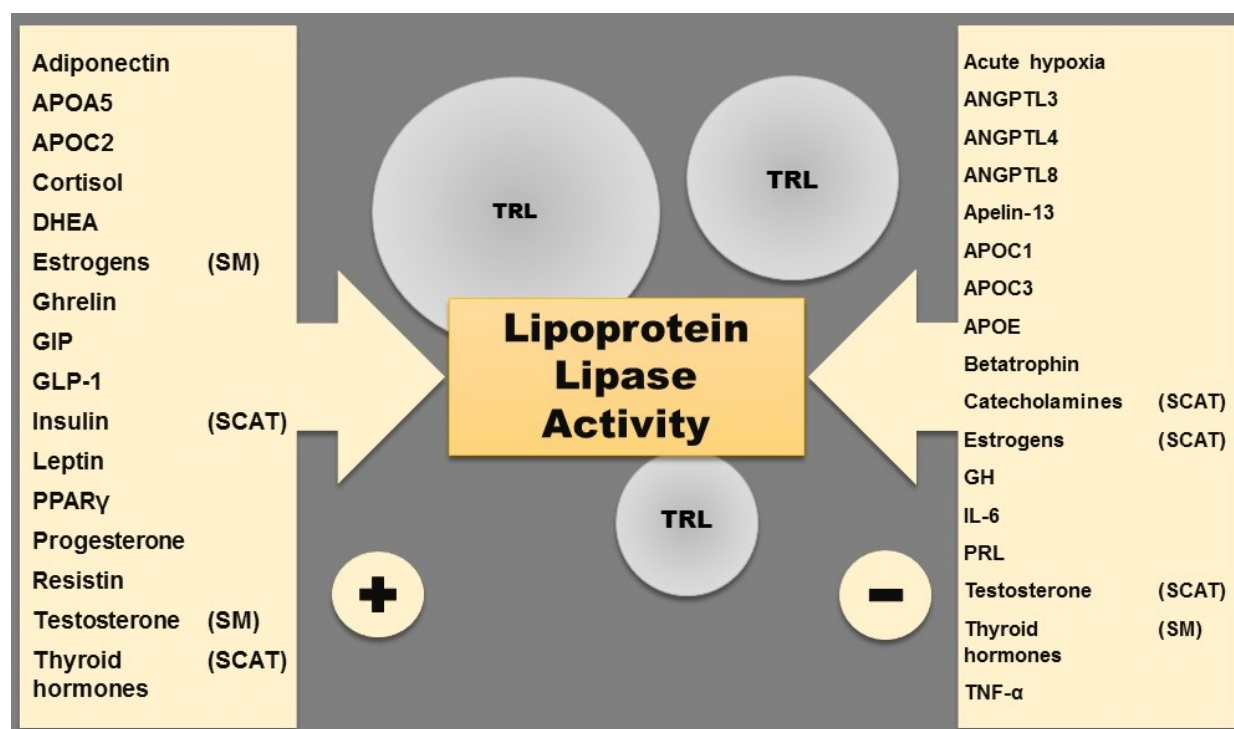

Figure 3 Non-exhaustive list of physiological factors regulating lipoprotein lipase activity. The content of the Figure 3 was adapted from the following references [3,52,83,94-111]. Insulin action on adipose tissue and muscle is discussed in the text. Note: +, stimulation; -, inhibition; SM, skeletal muscle; SCAT, subcutaneous adipose tissue; TRL, triacylglycerol-rich lipoprotein; APOA5, apolipoprotein A5; APOC2, apolipoprotein C2; DHEA, dehydroepiandrosterone; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; PPARγ, peroxisome proliferator-activated receptor γ; ANGPTL3, angiopoietin-like protein 3; ANGPTL4, angiopoietin-like protein 4; ANGPTL8, angiopoietin-like protein 8; APOC1, apolipoprotein C1; APOC3, apolipoprotein C3; APOE, apolipoprotein E; GH, growth hormone; IL-6, interleukin-6; PRL, prolactin; TNF-α, tumor necrosis factor-α.

Exercise may be concisely defined as a series of specific movements for the purpose of training or developing the body through systematic practice, or as a bodily exertion for the promotion of physical health [112]. LPL has been found to be increased in the skeletal muscle and adipose tissue as well as in the plasma of people engaged in exercise compared to those not engaged in exercise [83,113]. Moreover, exercise induces an acute increase in postheparin LPL that in turn leads to enhanced TG clearance and decreases plasma clearance of HDL constituents [113]. It is known that during exercise, energy turnover increases and adrenergic mechanisms play an important role in this regulation [114]. Plasma catecholamines effectively inhibit LPL via the α1-adrenoceptors **(Figure 3)** [109]. Nonetheless, exercise induces LPL and GLUT4 protein in

the muscle independent of adrenergic-receptor signaling [115]. Both adipose tissue and intramuscular fat can be stimulated by catecholamines, and both LPL and hormone-sensitive lipase (HSL; EC 3.1.1.79) play important roles in this regulation [114]. HSL is the predominant regulator of lipolysis from adipocytes, releasing FFAs from stored TGs [116]. In this dynamic metabolic process, LPL replenishes while HSL depletes the adipocyte fat store.

In the fed state, postprandial metabolism is essentially characterized by high insulin levels that are responsible for antilipolytic action (e.g., by inhibiting HSL) and antigluconeogenic action (by suppressing this metabolic pathway) as well as for lipogenic action (e.g., by stimulating LPL) [87,117]. Human insulin is a 51-amino acid peptide hormone that is produced by pancreatic β-cells in addition to be a major regulator of LPL activity **(Figure 3)** [110,118]. Briefly, insulin inhibits gluconeogenesis in the liver and the kidney because of the tissue-specific expression of hormone-sensitive metabolic enzymes involved in this process [119]. Thus, insulin may inhibit, for example, glucose-6-phosphatase (EC 3.1.3.9), among other gluconeogenic enzymes [120-122]. However, because higher insulin concentrations are required to suppress gluconeogenesis than to inhibit glycogenolysis (i.e., the breakdown of glycogen), or increase glycogen synthesis, gluconeogenically derived glucose-6-phosphate can be diverted into hepatic glycogen even during mild hyperinsulinemia [87,123]. Thus, the fed state is an insulin-sufficient state in which insulin affects the internal machinery of cells in the liver, adipose tissue, and muscles to promote energy production and storage [124]. Postprandially, LPL activity is elevated in adipose tissue compared with heart and muscle, resulting in the channeling of circulating TG fatty acids into lipid depots [125].

Conversely, the fasting state is characterized by low plasma insulin and high insulin counterregulatory hormones (e.g., glucagon, catecholamines) that determine the catabolic changes in fuel selection and the metabolite fluxes [87,126]. Reference [87] includes an overview of the hormonal and metabolic alterations during food deprivation. With such a hormonal profile, LPL activity is decreased in certain tissues (i.e., white adipose tissue) [83,127,128]. However, during fasting, relatively high heart and muscle LPL activities redirect TG fatty acids appropriately into these tissues and away from adipose stores [79,125]. Additionally, a study demonstrated that a ten-hour period of fasting caused a 25% decrease in LPL activity in adipose tissue whereas LPL activity in muscle remained unchanged, while a 30-hour period of fasting caused an incremental 50% decrease in LPL activity in adipose tissue and a 100% increase LPL activity in muscle; this likely reflects an increase in activity and mass of LPL in skeletal muscle [129]. Thus, a role for the tissue-specific regulation of LPL activity seems to be plausible, especially when LPL activity channels fatty acids to adipose tissue for storage in the fed state and to muscle tissues as energy fuel during times of food deprivation such as fasting [129]. Finally, intermittent fasting has been much discussed in the current literature for its potential health benefits [130-134]. In fact, LPL has been reported to accumulate in senile plaques of Alzheimer's disease (AD)

brains, and as a molecular chaperone to bind to amyloid-β peptide (the major component of the plaques) [130]. In one study, intermittent fasting (i.e., alternate-day fasting) alleviated the increase of LPL expression in the brain of a mouse model of AD possibly by mediation of an increase in ketone body levels (i.e., β-hydroxybutyrate) subsequent to the induced ketosis [130].

Fasting and starvation are not synonymous terms, but the expression "prolonged fasting" is currently used as a synonym for starvation [87]. The term starvation is used to describe a state of extreme hunger resulting from a prolonged lack of essential nutrients [87]. Starvation is, in principle, longer, potentially harmful, and may lead to a lethal outcome [87]. The response to starvation is also integrated at all levels of organization and is directed toward the survival of the species [87]. For example, in the presence of low insulin levels during starvation, LPL in the muscle is more active than in the adipose tissue, and fatty acids from triglyceride-rich VLDLs are shunted in addition to the readily available FFAs into skeletal muscle cells to produce energy by oxidation [135]. Thus, in extreme circumstances such as starvation, the enzymatic activity of LPL seems to be adjusted to the actual energy metabolism needs of the organism.

Lastly, it is important to mention the role of brown adipose tissue (BAT) in the rat in increasing LPL activity by β3-adrenergic stimulation during cold [83]. The development of BAT with its characteristic protein, uncoupling protein-1, likely had a role in determining the evolutionary success of mammals, because its thermogenesis enhances neonatal survival and allows active life even in cold surroundings [136]. However, in humans, BAT is retained into adulthood, and it also retains the capacity to have a significant role in energy balance [137]. BAT is currently a primary target organ in obesity prevention strategies [137].

Alterations of Lipoprotein Lipase Activity in Metabolic Disorders

Enzymes are very sensitive biomolecules that require optimum conditions for their maximal operation. Experimentally, researchers seek to define this ideal operational profile of the enzymes by testing various influential factors, such as different substrates, temperatures, pH, buffers, activators, inhibitors, and durations. Thus, it is possible to define enzymatic stability, i.e., the ability to retain the catalytic activity of the biomolecule [138]. Knowing the enzymatic stability makes it possible to adapt the enzyme use to the most diverse biotechnological activities, including those aimed at human health. However, it is not possible to directly extrapolate *in vitro* results to *in vivo* results, but there is a great variability of enzymatic activity (lato sensu) among, for example, microorganism strains and animal species, including humans [139-142].

As discussed above, LPL activity is regulated by multiple physiological factors and daily circumstances such as exercise and fasting. Additionally, numerous diseases may affect human metabolism and LPL activity. The most prevalent

metabolic disorders are obesity, diabetes mellitus, dyslipidemia, metabolic syndrome, and osteoporosis [143-145]. However, metabolic syndrome is composed of a constellation of interrelated cardiovascular risk factors of metabolic origin and includes visceral (or android) obesity, glucose intolerance, insulin resistance, dyslipidemia, and hypertension [146-148]. Consequently, metabolic syndrome is a heterogeneous entity rather than an unequivocal entity and it has profuse synonymy (e.g., plurimetabolic syndrome, syndrome X, Reaven syndrome, atherothrombogenic syndrome) [148,149]. Two common LPL gene variants (447 Ter and 291 Ser) were associated with metabolic syndrome through their effect on high TG and low HDL cholesterol [149].

Obesity may be broadly defined as an excess of body fat mass [150]. Adipogenesis is a process of adipocyte differentiation and lipid accumulation, and the expression of LPL mRNA has often been considered to be an early sign of adipocyte differentiation [151,152]. During adipogenesis, transcription of the LPL gene is stimulated by adipogenic transcription factor PPARγ, fatty acids, and other PPARγ agonists in differentiated adipocytes [83]. Additionally, insulin has a major effect on LPL activity in adipose tissue during adipocyte differentiation by increasing LPL gene transcription [89]. In mature adipocytes, insulin not only increases the level of LPL mRNA but also regulates LPL activity through both posttranscriptional and posttranslational mechanisms [89]. A major portion of available fatty acids for adipocyte uptake is derived from LPL-mediated hydrolysis of circulating lipoprotein particles; but in humans, de novo lipogenesis occurs mainly in the liver and to a lesser extent in the adipocyte [153-155]. Obesity studies in rodents and humans have revealed increased adipose tissue LPL activity [90]. Obese subjects also have elevated adipose tissue LPL activity per fat cell when compared with lean control subjects [156]. Remarkably, weight loss increases adipose tissue LPL activity probably in an attempt to maintain lipid stores [90]. Finally, obesity is a significant risk factor for type 2 diabetes mellitus [157]. It is estimated that approximately 80% of type 2 diabetic patients are obese, explaining the tight association of adiposity with insulin resistance and justifying the term diabesity [158,159].

Type 2 diabetes mellitus is the most common endocrine disorder in the world [160]. It is a chronic, progressive disease, characterized by multiple defects in glucose metabolism, the core of which is insulin resistance, which is the impaired ability to respond to insulin especially in muscle, liver, and adipocytes, and by a gradual β-cell failure [161,162]. Type 1 diabetes mellitus is, however, much less prevalent, and is characterized by profound insulin deficiency caused by pancreatic β-cell destruction [163,164]. A novel subtype of type 1 diabetes mellitus, known as fulminant type 1 diabetes, is responsible for approximately 20% of all ketosis-onset type 1 diabetes cases in the Japanese population [164]. As discussed above, LPL activity in both adipose tissue and skeletal muscle depends on insulin and varies in diabetes mellitus according to ambient insulin level and insulin sensitivity [165]. Briefly, in untreated type 1 diabetes mellitus, LPL activity in both adipose tissue and muscle tissue is low, but it increases with insulin therapy [165]. In chronically insulin-treated patients with good control, LPL activity in postheparin plasma is increased [165]. In untreated type 2 diabetic patients, the average LPL activity in adipose tissue and postheparin plasma is normal (or below normal) and therapy with oral agents or insulin results in good glycemic control, followed by an increase in LPL activity in both adipose tissue and postheparin plasma [165]. Of utmost interest are the alterations in lipoproteins following changes in LPL activity in diabetic patients. These changes include high VLDLs and low HDLs in insulin deficiency with low LPL activity, normal or low VLDLs and high HDLs in chronically insulin-treated patients with high LPL activity, and high TGs and low HDLs in untreated type 2 diabetic patients [165]. Thus, the most obvious lipid defect in uncontrolled diabetes mellitus is the elevated TG level and a corollary is the reduced HDL level [166]. These metabolic disorders must be clinically followed up and continuously treated.

Lastly, fatty liver may occur in up to 80% of diabetic patients and is more commonly associated with type 2 diabetes mellitus (in which the degree of hepatic lipid accumulation is related to the severity of the associated obesity) [167]. Thus, non-alcoholic fatty liver disease (NAFLD) is closely associated with several metabolic syndrome features and has even been recognized as the hepatic expression of metabolic syndrome [168,169]. In this pathophysiological context, de novo lipogenesis is thought to contribute to the origin of NAFLD, which is often associated with insulin resistance [78,170]. However, the high activity of LPL in the white adipose tissue of extremely obese individuals is impaired by insulin resistance [171,172]. Hence, the pathophysiological role of LPL activity in NAFLD remains elusive **(Figure 4)**.
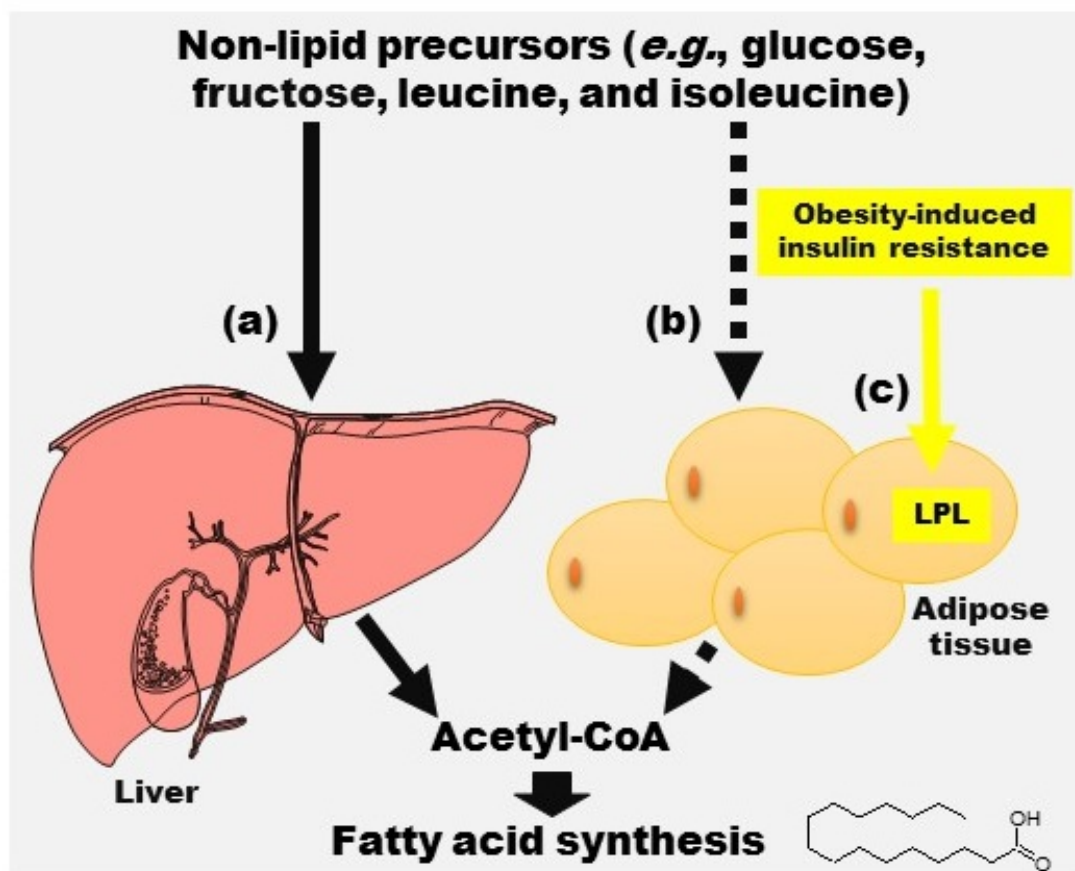
Figure 4 Potential role of the de novo lipogenesis in non-alcoholic fatty liver disease. Notably, acetyl-CoA is the principal building block of fatty acids for de novo lipogenesis after activation to malonyl-CoA by the multifunctional polypeptide acetyl-CoA carboxylase (EC 2.7.11.27) [170,173]. De novo lipogenesis is threefold higher in patients with NAFLD than in physiologically normal individuals, representing a key feature of fatty livers [174]. Note: (a) Full black arrow indicates major metabolic route. (b) Dotted black arrow indicates minor metabolic route. (c) Full yellow arrow indicates impaired enzymatic activity.

Drugs and Phytochemicals Affecting Lipoprotein Lipase Activity

Many compounds exert part of their beneficial effects on the disordered metabolism of lipoproteins through the modulation of LPL activity. Fibrates are one of the oldest lipid-lowering drugs, beginning in the late 1950s with the first-generation agent (clofibrate), subsequently, gemfibrozil, the second-generation fibrate that has been used worldwide, while the third-generation agents comprise fenofibrate, bezafibrate, and etofibrate [175]. Fibrates are derivatives of fabric acid whose mechanism of action relies on the activation of the nuclear receptor peroxisome proliferator-activated receptors alpha (PPARα), which leads to several changes in metabolism, including a reduction in the production of APOC3 (the already mentioned physiological inhibitor LPL) and an increase in the expression of LPL, both alterations leading to a significant rise in LPL activity and a reduction in TG level in bloodstream [9,175-177]. Nicotinic acid and its derivatives (pyridylcarbinol, xanthinol nicotinate, and acipimox) activate LPL, thereby mainly lowering TG levels [175,178,179]. However, at the start of nicotinic acid therapy, a prostaglandin-mediated vasodilation may occur with flushing, hypotension, that can be prevented by low doses of acetylsalicylic acid [178]. Some statins, such as pitavastatin, simvastatin, and atorvastatin, also increase the expression and the activity of LPL [180-183].

Phytochemicals may be defined as substances found in plants that exhibit a potential for modulating human metabolism in a manner that is beneficial for the prevention of chronic and degenerative diseases [184]. The growing interest in phytochemicals is in part due to the high prevalence of

metabolic disorders and an urgent need for new therapeutic avenues [19]. Among phytochemicals, polyphenols have drawn attention for their many health virtues, particularly their antioxidant activity [81]. In addition, many plants rich in these phytochemicals have been currently tested for their effects on LPL activity [185-187]. This research area holds promise for improving patients' quality of life.

Concluding Remarks

LPL plays a crucial physiological role not only in lipoprotein metabolism but also in fuel metabolism. LPL is strategically located at the dynamic blood-tissue interface (vascular endothelium) from where it can more easily redirect the use of energy-rich substrates, such as FFAs, according to the metabolic demands of the organism. LPL activity seems to adapt to even more extreme circumstances of energy shortage, such as prolonged fasting (or starvation), by favoring the energy supply to tissues such as the muscles. As discussed in this review, this complex tissue-specific regulation of LPL activity is physiologically desirable. Pathophysiologically, however, there are still gaps in the comprehension of the role played by LPL in metabolic disorders such as obesity, diabetes mellitus, and NAFLD, among others. Furthermore, the metabolic syndrome continues to expand (conceptually), making the understanding of the role of LPL activity in this heterogeneous illness even more difficult. Finally, complex diseases, such as metabolic disorders, require multifarious therapeutic approaches. Nonetheless, some LPL activators (e.g., fibrates) have been proven effective in the treatment of hypertriglyceridemia.

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Conflict of Interest

The author declares no conflict of interest.

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