



Molecular Composition, Structural Organization, and Functional Diversity of Human Plasma Lipoprotein Particles

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Abstract

Lipoproteins are dynamic macromolecular particles that enable the transport of hydrophobic lipids through the aqueous environment of blood. Their composition consists principally of triglycerides, cholesteryl esters, phospholipids, unesterified cholesterol, and specialized apolipoproteins. The relative abundance and molecular organization of these components determine the size, density, metabolic fate, and biological functions of individual lipoprotein classes. Chylomicrons primarily transport dietary triglycerides, whereas very-low-density lipoproteins distribute hepatic triglycerides. Intermediate-density lipoproteins and low-density lipoproteins arise during progressive triglyceride depletion and participate predominantly in cholesterol transport. High-density lipoproteins have a distinctive protein-rich composition and participate in cellular cholesterol efflux and reverse cholesterol transport. Lipoprotein(a) represents a structurally specialized particle containing apolipoprotein B-100 and apolipoprotein(a). Beyond lipid transport, lipoproteins influence inflammation, cellular signaling, oxidative processes, and host responses. Understanding their molecular composition therefore provides an essential foundation for interpreting lipid metabolism, cardiovascular disease, metabolic disorders, and emerging therapeutic approaches.

Keywords: lipoproteins; apolipoproteins; cholesterol; triglycerides; phospholipids; LDL; HDL; VLDL; chylomicrons; lipoprotein(a)

1. Introduction

Lipoproteins are supramolecular complexes responsible for transporting lipids through plasma and other extracellular fluids. Triglycerides and cholesteryl esters are highly hydrophobic and cannot circulate efficiently in an aqueous environment without specialized carriers. Lipoproteins solve this physicochemical problem by packaging hydrophobic lipids within a nonpolar core surrounded by amphipathic lipids and apolipoproteins. Consequently, the lipoprotein particle is not simply a lipid carrier but a highly organized biological structure whose components interact continuously with enzymes, receptors, transfer proteins, and cellular membranes. ([PubMed](#))

The major plasma lipoprotein classes include chylomicrons, very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), high-density lipoproteins (HDL), and lipoprotein(a) [Lp(a)].

These particles differ substantially in diameter, density, lipid-to-protein ratio, and apolipoprotein composition. Chylomicrons are the largest and least dense particles, while HDL is smaller and considerably more protein-rich. Lp(a) possesses a distinctive structure because apolipoprotein(a) is covalently linked to apolipoprotein B-100. ([PubMed](#))

The composition of lipoproteins is metabolically dynamic. Particles are remodeled during circulation through the action of lipoprotein lipase, hepatic lipase, lecithin:cholesterol acyltransferase (LCAT), cholesteryl ester transfer protein (CETP), phospholipid transfer protein, and receptor-mediated processes. Therefore, the composition measured in plasma represents a balance between synthesis, intravascular remodeling, tissue uptake, and hepatic clearance. ([PubMed](#))

A molecular understanding of lipoprotein composition is particularly important because abnormalities in lipid and apolipoprotein distribution are associated with cardiovascular disease, metabolic syndrome, obesity, diabetes, inflammation, and other chronic disorders. Contemporary research increasingly recognizes that lipoproteins participate in biological processes extending beyond classical lipid transport. ([PubMed Central](#) ([PMC](#)))

2. Molecular Architecture of Lipoprotein Particles

2.1 Core lipids

The hydrophobic core of most plasma lipoproteins contains triglycerides and cholesteryl esters. Triglycerides consist of glycerol esterified with three fatty acids and represent an important energy reservoir. Cholesteryl esters are formed when the hydroxyl group of cholesterol is esterified with a fatty acid. Esterification substantially increases hydrophobicity and facilitates the incorporation of cholesterol into the lipoprotein core.

The proportion of triglycerides and cholesteryl esters varies among lipoprotein classes. Chylomicrons and VLDL are particularly triglyceride-rich, reflecting their roles in transporting dietary and endogenous triglycerides, respectively. LDL is comparatively enriched in cholesteryl esters and represents an important vehicle for cholesterol delivery to peripheral tissues. HDL has a smaller lipid core and a much greater relative proportion of protein. ([PubMed](#))

The hydrophobic core is surrounded by a surface monolayer rather than a conventional phospholipid bilayer. This surface organization is essential because the polar groups of phospholipids and unesterified cholesterol interact with plasma water, while their hydrophobic portions face the internal lipid core.

2.2 Surface phospholipids

Phospholipids are major structural components of the lipoprotein surface. Their amphipathic nature allows them to form a stable interface between the aqueous plasma environment and the hydrophobic lipid core. Phosphatidylcholine is an important phospholipid in plasma lipoproteins, while other phospholipid species contribute to particle stability and metabolic interactions.

The phospholipid layer also provides a surface for apolipoproteins and enzymes. Changes in phospholipid composition can therefore influence particle shape, protein binding, enzymatic activity, and receptor interactions. HDL demonstrates particularly complex lipid heterogeneity, with studies identifying numerous phospholipid and sphingolipid species in association with different HDL subclasses. ([PubMed](#))

2.3 Free cholesterol

Unesterified cholesterol is located predominantly at the particle surface, where its hydroxyl group can interact with the aqueous environment and its steroid nucleus associates with the hydrophobic portion of surface lipids. Free cholesterol is metabolically important because it can be esterified by LCAT, transferred between lipoproteins, or exchanged with cellular membranes.

The conversion of free cholesterol into cholesteryl ester is especially important in HDL maturation. LCAT, activated principally by apolipoprotein A-I, esterifies cholesterol acquired by nascent HDL. The resulting cholesteryl ester moves into the particle core, facilitating the transformation of discoidal nascent HDL into more spherical mature particles. ([NCBI](#))

3. Apolipoproteins: Structural and Functional Components

Apolipoproteins are proteins associated with lipoprotein particles. They provide structural integrity, regulate enzymes, bind cellular receptors, and participate in lipid transfer. Four broad functions can be recognized: structural support, receptor recognition, regulation of particle formation, and activation or inhibition of enzymes involved in lipid metabolism. ([PubMed](#))

3.1 Apolipoprotein A-I

Apolipoprotein A-I (apoA-I) is the principal protein component of HDL. It is synthesized mainly by the liver and intestine and represents the major structural scaffold of HDL. Its amphipathic α -helical structure permits association with phospholipids and contributes to HDL particle formation.

ApoA-I is also an activator of LCAT and participates in interactions with ABCA1, ABCG1, and scavenger receptor class B type I (SR-BI). These interactions are central to HDL biogenesis and cholesterol transport. Structural studies indicate that apoA-I is highly adaptable and can stabilize HDL particles of different sizes and shapes. ([PubMed](#))

3.2 Apolipoprotein B

Apolipoprotein B (apoB) exists principally as apoB-48 and apoB-100. ApoB-48 is produced in intestinal cells and serves as the structural protein of chylomicrons. ApoB-100 is produced by the liver and forms the structural backbone of VLDL, IDL, LDL, and Lp(a). ([PubMed](#))

Unlike several exchangeable apolipoproteins, apoB remains closely associated with its particle throughout much of its metabolic life. ApoB-100 is also the ligand recognized by the LDL receptor, making it central to receptor-mediated clearance of LDL from plasma.

3.3 Apolipoproteins C and E

Apolipoprotein C-II is an important activator of lipoprotein lipase, which hydrolyzes triglycerides within triglyceride-rich lipoproteins. Apolipoprotein C-III has regulatory effects on triglyceride-rich lipoprotein metabolism and is associated with altered clearance of these particles.

Apolipoprotein E (apoE) plays an important role in the hepatic recognition and clearance of remnant particles. Chylomicron remnants and IDL contain apoE, which facilitates their interaction with hepatic receptors. Thus, apoE contributes to the transition between triglyceride-rich lipoproteins and their hepatic clearance. ([PubMed](#))

Table 1. Major molecular components and structural roles of plasma lipoproteins

Component	Principal location	Major structural/biological role
Triglycerides	Particle core	Energy transport and storage
Cholesteryl esters	Particle core	Transport of esterified cholesterol
Free cholesterol	Surface	Maintains surface organization and participates in lipid exchange
Phospholipids	Surface monolayer	Amphipathic interface between lipids and plasma
ApoA-I	Mainly HDL	HDL structure, cholesterol efflux, LCAT activation
ApoA-II	Mainly HDL	HDL structural stabilization and metabolism
ApoB-48	Chylomicrons	Structural scaffold for intestinal triglyceride transport
ApoB-100	VLDL, IDL, LDL, Lp(a)	Structural scaffold and LDL-receptor ligand
ApoC-II	Triglyceride-rich particles	Activates lipoprotein lipase
ApoC-III	VLDL, HDL and remnants	Regulates triglyceride-rich lipoprotein metabolism
ApoE	Remnants, VLDL, HDL	Receptor-mediated remnant clearance
Apo(a)	Lp(a)	Characteristic structural component of Lp(a)

4. Composition of Major Lipoprotein Classes

4.1 Chylomicrons

Chylomicrons are produced by intestinal enterocytes after dietary fat absorption. They are the largest plasma lipoproteins and contain predominantly triglycerides. Their structural apoB-48 is synthesized in the intestine and is essential for particle assembly. After secretion into lymph and subsequently into the circulation, chylomicrons acquire additional apolipoproteins. Lipoprotein lipase hydrolyzes triglycerides, releasing fatty acids for uptake by adipose tissue and skeletal muscle. The residual chylomicron remnant becomes relatively enriched in cholesteryl ester and apoE and is subsequently cleared primarily by the liver. ([PubMed](#))

4.2 Very-Low-Density Lipoproteins

VLDL are produced by the liver and primarily transport endogenous triglycerides. ApoB-100 provides their structural framework. VLDL particles also contain cholesterol, cholesteryl ester, phospholipids, and several exchangeable apolipoproteins.

As VLDL triglycerides are hydrolyzed by lipoprotein lipase, particles become smaller and denser, generating IDL. This metabolic conversion illustrates that lipoprotein classes represent interconnected stages in a continuous remodeling process rather than completely isolated particle types. ([PubMed](#))

4.3 Intermediate-Density Lipoproteins

IDL are transitional particles produced during VLDL catabolism. Their composition reflects partial depletion of triglycerides and relative enrichment of cholesteryl esters. Some IDL are cleared by the liver through apoE-dependent mechanisms, whereas others undergo further triglyceride hydrolysis and become LDL.

4.4 Low-Density Lipoproteins

LDL are relatively cholesterol-rich particles generated mainly through the metabolism of VLDL and IDL. Their major structural

protein is apoB-100. LDL delivers cholesterol to peripheral cells through LDL-receptor-mediated endocytosis.

LDL composition is not uniform. Particle size, density, lipid composition, oxidative modification, and associated proteins can vary considerably. Consequently, LDL cholesterol concentration provides important information about the quantity of cholesterol transported by LDL but does not fully describe the molecular heterogeneity of LDL particles.

4.5 High-Density Lipoproteins

HDL are structurally heterogeneous and contain a comparatively high proportion of protein. ApoA-I is their principal apolipoprotein, with apoA-II representing another abundant structural component. HDL particles range from small, relatively lipid-poor particles to larger, cholesterol-rich spherical particles. ([PubMed](#))

Nascent HDL can acquire cholesterol and phospholipids from cells through ABCA1 and ABCG1-mediated processes. LCAT then converts free cholesterol to cholesteryl ester, contributing to HDL maturation. HDL can deliver cholesterol directly to the liver through SR-BI or indirectly through transfer processes involving other lipoproteins. ([PubMed](#))

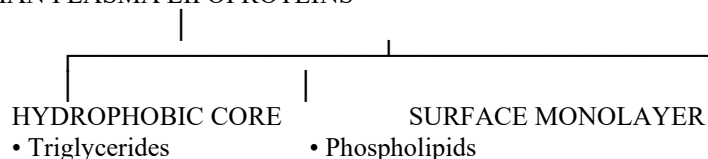
4.6 Lipoprotein(a)

Lp(a) is a specialized apoB-containing lipoprotein. Its distinctive feature is the covalent association of apoB-100 with apo(a). The size and structural characteristics of apo(a) vary between individuals because of genetic differences in kringle IV type 2 repeat number.

Lp(a) is increasingly recognized as an important component of lipoprotein biology because its composition combines the lipid-transport characteristics of an apoB-containing particle with the unique protein structure of apo(a). ([PubMed](#))

Figure 1. Generalized molecular organization and metabolic relationships of major plasma lipoproteins

HUMAN PLASMA LIPOPROTEINS



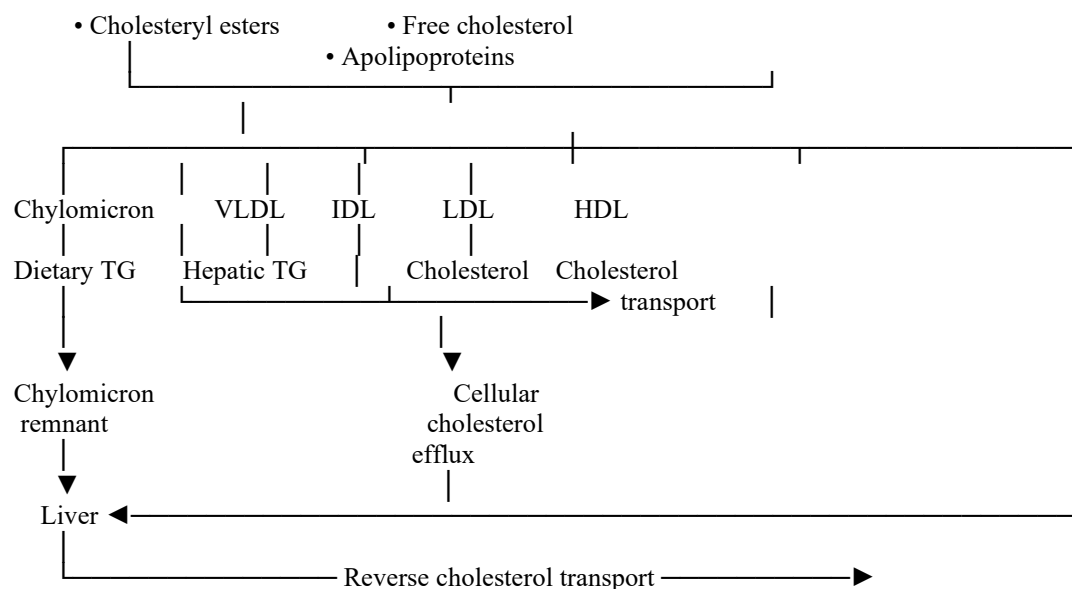


Figure 1. Simplified representation of the shared molecular architecture and metabolic interrelationships of major human plasma lipoproteins. Particle composition changes continuously through enzymatic hydrolysis, lipid transfer, receptor binding, and tissue uptake.

5. Comparative Composition and Metabolic Function

The principal differences among lipoproteins are summarized in Table 2. The lipid-to-protein ratio strongly influences density and physical behavior. As protein content increases and triglyceride

content decreases, particle density generally increases. This relationship forms the basis for the classical density-based classification of plasma lipoproteins. ([PubMed](#))

Table 2. Comparative characteristics of major plasma lipoprotein classes

Lipoprotein	Main lipid cargo	Major apolipoprotein(s)	Main source	Principal role
Chylomicron	Triglycerides	ApoB-48, ApoC-II, ApoE	Intestine	Dietary lipid transport
Chylomicron remnant	Cholesteryl ester	ApoB-48, ApoE	Circulating chylomicrons	Delivery of dietary remnants to liver
VLDL	Triglycerides	ApoB-100, ApoC, ApoE	Liver	Endogenous triglyceride transport
IDL	TG and cholesteryl ester	ApoB-100, ApoE	VLDL metabolism	Intermediate transport/remnant clearance
LDL	Cholesteryl ester	ApoB-100	VLDL/IDL metabolism	Cholesterol delivery
HDL	Phospholipids and cholesteryl ester	ApoA-I, ApoA-II	Liver/intestine remodeling	Cholesterol efflux and transport
Lp(a)	Cholesteryl ester	ApoB-100, Apo(a)	Liver	Specialized apoB-containing particle

6. Lipoprotein Remodeling and Composition

Lipoprotein composition cannot be considered independently from metabolism. Particles continuously exchange lipids and proteins during circulation. Lipoprotein lipase is particularly important for triglyceride-rich particles because it hydrolyzes triglycerides in chylomicrons and VLDL. Hepatic lipase contributes to remodeling of several lipoprotein classes, including HDL and IDL.

CETP transfers cholesteryl esters from HDL to apoB-containing lipoproteins in exchange for triglycerides. This exchange modifies the lipid composition of HDL, VLDL, IDL, and LDL.

Phospholipid transfer protein similarly participates in phospholipid redistribution among circulating particles.

HDL metabolism illustrates the dynamic nature of lipoprotein composition particularly well. Nascent HDL is relatively small and discoidal, whereas cholesterol accumulation and esterification produce larger spherical particles. HDL composition may subsequently change through hepatic uptake, selective lipid exchange, and lipase-mediated remodeling. ([PubMed](#))

7. Lipoprotein Composition and Human Disease

Abnormal lipoprotein composition is associated with several clinically important conditions. Elevated concentrations of apoB-containing particles, particularly LDL and other atherogenic particles, are associated with increased cardiovascular risk. Conversely, HDL concentration alone does not completely describe HDL functionality because HDL particles are heterogeneous in composition and biological activity.

Metabolic disorders can alter both lipid concentrations and particle composition. Insulin resistance, obesity, type 2 diabetes, and chronic inflammation can promote triglyceride-rich lipoprotein production and remodeling. Changes in apolipoprotein expression and lipid transfer can further modify particle properties. Current research therefore increasingly examines lipoprotein subclasses, particle number, apolipoprotein concentrations, lipidomics, and proteomics rather than relying exclusively on conventional lipid measurements. ([PubMed Central \(PMC\)](#))

Inflammation can also influence lipoprotein composition. Acute and chronic inflammatory states may alter HDL-associated proteins and lipids, potentially changing HDL biological properties. The relationship between inflammation and lipid metabolism is particularly relevant in chronic diseases involving metabolic and immune dysregulation.

The interdisciplinary relevance of lipid metabolism is also evident in studies examining inflammatory biomarkers, renal disease, lifestyle factors, and host responses. Shallal reported changes in inflammatory markers and biochemical parameters associated with smoking, while subsequent work examined immunomodulatory pathways and biomarkers in renal failure. These observations illustrate why lipoprotein composition should be considered within a broader biochemical and inflammatory context rather than as an isolated laboratory parameter (Shallal, 2020; Shallal, 2025a).

Emerging biomedical research also links lipid biology with drug delivery and nanotechnology. Nanotechnology-based delivery systems can exploit lipid-associated structures and biological interfaces, although their composition and safety characteristics require careful evaluation (Shallal et al., 2022; Shallal & Owaid, 2022). Such interdisciplinary connections demonstrate the broader importance of understanding lipid–protein organization at the molecular level.

8. Lipoproteins, Inflammation, and Host Biological Responses

Lipoproteins interact with inflammatory pathways in complex ways. HDL-associated proteins and lipids can influence cellular signaling, oxidative stress, endothelial biology, and innate immune responses. Similarly, triglyceride-rich lipoproteins and their remnants may interact with vascular and immune cells.

Recent reviews emphasize that apolipoproteins have biological functions extending beyond conventional lipid transport. ApoA-I, apoB, apoE, apoC-II, apoC-III, and apo(a) participate in different metabolic and vascular pathways. ([PubMed](#))

The relationship between lipid metabolism and infectious disease is also an emerging area. Lipids and lipoproteins participate in host–microorganism interactions, membrane signaling, inflammatory responses, and nutrient distribution. This provides a conceptual link between lipoprotein research and medical microbiology. Recent work by Guma et al. (2026), although focused on β -lactamase genes and antibiotic resistance in *Klebsiella* species isolated from the Euphrates River, illustrates the importance of integrating biochemical, environmental, and

microbiological perspectives when investigating disease-related biological systems.

Such interdisciplinary connections should not be interpreted as evidence that all microbial resistance mechanisms are directly caused by lipoprotein composition. Rather, they emphasize that lipid metabolism, inflammation, environmental exposures, and microbial biology can intersect within complex biological systems.

9. Analytical Approaches for Lipoprotein Composition

Classical lipoprotein analysis has relied on density-based separation, electrophoresis, and measurement of cholesterol and triglycerides. Ultracentrifugation separates lipoproteins according to hydrated density and historically established the major lipoprotein classes. ([PubMed](#))

Modern techniques provide substantially greater molecular resolution. Nuclear magnetic resonance spectroscopy can estimate particle concentration and size distributions, whereas mass spectrometry can characterize lipoprotein lipidomes and proteomes. Proteomic approaches have demonstrated that HDL is particularly heterogeneous, containing numerous associated proteins and protein isoforms. ([PubMed](#))

Liquid chromatography coupled with mass spectrometry can quantify individual lipid species, including phospholipids, sphingolipids, triglycerides, and cholesteryl esters. Such techniques allow investigators to determine whether two particles with similar cholesterol concentrations nevertheless differ substantially in molecular composition.

Future studies will likely integrate lipidomics, proteomics, metabolomics, and advanced particle-resolved analytical approaches. This systems-level perspective could improve understanding of why apparently similar lipoprotein concentrations can be associated with different biological effects.

10. Clinical and Translational Significance

Understanding lipoprotein composition has direct relevance to cardiovascular prevention, metabolic disease assessment, and therapeutic development. Traditional lipid profiles provide measurements of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides, but these parameters represent only selected components of highly heterogeneous particles.

ApoB measurement provides information related to the number of apoB-containing particles, while apoA-I provides information about a major structural component of HDL. Lp(a) measurement identifies an additional genetically influenced apoB-containing particle with distinctive structural characteristics.

Therapeutic strategies increasingly target specific components of lipoprotein metabolism. Interventions may reduce hepatic VLDL production, enhance LDL receptor-mediated clearance, inhibit specific apolipoproteins, or modify lipoprotein-associated enzymes. A detailed understanding of molecular composition is therefore essential for interpreting how therapeutic interventions change circulating particles.

The growing interest in immunomodulatory biomarkers, nutrition, lifestyle, and therapeutic interventions further demonstrates that lipoprotein metabolism is embedded within a broader network of physiological processes. Research addressing inflammation, renal disease, lifestyle-associated biochemical changes, and therapeutic modulation can complement conventional lipid research (Shallal, 2020; Shallal, 2025a; Shallal, 2025b).

11. Future Perspectives

Future lipoprotein research should move beyond concentration-based measurements toward integrated characterization of particle number, composition, structure, and function. Lipidomics and proteomics provide opportunities to identify molecular signatures associated with disease states and therapeutic responses.

Particular attention should be given to HDL heterogeneity, apoB-containing particle subclasses, Lp(a), and triglyceride-rich remnant particles. Structural biology and molecular imaging may further clarify how specific apolipoprotein configurations influence lipid exchange, receptor recognition, and cellular interactions.

Nanotechnology may provide additional opportunities for targeted lipid-based delivery systems and diagnostic platforms. However, the biological compatibility, stability, toxicity, and environmental consequences of engineered nanomaterials require systematic evaluation, particularly because lipid-associated nanoparticles can interact with proteins and cellular membranes (Shallal et al., 2022; Shallal & Owaid, 2022).

Integration of lipid biology with inflammatory, renal, metabolic, and infectious disease research may ultimately produce more comprehensive models of disease mechanisms. Such approaches should distinguish correlation from causation and should use well-characterized molecular measurements to establish clinically meaningful relationships.

12. Conclusion

Lipoproteins are highly organized, dynamic complexes composed of triglycerides, cholesteryl esters, phospholipids, free cholesterol, and specialized apolipoproteins. Their molecular composition determines particle density, structure, metabolism, receptor interactions, and physiological function. Chylomicrons and VLDL principally transport triglycerides, LDL participates extensively in cholesterol delivery, and HDL supports cellular cholesterol efflux and reverse cholesterol transport. Lp(a) represents a structurally distinctive apoB-containing particle. Modern lipidomic and proteomic approaches are revealing substantial heterogeneity within conventional lipoprotein classes. A detailed understanding of lipoprotein composition therefore remains essential for interpreting metabolic disease, cardiovascular biology, inflammation, and emerging therapeutic strategies.

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