LOW DENSITY LIPOPROTEIN (LDL) CHOLESTROL: THE BAD CHOLESTROL

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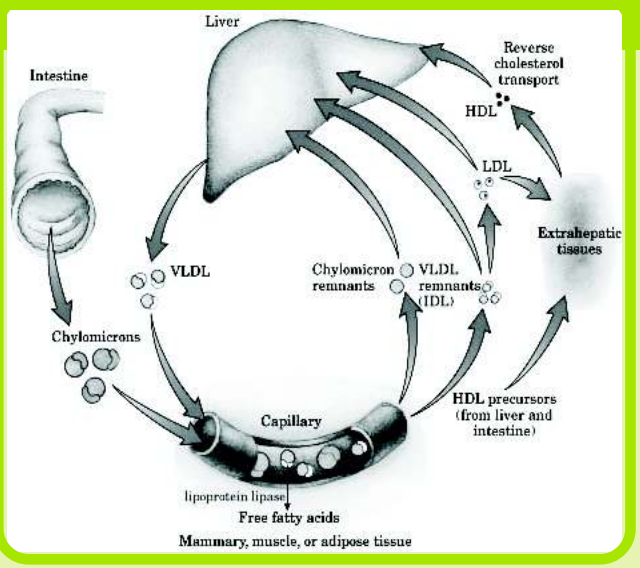
This article introduces cholesterol, its transport as a component of liproprotein and types of lipoproteins. Mechanism of plaque formation in arteries is also explained. High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL) cholesterol, their relative importance and foods that fight bad LDL cholesterol are discussed.



Introduction

Cholesterol is a waxy steroid. Much of the cholesterol synthesis in vertebrates takes place in the liver. A small fraction of the cholesterol made there is incorporated into the membranes of hepatocytes (liver cells), but most of it is exported. The name cholesterol originates from the Greek word *chole* - (bile) and *stereos* (solid), and the chemical suffix *-ol* for an alcohol. François Poulletier de la Salle first identified cholesterol in solid form in gallstones, in 1769. However, it was only in 1815 that chemist Eugène Chevreul named the compound, 'cholesterine'.

It is an essential structural component of mammalian cell membranes. It is required to establish proper membrane permeability and fluidity. In addition, cholesterol is an important component for the manufacture of bile acids, steroid hormones and Vitamin D. Although cholesterol is important and necessary for mammals, high levels of cholesterol in the blood can damage arteries and are potentially linked to diseases such as those associated with the cardiovascular system (heart disease). Cholesterol is recycled. It is excreted by the liver via the bile into the digestive tract. Typically about 50 per cent of the excreted cholesterol is reabsorbed by the small bowel back into the bloodstream.

Transport via Lipoprotein Complexes

Cholesterol and cholesteryl esters, like triacylglycerols and phospholipids, are essentially insoluble in water, yet must be removed from the tissue of origin to the tissues in which they will be

stored or consumed. They are carried in the blood plasma as plasma lipoproteins, macromolecular complexes of specific carrier proteins, apoliproteins, with various combinations of phospholipids, cholesterol, cholesteryl esters and triacylglycerols. Lipoproteins are complex discoidal particles which have an exterior composed of amphiphilic proteins and lipids whose outward-facing surfaces are water-soluble and inward-facing surfaces are lipid-soluble; triglycerides and cholesterol esters are carried internally. Phospholipids and cholesterol, being amphipathic, are transported in the surface monolayer of the lipoprotein particle. The apoliproteins serve as ligands for specific receptors on cell membranes. In this way, the lipoprotein particles are molecular addresses that determine the start- and end-points for cholesterol transport.

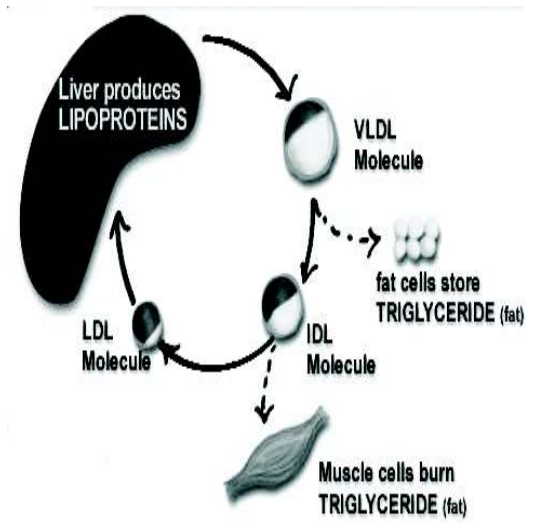


Fig. 1: Lifecycle of cholesterol carrying lipoproteins

Types of Lipoproteins

Different combinations of lipids and proteins produce lipoprotein particles of different densities. The densities are related to the relative amounts of lipid and protein in the complexes. Because, most proteins have densities of about 1.3 to 1.4 g/mL, and lipid aggregates usually possess densities of about 0.8 g/mL, the more protein and less lipid in a complex, the denser the lipoprotein. Thus, in order of increasing density, there are chylomicrons, Very-Low Density Lipoproteins (VLDL), intermediate density Lipoprotein (IDL), Low Density Lipoprotein (LDL) and High Density Lipoprotein (HDL). Each class of lipoprotein has a specific function, determined by its point of synthesis, lipid composition and apoliprotein content.

- **Chylomicrons** have the lowest protein-to-lipid ratio and thus are the lowest density lipoproteins. They are synthesised in the endoplasmic reticulum of epithelial cells that line the small intestine, then move through the lymphatic system and enter the blood stream. It carries dietary fatty acids to tissues where they will be consumed or stored as fuel. The remnants of chylomicrons (depleted most of their triacylglycerols but still containing cholesterol, apoliproteins) move through the blood stream to the liver. In the liver, remnants release their cholesterol and are degraded in lysosome.
- **VLDL:** When the diet contains more fatty acids than the needed immediately as fuel, they are converted to triacylglycerols in the liver and packaged with specific apoliproteins into VLDL. Excess

carbohydrates in the diet can also be converted to triacylglycerols in the liver and exported as VLDLs.

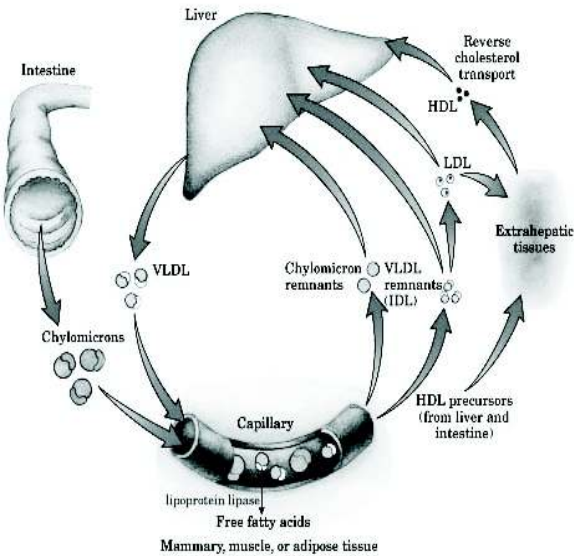


Fig. 2: Different classes of lipoproteins and fates

In addition to triacylglycerols, VLDLs contain some cholesterol and cholesteryl esters, as well as apoliproteins. These lipoproteins are transported in the blood from the liver to muscle and adipose tissue, where activation of lipoprotein lipase enzyme causes the release of free fatty acids from the VLDL triacylglycerols. Adipocytes take up these fatty acids, reconvert them into triacylglycerols, and store the products in intracellular lipid droplets; myocytes in contrast, primarily oxidise the fatty acids to supply energy.

- **IDL:** The loss of triacylglycerol converts some VLDL to VLDL remnants, also called as IDL. The IDL molecules have two possible fates: half are taken up by the liver for metabolism into other biomolecules and the rest is converted into LDL.

Table 1: Desirable, High and Very High Levels of Different Lipoproteins

Blood lipids measured	Desirable for those with heart disease	Desirable for general population	Borderline high	High	Very high
Total Cholesterol (mg/dl)		Less than 200	200-239	240 or more	
LDL Cholesterol (mg/dl)	Less than 100	Less than 130	130-159	160 or more	
HDL Cholesterol (mg/dl)		35 or more			
Triglycerides (mg/dl)		Less than 200	200-400	400-1000	1000 or more

- **LDL** particles are formed as IDL lipoproteins, further lose triacylglycerols through the action of lipoprotein lipase and they become smaller and denser (i.e., fewer fat molecules with same protein transport shell), containing a higher proportion of cholesterol esters.
- **HDL** (good cholesterol) originates in the liver and small intestine as small protein rich particle that contains relatively little cholesterol and no cholesteryl esters. These lipoprotein particles are thought to transport excess cholesterol back to the liver for excretion or to other tissues that use cholesterol to synthesise hormones in a process known as Reverse Cholesterol Transport (RCT). The higher HDL, the less bad cholesterol you'll have in one's blood.

Low Density Lipoprotein Cholestrol

LDL molecules are the major carriers of cholesterol in the blood. Each native LDL particle has a highly-hydrophobic core consisting of polyunsaturated fatty acid known as *linoleate* and about 1500 esterified cholesterol molecules. This core is surrounded by a shell of phospholipids and unesterified cholesterol, as well as a single copy of apoliprotein, i.e., ApoB-100, a large protein with 4,636 amino acid residues. LDL particles are approximately 22 nm in diameter and have a mass of about 3 million Daltons on the average since fatty acids of variable mass are associated with them. Determining structure of LDL has been a tough task because of its heterogeneous structure. First structure of LDL at human body temperature in native condition has been recently found using cryo-electron microscopy and it has resolution of 16 Angstrom.

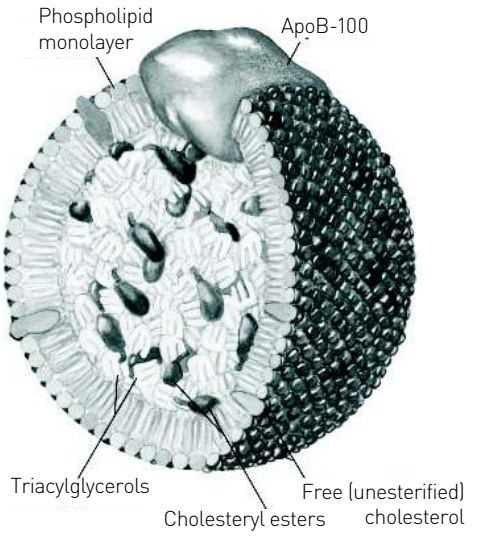


Fig. 3: Structure of LDL Cholestrol

Transport of LDL Particles into the Cell

When a cell requires cholesterol, it synthesises the necessary LDL receptors, and inserts them into the plasma membrane. The LDL receptors then diffuse freely until they associate with clathrin-coated pits. The shell of the LDL molecule contains just one molecule of apolipoprotein B-100, which is recognised by the LDL receptor in peripheral tissues. LDL particles in the blood stream bind to these extracellular LDL receptors. The clathrin-coated pits then form vesicles that are endocytosed into the cell. The vesicle then fuses with a lysosome, which has an enzyme, called lysosomal acid lipase that hydrolyses the cholesterol esters. Now, within

the cell, the cholesterol can be used for membrane biosynthesis or esterified and stored within the cell, so as not to interfere with cell membranes. The LDL receptors are recycled back to the plasma membrane.

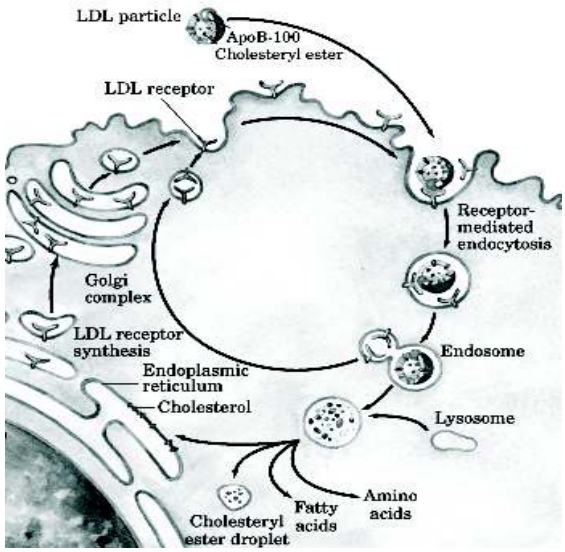


Fig. 4: Endocytosis and degradation of LDL

When the cell has abundant cholesterol, LDL receptor synthesis is blocked so that new cholesterol in the form of LDL molecules cannot be taken up. On the converse, more LDL receptors are made when the cell is deficient in cholesterol. When this system is deregulated, many LDL molecules appear in the blood without receptors on the peripheral tissues. These LDL molecules are oxidised and taken up by macrophages, which become engorged and form foam cells. These cells often become trapped in the walls of blood vessels and contribute to atherosclerotic plaque formation.

Mechanism of Plaque Formation and Atherosclerosis

LDL cholesterol is an important part of the process of narrowing arteries, called atherosclerosis.

Some LDL cholesterol circulating through the bloodstream tends to deposit in the walls of arteries. This process starts as early as childhood or adolescence.

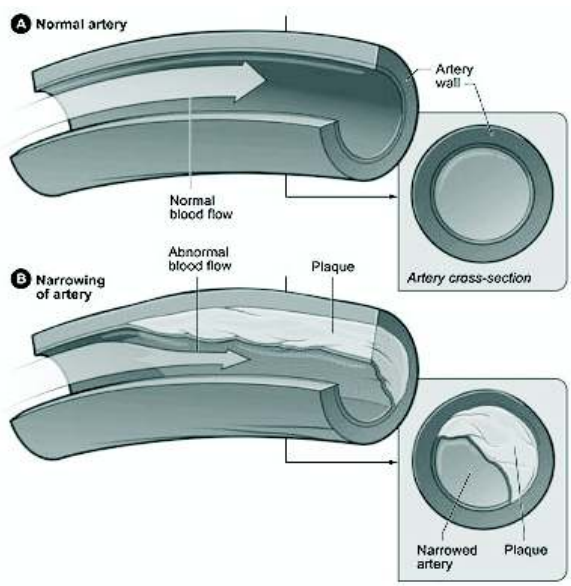


Fig.5: Plaque formation in artery

- White blood cells (macrophages) ingest and try to digest the LDL, possibly in an attempt to protect the blood vessels. In the process, the macrophages oxidise the LDL to a toxic form giving the macrophages foam like appearance.

- More macrophages and other cells migrate to the area, creating steady low-grade inflammation in the artery wall to form a visible fatty streak.
- Over time, more LDL cholesterol and cells collect in the area. The ongoing process creates a bump in the artery wall called a plaque. The plaque is made of cholesterol, cells and debris.
- Over time vulnerable plaques rupture, activate blood clotting and produce arterial stenosis, which if severe enough results in heart attack, stroke, and peripheral vascular disease symptoms and major debilitating events. The body's immune system sends in specialised white blood cells (macrophages and T-lymphocytes) to absorb the oxidised-LDL forming foam cells.

These white blood cells, though, are not able to process the oxidised-LDL, and ultimately grow then rupture, depositing a greater amount of oxidised cholesterol into the artery wall. This triggers more white blood cells to rush to the site, continuing the cycle. So the immune system becomes part of the causes of atherosclerosis. Eventually, the artery becomes inflamed. The cholesterol plaque causes the muscle cells to enlarge and form a hard cover over the affected area, where calcium and other substances accumulate that make the plaque hard and brittle. This hard cover is what causes a narrowing of the artery, reduces the blood flow and increases blood pressure. In addition, the brittle plaque can break off, travel through the blood stream and form a clot anywhere in the body. Also, blood clots can form on the plaque and cause obstruction of the artery or the plaque may weaken the artery wall so that it balloons out, forming an aneursm, which may burst and cause a haemorrhage or bleeding.

Atherosclerosis versus Arteriosclerosis

Healthy blood vessel should be flexible and strong, capable of containing the pulsating pressure of

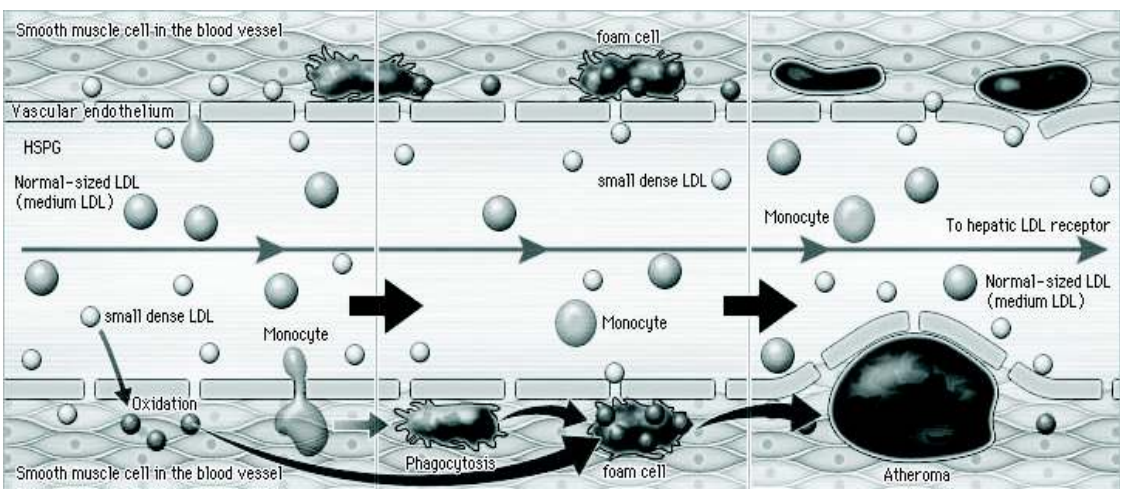


Fig.6: Role of white blood cells in atherosclerosis

rushing blood, heartbeat after heartbeat, for a lifetime. But they are also delicate and vulnerable and can easily get damaged.

Atherosclerosis is the most common form of arteriosclerosis, which refers to any hardening of the arteries with loss of elasticity. Atherosclerosis is a hardening of an artery specifically due to an atheromatous plaque which narrows the lumen of the arteries.

Atherosclerosis and Cholestrol

Although cholesterol in itself is not one of the main causes of atherosclerosis, the higher your LDL cholesterol level, the greater is the risk of developing life-threatening plaque and blocked arteries. This is why your LDL cholesterol should be low. According to the National Institute of Health (NIH), the optimal level of LDL cholesterol should be below 100 mg/dL. LDL level 160 mg/dL is considered as high but more than 130 mg/dL needs immediate attention.

HDL cholesterol, on the other hand, is like nature's plaque vacuum cleaner, because it picks up the vessel-clogging cholesterol and carries it away to the liver to be disposed of in the form of bile. The higher your HDL levels, the cleaner your blood vessels will be. So we need HDL to be high. According to the NIH, people with HDL of 60 mg/dL or higher have a lower risk of heart disease, whereas HDL below 40 mg/dL is considered too low. Because HDL is so important to the health of

Table 2: Factors which Raise or Lower the Levels of HDL and LDL

HDL		LDL	
Raise	Lower	Raise	Lower
Alcohol			
Niacin			Niacin
Fibrates	Certain drugs		Fibrates
Statins			Statins
		Dietary fats	Fat reduction
Smoking cessation	Smoking		
Estrogen	Progesterone		Estrogen
	Diabetes	Diabetes	
Weight loss	Obesity	Obesity	Weight loss
Metabolic syndrome	Thyroid disease		
		Renal disease	
Exercise	No exercise	Liver disease	
	Hightriglycerides	Genetics	Resins
			Bile acid sequestrants

blood vessels, some physicians prefer to talk about the cholesterol ratio — your total cholesterol divided by your HDL cholesterol. For example, if your total cholesterol number is 250 and your HDL is 50, your ratio is 250/50 or 5. A ratio of 3.5 is considered optimal and people are urged to aim for a ratio of 5 or less.

HDL versus LDL

Foods that Fight Bad LDL Cholesterol Levels

Several scientific clinical studies have proven the value and effectiveness of these foods in lowering bad LDL levels and/or increase good HDL levels.

- Almonds: Studies have found that eating just a quarter cup of almonds can lower LDL by 4.4 per cent.
- Oatmeal: Gives great results due to the high level of soluble fiber in oatmeal. The soluble fiber binds to the bile acids that are the precursor to the development of cholesterol and help flush it out.

Fig. 7: Foods that lower LDL level

- Fish: Omega-3 fatty acids are widely considered to be the best of the 'good' fats, and the best place to find them is in fish — especially fatty fishes like salmon, halibut and tuna. These fatty acids can also be obtained from walnuts and flaxseed (two tablespoons of flaxseed provides 3.5 grams) and in fish oil supplements.
- Red Wine: A glass of red wine, which contains *flavanols* (also found in red grape juice and dark cocoa), has been shown to have anti-inflammatory properties that may help lower cholesterol and stave off heart disease. But in this case, more is definitely not better.
- Soy Products: Like soybeans, soy nuts, and edamame beans, natto *(the green vegetable form of soybeans)*, plus any products made from soy (like tofu, soymilk, etc.) can help to reduce the production of new cholesterol. A little can go a long way—one may aim for about 25 grams of soy protein a day (the amount in a cup of edamame).
- Garlic: The active compound in garlic, called *allicin* seems to be responsible for lowering cholesterol. It also acts as a powerful antioxidant. It may affect the way LDL cholesterol is used in the body and reduce triglycerides. There is some evidence that garlic also lower homocysteine and reduce blood pressure.

Conclusion

One can safely take control of cholesterol levels by eating more of those foods that have scientific evidence for lowering bad LDL cholesterol levels and increasing good HDL cholesterol numbers. Lowering cholesterol can lower the risks for heart disease and other chronic illnesses.

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