Lipid metabolism

Lipids constitute a heterogeneous group of compounds of biochemical importance. Lipids may be defined as compounds that are relatively insoluble in water, but freely soluble in nonpolar organic solvents like benzene, chloroform, ether, hot alcohol, acetone, etc.,

Functions of Lipids:

1. Storage form of energy (triglycerides)
2. Structural components of biomembranes (phospholipids and cholesterol)
3. Metabolic regulators (steroid hormones and prostaglandins)
4. Act as surfactants, detergents and emulsifying agents (amphipathic lipids)
5. Act as electric insulators in neurons
6. Provide insulation against changes in external temperature (subcutaneous fat)
7. Give shape and contour to the body
8. Protect internal organs by providing a cushioning effect (pads of fat)
9. Help in the absorption of fat-soluble vitamins (A, D, E, and K)
10. Improve the taste and palatability of food.

Clinical Applications:

1. Excessive fat deposits cause obesity.
2. Abnormality in cholesterol and lipoprotein metabolism leads to atherosclerosis and cardiovascular diseases.
3. In diabetes mellitus, the metabolisms of fatty acids and lipoproteins are deranged, leading to ketosis.

CLASSIFICATION OF LIPIDS

Based on the chemical nature, lipids are classified:

I. Simple Lipids
They are esters of fatty acids with glycerol or other higher alcohols. They are subclassified as:

a) Triacylglycerol or Triglycerides or neutral fat.
b) Wax

II. Compound Lipids

They are fatty acids esterified with alcohol, but in addition, they contain other groups. Depending on these extra groups, they are subclassified as:

A) Phospholipids, Containing Phosphoric Acid

B) Non-phosphorylated Lipids such as Glycosphingolipids (carbohydrate)

III. Derived Lipids

They are compounds that are derived from lipids or precursors of lipids, e.g. fatty acids, steroids, prostaglandins, leukotrienes, terpenes, dolichols, etc. For details of cholesterol and steroids.

IV. Lipids Complexed to Other Compounds Proteolipids and lipoproteins.

Fatty acids:

Fatty acids are straight-chain hydrocarbons with a terminal carboxyl group. They are frequently identified by the number of carbon atoms and number of double bonds, as di-unsaturated linolic acid. The location of the double bond in the n- or omega (ω) numbering system designates the number of carbon atoms from the terminal methyl, thus linolic acid is designated as 18:2n-6 and called an ω-6 fatty acid.

Fatty acids exist mostly as an ester of glycerol in both triglycerides and some phospholipids and as esters of high–molecular–weight alcohols. The fatty acids of triglycerides are mostly C16 or C18, and in phospholipids, they are C18 to C22.

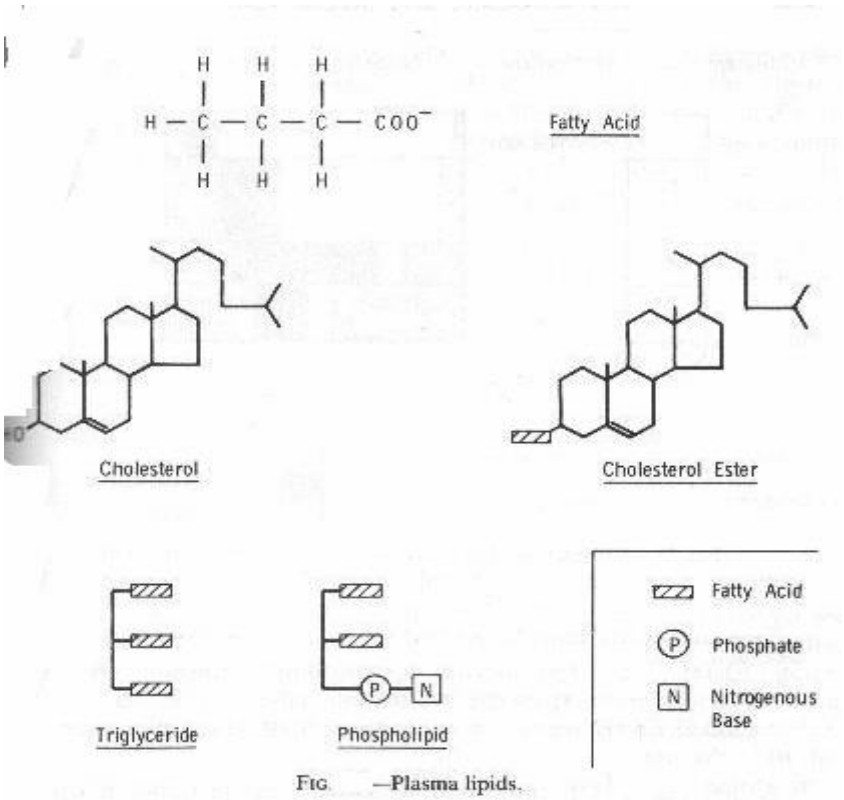
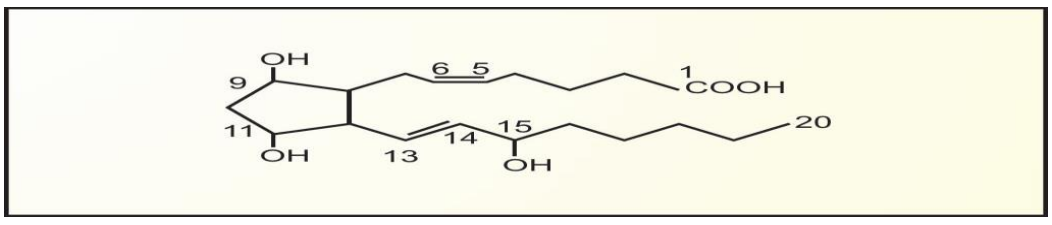


FIG. —Plasma lipids.

Prostaglandins

Prostaglandins (PGs) were originally isolated from prostate tissue and hence the name. But they are present in almost all tissues. They are the most potent biologically active substances; as low as one nanogram/ml of PG will cause smooth muscle contraction. The diverse physiological roles of prostaglandins confer on them the status of local hormones. Chemical Structure: All prostaglandins are considered to be derived from the 20 C cyclic saturated fatty acid, The five-carbon ring is saturated. All naturally occurring PGs have an alpha-oriented OH group at C15. Classification of Prostaglandins: According to the attachment of different substituent groups to the ring, PGs are named with capital letters such as A, B, E, and F. In the same series, depending on the number of double bonds on the side chains they are denoted by a subscript after the capital letter, *e.g.* PGE 1, PGE 2, PGE 3, etc. Series 2 have 2 double bonds at 13–14 (trans) and 5–6 (cis). The structure of PGF 2 is shown in the Figure below:



Triglycerides

Most of the fatty acids in the body are components of triglyceride and are stored in the depots (adipose tissue) as fat. Adipose cells convert fatty acids into triglycerides by esterification with glycerol-3-phosphate, compounds that arise from glucose metabolism. cells must contain glucose for triglyceride formation. Glucose is absent during periods of fasting, starvation, or uncontrolled diabetes mellitus, and in this condition, hydrolysis of triglycerides, and withdrawal of their fatty acids from the depots predominate. Excess carbohydrates ingested during a meal may be stored temporarily as triglycerides after the conversion of glucose to fatty acids. The hormone insulin promotes the synthesis of triglycerides by adipose cells, whereas its deficiency accelerated triglyceride hydrolysis. The first step in the catabolism of triglycerides begins with their hydrolysis. The fatty acids appear in the plasma as non-esterified (free) fatty acids bound to albumin as a carrier.

Phosphosholipids

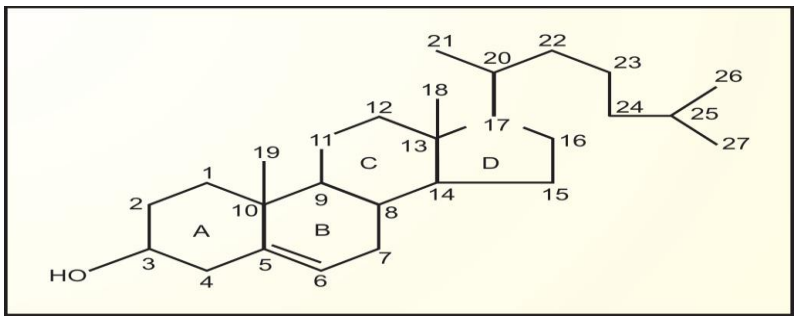
The principal phospholipids are composed of triglyceride esterified with phosphoric acid, which in turn, is bound as an ester to a nitrogen-containing base (choline, ethanolamine) or to serine, and inositol are sometimes collectively referred to as cephalins. Phospholipids are essential compounds of cell membranes because of their ability to align themselves between the water and lipids phase. Phosphoethanolamine, a constituent of blood platelets, is a necessary participant in the clotting process. Phospholipids in lipoproteins also supply the fatty acids necessary for the esterification of cholesterol. The phospholipids play a role in mitochondrial metabolism, blood coagulation, and lipid transport as part of lipoproteins, and are important structural components of membranes.

Sphingolipids

The sphingolipids are all compounds containing the long-chain, dihydroxyamino alcohol sphingosine. All the sphingolipids bind a fatty acid in amide linkage to the amino group and are also known as ceramides because they are cerebral lipids containing an amide group.

Cholesterol

Cholesterol, the principal body sterol, is complex alcohol formed of four fused rings and a side chain, pure cholesterol is a solid at body temperature. The major sites of synthesis of cholesterol are the liver, adrenal cortex, testis, ovaries, and intestine.



Structure of cholesterol

Approximately 70 % of plasma cholesterol exists in an acyl ester form. The esterification takes place almost exclusively in the high-density lipoprotein (HDL) complex. Most of the cholesterol in the body is synthesized from acetyl CoA, but we also ingest some when we eat meat, dairy products, or eggplants do not contain cholesterol, although they do have closely related sterols. Cholesterol is catabolized in hepatic cells by oxidation to bile acids (cholic and chenodeoxycholic acids that conjugate with glycine or taurine before secretion into bile. These bile acids and conjugates are emulsifying agents that are essential for the digestion and absorption of fats. Some of the cholesterol is also secreted as such into the bile. Both the bile acids and biliary cholesterol are reabsorbed to some extent in the intestine by enterohepatic circulation. *Thus*, the liver

is the site of cholresterol disposal or degradation, as well as its major sit of synthesis.

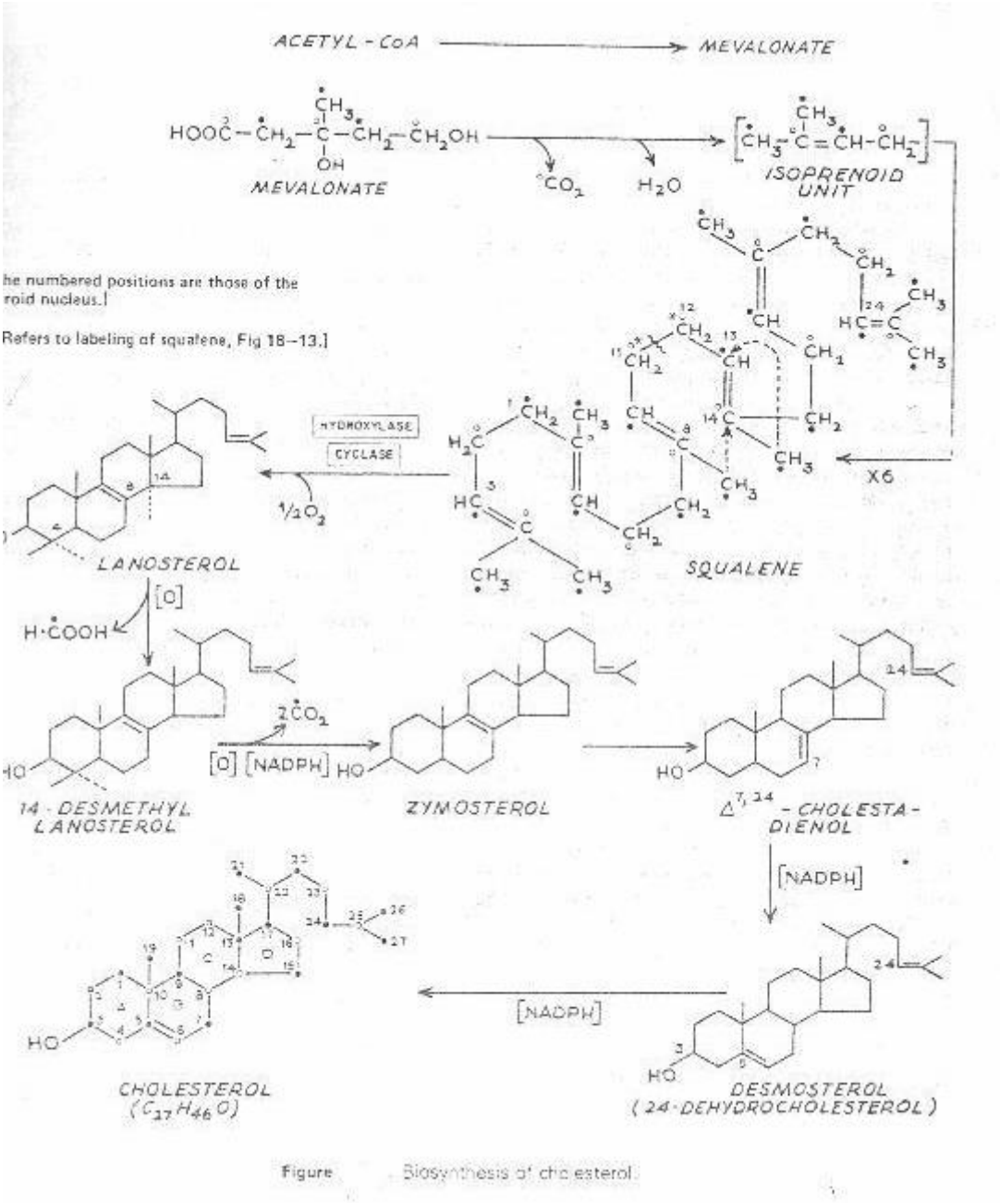


Figure Biosynthesis of cholesterol

A negative feedback mechanism controls to a limited extent the rate of synthesis of cholesterol. When the diet is high in cholesterol, the increased amount of cholesterol brought to the liver decrease the receptors – mediates hepatic intake of cholesterol and inhibits the rate-

limiting enzyme (β-hydroxy- β-methylglutaryl CoA reductase) essential for the synthesis of mevalonic acid, step in the synthesis of cholesterol. *Furthermore*, the reabsorption of bile acids and cholesterol in the enterohepatic circulation is decreased, so more cholesterol is excreted in the form of bile acids and free cholesterol.

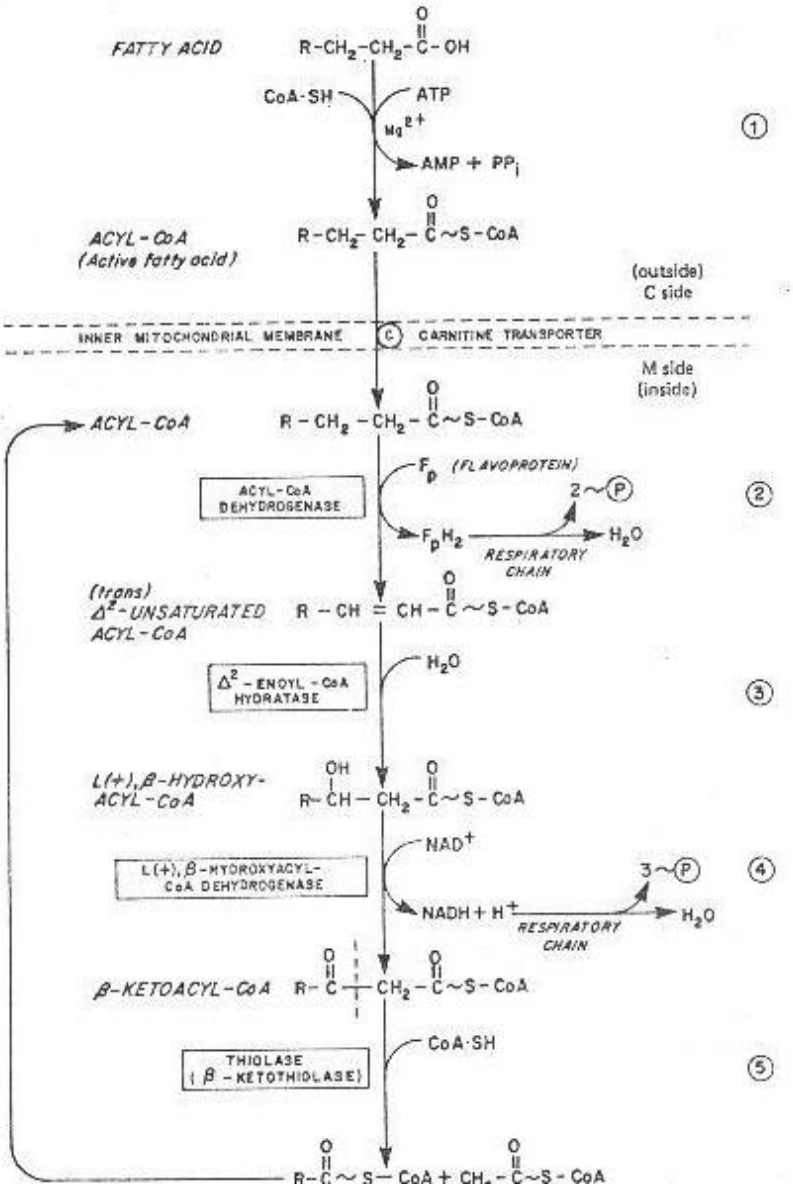
Serum cholesterol concentration can rise to high levels in some pathological states. An elevated cholesterol concentration has been implicated as one of several risk factors leading to coronary artery disease (atherosclerosis or myocardial infraction); *thus* the measurement of serum cholesterol is a fairly common lab. procedure.

Significance and Functions of Cholesterol:

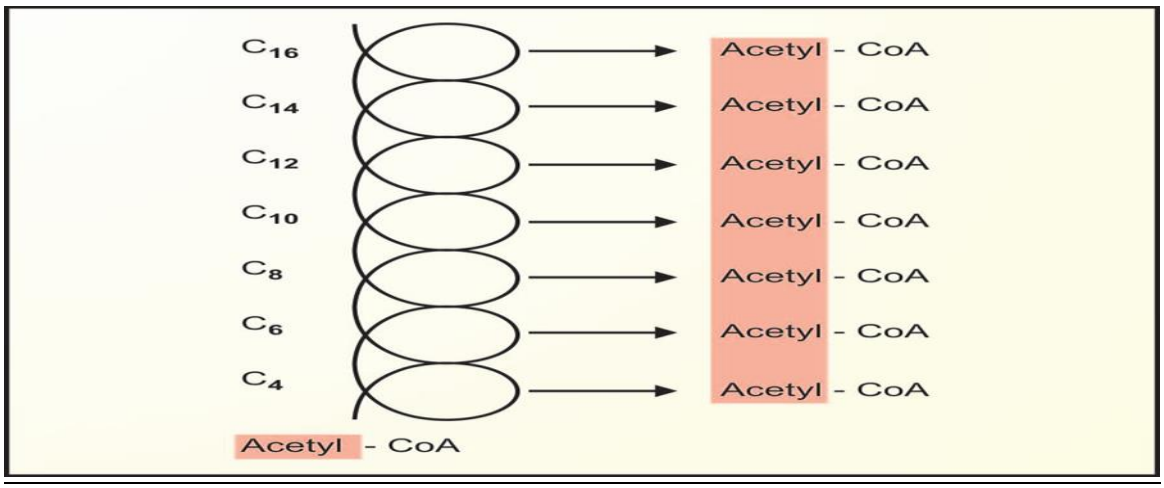
1. Heart diseases: The level of cholesterol in blood is related to the development of atherosclerosis. Abnormality of cholesterol metabolism may lead to cardiovascular accidents and heart attacks.
2. Cell membranes: Cholesterol is a component of membranes and has a modulating effect on the fluid state of the membrane.
3. Nerve conduction: Cholesterol is a poor conductor of electricity, and is used to insulate nerve fibers.
4. Bile acids and bile salts: The 24 carbon bile acids are derived from cholesterol. Bile salts are important for fat absorption.
5. Steroid hormones: 21 carbon glucocorticoids, 19 carbon androgens and 18 carbon estrogens are synthesized from cholesterol.
6. Vitamin D: It is synthesized from cholesterol.

β oxidation

The major pathway for the catabolism of saturated fatty acid is a mitochondrial pathway called β-oxidation, which was proposed by Knoop. In this process, oxidation of fatty acids occurs at the β-carbon atom, and two carbon fragments are successively removed from the carboxyl end of fatty acetyl-CO A. this result in the elimination of two terminal carbon atoms as acetyl CoA, thereby leaving fatty acyl CoA that has two carbons less than the original fatty acid.



The β-oxidation



Summary of beta-oxidation of palmitic acid (16 C). It undergoes 7 cycles, which give rise to 8 molecules of acetyl CoA

Table 10.1. Difference in the two pathways

	Beta-oxidation	Fatty acid synthesis
Site	Mitochondria	Cytoplasm
Intermediates	Present as CoA derivatives	Covalently linked to SH group of ACP
Enzymes	Present as inde-pendent proteins	Multi-enzyme complex
Sequential units	2 carbon units split off as acetyl CoA	2 carbon units added, as 3 carbon malonyl CoA
Co-enzymes	NAD^+ and FAD are reduced	NADPH used as reducing power

Energetics of Beta-oxidation (ATP Yield)

Palmitic acid (16 C) needs 7 cycles of beta-oxidation, which give rise to 8 molecules of acetyl CoA (Fig. 10.7). Every molecule of acetyl CoA when oxidized in the TCA cycle gives 12 molecules of ATP. Each molecule of FADH 2 produces 2 molecules of ATP and each NADH generates 3 molecules of ATP when oxidized in the electron transport chain.

Hence, the energy yield from one molecule of palmitate may be calculated as:

8 acetyl CoA × 12 = 96 ATP

7 FADH 2 × 2 = 14 ATP

7 NADH × 3 = 21 ATP
Gross total = 131 ATP
Net yield = 131 minus 2 =129 ATP
(In the initial activation reaction, the equivalent of 2 high-energy bonds are utilized). The efficiency of beta-oxidation is about 40 percent.

DE NOVO SYNTHESIS OF FATTY ACIDS

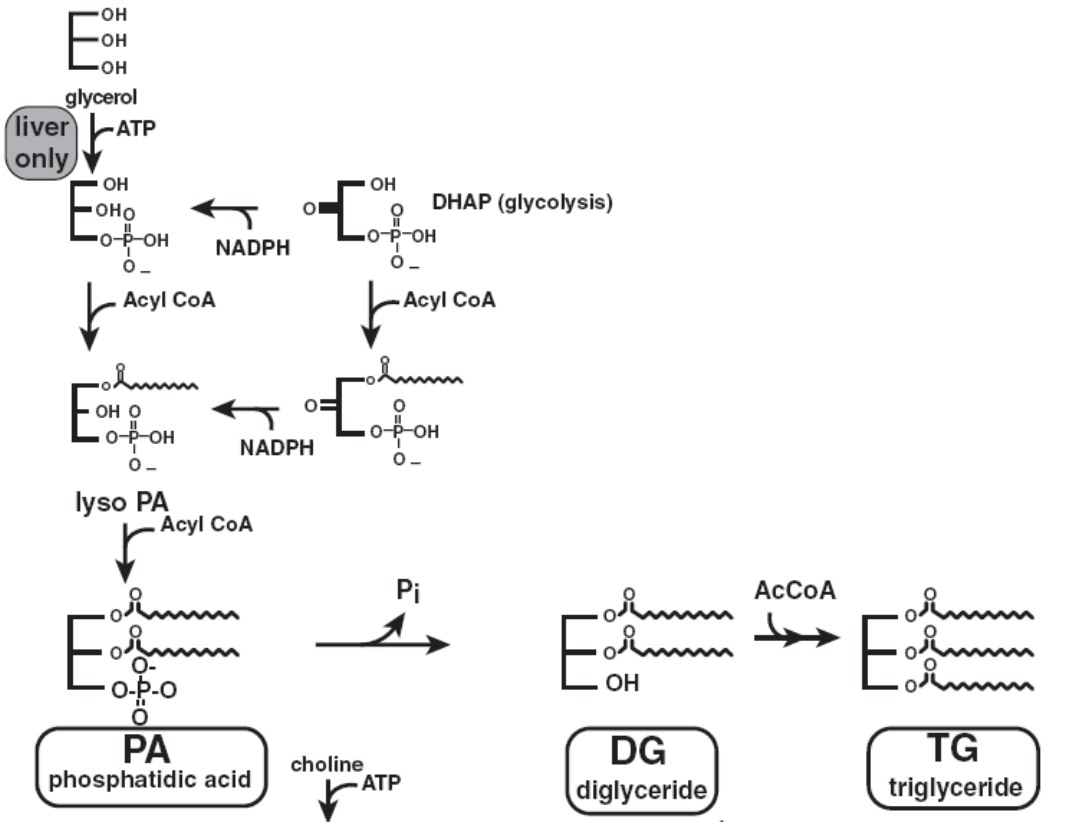
The process of fatty acid synthesis was studied by Feodor Lynen, who got a Nobel prize in 1964. The pathway is referred to as Lynen's spiral. It is not a reversal of oxidation. Important differences in synthesis and breakdown of fatty acids are given in Fatty acids are synthesized mainly by a de novo synthetic pathway operating in the cytoplasm. So, it is referred to as the extramitochondrial or cytoplasmic fatty acid synthase system. The major fatty acid synthesized de novo is palmitic acid, the 16 C saturated fatty acid. The process occurs in the liver, adipose tissue, kidney, brain, and mammary glands. Summary of de novo Synthesis The net reaction of de novo synthesis of fatty acid may be summarized as:
1Acetyl CoA +7Malonyl CoA +14NADPH +14H +
→ 1Palmitate + 7CO 2 +14NADP + + 8CoA+ 6H 2 O
Fatty acid synthesis is not an exact reversal of beta-oxidation.

Stages of FA Synthesis
1. Transfer of acetyl-CoA from mitochondria to cytosol.
2. Activation of acetyl-CoA; synthesis of malonyl-CoA.
3. Five-step elongation cycle of FA synthesis via ACP intermediates.

FA are synthesized by the repetitive condensation of two-carbon units derived from malonyl CoA
Loading of precursors via thioester derivatives, followed by chain elongation
(1) Condensation of the precursors
(2) Reduction
(3) Dehydration
(4) Reduction

TRIGLYCERIDE AND PHOSPHOLIPID SYNTHESIS

Glycerol phosphate comes from glycerol (*not in adipose*) or from dihydroxyacetone phosphate (in *liver* and *adipose*).
Nitrogen-containing phospholipids are made from diglyceride. Other phospholipids are made from phosphatidic acid.



Liver and adipose tissue are the major sites of triacylglycerol (TAG) synthesis. The TAG synthesis in adipose tissue is for storage of energy whereas in liver it is mainly secreted as VLDL and is transported. The TAG is synthesized by esterification of fatty acyl CoA with either glycerol-3-phosphate or dihyroxy acetone phosphate (DHAP). The glycerol part of the fat is derived from the metabolism of glucose. DHAP is an intermediate of glycolysis. In adipose tissue, glycerol kinase is deficient and the major source is DHAP derived from glycolysis. However, in liver glycerol kinase is active. The fatty acyl CoA molecules transfer the fatty acid to the hydroxyl groups of glycerol by specific acyl transferase Exogenous and endogenous pathways.

The body lipids are derived from two sources that require separate metabolic pathways. The first source is fats, oils, and tissue lipids in the diet. After ingestion, the dietary lipids are hydrolyzed in the intestine and absorbed and transported to various tissues. The rout is the exogenous pathway, dealing with lipids from outside. The liver, however, readily synthesized saturated and monounsaturated fatty acids from Acetyl CoA and converts them to triglycerides that atre distrbuted to tissues. Cholesterol is also synthesis in liver from acetyl CoA units. The internal synthesis and distribution of lipids is the endogenous

pathway. Both pathways require a means for soluilization and transportation of water insoluble lipids throught the body stream. Lipoprotiens are the particles that transport and distribute the lipids.

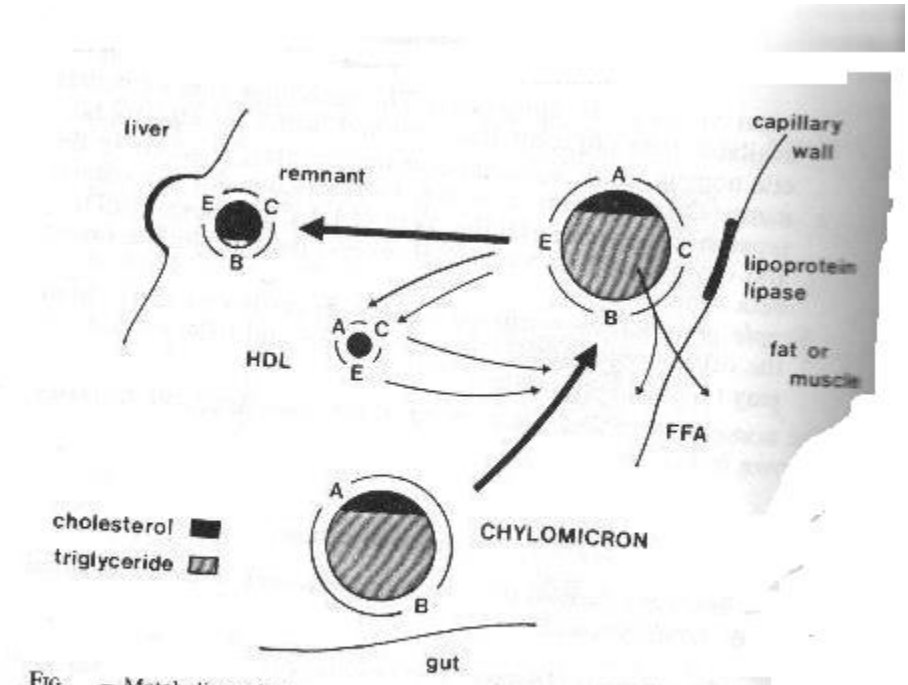
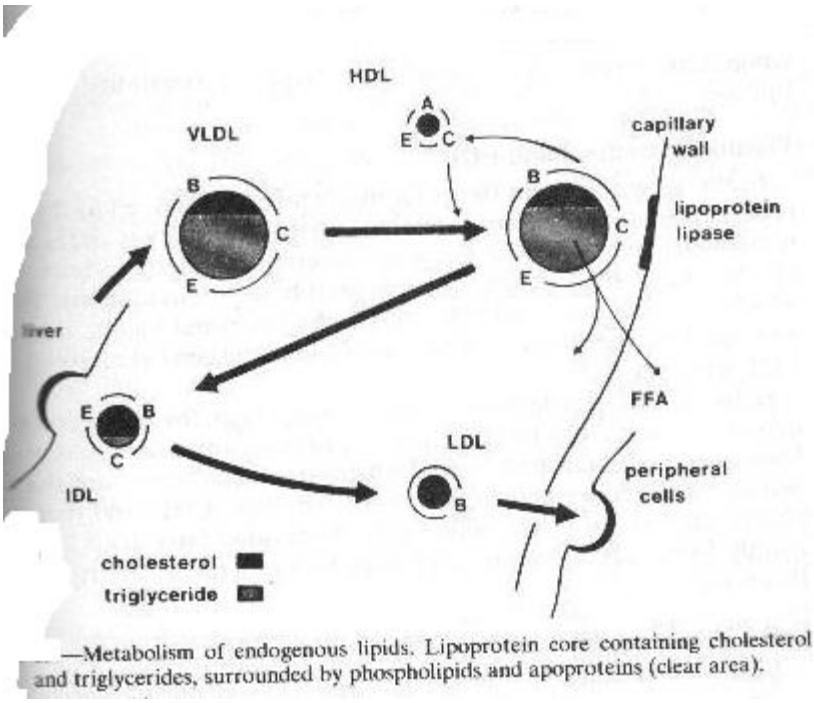


FIG. —Metabolism of exogenous lipids. Lipoprotein core containing cholesterol and triglycerides, surrounded by phospholipids and apoproteins (clear area).



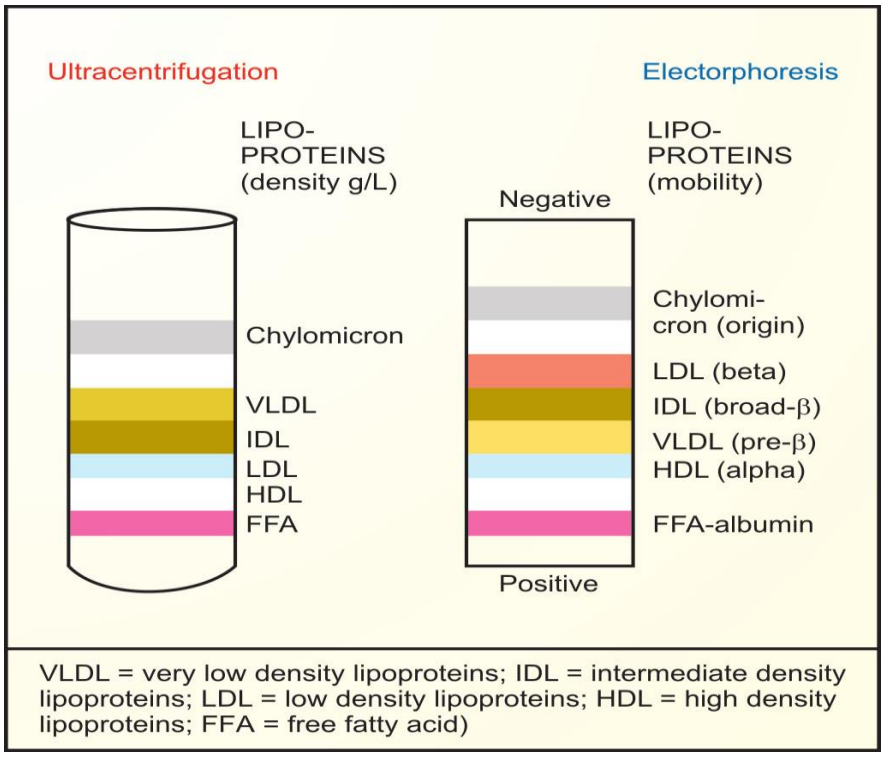
—Metabolism of endogenous lipids. Lipoprotein core containing cholesterol and triglycerides, surrounded by phospholipids and apoproteins (clear area).

Lipoproteins and apoplipoproteins:

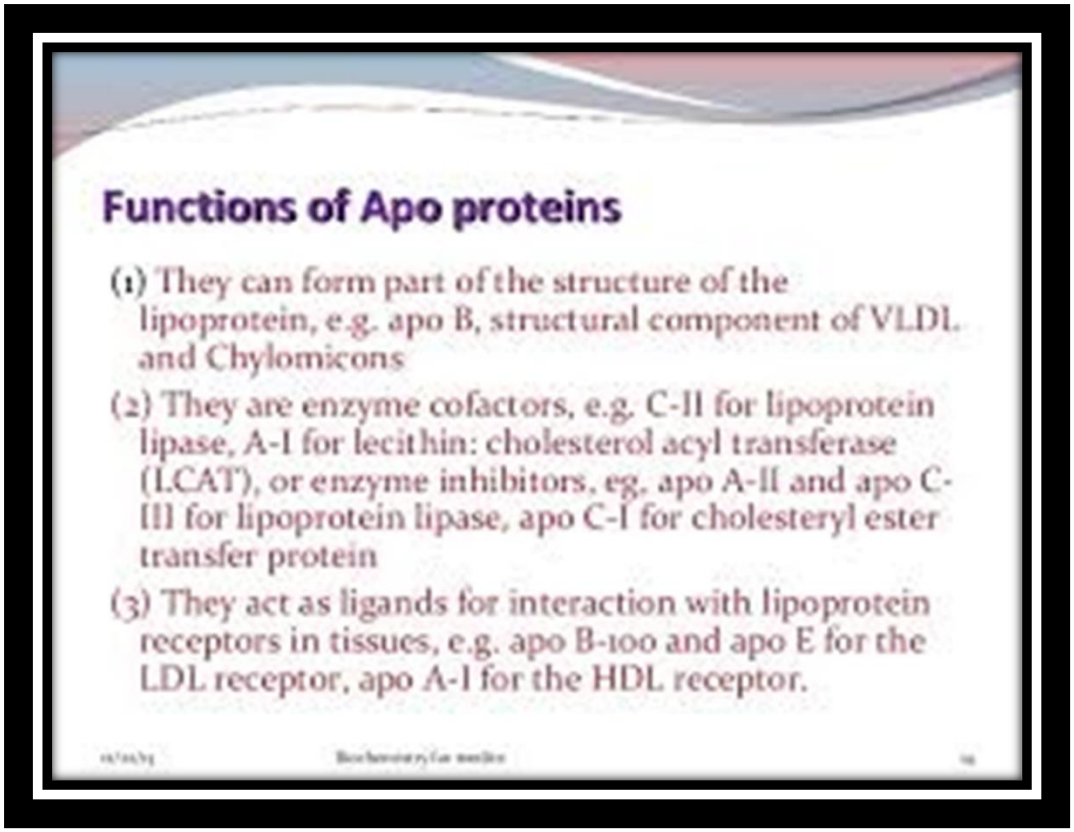
Lipoproteins are lipids–filled particles that have an outer membrane consisting of a monolayer of special proteins called apolipoproteins interspersed with the polar lipids (phospholipids and nonesterified cholesterol) the polar lipids are aligned with their charged heads facing outward and the hydrophobic tails pointing inward. The outer membrane surrounds a central core of neutral lipids (triglycerides and cholesterol esters).

Classes of lipoprotiens

The five different classes of lipoproteins have distinctive physical properties structures. Each class of lipoproteins has a specific set of apolipoproteins in the membrane and different of lipids in the core. The most commonly used names of lipoproteins clases are derived frome their relative densities upon ultracenterfugation. The structure and function of lipoproteins are described in more details in a subsequent section.



VLDL = very low density lipoproteins; IDL = intermediate density lipoproteins; LDL = low density lipoproteins; HDL = high density lipoproteins; FFA = free fatty acid)



1. chylomicrons

Chylomicrons are the largest and least dense of all lipoproteins. they arise in the intestine and transport ingested triglycerides to adipose tissue and muscle cells.

1. very low density lipoprotein (VLDL)

VLDL is a lipoprotein made in the liver and is designed primarily to transport triglycerides synthesized by the liver to muscle and adipose cells.

3. intermediate-density lipoprotein (IDL)

IDL is a transitory remnant of VLDL, circulating in plasma after about half of VLDL triglyceride has been transferred to adipose tissue or muscle cells. Most of the IDL undergoes further delipidation, transfers to

HDL all its apolipoproteins except ApoB, and thus becomes LDL. A small percentage of IDL binds to liver cells, where it is degraded.

4. Low density lipoproteins (LDL)

LDL, rich in cholesterol, arise in plasma from IDL, LDL delivers cholesterol either to the liver for bile acid formation or to other tissues for use as a structural component of new cells membrane, as a precursor of steroid hormones, or for storage as cholesterol esters.

5. High-density lipoprotein (HDL)

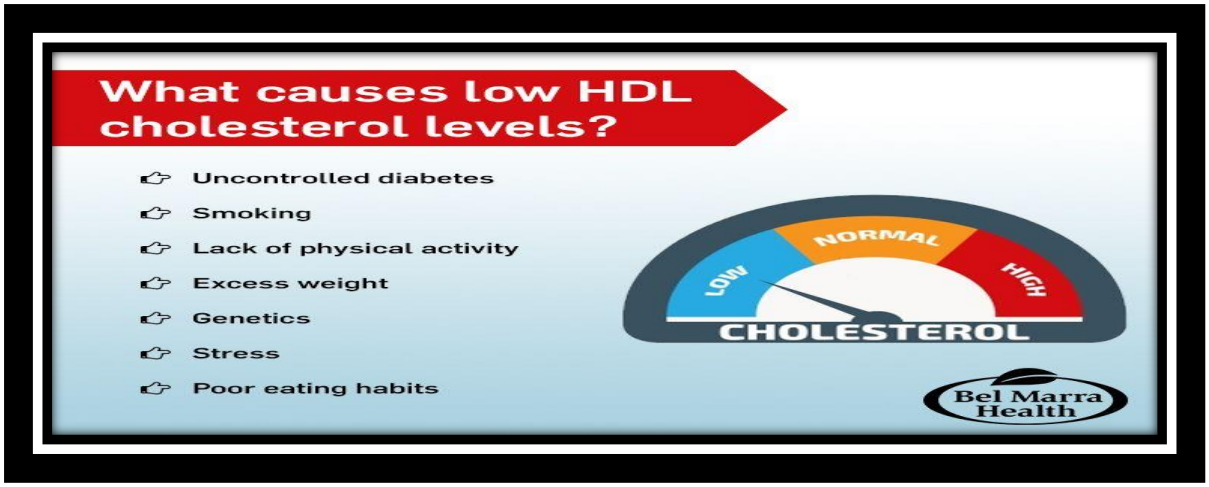
HDL has a complicated life cycle and undergoes growth and change after its initial formation. HDL particles are made both by the liver and intestinal mucosa cells. A newly formed (nascent) HDL particle forms a complex with some lipoproteins, LCAT (lecithin cholesterol acyltransferase) esterifies cholesterol by transferring to it a fatty acids from lecithin. HDL also transfers some apolipoproteins baack and froth to other lipoproteins at various stages in their life cycles.

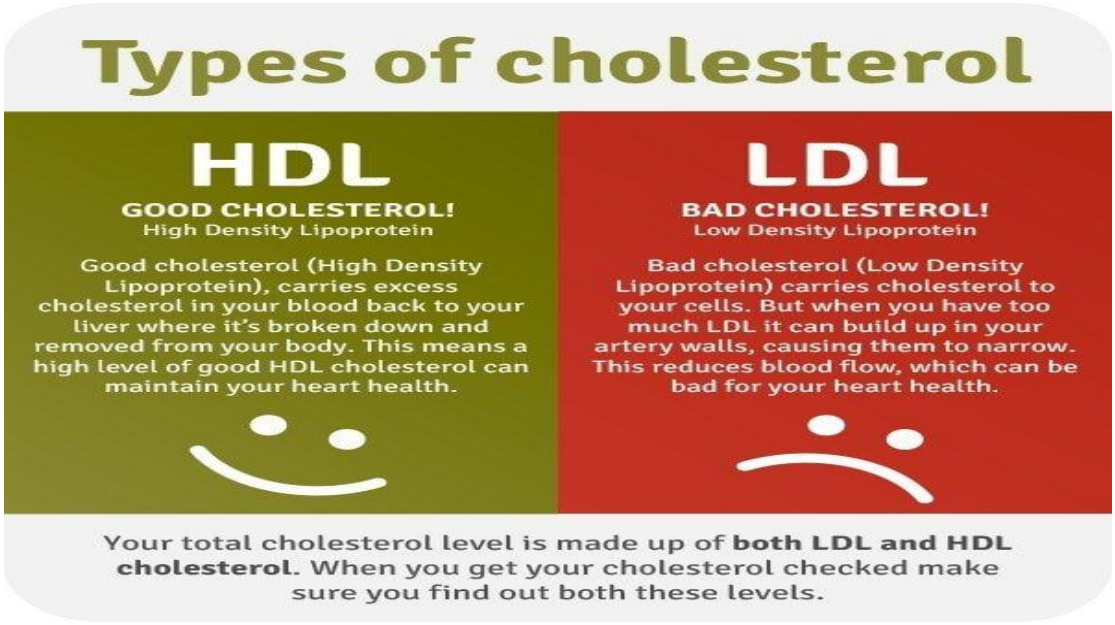
Function of HDL

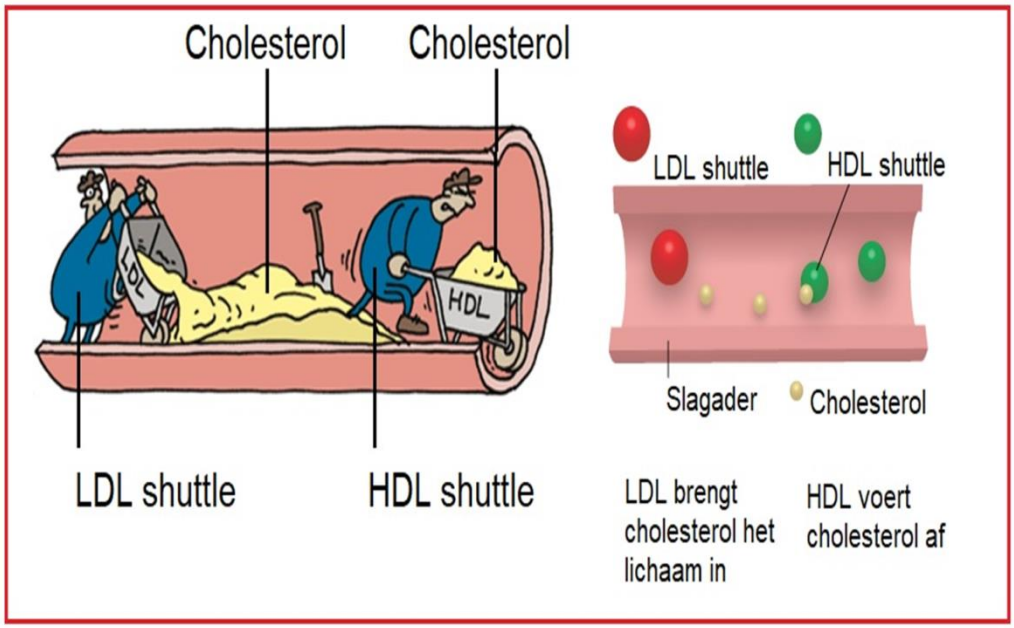
i. HDL is the main transport form of cholesterol from peripheral tissue to the liver, which is later excreted through bile. This is called reverse cholesterol transport by HDL.

ii. The only excretory route of cholesterol from the body in the bile.

iii. Excretion of cholesterol needs prior esterification with polyunsaturated fatty acids. These polyunsaturated fatty acids will help in lowering cholesterol in the body, and so polyunsaturated fatty acids is anti-atherogenic.


What causes low HDL cholesterol levels?
Uncontrolled diabetes
Smoking
Lack of physical activity
Excess weight
Genetics
Stress
Poor eating habits
LOW
NORMAL
HIGH
CHOLESTEROL
Bel Marra Health


Types of cholesterol
HDL
GOOD CHOLESTEROL!
High Density Lipoprotein
Good cholesterol (High Density Lipoprotein), carries excess cholesterol in your blood back to your liver where it's broken down and removed from your body. This means a high level of good HDL cholesterol can maintain your heart health.
LDL
BAD CHOLESTEROL!
Low Density Lipoprotein
Bad cholesterol (Low Density Lipoprotein) carries cholesterol to your cells. But when you have too much LDL it can build up in your artery walls, causing them to narrow. This reduces blood flow, which can be bad for your heart health.
Your total cholesterol level is made up of both LDL and HDL cholesterol. When you get your cholesterol checked make sure you find out both these levels.


Cholesterol
Cholesterol
LDL
HDL
LDL shuttle
HDL shuttle
LDL shuttle
HDL shuttle
Slagader
Cholesterol
LDL brengt cholesterol het lichaam in
HDL voert cholesterol af