Disorders of lipid metabolim

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Introduction:

Lipids: are defined as compounds which are relatively insoluble in water, but freely soluble in non-polar organic solvent like benzene, chloroform, ether, hot alcohol, acetone, etc.

- Functions of lipids:

- 1. Storage form of energy (triglycerides) firstly because of their high energy content.

2. Structural components of biomembranes (phospholipids and cholesterol).
3. As protective coating on the surface of many organs such as kidney, against injury.
4. Facilitation the absorption of the fat soluble vitamins A, D, E and K.
5. Providing insulation against changes in external temperature (subcutaneous fat).
6. Metabolic regulators (steroid hormone and prostaglandins).
7. As transport forms of various metabolic fuel.
8. Acting as electric insulator in neurons.

- The major lipids present in the plasma are fatty acids, triglycerides, cholesterol and phospholipids. Other lipid-soluble substances, present in much smaller amounts but of considerable physiological importance, include steroid hormones and fat-soluble vitamins; Elevated plasma concentrations of lipids, particularly cholesterol, are causally related to the pathogenesis of atherosclerosis, the process responsible for the majority cardiovascular disease (coronary, cerebrovascular and peripheral vascular disease).

- Cardiovascular disease is the commonest cause of death in the UK: about a quarter of all deaths (more in women than in men) are due to coronary heart disease (CHD). Many of these are in people under the age of 60. Effective management of hypercholesterolaemia and other risk factors is of proven benefit in reducing cardiovascular disease mortality.

- **TRIGLYCERIDES, CHOLESTEROL AND PHOSPHOLIPIDS**
- Triglycerides are more correctly called triacylglycerols, They consist of glycerol esterified with three long-chain fatty acids, such as stearic (18 carbon atoms) or palmitic (16 carbon atoms) acids. Triglyceride is present in dietary fat, and can be , synthesized in the liver and adipose tissue to provide a source of stored energy; this can be mobilized when required, for example during starvation. Triglycerides containing both saturated and unsaturated fatty acids are important components of cell membranes.

- Cholesterol is also important in membrane structure and is the precursor of steroid hormones and bile acids. Cholesterol is present in dietary fat, and can be synthesized in the liver by a mechanism that is under close metabolic regulation. Phospholipids are compounds similar to the triglycerides but with one fatty acid residue replaced by phosphate and a nitrogenous base. Because they are not water soluble, lipids are transported in the plasma in association with proteins.

- Albumin is the principal carrier of free fatty acids (FFA); the other lipids circulate in complexes known as lipoproteins. These consist of a non-polar core of triglyceride and cholesteryl esters surrounded by a surface layer of phospholipids, cholesterol and proteins known as apolipoproteins (Fig. 14.1). The latter are important both structurally and in the metabolism of lipoproteins (Fig. 14.2).
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Apolipoprotein	Function
A-I	activates LCAT structural (in HDL)
A-II	inhibits HTGL at high concentration structural (in HDL)
B-100	structural (in LDL and VLDL) receptor binding
B-48	structural (in chylomicrons)
C-I	cofactor for LCAT
C-II	activator of LPL
C-III	inhibits LPL inhibits clearance of CM and VLDL remnant particles
E	binding to LDL and remnant receptors

Fig. 14.2 Functions of the major apolipoproteins. Abbreviations are explained in the text.

- **CLASSIFICATION OF LIPOPROTEINS**

Lipoproteins are classified on the basis of their densities as demonstrated by their ultracentrifugal separation. Density increases from chylomicrons (CM, of lowest density) through lipoproteins of very low density

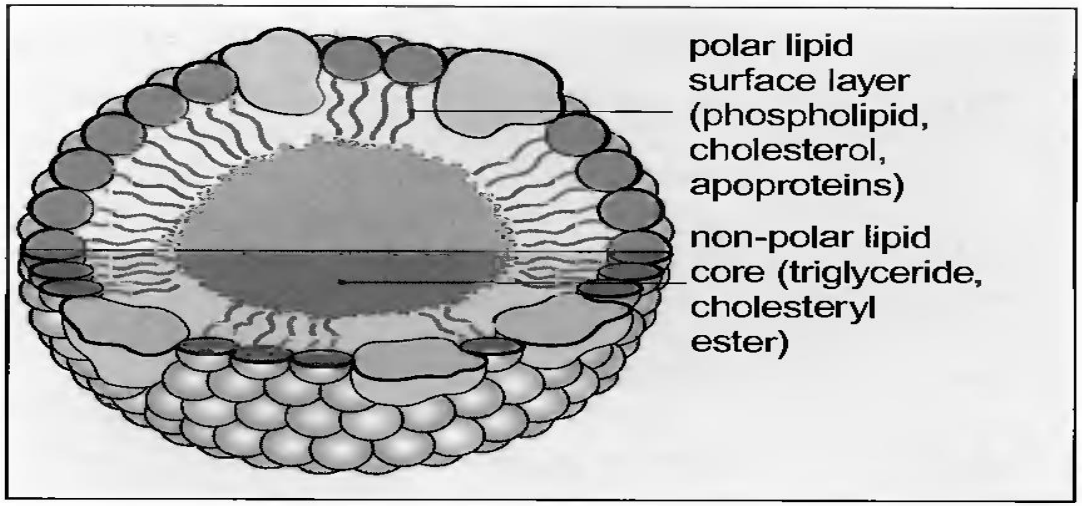

Fig. 14.1 Diagram showing the composition of a lipoprotein particle. A segment has been removed to reveal the non-polar core of cholesteryl ester and triglyceride surrounded by phospholipids and apoprotein.

- (VLDL), intermediate density (IDL) and low density(LDL) to high density lipoproteins (HDL). HDL can be separated, on the basis of density, into two metabolically distinct subtypes, HDL2 (density 1.064-1.125) and HDL3 (density 1.126-1.21). Distinct sub-types of LDL (LDL-I, II and III, in increasing order of density) are also recognized. IDL are normally present in the blood- stream in only small amounts but can accumulate in pathological disturbances of lipoprotein metabolism.

- Lipoprotein(a), or Lp(a), is an atypical lipoprotein of unknown function. It is larger and more dense than LDL but has a similar composition, except that it contains in addition one molecule of apo(a) for every molecule of apo B-100. Apo(a) shows considerable homology with plasminogen. The concentration of Lp(a) in the plasma varies considerably between individuals, ranging from 0 to 1000 mg/L. An elevated concentration of Lp(a) appears to be an independent risk factor for CHD. Conventional drug treatments that lower LDL have little effect on Lp{a) concentration.

Classification and characteristics of lipoproteins

lipoprotein	density (g/mL)	mean diameter (nm)	electrophoretic mobility	source	principal function
CM	<0.95	500	remains at origin	intestine	transport of exogenous triglyceride
VLDL	0.96–1.006	43	pre-β	liver	transport of endogenous triglyceride
IDL	1.007–1.019	27	'broad β'	catabolism of VLDL	precursor of LDL
LDL	1.02–1.063	22	β	catabolism of VLDL, via IDL	cholesterol transport
HDL	1.064–1.21	8	α	liver, intestine; catabolism of CM & VLDL	reverse cholesterol transport

Fig. 14.3 Classification and characteristics of lipoproteins.

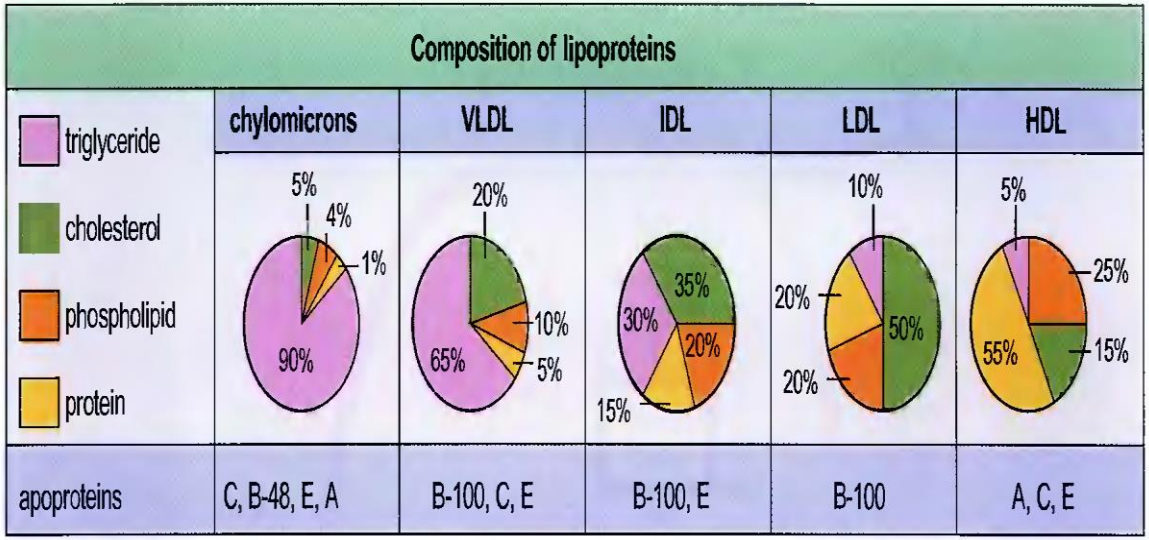

Fig. 14.4 Composition of lipoproteins; although the composition in each class is similar, the particles are heterogeneous so the percentages given are approximate. Figures shown for HDL are for HDL3; HDL2 contains less protein and more lipid. Only the principal apoproteins are shown.

- **Chylomicrons:**
- Chylomicrons (Fig. 14.5) are formed from dietary fat (principally triglycerides, but also cholesterol) in enterocytes; they enter the lymphatics and reach the systemic circulation via the thoracic duct. Chylomicrons are the major transport form of exogenous (dietary) fat. Triglycerides constitute about 90% of the lipid. Triglycerides are removed from chylomicrons by the action of the enzyme lipoprotein lipase (LPL), located on the luminal surface of the capillary endothelium of adipose tissue, skeletal and cardiac muscle and lactating breast, with the result that free fatty acids are delivered to these tissues to be used either as energy substrates or, after re-esterification to triglyceride, for energy storage.

- . LPL is activated by apo C-II. Apo A and apo B-48 are synthesized in the gut and are present in newly formed chylomicrons; apo C-II and apo E are transferred to chylomicrons from HDL. As triglycerides are removed from chylomicrons by the action of lipoprotein lipase, these become smaller; cholesterol, phospholipids, apo A and apo C-II are released from the surface of the particles and taken up by HDL. Esterified cholesterol is transferred to the chylomicron remnants from HDL, in exchange for triglyceride, by cholesteryl ester transfer protein.

- The chylomicron remnants, depleted of triglyceride and enriched in cholesteryl ester, are cleared rapidly from the circulation by hepatic parenchymal cells. This hepatic uptake depends on the recognition of apo E by hepatic remnant receptors (also known as LDL-related receptor protein). Although their major function is the transport of dietary triglyceride, chylomicrons also transport dietary cholesterol and fat-soluble vitamins to the liver.

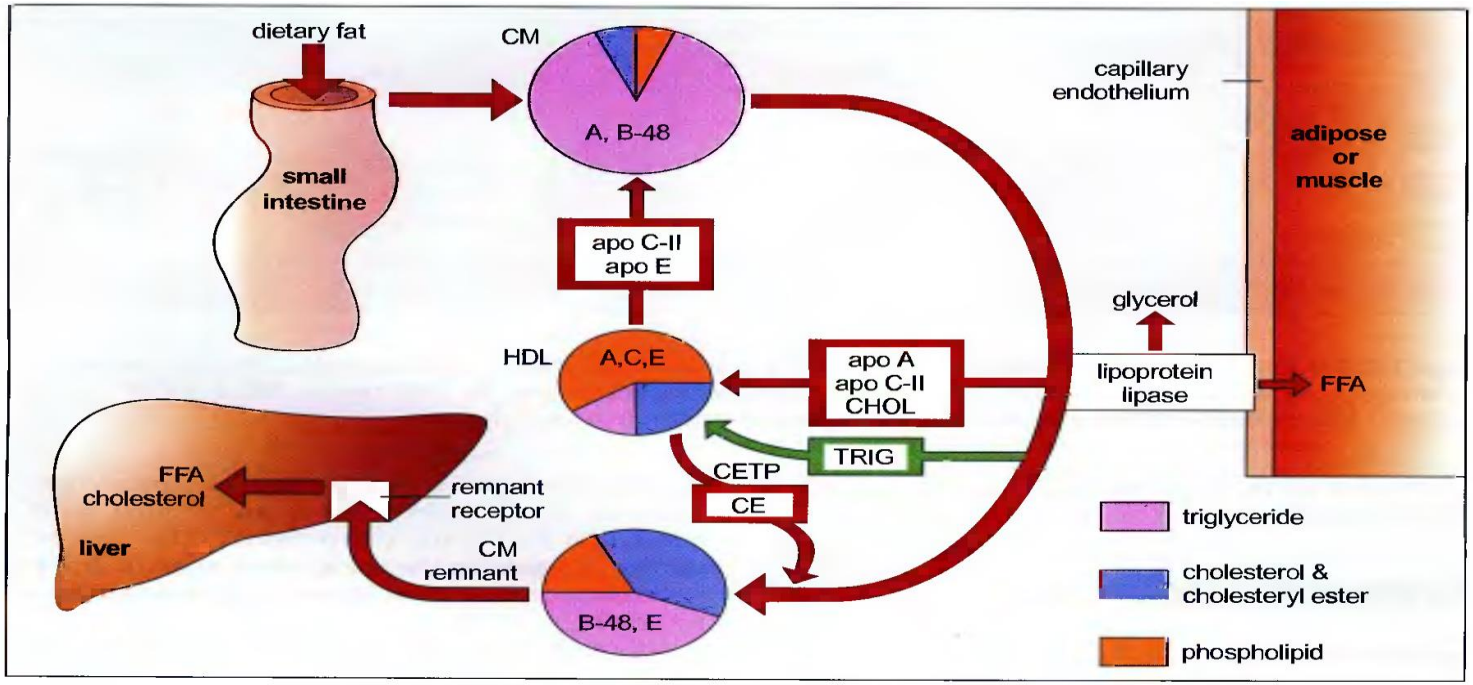

Fig. 14.5 Chylomicrons transport dietary triglycerides to tissue where they are removed by the action of lipoprotein lipase. The resulting remnant particles are removed by the liver. They bind to remnant receptors (which recognize apo E) on hepatic cells, are internalized and catabolized. Apolipoproteins A and B-48 are synthesized in intestinal cells; apo C and apo E are acquired, together with cholesteryl esters (CE), from HDL. Apolipoprotein C-II activates lipoprotein lipase. As triglycerides are removed from chylomicrons, apo A, apo C, cholesterol and phospholipids are released from their surfaces and transferred to HDL where the cholesterol is esterified. Cholesteryl ester is transferred back to the remnant particles in exchange for triglycerides by cholesteryl ester transport protein (CETP).

- **Very low density lipoproteins:**
- VLDL (Fig. 14.6) are formed from triglycerides synthesized in the liver either de novo or by re- esterification of free fatty acids. VLDL also contain some cholesterol, apo B, apo C and apo E; the apo E and some of the apo C is transferred from circulating HDL. VLDL are the principal transport form of endogenous triglycerides and initially share a similar fate to chylomicrons, triglycerides being removed by the action of LPL. As the VLDL particles become smaller, phospholipids, free cholesterol and apolipoproteins are released from their surfaces and taken up by HDL thus converting the VLDL to denser particles, IDL

- Cholesterol that has been transferred to HDL is esterified and the cholesteryl ester is transferred back to IDL by cholesteryl ester transfer protein in exchange for triglyceride. More triglycerides are removed by hepatic triglyceride lipase, located on hepatic endothelial cells, and IDL are thereby converted to LDL composed mainly of cholesteryl esters, apo B-IO0 and phospholipid. Some IDL are taken up by the liver via LDL receptors. These receptors, also known as B, E receptors, are capable of binding apo B-IO0 and apo E. Under normal circumstances, there are very few IDL in the circulation because of their rapid removal or conversion to LDL.

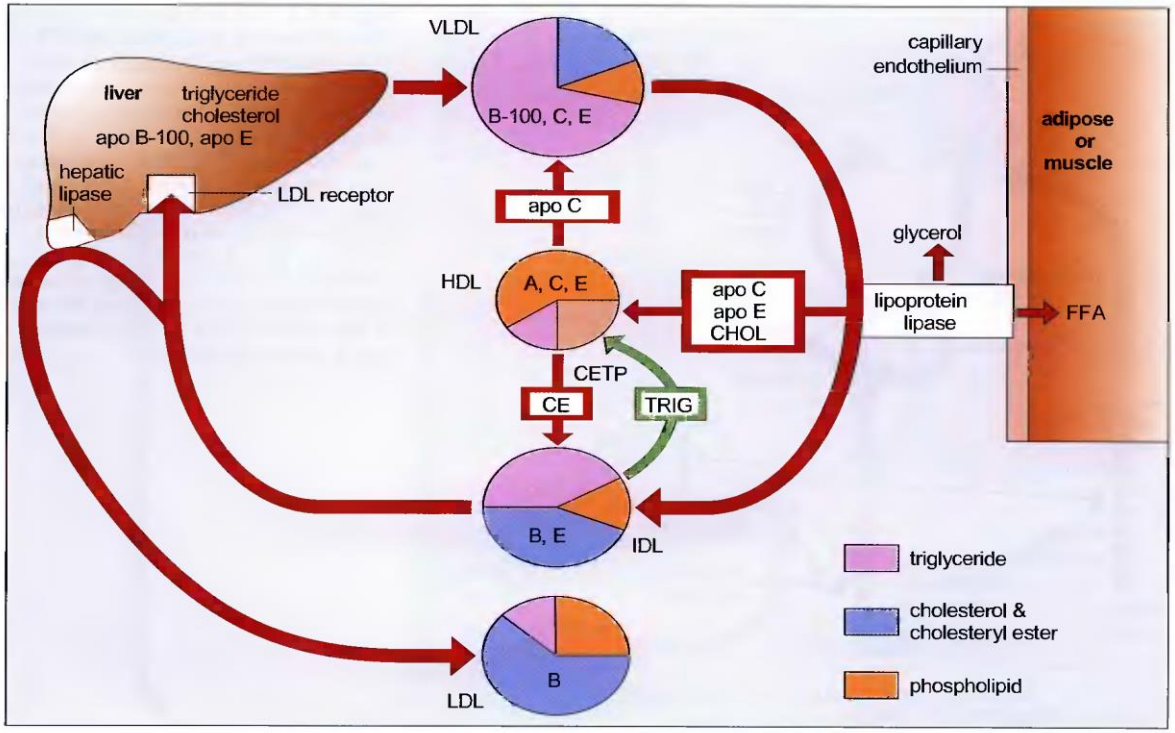

Fig. 14.6 VLDL are synthesized in the liver and transport endogenous triglyceride from the liver to other tissues where it is removed by the action of lipoprotein lipase. At the same time, cholesterol, phospholipids and apo C and apo E are released and transferred to HDL. By this process VLDL are converted to IDL. Cholesterol is esterified in HDL and cholesteryl ester is transferred to IDL by cholesteryl ester transfer protein. Some IDL is removed by the liver but most has more triglyceride removed by hepatic triglyceride lipase and is thereby converted into LDL. Thus the triglyceride-rich VLDL are precursors of LDL, which comprise mainly cholesteryl ester and apo B-100.

- **Low density lipoproteins:**
- LDL are the principal carriers of cholesterol, mainly in the form of cholesteryl esters. LDL are formed from VLDL via IDL {Fig. 14.6). LDL can pass through the junctions between capillary endothelial cells and attach to LDL receptors on cell membranes that recognize apo B-IO0. This is followed by internalization and lysosomal degradation with release of free cholesterol {Fig. 14.7).

- Cholesterol can also be synthesized in these tissues, but the rate-limiting enzyme, HMG-CoA reductase {hydroxymethylglutaryl CoA reductase), is inhibited by cholesterol with the result that, in the average adult, cholesterol synthesis in peripheral calls probably does not occur. Free cholesterol also stimulates its own esterification to cholesteryl ester by stimulating the enzyme acyl -CoA:cholesterol acyl transferase (ACAT). LDL receptors are saturable and subject to down regulation by an increase in intracellular cholesterol.

- Macrophages derived from circulating monocytes can take up LDL via scavenger receptors. This process occurs at normal LDL concentrations but is enhanced when LDL concentrations are increased and by modification (e.g. oxidation) of LDL. Uptake of LDL by macrophages in the arterial wall is an important event in the pathogenesis of atherosclerosis. When macrophages become overloaded with cholesteryl esters, they are converted to 'foam cells', the classic components of atheromatous plaques. In human neonates, plasma LDL concentrations are much lower than in adults and cellular cholesterol uptake is probably all receptor mediated and controlled. LDL concentrations increase during childhood and reach adult levels after puberty.

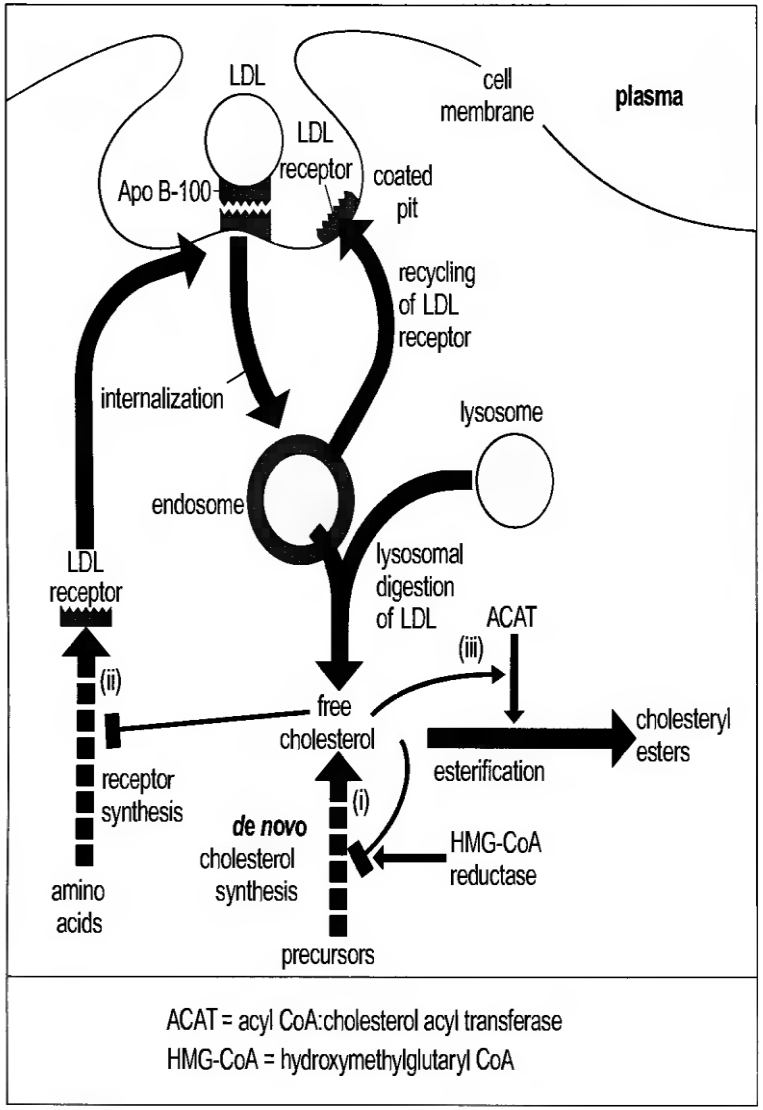

Fig. 14.7 LDL uptake and catabolism. LDL are derived from VLDL, via IDL. They are removed by the liver and other tissues by a receptor-dependent process involving the recognition of apo B-100 by the LDL receptor. The LDL particles are hydrolyzed by lysosomal enzymes, releasing free cholesterol which (i) inhibits HMG-CoA reductase, the rate-limiting step in cholesterol synthesis, (ii) inhibits LDL receptor synthesis and (iii) stimulates cholesterol esterification by augmenting the activity of the enzyme acyl CoA:cholesterol acyl transferase (ACAT).

- **High density lipoproteins:**
- HDL (Fig. 14.8) are synthesized primarily in the liver and, to a lesser extent, in small intestinal cells, as a precursor ('nascent HDL') comprising phospholipid, cholesterol, apo E and apo A. Nascent HDL is disc- shaped; in the circulation, it acquires apo C and apo A from other lipoproteins and from extrahepatic tissues, and in doing so assumes a spherical conformation. The free cholesterol is esterified by the enzyme lecithin-cholesterol acyltransferase (LCAT),

-), which is present in nascent HDL and activated by its cofactor, apo A-I. This increases the density of the HDL particles, which are thus converted from HDL3 to HDL2. Cholesteryl esters are transferred from HDL2 to remnant particles in exchange for triglycerides, this process being mediated by cholesteryl ester transfer protein. Cholesteryl esters are taken up by the liver in chylomicron remnants and IDI. and excreted in bile,

- partly after metabolism to bile acids. The triglyceride-enriched HDL2 is converted back to HDL3 by the removal of triglycerides by the enzyme hepatic triglyceride lipase, located on the hepatic capillary endothelium. Some HDL2 is probably removed from the circulation by the liver, through receptors that recognize apo A-I.

- Thus HDL has two important functions: it is a source of apoproteins for chylomicrons and VLDL, and it mediates reverse cholesterol transport, taking up cholesterol from senescent cells and other lipoproteins and transferring it to remnant particles, which are taken up by the liver. Cholesterol is excreted by the liver in bile, both as free and esterified cholesterol and after metabolism to bile acids.

- The essential features of lipoprotein metabolism are as follows.
- Dietary triglycerides are transported in chylomicrons to tissues where they can be used as an energy source or stored.
- Endogenous triglycerides, .synthesized in the liver, are transported in VLDL and are also available to tissues as an energy source or for storage.
- Cholesterol .synthesized in the liver is transported to tissues in LDL, derived from VLDL; dietary cholesterol reaches the liver in chylomicron remnants.
- HDL acquire cholesterol from peripheral cells and other lipoproteins and this is esterified by LCAT.
- Cholesteryl esters are transferred to remnant particles, which are taken up by the liver, whence the cholesterol is excreted.

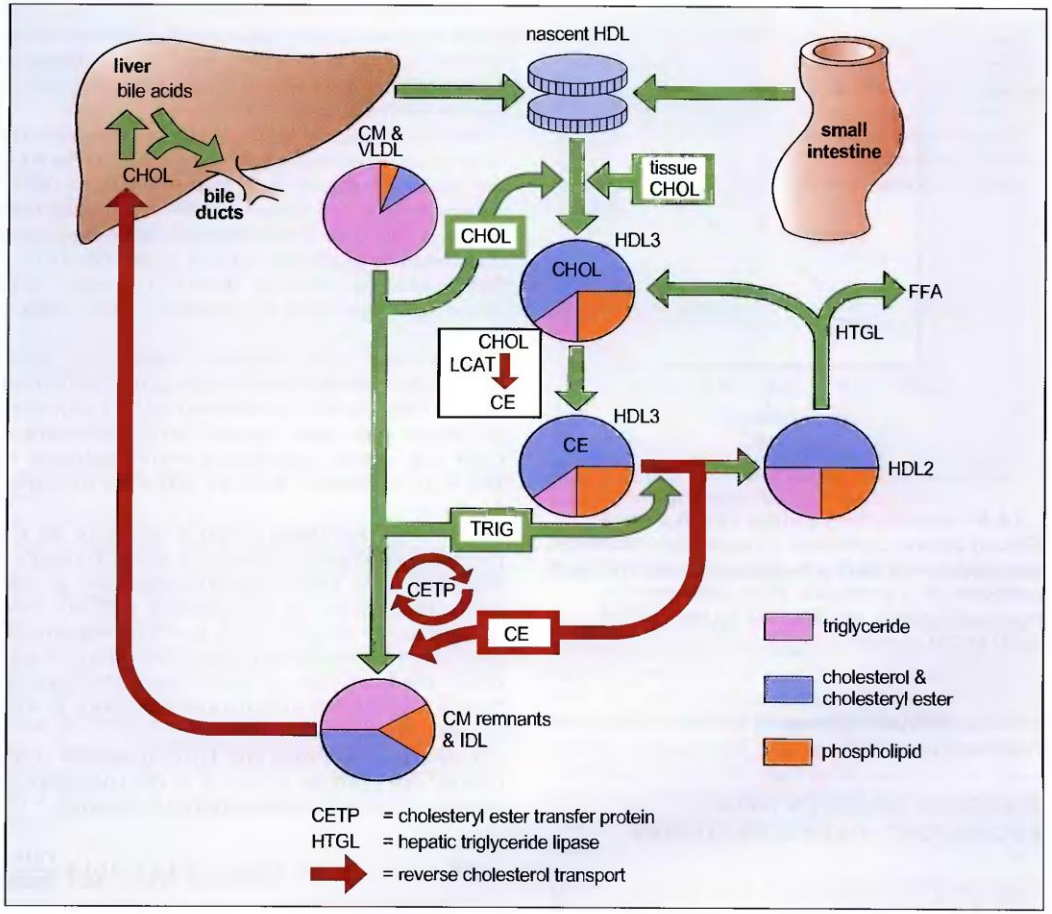

Fig. 14.8 HDL metabolism and reverse cholesterol transport. Nascent HDL acquires free cholesterol from extrahepatic cells, chylomicrons and VLDL and is thereby converted to HDL3. The cholesterol is esterified by the enzyme LCAT and cholesteryl ester is transferred to remnant lipoproteins by CETP in exchange for triglyceride. Remnant particles are removed from the circulation by the liver whence the cholesterol is excreted in bile both *per se* and as bile acids. Much HDL is recycled although some is probably taken up by the liver and catabolized. Apoprotein transfers have been omitted for clarity.

- **Metabolic disease related to lipids:**
- **Familial hypercholesterolemia: (Type ||)**
- Familial hypercholesterolemia is a genetic disorders characterized by elevated total cholesterol and LDL-Cholesterol. People with this disorders have a defect in the LDL receptor, which reduces the normal rate of removal of cholesterol from the blood stream. Cholesterol levels in people with familial hypercholesterolemia are elevated from birth.one in every 500 people in the united states is affected by familial hypercholesterolemia. Adult with this disorders frequently exhibit small fat deposits under skin along the tendons,with the acilles tendon and finger tendons most commonly affected.

- . minute fat deposits called xanthelasmas also characteristically develop on the eyelids. People with familial hypercholesterolemia are at significantly increased risk for coronary heart disease and heart attack at a young age.
- There are 2 types of familial hypercholesterolemia (Type II**)**
- **Type ||a:** Defective LDL receptor or mutation in ligand region of apo B-100.
- **Type ||b :**Tendency for VLDL to be elevated in addition.
- Remarks of familial hypercholesterolemia: reduced rate of LDL clearance leads to elevated LDL levels and hypercholesterolemia, resulting in atherosclerosis and coronary disease.

- **Hyperlipoproteinemias:(** Familial lipoprotein lipase deficiency) (type I)

Hypertriacylglycerolemia due to deficiency of LPL, production of abnormal LPL, or apo C-II deficiency causing inactive LPL.

Remarks:

Slow clearance of chylomicrons and VLDL. Low levels of LDL and HDL. No increased risk of coronary disease.

- Familial dysbetalipoproteinemia: (hyperlipoproteinemia)(Type III)
- Familial dysbetalipoproteinemia ,also known as type III hyperlipoproteinemia,is an uncommon inherited disorder characterized by elevated cholesterol,TG and VLDL.Fat deposits within the skin commonly occure with familial dysbetalipoproteinemia. People with this disorders are at significantly increased risk for early onset coronary heart disease, stroke and peripheral arterial disease, with peripheral arterial disease,fatty deposits called plaques accumulate in the arteries of the extremities, partially obstructing blood flow.

- People with peripheral arterial disease characteristically develop pain in the legs with physical activity due to decreased blood supply to the leg muscles. The main defect of familial dysbetalipoproteinemia is due to deficiency in remnant clearance by the liver is due to abnormality in apo E.

- Familial hypertriacylglyceroma: Type
- Defect: over production of VLDL often associated with glucose intolerance and hyperinsulinemia,which may be a cause of the production.
- Remarks: Cholesterol levels rise with VLDL concentration. LDL and HDL tend to be subnormal .This type of pattern is commonly associated with coronary heart disease, type 2 non-insulin-dependent diabetes mellitus,obesity,alcoholism,and administration of progestational hormones.

- Familial type hyperlipoproteinemia:
- Defect: Elevated chylomicrons and VLDL.Not completely understood,but defects in lipoprotein lipase or apo C- are possible.
- Remarks: Hypertriacylglycerlemia and hypercholesterolemia with low LDL and HDL.Inceased coronary heart disease risk in some patiens.

- Familial hyperalphalipoproteinemia:
- Defect: Increased concentrations of HDL.
- Remarks: A rare condition apparently beneficial to health and longesity.
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- Hepatic lipase deficiency:
- Defect: Deficiency of the enzyme leads to accumulation of large triacylglycerol rich HDL and VLDL remnants.
- Remarks:Patients have xanthomas and coronary heart disease.
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- Familial lipoprotein (a)excess:
- Defect: LP(a) consists of 1 mol of apo(a).Apo (a)shows structural to 1 mol of apo (a).apo (a) shows structural homologies to plasminogen.
- Remarks premature coronary heart disease due to atherosclerosis,plus thrombosis due to inhibition of fibrinolysis.
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- Familial hypobetalipoproteinemia:
- Defect:LDL concentration is 10-60 of normal
- Remarks:chylomicron formation still occurs, most individuals healthy and long lived.
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- Familial lecithin:cholesterol acyltransferase (LCAT)deficiency:
- Defect: Absence of LCAT leads to block in revers cholesterol transport. HDL remains as nascent disks in stacks ,incapable of taking up and esterifying cholesterol.
- Remarks: Plasma concentrations of cholesteryl esters and lysolecithin are low.

TABLE 26–1 Primary Disorders of Plasma Lipoproteins (Dyslipoproteinemias)

Name	Defect	Remarks
Hypolipoproteinemias Abetalipoproteinemia	No chylomicrons, VLDL, or LDL are formed because of defect in the loading of apo B with lipid.	Rare; blood acylglycerols low; intestine and liver accumulate acylglycerols. Intestinal malabsorption. Early death avoidable by administration of large doses of fat-soluble vitamins, particularly vitamin E.
Familial alpha-lipoprotein deficiency Tangier disease Fish-eye disease Apo-A-I deficiencies	All have low or near absence of HDL.	Tendency toward hypertriacylglycerolemia as a result of absence of apo C-II, causing inactive LPL. Low LDL levels. Atherosclerosis in the elderly.
Hyperlipoproteinemias Familial lipoprotein lipase deficiency (type I)	Hypertriacylglycerolemia due to deficiency of LPL, abnormal LPL, or apo C-II deficiency causing inactive LPL.	Slow clearance of chylomicrons and VLDL. Low levels of LDL and HDL. No increased risk of coronary disease.
Familial hypercholesterolemia (type IIa)	Defective LDL receptors or mutation in ligand region of apo B-100.	Elevated LDL levels and hypercholesterolemia, resulting in atherosclerosis and coronary disease.
Familial type III hyperlipoproteinemia (broad beta disease, remnant removal disease, familial dysbetalipoproteinemia	Deficiency in remnant clearance by the liver is due to abnormality in apo E. Patients lack isoforms E3 and E4 and have only E2, which does not react with the E receptor.[1]	Increase in chylomicron and VLDL remnants of density < 1.019 (β-VLDL). Causes hypercholesterolemia, xanthomas, and atherosclerosis.
Familial hypertriacylglycerolemia (type IV)	Overproduction of VLDL often associated with glucose intolerance and hyperinsulinemia.	Cholesterol levels rise with the VLDL concentration. LDL and HDL tend to be subnormal. This type of pattern is commonly associated with coronary heart disease, type II diabetes mellitus, obesity, alcoholism, and administration of progestational hormones.
Familial hyperalphalipoproteinemia	Increased concentrations of HDL.	A rare condition apparently beneficial to health and longevity.
Hepatic lipase deficiency	Deficiency of the enzyme leads to accumulation of large triacylglycerolrich HDL and VLDL remnants.	Patients have xanthomas and coronary heart disease.
Familial lecithin:cholesterol acyltransferase (LCAT) deficiency	Absence of LCAT leads to block in reverse cholesterol transport. HDL remains as nascent disks incapable of taking up and esterifying cholesterol.	Plasma concentrations of cholesteryl esters and lysolecithin are low. Present is an abnormal LDL fraction, lipoprotein X, found also in patients with cholestasis. VLDL is abnormal (β-VLDL).
Familial lipoprotein(a) excess	Lp(a) consists of 1 mol of LDL attached to 1 mol of apo(a). Apo(a) shows structural homologies to plasminogen.	Premature coronary heart disease due to atherosclerosis, plus thrombosis due to inhibition of fibrinolysis.

[1]There is an association between patients possessing the apo E4 allele and the incidence of Alzheimer's disease. Apparently, apo E4 binds more avidly to β-amyloid found in neuritic plaques.

THANK YOU