

# 13

## Plasma lipids and lipoproteins

### Lec. 5

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Lipids play a critical role in almost all aspects of biological life – they are structural components in cells and are involved in metabolic and hormonal pathways. The importance of having a knowledge of lipid disorders cannot be overstated, not least because they are common in clinical practice and, in some cases associated with atherosclerosis such as coronary heart disease, one of the biggest killers in urbanized societies.

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.

### PLASMA LIPIDS

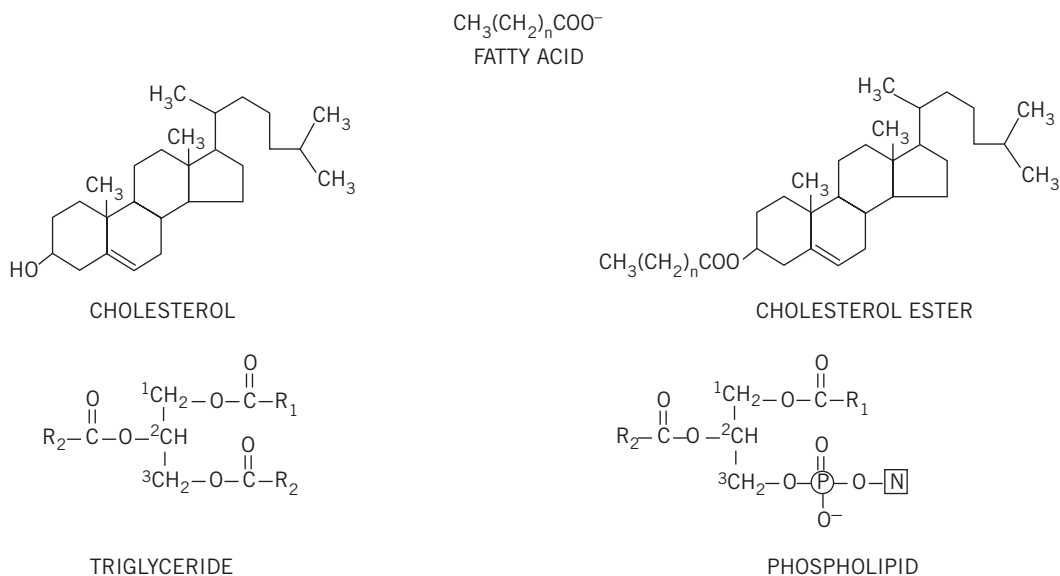
The chemical structures of the four main forms of lipid present in plasma are illustrated in Figure 13.1.

### FATTY ACIDS

These are straight-chain carbon compounds of varying lengths. They may be saturated, containing no double bonds, monounsaturated, with one double bond, or polyunsaturated, with more than one double bond (Table 13.1).

Fatty acids can esterify with glycerol to form triglycerides or be non-esterified (NEFAs) or free. Plasma NEFAs liberated from adipose tissue by lipase activity are transported to the liver and muscle mainly bound to albumin. The NEFAs provide a significant proportion of the energy requirements of the body. Summary diagrams of fatty acid synthesis and oxidation 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-polar lipids and cholesterol in lipoproteins.

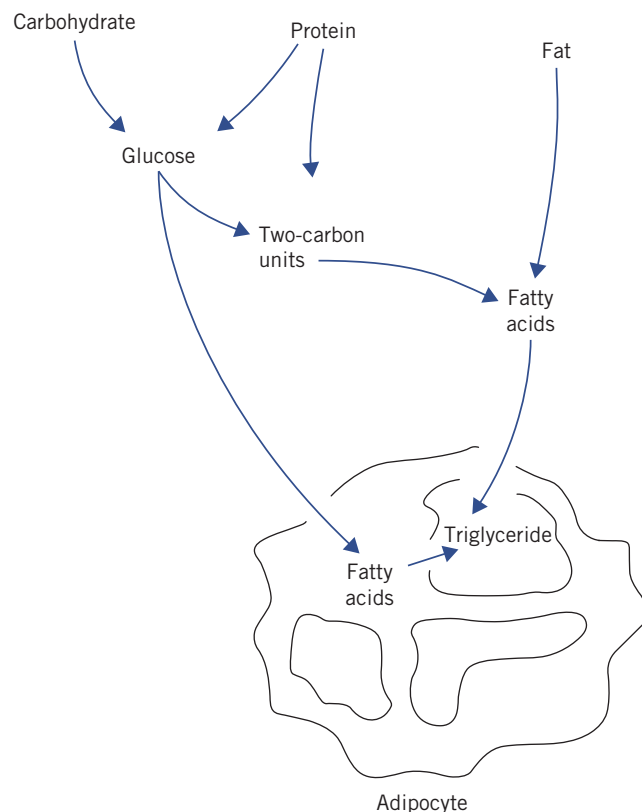
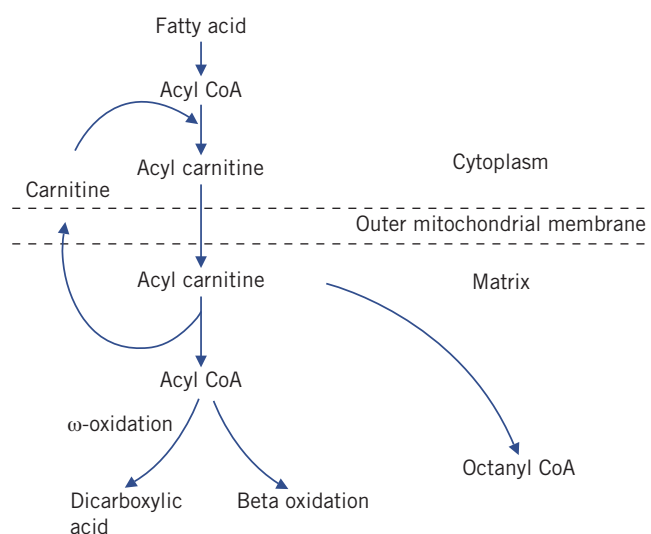
A family of nuclear receptors that are activated by fatty acids – called peroxisome proliferator-activated receptors (PPARs) – has been described and implicated in insulin resistance and dyslipidaemia. The PPARs can be subdivided into  $\alpha$ -PPARs, which are activated by fibrate drugs, and  $\gamma$ -PPARs, which are activated by thiazolidinedione drugs, for example pioglitazone or rosiglitazone.

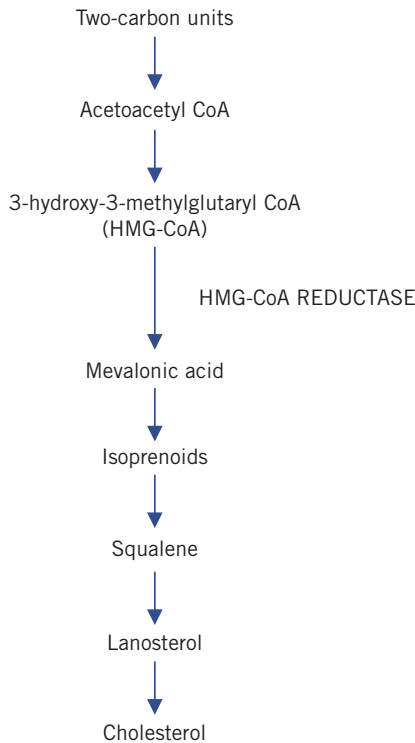
## CHOLESTEROL

Cholesterol is a steroid alcohol found exclusively in animals and present in virtually all cells and body fluids. It is a precursor of numerous physiologically important steroids, including bile acids and steroid hormones. A summary of the cholesterol synthetic pathways is shown in Figure 13.4. The rate-limiting enzyme is 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), which is controlled by negative feedback by the intracellular concentration. About two-thirds of the plasma cholesterol is esterified with fatty acids to form cholesterol esters.

## LIPOPROTEINS

Because lipids are relatively insoluble in aqueous media, they are transported in body fluids as, often spherical,

**Figure 13.2** Summary of fatty acid synthesis and adipose tissue substrates. Reproduced with kind permission from Candlish JK and Crook M. *Notes on Clinical Biochemistry*. Singapore: World Scientific Publishing, 1993.**Figure 13.3** Summary of fatty acid oxidation. CoA, coenzyme A. Reproduced with kind permission from Candlish JK and Crook M. *Notes on Clinical Biochemistry*. Singapore: World Scientific Publishing, 1993.



**Figure 13.4** Summary of pathways of cholesterol synthesis. CoA, coenzyme A. Reproduced with kind permission from Candlish JK and Crook M. *Notes on Clinical Biochemistry*. Singapore: World Scientific Publishing, 1993.

soluble protein complexes called lipoproteins. Lipids can be derived from food (exogenous) or synthesized in the body (endogenous). The water-soluble (polar) groups of proteins, phospholipids and free cholesterol face outwards and surround an inner insoluble (non-polar) core of triglyceride and cholesterol esters.

Lipoproteins are classified by their buoyant density, which inversely reflects their size. The greater the lipid to protein ratio, the larger their size and the lower the density. Lipoproteins can be classified into five main groups (Table 13.2). The first three are triglyceride

rich and, because of their large size, they scatter light, which can give plasma a turbid appearance (lipaemic) if present in high concentrations:

- Chylomicrons are the largest and least dense lipoproteins and transport exogenous lipid from the intestine to all cells.
- Very low-density lipoproteins (VLDLs) transport endogenous lipid from the liver to cells.
- Intermediate-density lipoproteins (IDLs), which are transient and formed during the conversion of VLDL to low-density lipoprotein (LDL), are not normally present in plasma.

The other two lipoprotein classes contain mainly cholesterol and are smaller in size:

- Low-density lipoproteins are formed from VLDLs and carry cholesterol to cells.
- High-density lipoproteins (HDLs) are the most dense lipoproteins and are involved in the transport of cholesterol from cells back to the liver (reverse cholesterol transport). These lipoproteins can be further divided by density into HDL<sub>2</sub> and HDL<sub>3</sub>.

If a lipaemic plasma sample, for example after a meal, is left overnight at 4°C, the larger and less dense chylomicrons form a creamy layer on the surface. The smaller and denser VLDL and IDL particles do not rise, and the sample may appear diffusely turbid. The LDL and HDL particles do not contribute to this turbidity because they are small and do not scatter light. Fasting plasma from normal individuals contains only VLDL, LDL and HDL particles.

In some cases of hyperlipidaemia, the lipoprotein patterns have been classified (Fredrickson’s classification) according to their electrophoretic mobility. Four principal bands are formed, based on their relative positions, by protein electrophoresis, namely α (HDL), pre-β (VLDL), β (LDL) and chylomicrons (Table 13.3).

**Table 13.2** Characteristics of major lipoproteins

Lipoprotein	Source	Composition (% mass)				Apolipoprotein	Electrophoretic mobility
		Pro	Cho	Tg	PL		
Chylomicrons	Gut	1	4	90	5	A, B, C, E	Origin
VLDL	Liver	8	25	55	12	B, C, E	Pre-β
LDL	VLDL via IDL	20	55	5	20	B	β
HDL	Gut/liver	50	20	5	25	A, C, E	α

Cho, cholesterol; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; PL, phospholipid; Pro, protein; Tg, triglyceride; VLDL, very low-density lipoprotein.

**Table 13.3** Fredrickson's classification of hyperlipidaemias

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

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

Intermediate-density lipoproteins in excess may produce a broad  $\beta$ -band. Some individuals with hyperlipidaemia may show varying electrophoretic patterns at different times.

Ultracentrifugation (separation based upon particle buoyant density) or electrophoretic techniques are rarely used in routine clinical practice as these may require completed apparatus and experienced operators. Instead, the lipoprotein composition of plasma may be inferred from standard clinical laboratory lipid assays. As fasting plasma does not normally contain chylomicrons, the triglyceride content reflects VLDL. Furthermore, generally about 70 per cent of plasma cholesterol is incorporated as LDL and 20 per cent as HDL. The latter particles, because of their high density, can be quantified by precipitation techniques that can assay their cholesterol content by subtraction, although direct HDL assays are now often used.

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

$$\begin{aligned} \text{LDL cholesterol} \\ = \text{total cholesterol} - \text{HDL cholesterol} \\ - \frac{[\text{triglyceride}]}{2.2} \end{aligned} \quad (13.1)$$

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).

There has been recent interest in the subdivision of LDL particles into small dense LDL<sub>2</sub> and LDL<sub>3</sub>, which appear to be more atherogenic and more easily oxidized than the larger LDL<sub>1</sub> particles. Additionally,

another lipoprotein called lipoprotein (a), or Lp(a), has been found. This is similar in lipid composition to LDL but has a higher protein content. One of its proteins, called apolipoprotein (a), shows homology to plasminogen and may disrupt fibrinolysis, thus evoking a thrombotic tendency. The plasma concentration of Lp(a) is normally less than 0.30 g/L and it is thought to be an independent cardiovascular risk factor.

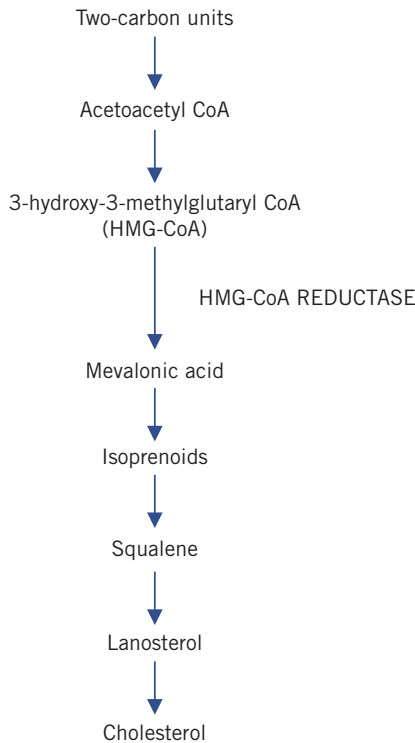
The proteins associated with lipoproteins are called apolipoproteins (apo). ApoA (mainly apoA<sub>1</sub> and apoA<sub>2</sub>) is the major group associated with HDL particles. The apoB series (apoB<sub>100</sub>) is predominantly found with LDL particles and is the ligand for the LDL receptor. Low-density lipoprotein has one molecule of apoB<sub>100</sub> per particle. Some reports have suggested that the plasma apoA<sub>1</sub> to apoB ratio may be a useful measure of cardiovascular risk (increased if the ratio is less than 1) and it is not significantly influenced by the fasting status of the patient. The apoC series is particularly important in triglyceride metabolism and, with the apoE series, freely interchanges between various lipoproteins. Some of the functions of these apolipoproteins are described in Table 13.4.

Lipoprotein-associated phospholipase A<sub>2</sub> [also called platelet-activating factor acetylhydrolase (PAF-AH)] is present mainly on LDL and to a lesser degree HDL. It is produced by inflammatory cells and is involved in atherosclerosis formation and levels are associated with increased risk of coronary artery disease and stroke.

**Table 13.4** The main apolipoproteins and their common functions

Apolipoprotein	Associated lipoprotein	Function
A <sub>1</sub>	Chylomicrons and HDL	LCAT activator
A <sub>2</sub>	Chylomicrons and HDL	LCAT activator
B <sub>48</sub>	Chylomicrons and VLDL	Secretion of chylomicrons/VLDL
B <sub>100</sub>	IDL, VLDL, LDL	LDL receptor binding
C <sub>2</sub>	Chylomicrons, HDL, VLDL, IDL	Lipoprotein lipase activator
C <sub>3</sub>	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; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.



**Figure 13.4** Summary of pathways of cholesterol synthesis. CoA, coenzyme A. Reproduced with kind permission from Candlish JK and Crook M. *Notes on Clinical Biochemistry*. Singapore: World Scientific Publishing, 1993.

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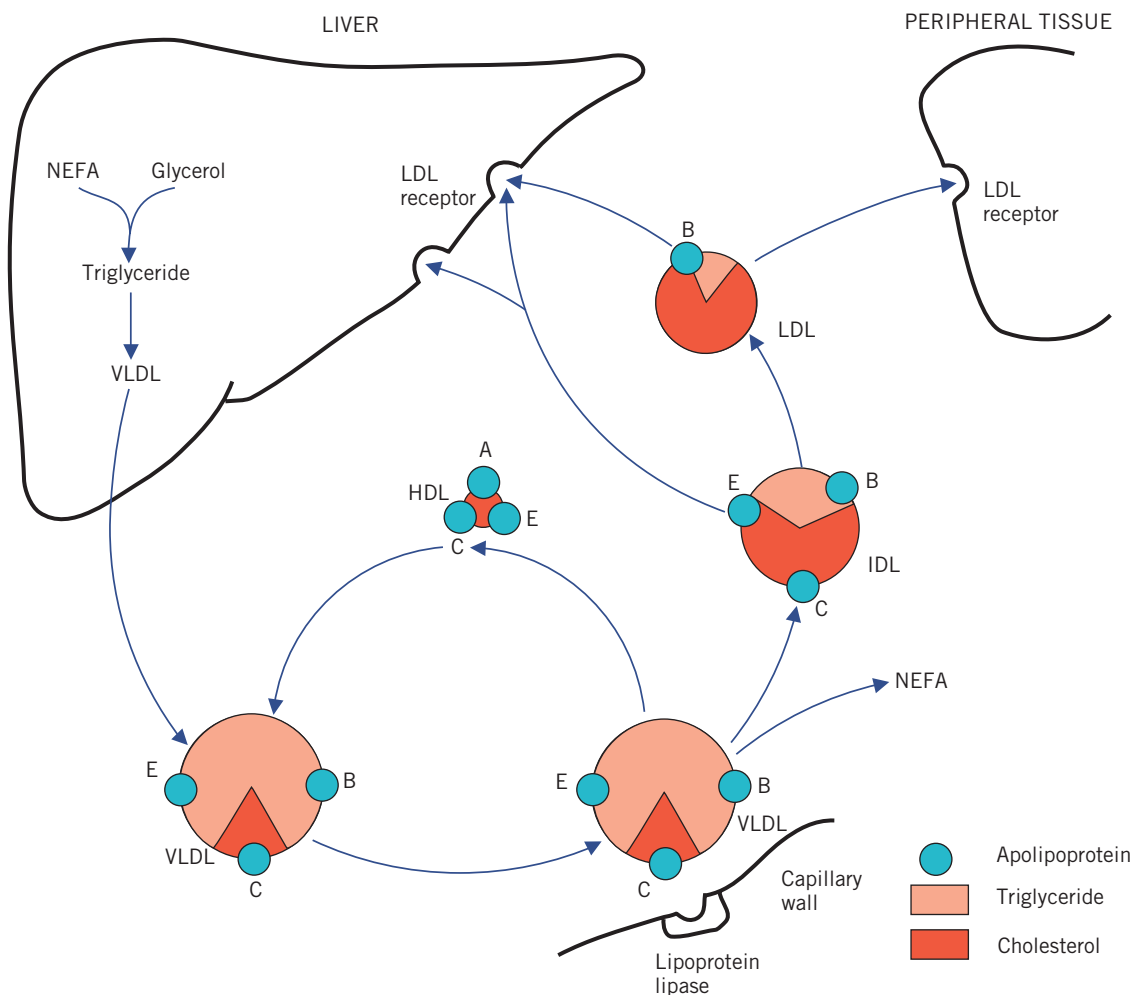
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Cho, cholesterol; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; PL, phospholipid; Pro, protein; Tg, triglyceride; VLDL, very low-density lipoprotein.



**Figure 13.6** Endogenous lipid pathways. HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; NEFA, non-esterified (free) fatty acid; VLDL, very low-density lipoprotein.

from chylomicron remnants via the exogenous pathway or synthesized locally. These lipids are transported from the liver as VLDL.

Very low-density lipoprotein is a large triglyceride-rich particle consisting also of apoB<sub>100</sub>, apoC and apoE. Following hepatic secretion, it incorporates additional apoC from HDL particles within the circulation. Like chylomicrons, VLDL is hydrolysed by lipoprotein lipase in the peripheral tissues, albeit more slowly. The resulting VLDL remnant or IDL contains cholesterol and triglyceride as well as apoB and apoE and is rapidly taken up by the liver or converted by the action of hepatic lipase to LDL by losing apoE and triglyceride.

Low-density lipoprotein is a small cholesterol-rich lipoprotein containing only apoB. It represents about 70 per cent of the total plasma cholesterol concentration. It can be taken up by most cells, although mainly the liver by the LDL or B/E receptor which recognizes and

binds apoB<sub>100</sub>. Within the cell, the LDL particles are broken down by lysosomes, releasing cholesterol. This cholesterol can be incorporated into cell membranes or in specific tissues such as the adrenal cortex or gonads and utilized in steroid synthesis.

Most cells are able to synthesize cholesterol, but, to avoid intracellular accumulation, there is a feedback control system reducing the rate of synthesis of the LDL receptors. Although most of the plasma LDL is removed by LDL receptors, if the plasma cholesterol concentration is excessive, LDL particles, by virtue of their small size, can infiltrate tissues by passive diffusion and can even cause damage, as in atheroma formation within arterial walls. An alternative route of removal of LDL is via the reticuloendothelial system, collectively termed the scavenger cell pathway, which recognizes only chemically modified LDL, for example oxidized LDL.



The liver has a central role in cholesterol metabolism:

- it contains most of the LDL receptors,
- it is responsible for most of the endogenous cholesterol synthesis,
- it takes up cholesterol from the diet via lipoproteins,
- it can excrete cholesterol from the body in bile.

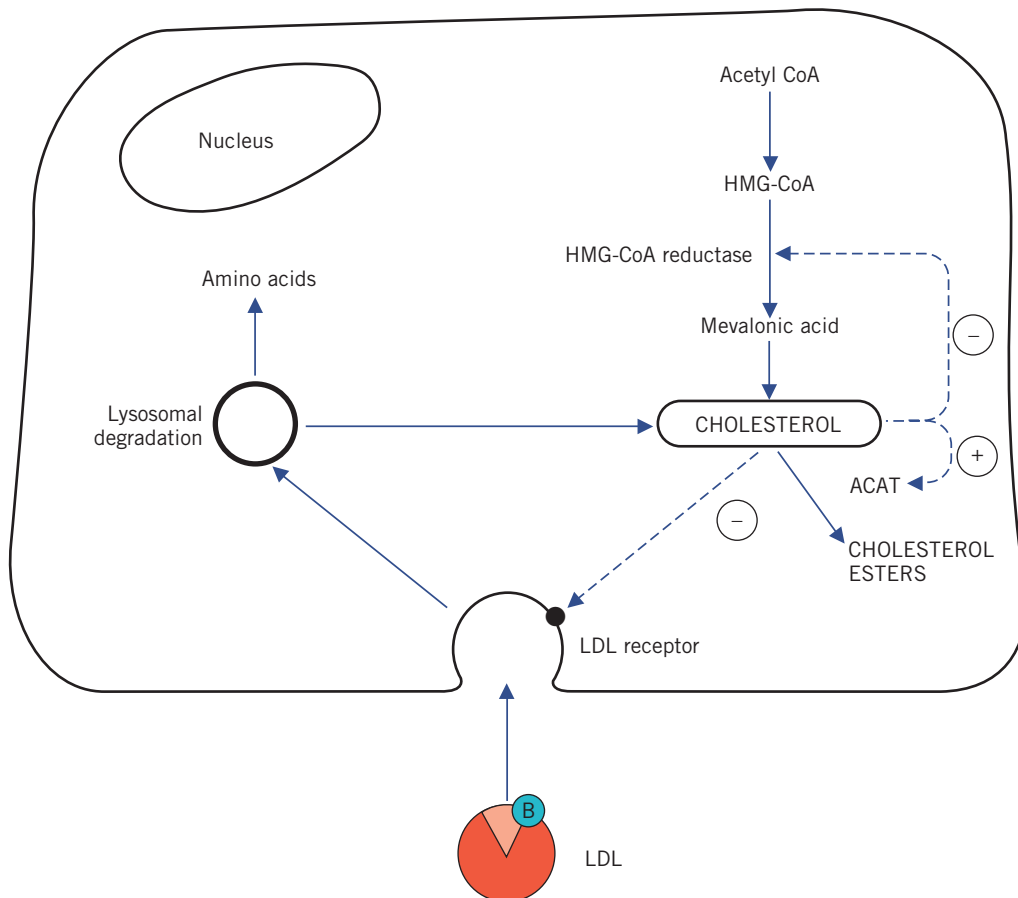
Cholesterol is synthesized via a series of enzymatic steps, with HMG-CoA reductase being the rate-limiting enzyme (Fig. 13.4). Suppression of this enzyme may occur if cholesterol synthesis is excessive. Involved in these processes is a family of transcription-regulating proteins called sterol regulatory element-binding proteins. Intracellular cholesterol accumulation also reduces the number of hepatic LDL receptors, and therefore LDL entry into cells declines and the plasma concentration rises. However, if the dietary intake of cholesterol is excessive, intracellular accumulation can still occur. About 30–60 per cent of the dietary intake of cholesterol (of 1–2 mmol) is absorbed, this amount being increased if the diet is rich in saturated fat. High

saturated fat intake can also suppress LDL receptor activity and is a bigger driver of cholesterol metabolism than dietary cholesterol. The richest dietary sources of cholesterol are egg yolks, dairy products and red meat.

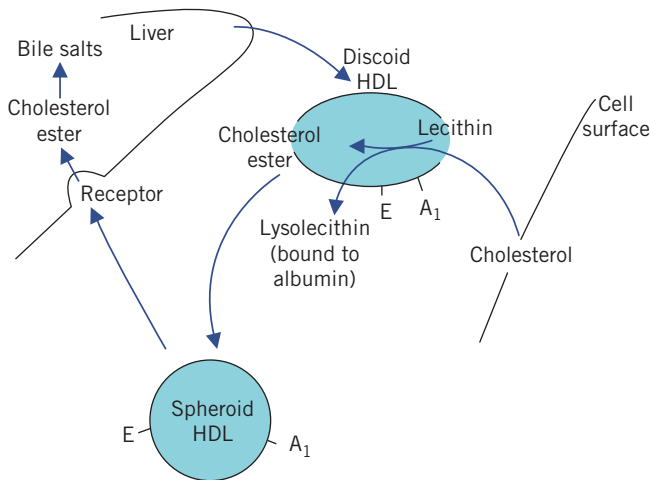
Net loss of body cholesterol can occur by bile excretion. Some bile salts are reabsorbed from the intestinal lumen and return to the liver via the enterohepatic circulation. Interruption of this process results in enhanced conversion of cholesterol to bile salts, reduced hepatic cholesterol stores and increased LDL receptors (Fig. 13.7). The rate of LDL receptor synthesis is also increased by thyroxine and oestrogens and decreases with age.

### High-density lipoprotein

The transport of cholesterol from non-hepatic cells to the liver involves HDL particles, in a process called reverse cholesterol transport (Fig. 13.8). The HDL is synthesized in both hepatic and intestinal cells and secreted from them as small, nascent HDL particles rich in free cholesterol, phospholipids, apoA and



**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.



**Figure 13.8** Reverse high-density lipoprotein (HDL) cholesterol transport. A1, apoA1; E, apoE. Reproduced with kind permission from Candlish JK and Crook M. *Notes on Clinical Biochemistry*. Singapore: World Scientific Publishing, 1993.

apoE. This cholesterol acquisition is stimulated by adenosine triphosphate-binding cassette protein 1 (ABC1). If the plasma concentration of VLDL or chylomicrons is low, apoC is also carried in HDL, but as the plasma concentrations of these lipoproteins rise, these particles take up apoC from HDL. In addition, HDL can be formed from the surface coat of VLDL and chylomicrons. Various factors control the rate of HDL synthesis, including oestrogens, thus explaining why plasma concentrations are higher in menstruating women than in menopausal women or men.

The enzyme lecithin–cholesterol acyltransferase (LCAT) is present on HDL and catalyses the esterification of free cholesterol and is activated by apoA<sub>1</sub>, the predominant apolipoprotein of HDL. Some HDL particles also contain apoA<sub>2</sub>. Most of this esterified cholesterol is transferred to LDL, VLDL and chylomicron remnants and thus ultimately reaches the liver. Some may be stored within the core of the HDL particle and taken directly to the liver. Cholesterol ester transfer protein (CETP) is involved in these processes.

The HDL particles can be divided into pre- $\beta$  (or precursor) HDL, HDL<sub>2</sub> and HDL<sub>3</sub>. The HDL<sub>2</sub>, which is a precursor of smaller HDL<sub>3</sub> particles, interconverts as a result of the acquisition of cholesterol by HDL<sub>3</sub> through the actions of LCAT and hepatic lipase.

High-density lipoprotein also contains other enzymes, including paroxanase, which may have an

antioxidant role. Removal of HDL may occur by endocytosis, although there may be specific receptors such as the murine class B type I scavenger receptor (SR-BI) in liver and steroidogenic tissue, for example adrenal glands, ovaries and testes. Thus HDL-derived cholesterol can be ‘off-loaded’ in the liver and secreted in bile or taken up and utilized for steroid synthesis.

In hypertriglyceridaemia there is increased VLDL concentration and, under the action of hepatic lipase, the HDL becomes overloaded with triglyceride; they reduce in size, losing apoA<sub>1</sub>, and the concentration of HDL cholesterol falls. Thus, in hypertriglyceridaemia one often sees an inverse relationship between plasma triglyceride and HDL cholesterol concentrations.

High-density lipoprotein cholesterol is cardioprotective not only because of the reverse cholesterol transport system, which helps to remove cholesterol from the peripheral tissues, but also because of the mechanisms that include increased atherosclerotic plaque stability, protection of LDL from oxidation, and maintaining the integrity of the vascular endothelium.

A plasma HDL cholesterol concentration of less than 1.0 mmol/L confers increased cardiovascular risk and can be raised by various lifestyle changes, such as smoking cessation, regular exercise and weight loss. The fibrate drugs or nicotinic acid are sometimes used if these measures fail (see later). A low HDL cholesterol concentration is associated with diabetes mellitus type 2, obesity and the metabolic syndrome (see Chapter 12). Concentration of plasma non-HDL cholesterol (total cholesterol – HDL cholesterol) may be a better indicator of cardiovascular risk than that of LDL cholesterol.

## DISORDERS OF LIPID METABOLISM

The study of hyperlipidaemias is of considerable importance, mainly because of the involvement of lipids in cardiovascular disease. Fredrickson, Levy and Lees first defined the hyperlipidaemias in a classification system based on which plasma lipoprotein concentrations were increased (Table 13.3). Although this so-called Fredrickson’s classification helped to put lipidology on the clinical map, it was not a diagnostic classification. It gives little clue as to the aetiology of the disorder; indeed, all of the phenotypes can be either primary or secondary. Furthermore, the Fredrickson type can change as a result of dietary or drug intervention. Nowadays, a more descriptive classification is used for the primary hyperlipidaemias, as follows.



### Chylomicron syndrome

This can be due to familial lipoprotein lipase deficiency, an autosomal recessive disorder affecting about 1 in 1 000 000 people. The gene for lipoprotein lipase is found on chromosome 8, and genetic studies have shown insertions or deletions within the gene. Lipoprotein lipase is involved in the exogenous lipoprotein pathway by hydrolysing chylomicrons to form chylomicron remnants, and also in the endogenous pathway by converting VLDL to IDL particles.

Presentation as a child with abdominal pain (often with acute pancreatitis) is typical. There is probably no increased risk of coronary artery disease. Gross elevation of plasma triglycerides due to the accumulation of uncleared chylomicron particles occurs (Fig. 13.9). Lipid stigmata include eruptive xanthomata, hepatosplenomegaly and lipaemia retinalis (Fig. 13.10).

Other variants of the chylomicron syndrome include circulating inhibitors of lipoprotein lipase and deficiency of its physiological activator apoC<sub>2</sub>. Apolipoprotein C<sub>2</sub> deficiency is also inherited as an autosomal recessive condition affecting about 1 in 1 000 000 people. The gene for apoC<sub>2</sub> is located on chromosome 19 and mutations resulting in low plasma concentrations have been found.



**Figure 13.9** Whole blood of a patient with lipoprotein lipase deficiency. Note chylomicron creamy appearance. Reproduced with kind permission from Nyhan WL and Barshop BA. *Atlas of Inherited Metabolic Diseases*, 3rd edition. London: Hodder Arnold, 2012.



**Figure 13.10** Lipaemia retinalis in a patient with lipoprotein lipase deficiency. Reproduced with kind permission from Nyhan WL and Barshop BA. *Atlas of Inherited Metabolic Diseases*, 3rd edition. London: Hodder Arnold, 2012.

Treatment of the chylomicron syndrome involves a low-fat diet, aiming for less than 20 g of fat a day, if possible, although compliance on such a diet may be difficult. Some clinicians supplement the diet with medium-chain triglycerides and also give 1 per cent of the total calorie intake as linoleic acid.

In cases of apoC<sub>2</sub> deficiency, fresh plasma may temporarily restore plasma apoC<sub>2</sub> levels. 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.

If apoC<sub>2</sub> deficiency is suspected, the plasma concentrations of this activator can be assayed. Patients may show a type I or type V Fredrickson's phenotype. Family members should be investigated.

### Familial hypercholesterolaemia

This condition is usually inherited as an autosomal dominant trait and was described by Goldstein and Brown. The inheritance of one mutant gene that encodes for the LDL receptor affects about 1 in every 500 people (more common in certain groups such as Afrikaners and French Canadians), resulting in

impaired LDL catabolism and hypercholesterolaemia. 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.

According to the Simon Broome register, definite familial hypercholesterolaemia (FH) is defined as a 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. Possible FH is defined as a 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, plus a family history of either an elevated plasma cholesterol concentration of more than 7.5 mmol/L in a first-degree or second-degree relative or myocardial infarction below the age of 50 years in a first-degree

relative or below the age of 60 years in a second-degree relative.

Typically, patients manifest severe hypercholesterolaemia, with a relatively normal plasma triglyceride concentration in conjunction with xanthomata, which can affect the back of the hands, elbows, Achilles tendons or the insertion of the patellar tendon into the pretibial tuberosity (Fig. 13.11). Premature cardiovascular disease is often observed, along with premature corneal arcus (Fig. 13.12).

Using the Fredrickson's classification, this condition has also been termed familial type IIa

## CASE 1

A 23-year-old woman had her plasma lipids checked by her general practitioner because her father had died of a myocardial infarction aged 44 years. Her 24-year-old brother had hyperlipidaemia. Her renal, liver and thyroid function tests were normal, as was her blood glucose.

### *Plasma (fasting)*

Cholesterol 11.4 mmol/L (3.5–5.0)

Triglyceride 1.1 mmol/L (0.3–1.5)

HDL cholesterol 1.2 mmol/L (1.0–1.8)

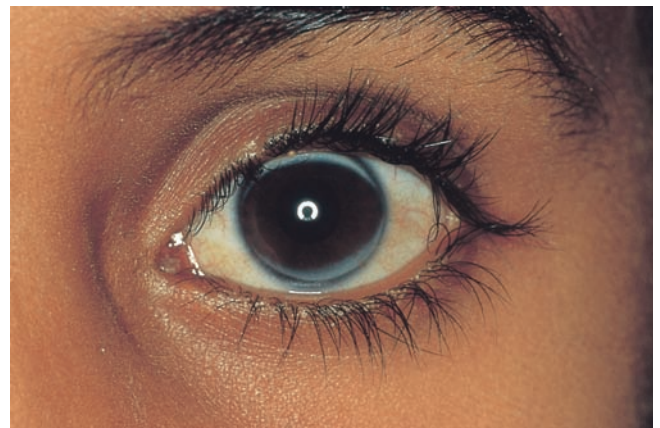
On examination, she had tendon xanthomata on her Achilles tendons and bilateral corneal arcus.

### DISCUSSION

Note the considerably raised plasma cholesterol concentration. The absence of an obvious secondary hyperlipidaemia, in conjunction with the family history of a first-degree relative with premature cardiovascular disease and hyperlipidaemia, suggests a genetic hyperlipidaemia. The presence of tendon xanthomata and premature corneal arcus supports the diagnosis of familial hypercholesterolaemia. This is usually an autosomal dominant disorder and usually a defect of the low-density lipoprotein (LDL) receptor.



**Figure 13.11** Tendinous xanthomas in familial hypercholesterolaemia. Reproduced with kind permission from Nyhan WL and Barshop BA. *Atlas of Inherited Metabolic Diseases*, 3rd edition. London: Hodder Arnold, 2012.



**Figure 13.12** Corneal arcus in familial hypercholesterolaemia. Reproduced with kind permission from Nyhan WL and Barshop BA. *Atlas of Inherited Metabolic Diseases*, 3rd edition. London: Hodder Arnold, 2012.

hyperlipoproteinaemia, although some patients may show a type IIb phenotype. Plasma HDL cholesterol concentration can vary in different individuals, although low concentrations may increase the likelihood of cardiovascular disease. It has been shown that in heterozygote FH there is more likely to be an increased amount of plasma Lp(a) in those subjects with cardiovascular disease.

The diagnosis of FH is usually obvious from the markedly elevated plasma cholesterol concentration and the presence of tendon xanthomata in the patient or first-degree relation. The diagnosis may not be so clear cut in patients without the lipid stigmata. A functional assay of the LDL receptors has recently been described using cultured lymphocytes, but this has not yet gained wide routine acceptance, and deoxyribonucleic acid (DNA) screening is now important. The response to a lipid-lowering diet is often disappointing and the treatment is usually with the HMG-CoA reductase inhibitors, that is, the statins.

Homozygous FH can be very severe. There is a considerable risk of coronary artery disease, aortic stenosis and early fatal myocardial infarction before the age of 20 years. Florid xanthoma occurs in childhood including tendon, planar and cutaneous types. Atheroma of the aortic root may manifest before puberty, associated with coronary ostial stenosis.

In homozygous FH, treatment to lower the plasma cholesterol concentration (which can be as high as 20 mmol/L or more) is essential in order to try to reduce the likelihood of sudden death due to coronary artery disease. Plasma exchange, LDL apheresis or heparin extracorporeal LDL precipitation (HELP) can be used in an attempt to remove the plasma LDL particles and thus reduce the plasma cholesterol concentration.

There is a rare recessive form of FH and also a form of FH associated with increased proprotein convertase subtilisin/kexin type 9 (PCSK9) expression which regulates LDL receptors.

#### Familial defective apoB<sub>3500</sub>

This condition is due to a 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. The treatment is similar to that for heterozygote FH. The apoB gene is located upon chromosome 2.

#### Familial combined hyperlipidaemia

In familial combined hyperlipidaemia (FCH), the plasma lipids may be elevated, plasma cholesterol concentrations often being between 6 mmol/L and 9 mmol/L and plasma triglyceride between 2 mmol/L and 6 mmol/L. The Fredrickson's phenotypes seen in this condition include IIa, IIb and IV. Familial combined hyperlipidaemia may be inherited as an autosomal dominant trait (although others suggest that there may be co-segregation of more than one gene). About 0.5 per cent of the European population is affected, and there is an increased incidence of coronary artery disease in family members. The metabolic defect is unclear, although plasma apoB is often elevated due to increased synthesis; LDL and VLDL apoB concentration is increased. The synthesis of VLDL triglyceride is increased in FCH and there may also be a relationship with insulin resistance.

The diagnosis of FCH is suspected if there is a family history of hyperlipidaemia, particularly if family members show different lipoprotein phenotypes. There is often a family history of cardiovascular disease. However, 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. Dietary measures and, if indicated, either a statin or a fibrate are sometimes used.

#### Familial hypertriglyceridaemia

Familial hypertriglyceridaemia is often observed with low HDL cholesterol concentration. The condition usually develops after puberty and is rare in childhood. The exact metabolic defect is unclear, although overproduction of VLDL or a decrease in VLDL conversion to LDL is likely. There may be an increased risk of cardiovascular disease. 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. Dietary measures, and sometimes lipid-lowering drugs such as the fibrates or  $\omega$ -3 fatty acids, are used to treat the condition.

#### Type III hyperlipoproteinaemia

This condition is also called familial dysbeta-lipoproteinaemia or broad  $\beta$ -hyperlipidaemia. The



underlying biochemical defect is one of a reduced clearance of chylomicron and VLDL remnants. The name broad  $\beta$ -hyperlipidaemia is sometimes used because of the characteristic plasma lipoprotein electrophoretic pattern that is often observed (the broad  $\beta$ -band that is seen being remnant particles).

An association with type III/broad  $\beta$ -hyperlipidaemia and homozygosity for apoE<sub>2</sub> or variants of apoE<sub>2</sub> has been described. Apolipoprotein E shows three common alleles, E<sub>2</sub>, E<sub>3</sub> and E<sub>4</sub>, coded for on chromosome 19, which are important for the binding of remnant particles to the remnant receptor.

The mechanism for the disorder seems to be that apoE<sub>2</sub>-bearing particles have poor binding to the apoB/E (remnant) receptor and thus are not effectively cleared from the circulation.

It is becoming apparent that it is not just inheriting the apoE<sub>2</sub> genotype that is important in developing broad  $\beta$ -hyperlipidaemia. The prevalence of the apoE<sub>2</sub>/E<sub>2</sub> genotype is about 1 in 100 in the general population, yet only about 1 in 5000–10 000 individuals manifest

type III hyperlipoproteinaemia. A concurrent increase in plasma VLDL concentration also seems necessary for the condition to be expressed, such as might occur in diabetes mellitus, hypothyroidism or obesity. Some patients may show either an autosomal recessive or a dominant mode of inheritance of the condition.

The palmar striae (palmar xanthomata) are considered pathognomonic for the disorder, but tuberoeruptive xanthomata, typically on the elbows and knees, xanthelasma and corneal arcus have also been described in this condition. Peripheral vascular disease is a typical feature of this hyperlipidaemic disorder, as is premature coronary artery disease.

Plasma lipid determination frequently reveals hypercholesterolaemia and hypertriglyceridaemia, often in similar molar proportions with plasma concentrations of around 9–10 mmol/L. Plasma HDL cholesterol concentration is usually low. Plasma LDL concentration may also be low due to the fact that there is reduced conversion from IDL particles, although it may also be normal or elevated.

Plasma lipoprotein electrophoresis can show the classic type III picture with a broad  $\beta$ -band composed of remnant particles, although this is not always present. An association of type III hyperlipoproteinaemia with homozygosity for apoE<sub>2</sub> has been described, and thus apoE phenotyping or genotyping by a specialized laboratory can be useful, although some patients with broad  $\beta$ -hyperlipidaemia can show other apoE phenotypes or variants.

Another investigation that can be useful in establishing the diagnosis is ultracentrifugation to separate the lipoprotein particles. The cholesterol of the VLDL particles is then quantified and expressed as a total of the plasma triglyceride concentration. In molar terms, normal individuals show a ratio of less than 0.30, while ratios more than 0.30 are more likely in type III hyperlipoproteinaemia, particularly nearer 0.60. Treatment consists of dietary measures, correcting the precipitating causes and either the statin or fibrate drugs.

#### Polygenic hypercholesterolaemia

This is one of the most common causes of a raised plasma cholesterol concentration. This condition is the result of a complex interaction between multiple environmental and genetic factors. In other words, it is not due to a single gene abnormality, and it is likely that it is the result of more than one metabolic defect. There is usually either an increase in LDL production

## CASE 2

A 43-year-old man attended the vascular surgery outpatient clinic for peripheral vascular disease. He was a non-smoker but had undergone a coronary artery bypass graft the year before. Some of his laboratory results were as follows:

#### Plasma (fasting)

Cholesterol 8.7 mmol/L (3.5–5.0)

Triglyceride 9.1 mmol/L (0.3–1.5)

HDL cholesterol 0.86 mmol/L (1.0–1.8)

His apolipoprotein E genotype was E<sub>2</sub>/E<sub>2</sub>

On examination, he had tuberous xanthomata and palmar striae.

#### DISCUSSION

The diagnosis was type III hyperlipoproteinaemia (familial dysbetalipoproteinaemia or broad  $\beta$ -hyperlipidaemia). Note the mixed hyperlipidaemia (both cholesterol and triglyceride concentrations raised) in an approximately 1:1 molar ratio and also apoE genotype E<sub>2</sub> homozygote (usual is apoE<sub>3</sub>/E<sub>3</sub>). The type III hyperlipoproteinaemia is associated with raised concentration of remnant lipoprotein particles, which are particularly atherogenic. Note also the characteristic lipid stigmata and premature peripheral vascular and coronary heart disease.

or a decrease in LDL catabolism. The plasma lipid phenotype is usually either IIa or IIb Fredrickson's phenotype. The plasma cholesterol concentration is usually either mildly or moderately elevated. An important negative clinical finding is the absence of tendon xanthomata, the presence of which would tend to rule out the diagnosis. Usually less than 10 per cent of first-degree relations have similar lipid abnormalities, compared with FH or FCH in which about 50 per cent of first-degree family members are affected. There may also be a family history of premature coronary artery disease. Individuals may have a high intake of dietary fat and be overweight. Treatment involves dietary intervention and sometimes the use of lipid-lowering drugs such as the statins.

### Hyperalphalipoproteinaemia

Hyperalphalipoproteinaemia results in elevated plasma HDL cholesterol concentration and can be inherited as an autosomal dominant condition or, in some cases, may show polygenic features. The total plasma cholesterol concentration can be elevated, with normal LDL cholesterol concentration. There is no increased prevalence of cardiovascular disease in this condition; in fact, the contrary probably applies, with some individuals showing longevity. Plasma HDL concentration is thought to be cardioprotective, and individuals displaying this should be reassured. Box 13.1 gives the causes of raised plasma HDL cholesterol concentrations.

### Secondary hyperlipidaemias

One should not forget that there are many secondary causes of hyperlipidaemia. These may present alone or sometimes concomitantly with a primary hyperlipidaemia. Some of the causes of secondary hyperlipidaemia are listed in Box 13.2. Secondary causes

#### Box 13.1 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

of hyperlipidaemia include obesity, type 2 diabetes mellitus, hypothyroidism, chronic kidney disease, cholestasis and certain drugs. The reader should refer to the other chapters in this book for details of the relevant diseases.

### Other lipid abnormalities

Inherited disorders of low plasma HDL concentration (hypoalphalipoproteinaemia) occur, and plasma HDL cholesterol concentration should ideally be more than 1.0 mmol/L. A number of such conditions have been described (such as apoA<sub>1</sub> deficiency), many of which are associated with premature cardiovascular disease. In Tangier's disease, individuals have very low levels of HDL, large, yellow tonsils, hepatomegaly and accumulation of cholesterol esters in the reticuloendothelial system. There is a defect in the *ABCI* gene involved in HDL transport. The causes of a low plasma HDL cholesterol concentration are shown in Box 13.3.

Defects of apoB metabolism have also been described. In abetalipoproteinaemia or LDL deficiency there is impaired chylomicron and VLDL synthesis. This results in a failure of lipid transport from the liver and intestine. Transport of fat-soluble vitamins is impaired and steatorrhoea, progressive ataxia, retinitis

#### Box 13.2 Some important causes of secondary hyperlipidaemia

##### 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,  $\beta$ -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

**Box 13.3** Causes of low plasma high-density lipoprotein (HDL) cholesterol**Primary**

Familial hypoalphalipoproteinaemia  
 ApoA<sub>1</sub> abnormalities  
 Tangier's disease  
 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, probutol,  $\beta$ -blockers (without intrinsic sympathomimetic activity), progestogens, anabolic steroids, bexarotene

pigmentosa and acanthocytosis (abnormal erythrocyte shape) can result. In hypobetalipoproteinaemia, a less severe syndrome occurs, sometimes due to a truncated form of apoB.

In LCAT deficiency, the accumulation of free unesterified cholesterol in the tissues results in corneal opacities, renal damage, premature atherosclerosis and haemolytic anaemia. The enzyme LCAT catalyses the esterification of free cholesterol. Another condition that is probably due to a defect of LCAT is fish-eye disease, in which there may be low HDL cholesterol concentrations and eye abnormalities.

**Lipid-lowering therapy**

The help of a dietitian is invariably useful in treating dyslipidaemias. Low-saturated fat/reduced cholesterol diets are instigated. Total fat intake should be less than 30 per cent of the total calorie intake, with an increase in monounsaturated fat intake up to 20 per cent of total calories. Dietary cholesterol intake should not exceed about 200 mg/day. Five daily portions of fruit and vegetables are advisable. Ideally, patients should aim to achieve their recommended body mass index. Alcohol intake should be less than 14 units/week for females and 21 units/week for males. Increased intake of plant sterols and stanols may lead to competition for cholesterol intestinal absorption, thereby reducing the plasma cholesterol concentration. If diet and lifestyle measures fail, drug therapy may be indicated (Table 13.5).

**Table 13.5** Some lipid-lowering drugs and their effects on plasma lipoprotein fractions

Drug	Cho	Tg	HDL	LDL
Statins	↓↓↓	↓	↑	↓↓↓
Fibrates	↓/-	↓↓↓	↑↑	↓/-
Bile salt-sequestering agents	↓	↑/-	↑	↓
Ezetimibe	↓↓	↓	↑	↓↓
Nicotinic acid	↓↓	↓↓↓	↑↑↑	↓↓
$\omega$ -3 fats	↓/-	↓↓	↑/-	↓/-

Cho, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Tg, triglyceride.

↓, reduced; -, no major change; ↑, raised.

The rate-limiting enzyme of cholesterol synthesis, HMG-CoA reductase, is inhibited by HMG-CoA reductase inhibitors, also known as the statins, which can be used to treat hypercholesterolaemia. These agents include lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin and rosuvastatin. The HDL cholesterol concentration is modestly increased and triglyceride concentration reduced by varying degrees by these agents. The side effects notably include myalgia, myositis (and rarely rhabdomyolysis) and abnormal liver function.

Bile salt sequestrants such as colestipol and colestyramine bind bile salts in the intestinal lumen and thus interrupt their reabsorption and reutilization. The removal of bile acids stimulates hepatic cholesterol synthesis, which in turn results in an increase in hepatic LDL receptors, resulting in decreased plasma LDL concentration. The side effects include gastrointestinal symptoms, such as constipation. To avoid interference with their absorption, these drugs should not be given at the same time as other drugs. They lower plasma cholesterol concentration by about 10–20 per cent; although HDL cholesterol concentration is also modestly raised, triglyceride concentrations can be paradoxically increased. Another agent acting on the gut is ezetimibe, which inhibits intestinal cholesterol uptake specifically.

The fibrate drugs include gemfibrozil, bezafibrate, fenofibrate and ciprofibrate. These drugs have good triglyceride-lowering and HDL-raising abilities, although LDL cholesterol concentration may not be much changed. They are PPAR  $\alpha$ -agonists and work on a number of lipid pathways, including increasing lipoprotein lipase activity, reducing apoC<sub>3</sub> and VLDL synthesis and increasing apoA<sub>1</sub> synthesis. The side



effects include myalgia, myositis and gastrointestinal disturbance, and they should not be used in patients with active gallstones or significant renal disease. They can lower plasma alkaline phosphatase concentration, which can be used to monitor drug compliance.

Nicotinic acid and its derivatives have been used to reduce VLDL secretion and LDL concentration and, interestingly, also Lp(a) levels. This drug is good at raising HDL cholesterol. However, the side effects include hepatic toxicity, hyperuricaemia, impaired glucose tolerance and flushing.  $\omega$ -3 fatty acids in the form of fish oils or flaxseed oil can lower plasma triglyceride concentrations by reducing VLDL synthesis. They also have an antiplatelet aggregatory action. They can sometimes be used to treat severe hypertriglyceridaemia. However, they show little, if any, LDL-lowering activity. Their side effects may include gastrointestinal upset or bruising. The plant sterols and stanols can also lower serum LDL-cholesterol, probably by interrupting gut micelle formation, and hence reduce cholesterol absorption.

Combination drug therapy is sometimes used, for example statin/ezetimibe or statin/nicotinic acid, but is best instigated by an expert with close monitoring, as dangerous side effects may be increased.

#### Coronary artery disease and prevention: the importance of lipid lowering

Coronary artery disease remains one of the major causes of morbidity and mortality in the industrial world. Traditionally, the major risk factors are hyperlipidaemia, hypertension and smoking, to which can be added diabetes mellitus, a family history of premature coronary heart disease and obesity.

With primary (the prevention of the occurrence) and secondary (the prevention of further occurrences) coronary heart disease prevention in mind, the usual strategy adopted is to try to reduce the modifiable risk factors. Cardiovascular risk factors tend to cluster together in individuals and interact in such a way that the overall combined effect is greater than the combined risk of individual factors (see Chapter 22).

#### INVESTIGATION OF HYPERLIPIDAEMIAS

Before collecting blood, consider whether the patient is on lipid-lowering therapy, including lipid-containing infusions. Also ensure that the patient fasts overnight for around 12 h (if safe to do so) and is allowed only water to drink, if required. Although plasma cholesterol

### CASE 3

A 15-year-old woman presented to the surgical unit with acute pancreatitis. Some of her laboratory results were as follows:

#### *Plasma (fasting)*

Cholesterol 33.4 mmol/L (3.5–5.0)  
Triglyceride 69.1 mmol/L (0.3–1.5)  
HDL cholesterol 0.9 mmol/L (1.0–1.8)  
Amylase < 20 U/L (<200)

On examination, she had eruptive xanthomata on her arms and thighs and fundoscopy revealed lipaemia retinalis.

#### DISCUSSION

This patient has grossly elevated lipid concentrations with severe hypertriglyceridaemia. The blood sample would be lipaemic and some plasma sodium assays (indirect ion electrodes) may show pseudohyponatraemia. She was found to have lipoprotein lipase deficiency when this enzyme was measured before and after heparin administration, which releases the enzyme from capillaries into the circulation. Lipoprotein lipase deficiency can result in the chylomicron syndrome and eruptive xanthomata may be present. Plasma amylase concentration is normally elevated in acute pancreatitis but, due to the gross lipaemia, the assay was unsatisfactory, giving a spuriously low result. The latter is an important practical point and a spot urinary amylase may be preferable, or assay of plasma amylase after separation from the lipid fraction, under such circumstances.

concentration is little affected by fasting, triglyceride concentrations rise and HDL cholesterol concentration decreases if not, and thus ideally fasting samples should be requested. The patient should be on his or her usual diet for a couple of weeks preceding the test.

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.

Posture can alter plasma lipid concentrations: in the upright position, plasma cholesterol concentration can be 10 per cent higher than in the recumbent position.

The blood sample should be taken to the laboratory and assayed promptly. The usual fasting lipid profile consists of plasma cholesterol, triglyceride and HDL cholesterol concentrations.

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 arcus 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.

It is generally wise to retest patients' lipids, a few months apart, as it is recognized that the within-individual variation of lipids can be significant, and reliance cannot be placed on just one set of readings.

It is also useful to assess the patient for other cardiovascular risk factors, including smoking habits, diabetes mellitus, blood pressure, body weight and family history of cardiovascular disease. These should also be managed in their own right. Assessment should also be made for possible atherosclerotic disease, for example does the patient have evidence of coronary, peripheral or carotid artery disease?

If the patient is known to have coronary artery disease, aim for a plasma LDL cholesterol concentration of about 2.0 mmol/L. Statins are first-line drugs for patients with raised LDL cholesterol concentration.

Alternatively, there may be a place for a fibrate drug if fasting plasma triglyceride concentrations are raised by more than 5 mmol/L, particularly if there is also a low HDL cholesterol concentration and LDL cholesterol concentration is not much raised. The ideal is to aim for fasting plasma cholesterol concentration of about 4.0 mmol/L, triglyceride concentration less than 1.5 mmol/L and HDL cholesterol concentration more than 1.0 mmol/L.

Severe hypertriglyceridaemia, particularly if the plasma triglyceride concentration is more than 10 mmol/L, is a risk factor for acute pancreatitis. Low-fat diets may help in conjunction with a fibrate (sometimes  $\omega$ -3 fatty acids are used), aiming ideally for a fasting plasma triglyceride concentration lower than about 1.5 mmol/L. Remember that severe hypertriglyceridaemia can cause problems with certain assays, for example falsely low plasma amylase concentration or pseudohyponatraemia.

In terms of primary coronary heart disease prevention, the use of a cardiovascular risk factor assessment may be helpful to determine if a lipid-lowering drug is indicated, for example Framingham Study-based or QRISK cardiovascular risk calculators. Close family members should be screened in cases of genetic hyperlipidaemias such as FH.

Specialist lipid assays may help define the abnormality. The apoE genotype is useful in the diagnosis of type III hyperlipoproteinaemia, as many of these patients are apoE<sub>2</sub>/E<sub>2</sub>. Plasma lipoprotein lipase and apoC<sub>2</sub> (its activator) assays may be useful in chylomicron syndrome, and LDL receptor DNA studies for familial hypercholesterolaemia. Plasma apoA<sub>1</sub> and apoB concentrations and also Lp(a) may help define risk status.

## SUMMARY

- Lipids are essential for health, but raised plasma cholesterol and triglyceride concentrations are associated with an increased incidence of cardiovascular disease.
- Conversely, plasma HDL cholesterol is cardioprotective, partly because of its central role in reverse cholesterol transport returning cholesterol from the tissues to the liver.
- There are many cases of secondary hyperlipidaemias, including obesity, alcohol excess, diabetes mellitus, hypothyroidism, chronic kidney disease and cholestasis.
- The genetic hyperlipidaemias include FH, FCH and type III hyperlipoproteinaemia. Familial hypercholesterolaemia usually results from a defect of the LDL receptor.
- The statins or HMG-CoA reductase inhibitors lower plasma cholesterol concentration and are associated with decreased cardiovascular disease.