Disorders of lipid metabolism

By

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Topics to be discussed

1-Introduction

2-Transport of lipids

3-lipid disorders :

A.primary hyperlipidemias

B.secondary hyperlipidemias

4-Investigation

Definition of lipids

- Lipids are defined as organic compounds that are poorly soluble in water but miscible in organic solvents.
- Lipidology is the study of abnormal lipid Metabolism.
- An understanding of the pathophysiology of plasma lipid metabolism is usefully based on the concept of lipoproteins, the form in which lipids circulate in plasma.

Biological functions of lipids

- Storage of energy
- Cell membrane formation
- Prostaglandin precursors
- Bile acids , steroidal hormones, vit.D presursors (cholesterol)
- Chemical messengers
- Maintenance of body temperature

lipoproteins, the form in which lipids circulate in plasma.

PLASMA LIPIDS

The chemical structures of the four main forms of lipid present in plasma are illustrated in Figure 13.1.

are shown in Figures 13.2 and 13.3.

Triglycerides are transported from the intestine to various tissues, including the liver and adipose tissue, as lipoproteins. Following hydrolysis, fatty acids are taken up, re-esterified and stored as triglycerides. Plasma

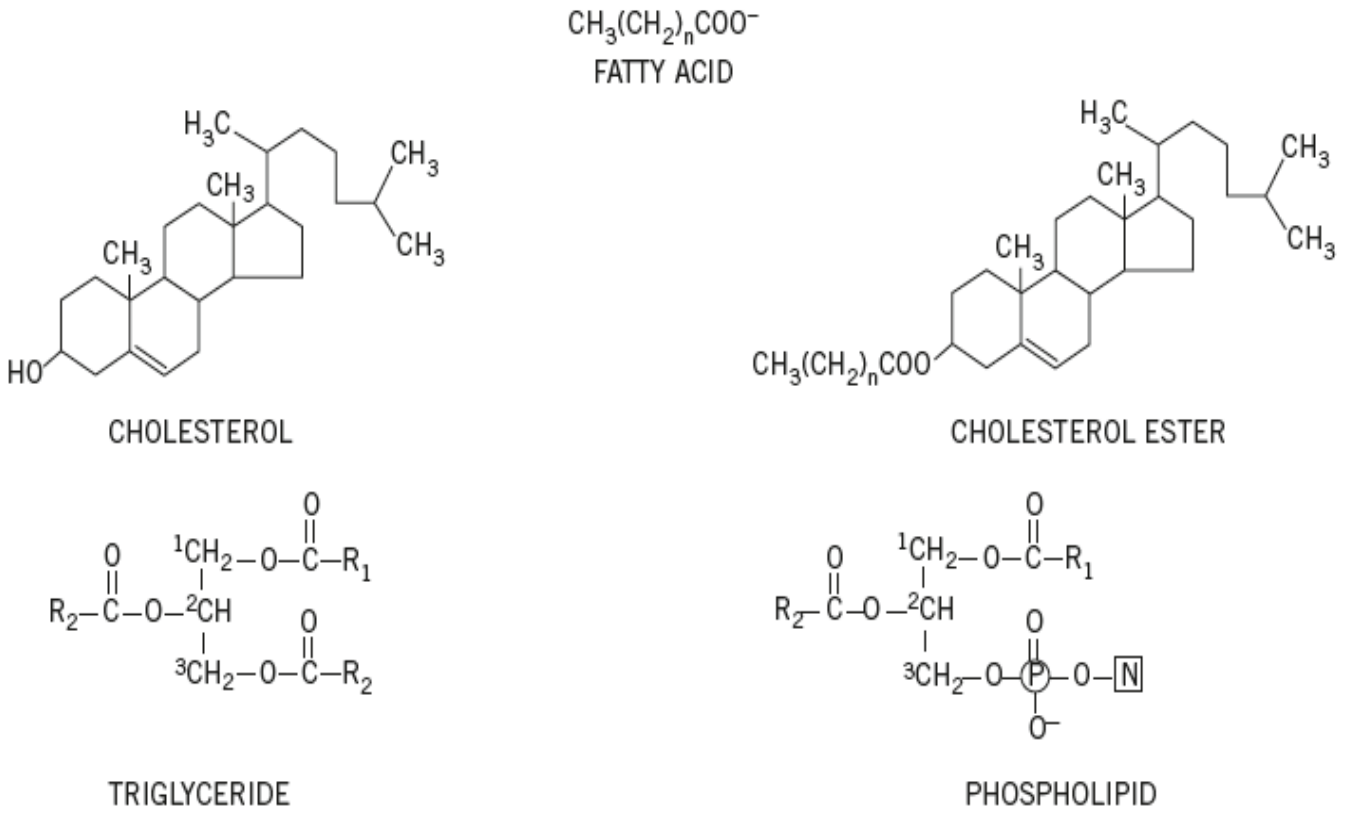

Figure 13.1 Lipid structures. P, phosphate; N, nitrogenous base; R, fatty acid.

Table 13.1 Some of the major fatty acids found in the plasma

Group	Name	Carbon-chain length	Source
Monounsaturated	Palmitoleic	C16	Plant oil
	Oleic	C18	Olive oil
Polyunsaturated	Linoleic	C18	Plant oil
	Linolenic	C18	Plant oil
	Arachidonic	C20	Plant oil
	Eicosapentaenoic	C20	Fish oil
Saturated	Myristic	C14	Coconut oil
	Palmitic	C16	Animal/plant oil
	Stearic	C18	Animal/plant oil

triglyceride concentrations rise after a meal, unlike that of plasma cholesterol.

Phospholipids are complex lipids, similar in structure to triglycerides but containing phosphate and a nitrogenous base in place of one of the fatty acids. They fulfil an important structural role in cell membranes, and the phosphate group confers solubility on non-

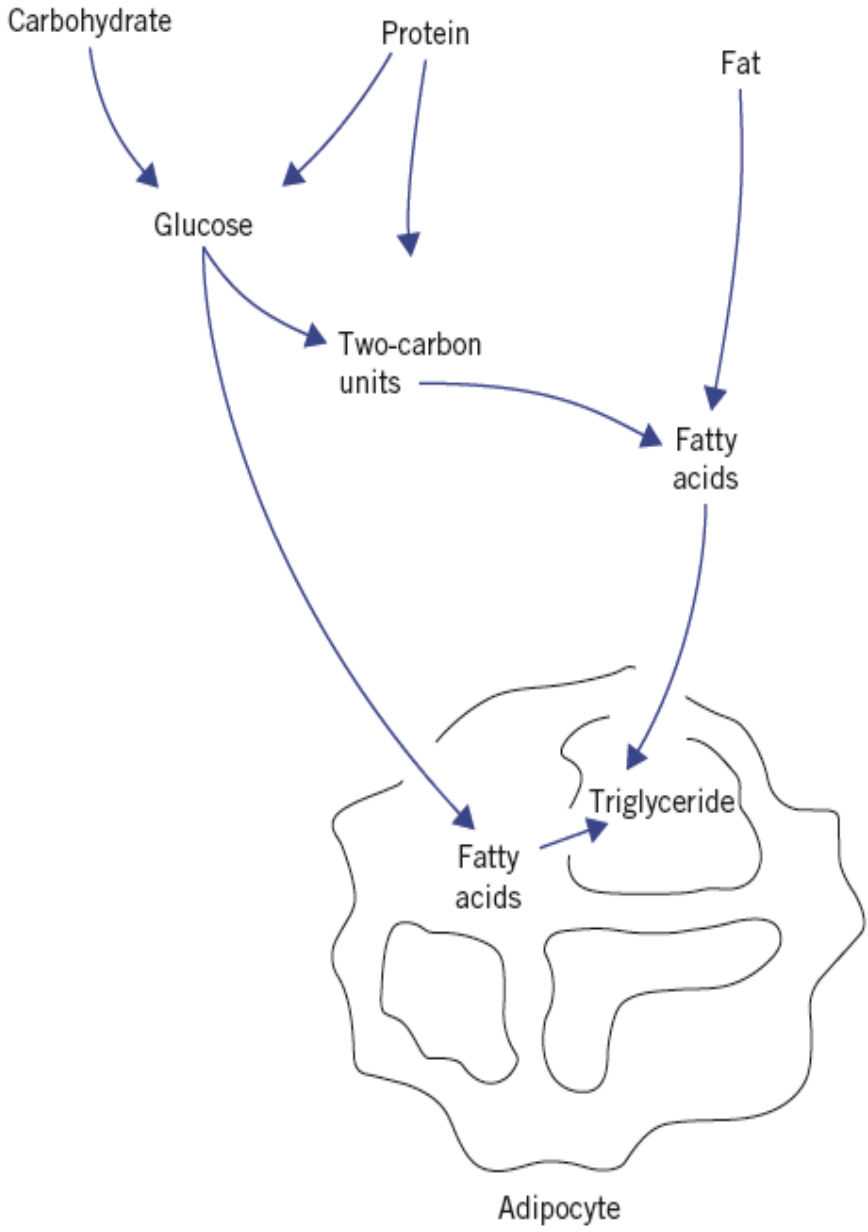

Figure 13.2 Summary of fatty acid synthesis and

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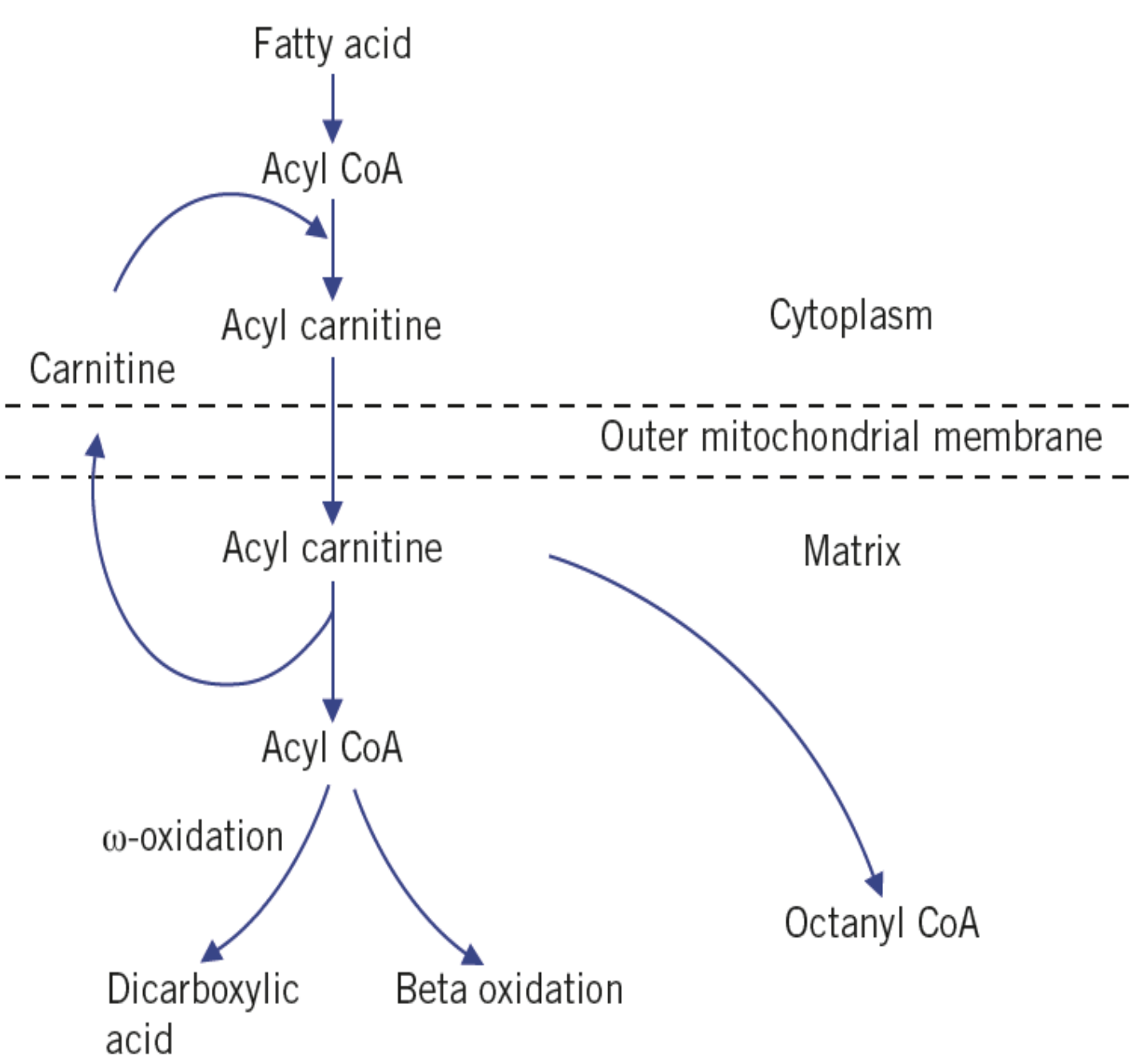


Figure 13.3 Summary of fatty acid oxidation. CoA,

LIPIDS ARE TRANSPORTED IN THE PLASMA AS LIPOPROTEINS

- Plasma lipids consist of **triacylglycerols (16%), phospholipids** (30%), **cholesterol (14%), and cholesteryl esters (36%) and a much smaller fraction of unesterified** long-chain fatty acids (free fatty acids) (4%). This latter fraction, the **free fatty acids (FFA), is metabolically** the most active of the plasma lipids.

Four Major Groups of Plasma Lipoproteins Have Been Identified

(1) **chylomicrons** derived from intestinal absorption of triacylglycerol and other lipids

(2) **Very low density lipoproteins (VLDL, or pre-β-lipoproteins)**, derived from the liver for the export of triacylglycerol

(3) **low-density lipoproteins (LDL, or β-lipoproteins)**, representing a final stage in the catabolism of VLDL

(4) **high-density lipoproteins (HDL, or α-lipoproteins)** (reverse cholesterol transport system)

Table 25–1. Composition of the lipoproteins in plasma of humans.

Lipoprotein	Source	Diameter (nm)	Density (g/mL)	Composition		Main Lipid Components	Apolipoproteins
				Protein (%)	Lipid (%)		
Chylomicrons	Intestine	90–1000	< 0.95	1–2	98–99	Triacylglycerol	A-I, A-II, A-IV,[1] B-48, C-I, C-II, C-III, E
Chylomicron remnants	Chylomicrons	45–150	< 1.006	6–8	92–94	Triacylglycerol, phospholipids, cholesterol	B-48, E
VLDL	Liver (intestine)	30–90	0.95–1.006	7–10	90–93	Triacylglycerol	B-100, C-I, C-II, C-III
IDL	VLDL	25–35	1.006–1.019	11	89	Triacylglycerol, cholesterol	B-100, E
LDL	VLDL	20–25	1.019–1.063	21	79	Cholesterol	B-100
HDL	Liver, intestine, VLDL, chylo-microns					Phospholipids, cholesterol	A-I, A-II, A-IV, C-I, C-II, C-III, D,[2] E
HDL_1		20–25	1.019–1.063	32	68		
HDL_2		10–20	1.063–1.125	33	67		
HDL_3		5–10	1.125–1.210	57	43		
Preβ-HDL[3]		< 5	> 1.210				A-I
Albumin/free fatty acids	Adipose tissue		> 1.281	99	1	Free fatty acids	

Abbreviations: HDL, high-density lipoproteins; IDL, intermediate-density lipoproteins; LDL, low-density lipoproteins; VLDL, very low density lipoproteins.

[1]Secreted with chylomicrons but transfers to HDL.

[2]Associated with HDL and HDL fractions

Lipoproteins Consist of a Nonpolar Core & a Single Surface Layer of Amphipathic Lipids

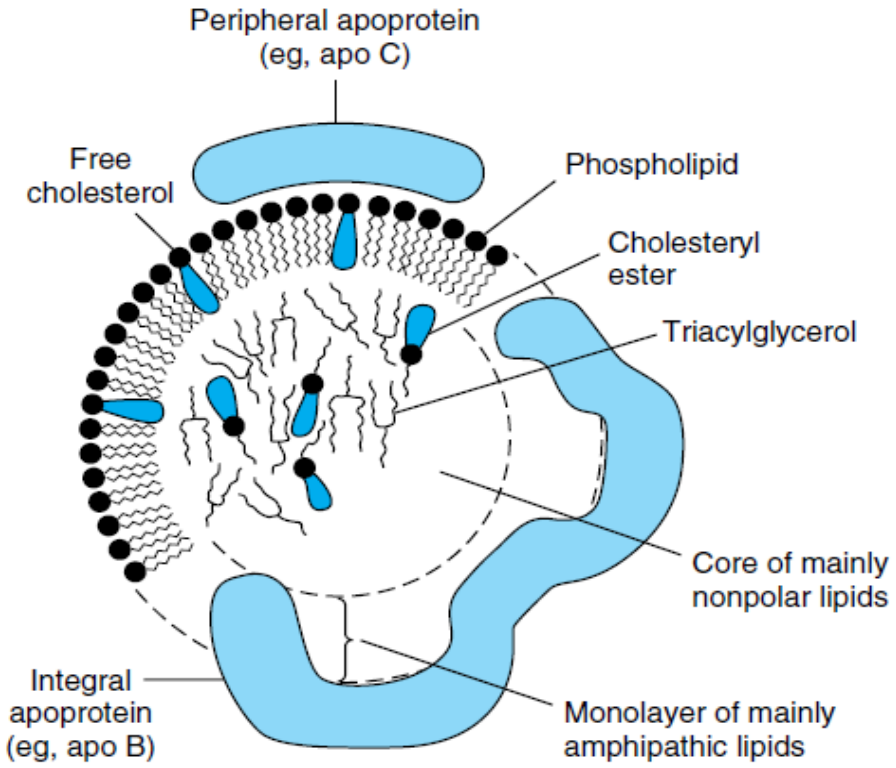


Figure 25–1. Generalized structure of a plasma lipoprotein. The similarities with the structure of the plasma membrane are to be noted. Small amounts of cholesteryl ester and triacylglycerol are to be found in the surface layer and a little free cholesterol in the core.

are also to be found in chyle; howeve
plasma **VLDL** are of hepatic origin. **The**
cles of transport of triacylglycerol fro
the extrahepatic tissues.

There are striking similarities in the
formation of chylomicrons by intestin
VLDL by hepatic parenchymal cells (Fig
haps because—apart from the mamma
intestine and liver are the only tissues fr
ticulate lipid is secreted. Newly secrete
chylomicrons and VLDL contain only a
of apolipoproteins C and E, and the full
acquired from HDL in the circulation
and 25–4). Apo B is essential for ch
VLDL formation. In **abetalipoproteine**
ease), lipoproteins containing apo B are
lipid droplets accumulate in the intestine

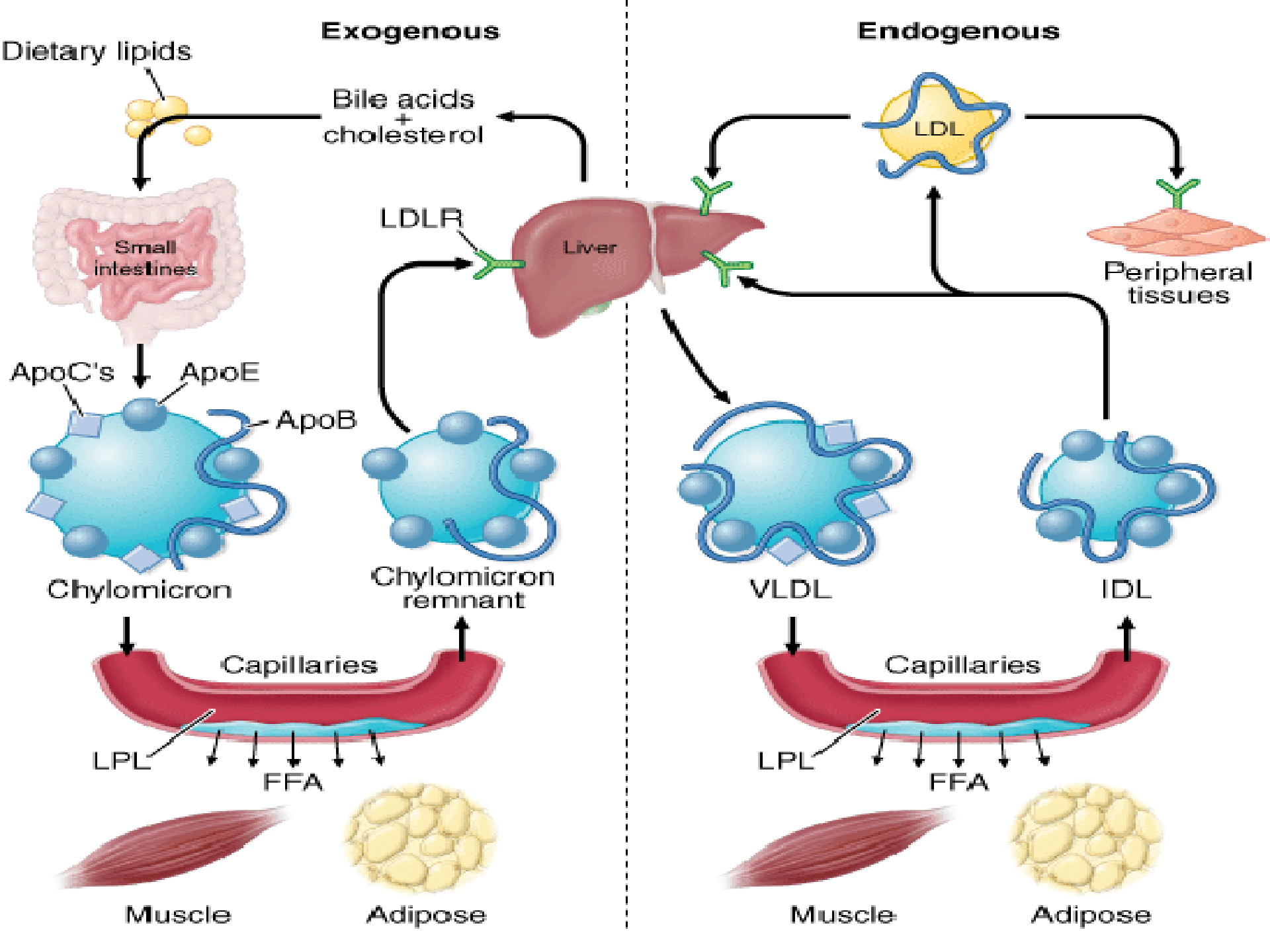
A more detailed account of the fact
hepatic VLDL secretion is given below.

CHYLOMICRONS & VERY LOW DENSITY LIPOPROTEINS ARE RAPIDLY CATABOLIZED

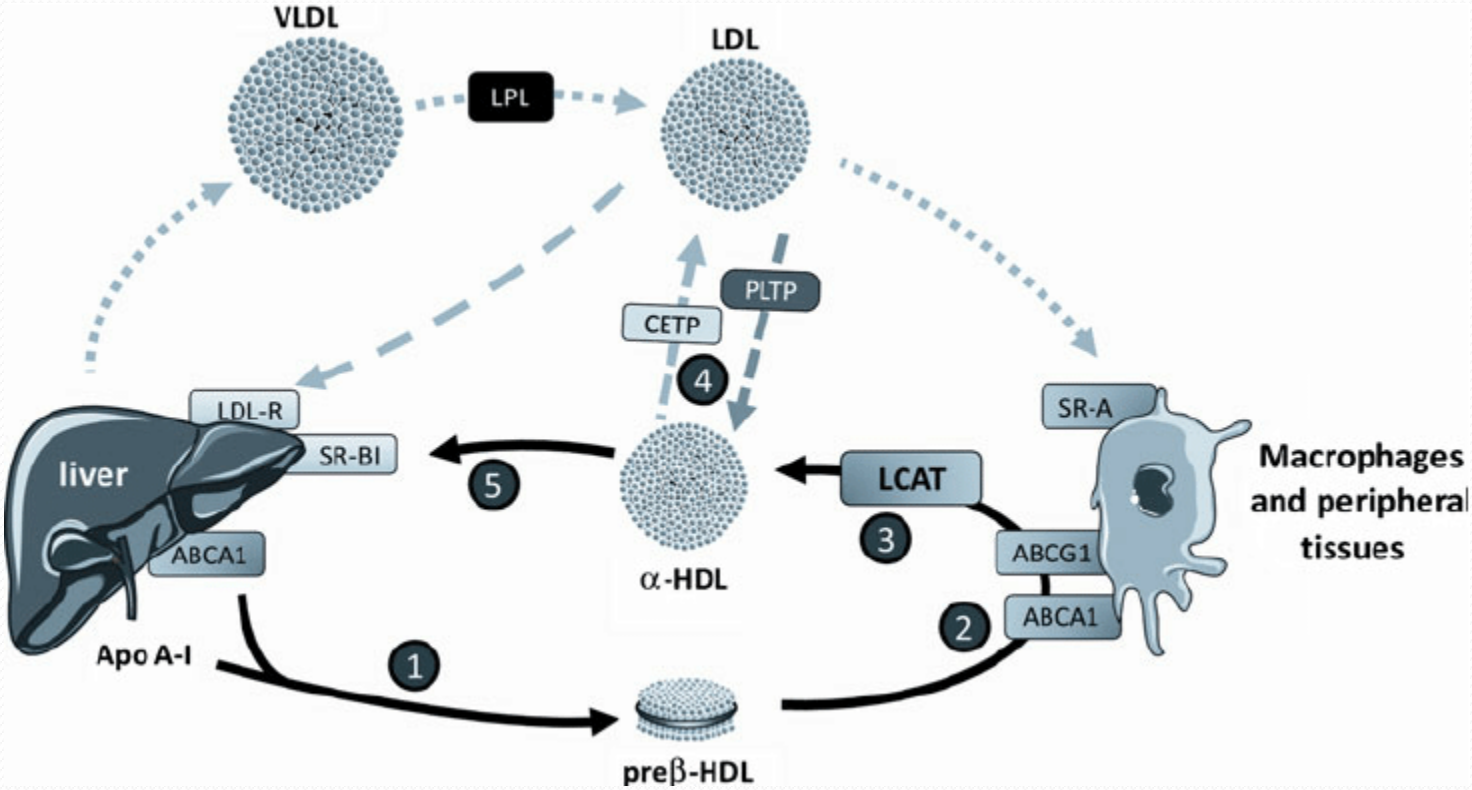
Table 13.4 The main apolipoproteins and their common functions

Apolipoprotein	Associated lipoprotein	Function
A_1	Chylomicrons and HDL	LCAT activator
A_2	Chylomicrons and HDL	LCAT activator
B_{48}	Chylomicrons and VLDL	Secretion of chylomicrons/VLDL
B_{100}	IDL, VLDL, LDL	LDL receptor binding
C_2	Chylomicrons, HDL, VLDL, IDL	Lipoprotein lipase activator
C_3	Chylomicrons, HDL, VLDL, IDL	Lipoprotein lipase inhibitor
E	Chylomicrons, HDL, VLDL, IDL	IDL and remnant particle receptor binding

HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein;


Exogenous
Endogenous
Dietary lipids
Bile acids
+
cholesterol
LDL
Small intestines
LDLR
Liver
Peripheral tissues
ApoC's
ApoE
ApoB
Chylomicron
Chylomicron remnant
VLDL
IDL
Capillaries
Capillaries
LPL
FFA
LPL
FFA
Muscle
Adipose
Muscle
Adipose

Reverse cholesterol transport pathway



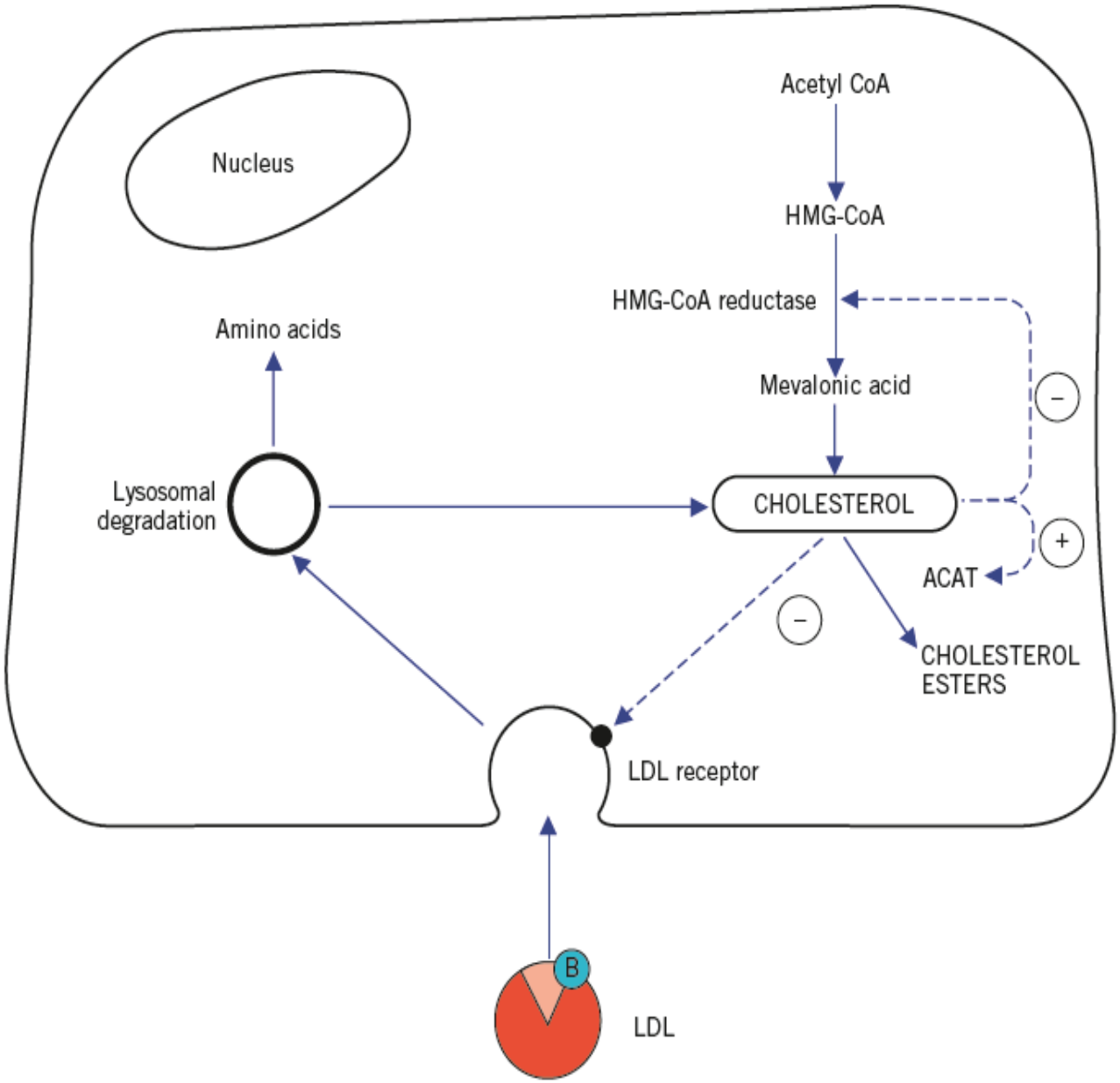


Figure 13.7 The low-density lipoprotein (LDL) receptor. ACAT, acyl coenzyme A acyl transferase; CoA, coenzyme A; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

	Unit	Optimal	Intermediate	High
Total Cholesterol	mg / dL	< 200	200 – 239	> 239
	mmol / dL	< 5.2	5.2 – 6.2	> 6.2
LDL Cholesterol (calculated)	mg / dL	< 130	130 – 159	> 159
	mmol / dL	< 3.36	3.36 – 4.11	> 4.11
HDL Cholesterol	mg / dL	> 60	60 – 40	< 40
	mmol / dL	> 1.55	1.55 – 1.03	< 1.03
Triglycerides	mg / dL	< 150	150 – 199	> 199
	mmol / dL	< 1.69	1.69 – 2,25	> 2,25
Non-HDL-C (calculated)	mg / dL	< 130	130 – 159	> 159
	mmol / dL	< 3.3	3.3 – 4.1	> 4.1
TG to HDL ratio (calculated)	mg / dL	< 3	3 – 3.8	> 3.8
	mmol / dL	< 1.33	1.33 – 1.68	> 1.68

LIPID PROFILE

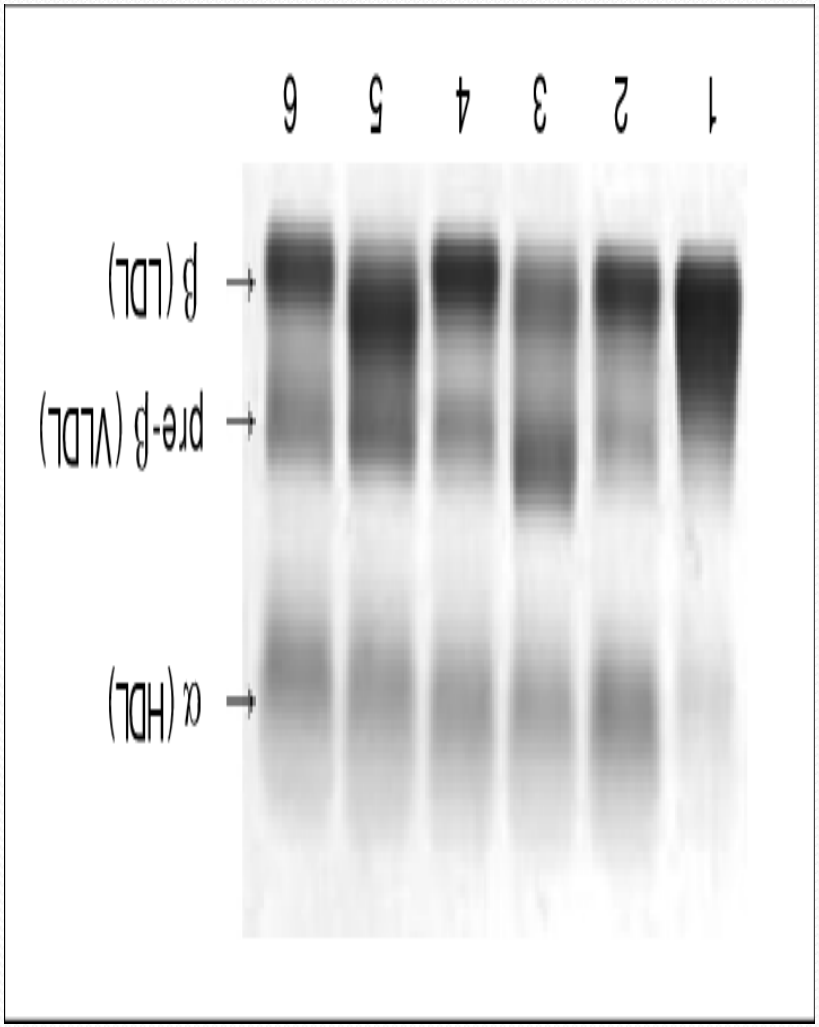
	DESIRABLE	BORDERLINE	HIGH RISK
Cholesterol	<200 mg/dl	200-239 mg/dl	240 mg/dl
Triglycerides	<150 mg/dl	150-199 mg/dl	200-499 mg/dl
HDL cholesterol	60 mg/dl	35-45 mg/dl	<35 mg/dl
LDL cholesterol	60-130 mg/dl	130-159 mg/dl	160-189 mg/dl
Cholesterol/ HDL ratio	4.0	5.0	6.0

Calculated LDL

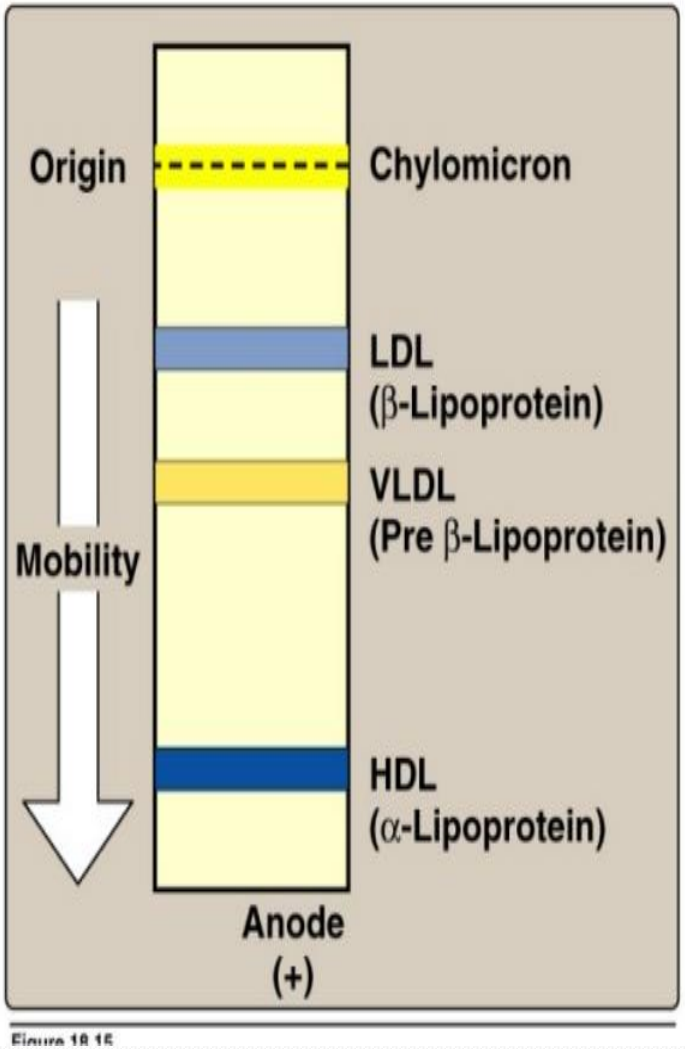
The Friedewald equation enables plasma LDL cholesterol concentration to be calculated and is often used in clinical laboratories:

LDL cholesterol (VLDL)
= total cholesterol – HDL cholesterol – [triglyceride/2.2]

This equation makes certain assumptions, namely that the patient is fasting and the plasma triglyceride concentration does not exceed 4.5 mmol/L (otherwise chylomicrons make the equation inaccurate).



Lipoprotein Electrophoresis



DISORDERS OF LIPID METABOLISM

Table 13.3 Fredrickson's classification of hyperlipidaemias

Type	Electrophoretic	Increased lipoprotein
I	Increased chylomicrons	Chylomicrons
IIa	Increased β-lipoproteins	LDL
IIb	Increased β and pre-β-lipoproteins	LDL and VLDL
III	Broad β-lipoproteins	IDL
IV	Increased pre-β-lipoproteins	VLDL
V	Increased chylomicrons and pre-β-lipoproteins	Chylomicrons and VLDL

IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

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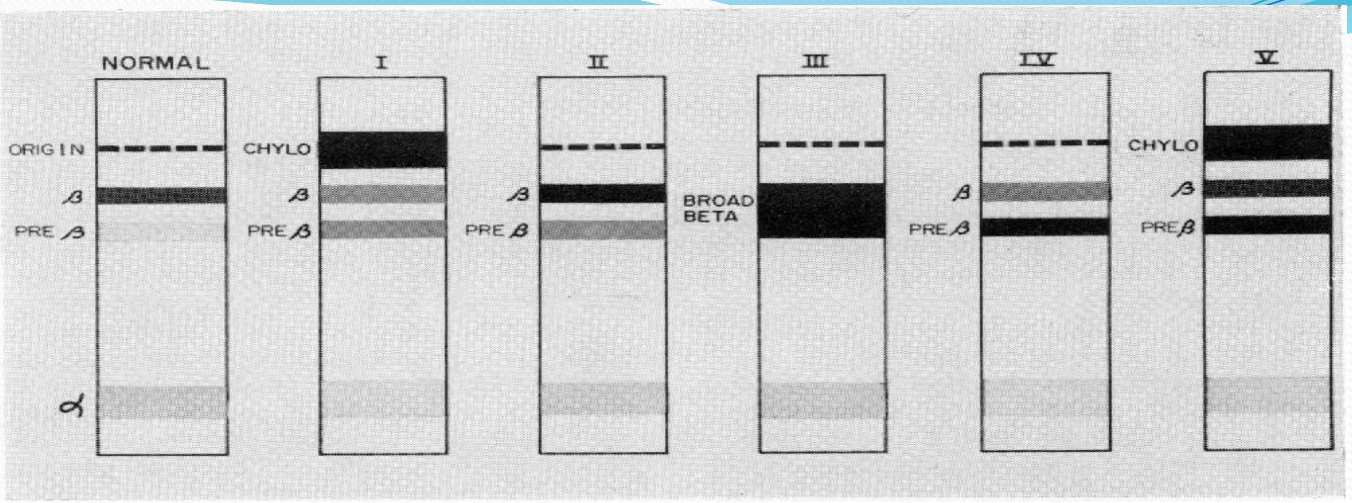
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α
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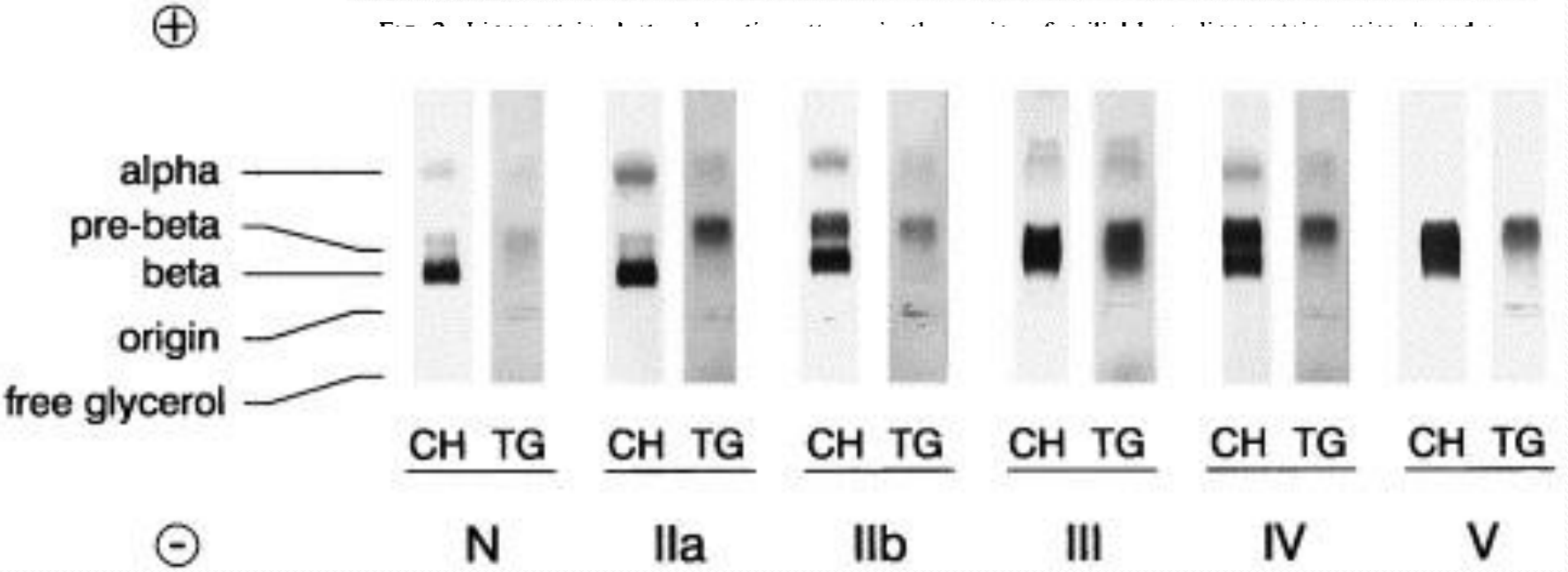
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1-Chylomicron syndrome

Causes:

1-Lipoprotein lipase deficiency.

2-Circulating inhibitors of lipoprotein lipase.

3-ApoC2 deficiency.

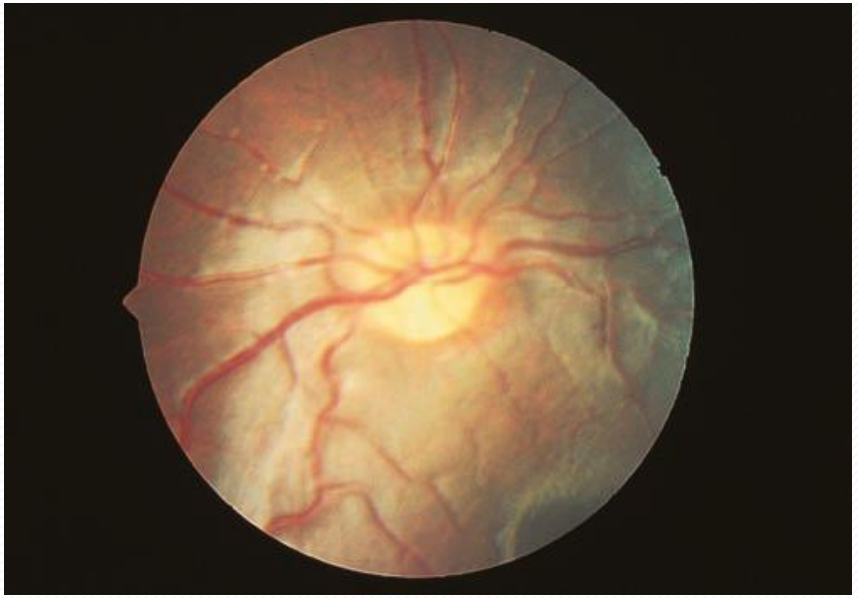
Clinical features:

Abdominal pain (often with acute pancreatitis) is typical., Lipid stigmata include eruptive xanthomata,hepatosplenomegaly and lipaemia retinalis .

To confirm the diagnosis of familial lipoprotein lipase deficiency,

plasma lipoprotein lipase can be assayed after the intravenous administration of heparin, which releases the enzyme from endothelial sites. The assay is complicated in that other plasma lipases (hepatic lipase and phospholipase, for example) contribute to the overall plasma lipase activity. Inhibition of lipoprotein lipase can be performed using protamine, high saline concentrations or specific antibodies and its overall activity can be calculated by subtraction.

Creamy layer and Lipaemia retinalis



2-Familial hypercholesterolaemia (FH)

Causes:

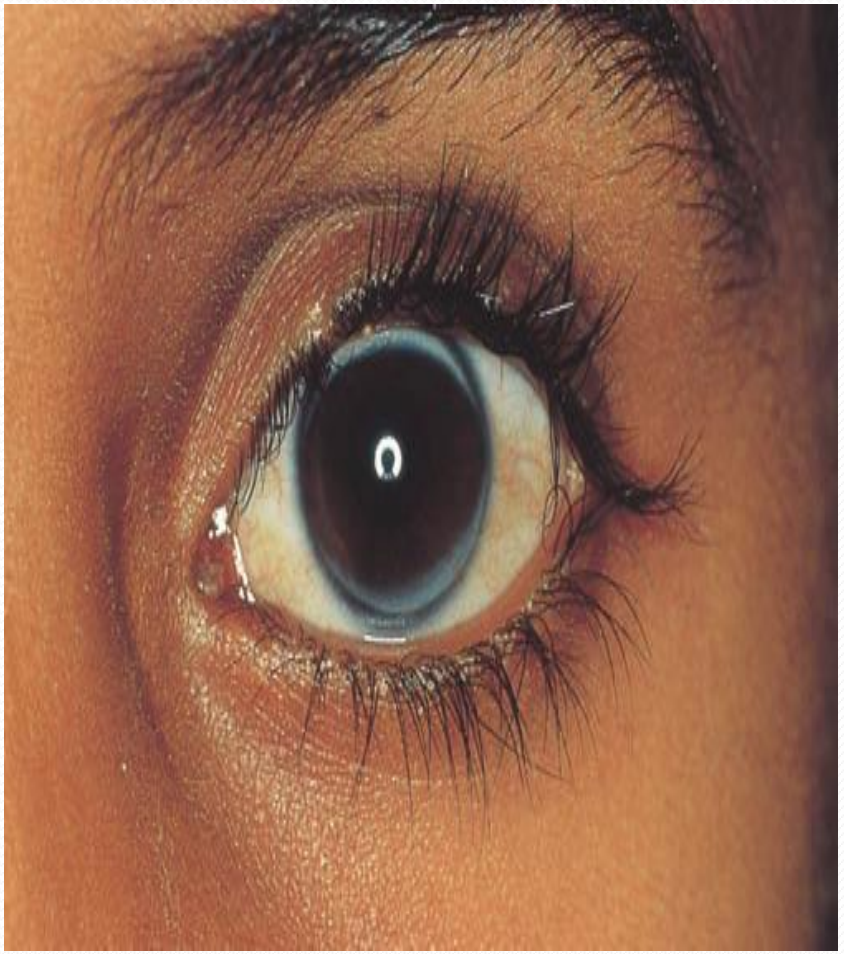
At least five types of mutation of the LDL receptor have been described, resulting in reduced synthesis, failure of transport of the synthesized receptor to the Golgi complex within the cell, defective LDL binding or inadequate expression or defective recycling of the LDL receptor at the cell surface.

Clinical features:

plasma cholesterol concentration of more than 7.5 mmol/L in an adult (more than 6.7 mmol/L in children under 16 years) or a plasma LDL cholesterol concentration of more than 4.9 mmol/L in an adult in the presence of tendon xanthoma. with a relatively normal plasma triglyceride . **type IIa and type IIb phenotype .**

The diagnosis of FH : assay of the LDL receptors and (DNA) screening is now important

Tendinous xanthomas and Corneal arcus in familial hypercholesterolaemia.



3-Familial defective apoB3500

Causes: mutation in the apoB gene resulting in a substitution of arginine at the 3500 amino acid position for glutamine. Apolipoprotein B is the ligand upon the LDL particle for the LDL receptor.

It may be indistinguishable clinically from FH and is also associated with hypercholesterolaemia and premature coronary artery disease.

4-Familial combined hyperlipidaemia (FCH)

Plasma cholesterol and plasma triglyceride are elevated . The Fredrickson's phenotypes seen in this condition include IIa, IIb and IV.

Plasma apoB is often elevated due to increased synthesis; LDL and VLDL .

The diagnosis can be difficult and it sometimes needs to be distinguished from FH (xanthomata are not usually present in FCH) and familial hypertriglyceridaemia (the IIa and IIb phenotypes are not usually found in familial hypertriglyceridaemia, although they are in FCH).

Children with FCH usually show hypertriglyceridaemia and not the type IIa phenotype (unlike the situation found in FH). Unlike familial hypertriglyceridaemia, plasma VLDL particles are usually smaller in FCH.

5-Familial hypertriglyceridaemia

Overproduction of VLDL or a decrease in VLDL conversion to LDL is likely . Often observed with low HDL cholesterol concentration.

Acute pancreatitis may also occur and is more likely

when the concentration of plasma triglycerides is more than 10 mmol/L. Some patients show hyperinsulinaemia and insulin resistance.

6-Type III hyperlipoproteinaemia

Also called familial dysbetalipoproteinaemia

or broad b-hyperlipidaemia. The underlying biochemical defect is one of a reduced clearance of chylomicron and VLDL remnants.

The name broad b-hyperlipidaemia is sometimes used

because of the characteristic plasma lipoprotein

electrophoretic pattern that is often observed (the

broad b-band that is seen being remnant particles).

The palmar striae (palmar xanthomata), hypercholesterolaemia and hypertriglyceridaemia, HDL

cholesterol concentration is usually low . The diagnosis is ultracentrifugation to separate the lipoprotein particles.

7-Hyperalphalipoproteinaemia

Elevated plasma HDL cholesterol concentration, total plasma cholesterol concentration can be elevated, with normal LDL cholesterol concentration. There is no increased prevalence of cardiovascular disease . Some causes of raised plasma high-density lipoprotein (HDL) cholesterol :

Primary

Hyperalphalipoproteinaemia

Cholesterol ester transfer protein deficiency

Secondary

High ethanol intake

Exercise

Certain drugs, e.g. estrogens, fibrates, nicotinic acid,

statins, phenytoin, rifampicin

hypoalphalipoproteinaemia

Primary

Familial hypoalphalipoproteinaemia

ApoA1 abnormalities

Tangier's disease (defect in the *ABC1) (*large, yellow tonsils, hepatomegaly and accumulation of cholesterol esters in the reticuloendothelial system.

Lecithin–cholesterol acyltransferase (LCAT) deficiency (Fish-eye disease)

Secondary

Tobacco smoking

Obesity

Poorly controlled diabetes mellitus

Insulin resistance and metabolic syndrome

Chronic kidney disease

Certain drugs, e.g. testosterone, probucol, b-blockers (without intrinsic sympathomimetic activity), progestogens, anabolic steroids, bexarotene

Abetalipoproteinaemia or LDL deficiency

Defects of apoB metabolism, impaired chylomicron and VLDL synthesis. failure of lipid transport from the liver and intestine. Transport of fat-soluble vitamins is impaired and steatorrhoea, progressive ataxia, retinitis pigmentosa and acanthocytosis (abnormal erthyrocyte shape) can result.

Secondary hyperlipidaemias

Predominant hypercholesterolaemia
Hypothyroidism
Nephrotic syndrome
Cholestasis, e.g. primary biliary cirrhosis
Acute intermittent porphyria
Anorexia nervosa/bulimia
Certain drugs or toxins, e.g. ciclosporin and chlorinated hydrocarbons

Predominant hypertriglyceridaemia
Alcohol excess
Obesity
Diabetes mellitus and metabolic syndrome
Certain drugs, e.g. estrogens, b-blockers (without intrinsic sympathomimetic activity), thiazide diuretics, acitretin, protease inhibitors, some neuroleptics and glucocorticoids
Chronic kidney disease
Some glycogen storage diseases, e.g. von Gierke's type I
Systemic lupus erythematosus
Paraproteinaemia

Patient preparation for lipid profile test

1-Consider whether the patient is on lipid-lowering therapy, including lipid-containing infusions.

2-overnight fasting for around 12 h and is allowed only water to drink .

3-The patient should be on his or her usual

diet for a couple of weeks preceding the test.

4-Plasma lipids should not be assessed in patients who

are acutely ill, for example acute myocardial infarction,

as plasma cholesterol concentration may be decreased

due to the acute-phase response. Wait for about

3 months after the event, although if a sample is taken

within 12 h of an event, a ‘true’ result may be obtained.

INVESTIGATION OF HYPERLIPIDAEMIAS

When faced with a hyperlipidaemia, decide whether it is primary or secondary. A family history, clinical features and appropriate blood tests can be useful to help make this decision. Lipid stigmata such as tendon xanthomata or premature corneal arci may point to familial hypercholesterolaemia, and tuberous xanthomata or

palmar striae to type III hyperlipoproteinaemia.

Blood glucose concentration is useful to help assess for diabetes mellitus, liver function tests for liver disease such as cholestasis, urinary protein and plasma albumin concentrations for nephrotic syndrome and thyroid function tests for hypothyroidism. It is also important to determine alcohol consumption and medications

from the clinical history.

Retest patients' lipids, a few months apart, reliance cannot be placed on just one set of readings