**Lipoproteins**

 **Lipoproteins** are complex aggregates ('particles') of lipids and proteins that render the hydrophobic lipids compatible with the aqueous environment of body fluids and enable their transport throughout the body of all vertebrates and insects to tissues where they are required.

 Lipoproteins are synthesised mainly in the intestines and liver. Within the circulation, these aggregates are in a state of constant flux, changing in composition and physical structure as the peripheral tissues take up the various components before the remnants return to the liver. The most abundant lipid constituents are triacylglycerols, free cholesterol, cholesterol esters and phospholipids (phosphatidylcholine and sphingomyelin especially), although fat-soluble vitamins and antioxidants are also transported in this way. Free (unesterified) fatty acids and lysophosphatidylcholine are bound to the protein albumin by hydrophobic forces in plasma and in effect are detoxified.

### 1.   Composition and Structure

**Lipoprotein classes:** Ideally, the lipoprotein aggregates should be described in terms of the different protein components known as **apoproteins** (or 'apolipoproteins'), as these determine the overall structures and metabolism, and the interactions with receptor molecules in liver and peripheral tissues.

lipoprotein groups are classified as :

- Chylomicrons (**CM**)

-Very-low-density lipoproteins (**VLDL**)

-Low-density lipoproteins (**LDL**)

-High-density lipoproteins (**HDL**), which are based on the relative densities of the aggregates on ultracentrifugation and with fortuitously broadly distinct functions. However, these classes can be further refined by improved separation procedures, and intermediate-density lipoproteins (**IDL**) and subdivisions of the HDL (e.g. HDL1, HDL2, HDL3 and so forth) are often defined, and each of these may have distinctive apoprotein compositions and biological properties that for example can be relevant to cardiovascular disease.

 Density is determined largely by the relative concentrations of triacylglycerols (lighter) and proteins and by the diameters of the broadly spherical particles, which vary from about 6000Å in CM to 100Å or less in the smallest HDL. Some compositional details are listed in **Table 1**.

**Characterization of lipoproteins in human plasma**[[3]](https://en.wikipedia.org/wiki/Lipoprotein#cite_note-3)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Chylomicrons** | **VLDL** | **LDL** | **HDL** |
| [Electrophoretic mobility](https://en.wikipedia.org/wiki/Serum_protein_electrophoresis) | Origin | Pre-Beta | Beta | Alpha |
| [Density](https://en.wikipedia.org/wiki/Density) | less than 0.96 | 0.96-1.006 | 1.006-1.063 | 1.063-1.21 |
| [Diameter](https://en.wikipedia.org/wiki/Diameter) (nm) | 100-1000 | 30-90 | 20-25 | 10-20 |
| Apolipoproteins | B48, Al, All | B100 CI, CII | B100 | AI, AII, CI |
| **Composition**(% of total content) |  |  |  |  |
| Protein | 2 | 10 | 20 | 40 |
| Lipid | 98 | 90 | 80 | 60 |
| **Lipid component**(% of total lipid content) |  |  |  |  |
| Triacylglycerols | 88 | 55 | 12 | 12 |
| Cholesterol esters | 4 | 24 | 59 | 40 |
| Phospholipids | 8 | 20 | 28 | 47 |
| Free fatty acids | - | 1 | 1 | 1 |

 The data for the relative compositions of the various lipid components should not be considered as absolute, as they are in a state of constant flux, but in general the lower the density class, the higher the proportion of triacylglycerols and the lower the proportions of phospholipids and the other lipid classes. In fact, the VLDL and LDL exhibit a continuum of decreasing size and density.

**Apoproteins**: Although a wide variety of proteins of various kinds are transported in the form of lipoprotein complexes, the apoproteins are the defining components that are essential for their formation and subsequent metabolism. In general, these consist of a single polypeptide chain often with relatively little tertiary structure, and they are required to solubilize the non-polar lipids in the circulation and to recognize specific receptors, which direct their metabolism and that of the associated lipoproteins. The various types with their main (but not exclusive) lipoprotein associations,

**Lipoprotein structures**: Lipoproteins are spherical (VLDL, LDL, HDL) to discoidal (nascent HDL) in shape with a core of non-polar lipids, triacylglycerols and cholesterol esters, and a surface monolayer, ~20Å thick, consisting of apoproteins, phospholipids and non-esterified cholesterol, which serves to obscure the hydrophobic lipids and present a hydrophilic face to the aqueous phase as illustrated schematically for a triacylglycerol-rich chylomicron below.



The physical properties of apoproteins enable them to bind readily at the interface between water and phospholipids, and specifically they bind to the phospholipids on the surface of the lipoproteins. In effect, this outer shell of amphipathic lipids and proteins solubilizes the hydrophobic lipid core in the aqueous environment. Each apoprotein, other than apo B100, tends to have a helical shape with a hydrophobic domain on one side that binds to the lipid core and a hydrophilic face that orientates to the aqueous phase. As the lipid compositions of the lipoproteins change during circulation throughout the body, the apoproteins are able to adapt to the altering affinities at the surface by changing conformation. For example, some have very little tertiary structure so are flexible, while apo A1 has a mobile or hinge domain. The polar nature of the surface monolayer prevents the lipoprotein particles from aggregating to form larger units. In addition, apoproteins have many different functions, some of which are listed in Table 3 (and are discussed further below). For example, some are ligands for receptors on cell surfaces and specify the tissues to which the lipid components are delivered, while others are cofactors for lipases or regulate lipid metabolism in the plasma in various ways.

**LDL particles**, for example, average 22 nm in diameter with roughly 3000 lipid molecules in total, and they contain a hydrophobic core of approximately 170 triacylglycerol, 1600 cholesterol ester and 200 unesterified cholesterol molecules. The amphipathic surface monolayer has a single copy of apo B100 together with about 700 phospholipid and 400 free cholesterol molecules. Phosphatidylcholine, about 450 molecules, and sphingomyelin, about 185 molecules, are the main phospholipids, together with smaller numbers of lysophosphatidylcholine, phosphatidylethanolamine and other lipid molecules. The structure and physical functions of LDLs depend mainly on the core–lipid composition and the conformation of the apoB-100, which is able to interact with extracellular membranes such as blood vessel intima where the LDL lipids are susceptible to modification, e.g. by acetylation, enzymatic digestion and oxidation.

 **HDL are** highly heterogeneous in terms of their size, lipid and protein contents, and their functional properties, and they can be separated by various means, including ultracentrifugation and gel filtration, into subclasses, designated HDL1, HDL2, HDL3, etc, that reflect the differences in composition. Discoidal nascent HDL particles are believed to consist of a small unilamellar bilayer, containing approximately 160 molecules of phospholipid, which is surrounded by four apoprotein molecules, including at least two apo A1 monomers. Although most HDL particles in human plasma are spherical, the structures are poorly characterized in comparison to discoidal HDL. It is believed that the apoA1 molecule changes conformation from the discoidal state and adopts a helical structure with the C-terminal domain binding to the phospholipids. In addition to apo A1 and other apoproteins (especially apo C and E), HDL carry a number of proteins/enzymes with important functions, including lipases, acyltransferases, transport proteins and some with anti-oxidative or anti-inflammatory properties; some are concerned with metabolic processes that do not involve lipids.

Lipoproteins can be categorized simplistically according to their main metabolic functions. For example, the principal role of the chylomicrons and VLDL is to transport triacylglycerols ‘forward’ as a source of fatty acids from the intestines or liver to the peripheral tissues. In contrast, the HDL remove excess cholesterol from peripheral tissues and deliver it to the liver where some is excreted in bile in the form of [**bile acids**](https://www.lipidhome.co.uk/lipids/simple/bileacids/index.htm) (‘reverse cholesterol transport’). While these functions are considered separately for convenience in the discussion that follows, it should be recognized that the processes are highly complex and inter-related, and they involve transfer of apoproteins, enzymes and lipid constituents among the heterogeneous mix of all the lipoprotein fractions.

**Lipoprotein(a) (Lp(a))** is structurally and metabolically distinct from the other lipoproteins, and it consists of an LDL-like particle containing a specific highly polymorphic glycoprotein named apolipoprotein(a) (apo(a)), which is covalently bound via a disulfide bond to the apo B100 of the LDL-like particle. While its physiological function is uncertain, Lp(a) is of particular interest because clinical evidence strongly supports a causal relationship between high plasma concentrations and the increased risk of cardiovascular diseases, including myocardial infarctions and stroke (see below). Apo(a) should not be confused with apo A.

### 2.  Lipoprotein and Triacylglycerol Metabolism

[**Triacylglycerols**](https://www.lipidhome.co.uk/lipids/simple/tag1/index.htm) are the most energy-dense molecules available to the body as a source of fuel but are highly hydrophobic. For efficient transport from the intestine and the liver to other organs of the body, it is essential that they be packaged in a form compatible with the aqueous environment in plasma, i.e. in lipoproteins. Chylomicrons and VLDL are mainly involved, although some proteins that are shared with HDL are essential for the process to function normally. For example, exchangeable apoproteins protect triacylglycerol-rich particles from non-specific interactions in plasma and ensure that they have the correct configuration to be acted upon by lipases.

**Chylomicron formation:** Dietary fatty acids and monoacylglycerols are absorbed by the enterocytes in the intestines, where they must cross the cytoplasm to the endoplasmic reticulum with the aid of fatty acid binding proteins. These are immediately utilized to form new triacylglycerols, and are thus detoxified (see our web page on **[triacylglycerol biosynthesis](https://www.lipidhome.co.uk/lipids/simple/tag2/index.htm)**), mainly by the monoacylglycerol pathway. The triacylglycerols are incorporated together with dietary cholesterol, much of which is in cholesterol ester form, into spherical chylomicron particles. These have a surface layer of phospholipids to which is attached a single molecule of the truncated form of apo B, apo B48, which is diagnostic for triacylglycerol-rich lipoproteins of intestinal origin. Chylomicrons are the largest lipoproteins present in the circulation, with their size dependent on the fed/fasted state, the rate of absorption of fat and the type and amount of fat absorbed.

The synthesis of apo B100 and its truncated form, and the accumulation of lipids to form chylomicrons or VLDL in intestinal cells and liver, respectively, are complex processes that are still only partly understood. Simplistically, secretory proteins such as apo B are synthesised on ribosomes on the surface of the endoplasmic reticulum and translocated through the membrane to the lumen of the endoplasmic reticulum. VLDL are then assembled by accretion of lipids, for example with the aid of a microsomal triacylglycerol transfer protein (MTTP), an essential protein that transfers phospholipids and triacylglycerols to nascent apo B for the assembly of lipoproteins. This occurs in three stages - pre-VLDL (pre-chylomicrons - nascent lipoproteins), VLDL2, a triacylglycerol-poor form of VLDL that is assembled in the Golgi and is transported to the basolateral membrane, where the final triacylglycerol-rich VLDL1 or chylomicrons with the assistance of apo B48 and apo A4, are secreted by a process of reverse exocytosis into the intestinal lamina propria. Apo A1 is generated separately in the endoplasmic reticulum of enterocytes, and it is transported to the Golgi and added to the chylomicrons just before the mature particle is secreted into the lymph.

 The chylomicrons are transported via the intestinal lymphatic system and enter the blood stream at the left subclavian vein. During circulation throughout the body, triacylglycerols are removed by the peripheral tissues by endothelial-bound lipoprotein lipase with entry of fatty acids into muscle for energy production and adipocytes for storage. However, the apo B48 remains with the residual particle. The chylomicrons also contain some apo A1, which is synthesised in the intestines and liver, but this is transferred spontaneously to the HDL as soon as the chylomicrons reach the circulation, while transfer of apo E and apo C(1-3) in the reverse direction from the HDL to the surface of the chylomicrons, displacing apo A4, occurs at the same time. The depleted or ‘remnant’ chylomicrons, containing the dietary cholesterol, apo E and apo B48 mainly, eventually reach the liver where they are cleared from the circulation by a receptor-mediated process that requires the presence of apo E.

**Liver catabolism:** A high proportion of the VLDL remnants (or ‘IDL’) with apo B100 and apo E as the remaining proteins are sequestered in the liver perisinusoidal space (space of Disse) where they may undergo additional processing by lipases with further loss of triacylglycerols as they are converted to LDL. Both apoproteins are required for recognition of the VLDL remnants and LDL by the **LDL receptors** in the liver mainly, although many other tissues also contain analogous receptors. The main LDL receptor in liver is a polypeptide of 839 amino acids to which complex carbohydrate moieties are linked that spans the plasma membrane and has an extracellular domain, which is responsible for binding to apo B100 and apo E. Within the cell, the receptors cluster into regions of the plasma membrane known as ‘coated pits’, where the cytoplasmic leaflet is coated with the protein clathrin. After binding of the LDL and some of the VLDL remnants to the receptor, the LDL-receptor complexes are internalized by endocytosis of the coated pit and then dissociated by means of an ATP-dependent proton pump, which lowers the pH in the endosomes, enabling the receptors to be recycled to the plasma membrane. The LDL-containing endosomes fuse with lysosomes, and lipolytic enzymes, especially a lysosomal acid lipase (LAL), release free fatty acids and cholesterol from triacylglycerols and cholesterol esters, while acid hydrolases degrade the apoproteins. However, much of the apo E is believed to escape this process and is returned to the circulation and the HDL. An additional receptor, the LDL-receptor-related-protein, assists in the removal of chylomicron remnants.

After their release from lysosomes, the fatty acids and other lipid components serve as precursors for the synthesis of new lipid species and may also function in the regulation of many metabolic processes. For example, **[unesterified fatty acids](https://www.lipidhome.co.uk/lipids/simple/ffa/index.htm%22%20%5Cl%20%22function)** are able to interact with the peroxisome proliferator-activated receptor PPARα and so target gene expression.

**Secretion from the liver:** The triacylglycerols of the remnant chylomicrons, together with cholesterol and cholesterol esters, are secreted by the liver into the circulation in the form of VLDL, which contain one molecule of the full-length form of apo B, apo B100. In addition, an appreciable amount of triacylglycerol in VLDL is synthesised in the liver from free fatty acids reaching it from adipose tissue via the plasma in the post-absorptive and fasted states, and stored in triacylglycerol form in lipid droplets for mobilization upon demand. In effect, liver lipid droplets and VLDL serve to buffer the plasma free fatty acids released following lipolysis in adipose tissue in excess of the requirements of muscle and liver.

Within the liver, the nascent VLDLs are assembled from apo B100 and lipids, which consist largely of triacylglycerol droplets with some phospholipid, in the endoplasmic reticulum with the aid of chaperone, namely, microsomal triglyceride transfer protein (MTTP), before they are transported to the Golgi in a complex multistep process, involving a specific VLDL transport vesicle. In the lumen of the *cis*-Golgi, VLDLs undergo a number of essential modifications before they are transported to the plasma membrane and secreted into the circulatory system. The surface layer of the newly synthesised VLDL is enriched in phosphatidylethanolamine, which rapidly exchanges with the phosphatidylcholine of other lipoproteins. The newly synthesised VLDL contain a little apo C3, apo E and apo A5, which may have a role in the assembly process, but they rapidly take up apo C2 (10-20 molecules) and apo E from HDL after a few minutes in the circulation while the small amount of apo A1 of intestinal origin is transferred to HDL.

### 3.  VLDL, LDL and Cholesterol Metabolism

[**Cholesterol**](https://www.lipidhome.co.uk/lipids/simple/cholest/index.htm) has a vital role in life and is essential for the normal functioning of cells both as a cell membrane constituent and as a precursor of steroid hormones and other key metabolites. In the lumen of the small intestine, free cholesterol from the diet and from biliary secretion is solubilized in mixed micelles containing bile acids and phospholipids before it is absorbed by the enterocytes by a mechanism for which the apical protein Niemann-Pick C1-like 1 (NPC1L1) is crucial. Within the enterocyte, the metabolic fate of the absorbed cholesterol involves an integrated network of many different proteins. Most of it is transported to the endoplasmic reticulum where it is converted to cholesterol esters by the enzyme acyl-CoA:cholesterol acyltransferase 2 (ACAT2) and is selectively packaged into chylomicron particles, a process that requires a specific microsomal transfer protein and apoprotein B48, for transport out of the enterocyte into the lymphatic system and subsequently to the liver for uptake at the basolateral side of the hepatocytes as described above for triacylglycerols. Regulation of intestinal cholesterol uptake and secretion is mediated by the nuclear receptor Liver X Receptor (LXR).

LDL are the main carriers of cholesterol from the liver to the adrenals and adipose tissue, where there are receptors requiring apo B100, and they are able to take in the LDL by a similar process to that occurring in liver. Within these tissues, the cholesterol esters are hydrolysed to yield free cholesterol, which is incorporated into the plasma membranes as required. Any excess cholesterol is re-esterified by an acyl-CoA:cholesterol acyltransferase for intracellular storage. Other peripheral tissues have much lower requirements for cholesterol, but that delivered by the LDL may be helpful in suppressing synthesis of cholesterol *de novo* within cells. It may also inhibit the expression of lipoprotein receptors.

The cholesterol at the particle surface is essential to enable VLDL to carry triacylglycerols efficiently in the aqueous environment of plasma. However, once this has been accomplished, the cholesterol-rich, triacylglycerol-depleted remnant LDL by-products are potentially toxic and must be removed from the circulation. Some have argued that a significant part of the complexity of lipoprotein metabolism is concerned with the disposal of this LDL cholesterol before it can cause damage to the cardiovascular system. The liver is able to scavenge chylomicron remnants much more rapidly than LDL particles, and it seems likely that this specificity has evolved because the former are especially atherogenic. Therefore, further mechanisms such as that involving the HDL discussed next are required to return the excess LDL cholesterol to liver.

In macrophages, scavenger receptors mediate the uptake of LDL that has been damaged by oxidation or other means such that its affinity to the LDL receptor is reduced. This has the unfortunate effect that cholesterol can accumulate in macrophages in an unregulated manner, a possible first step in the development of atherosclerosis.

### 4.  High-Density Lipoprotein and Cholesterol Metabolism

HDL are the most complicated and diverse of the lipoproteins, as they contain many different protein constituents whose main purpose is to enable secretion of cholesterol from cells, esterification of cholesterol in plasma, transfer of cholesterol to other lipoproteins, and the return of cholesterol from peripheral tissues to the liver – a process that has been termed **‘reverse cholesterol transport’**, as this may eventually lead to elimination of the excess of this lipid. In addition, HDL have an important function in triacylglycerol transport by facilitating the activation of lipoprotein lipase, in the transfer of triacylglycerols between lipoprotein classes, and in the removal of chylomicron remnants and VLDL enriched in triacylglycerols. As well as the apoproteins, other key components of HDL include anti-oxidative enzymes and phospholipid transfer proteins (PLTP). The latter mediates a net transfer of phospholipids from apoB-containing triacylglycerol-rich lipoproteins into HDL, and also exchanges phospholipids between lipoproteins; it is believed to be a factor in the enlargement of HDL. As many of the lipid and protein constituents of HDL are exchangeable with other lipoproteins, many different types (subclasses) of HDL particle are generated with differing metabolic roles.

The nascent HDL are synthesised in the extracellular space of the liver and small intestine as protein-rich disc-shaped particles, but their compositions change and evolve as the HDL circulate in the plasma. Apo A1 synthesised in the liver together with that released spontaneously from chylomicrons is a key molecule that binds to phospholipids with a little cholesterol of cellular origin. It has been described as the scaffold for HDL assembly and is secreted as pro-apo A1, which is rapidly cleaved by a circulating metalloproteinase to generate the mature polypeptide. The apoproteins apo C1, apo C2, apo E and especially apo A2 also accumulate in HDL. It is believed that the origin of the cholesterol lies in **[caveolae](https://www.lipidhome.co.uk/lipids/sphingo/sph-rafts/index.htm%22%20%5Cl%20%22cav)** (a type of membrane 'raft') in the plasma membrane, and the process is receptor-mediated via a specific transporter molecule ‘ABCA1’, one of a superfamily of 48 ABC membrane transporters, that facilitates the transfer of phospholipids and cholesterol especially to lipid-poor apoproteins, especially apo A1, in the nascent HDL (preβ-1 HDL) particles.