Lipid Metabolism Disorders

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 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.

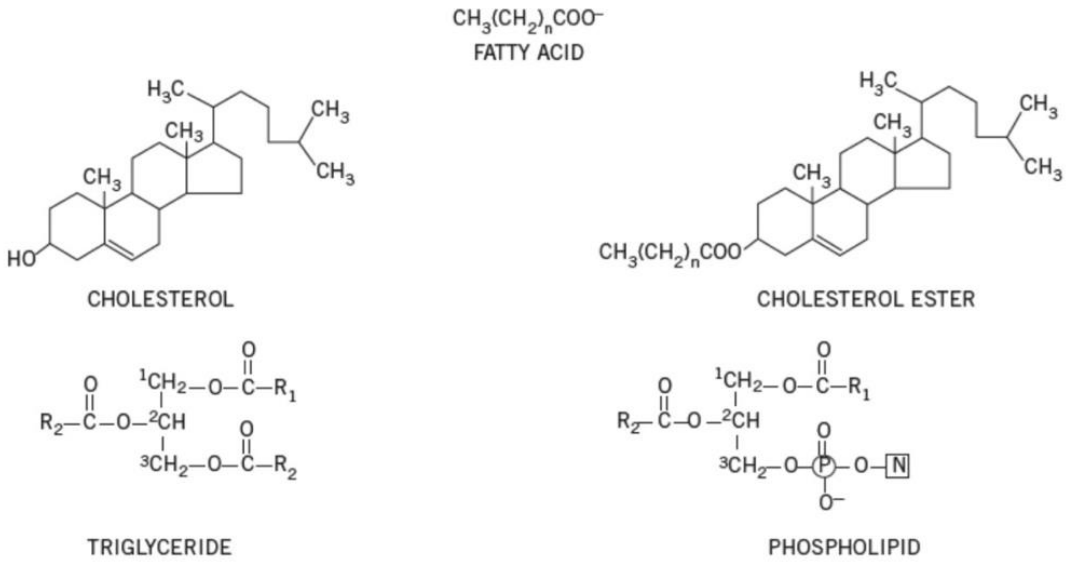

Figure 13.1 Lipid structures. P, phosphate; N, nitrogenous base; R, fatty acid.

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

➢ *lipoproteins*

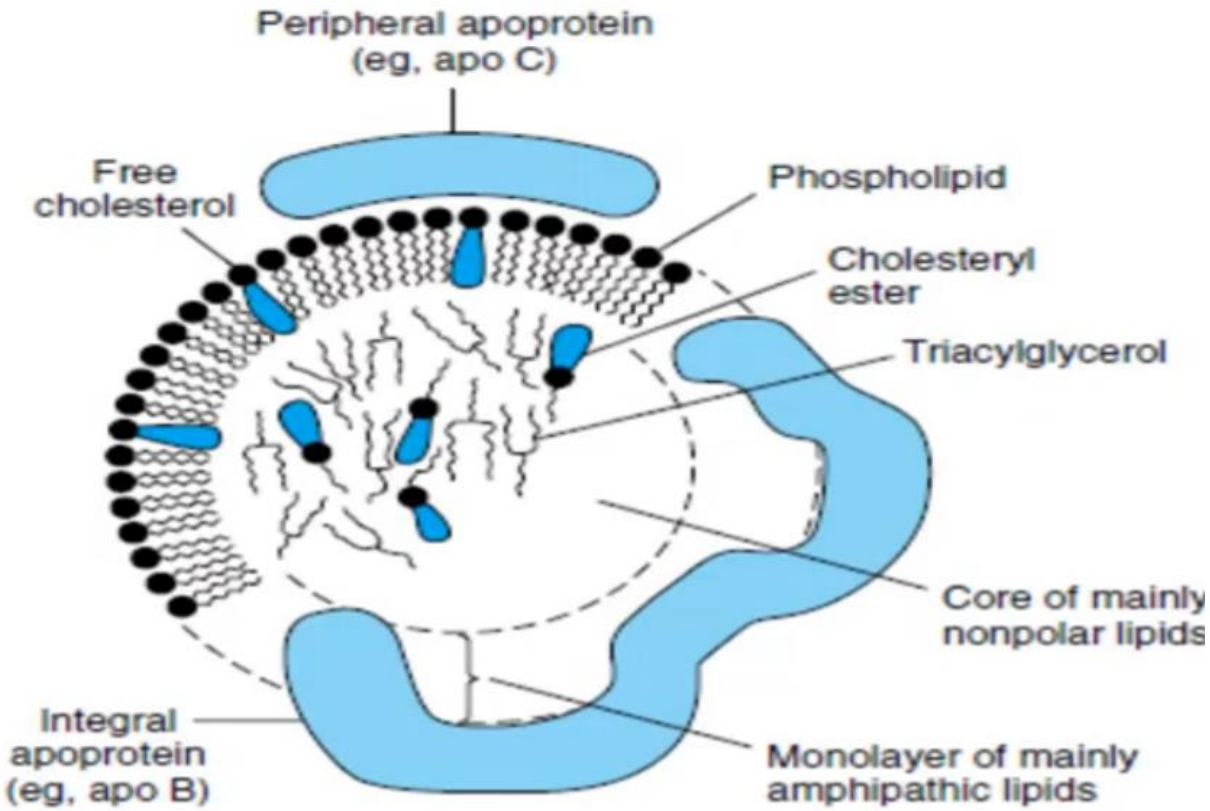

Figure 25–1. Generalized structure of a plasma lipoprotein. The similarities with the structure of the

- **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 LDL 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 densest 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 HDL2 and HDL3.**

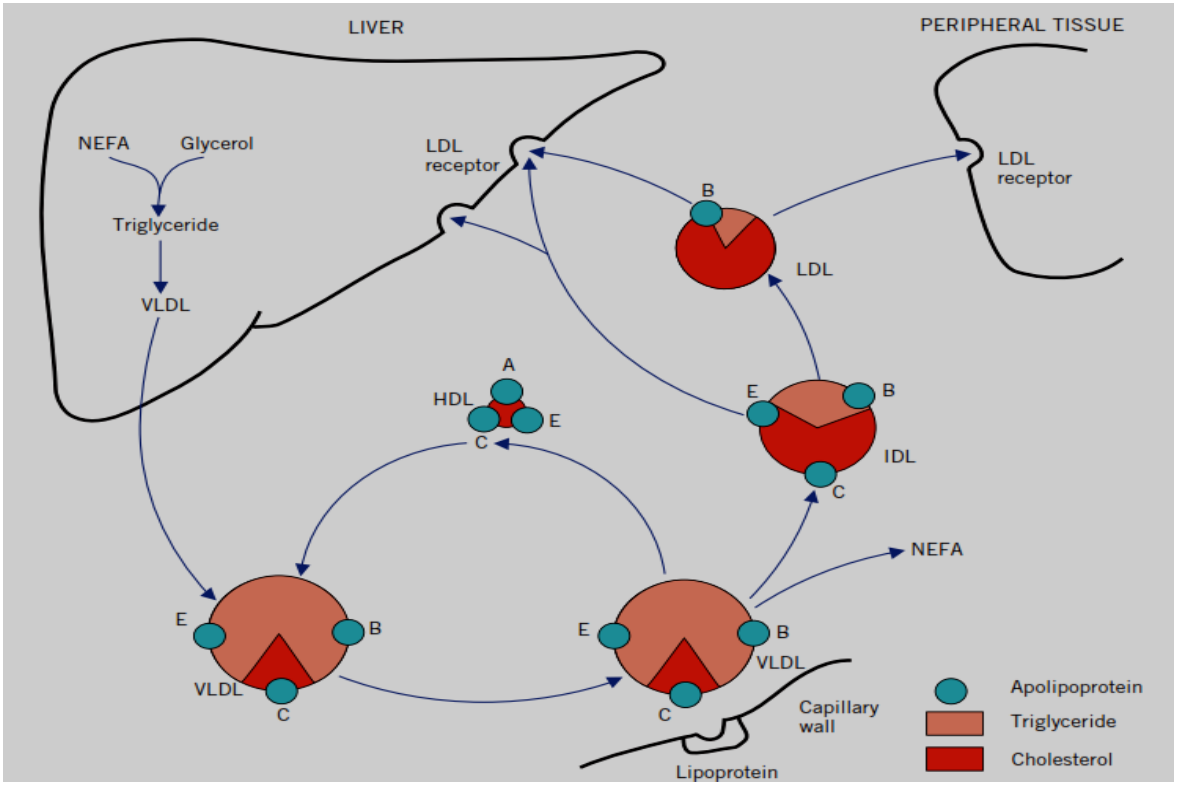

Figure 13.6 Endogenous lipid pathways. HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; NEFA, non-esterified (free) fatty acid; VLDL, very low-density lipoprotein.

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.

Figure 13.9 Whole blood of a patient with lipoprotein lipase deficiency. Note chylomicron creamy

DISORDERS OF LIPID METABOLISM

The study of hyperlipidemias 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.

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.

1. 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 hydrolyzing chylomicrons to form chylomicron remnants, and also in the endogenous pathway by converting VLDL to IDL particles.

There is probably no increased risk of coronary artery disease. Gross elevation of plasma triglycerides due to the accumulation of uncleared chylomicron particles occurs.

Lipid stigmata include eruptive xanthomata, hepatosplenomegaly and lipaemia retinalis

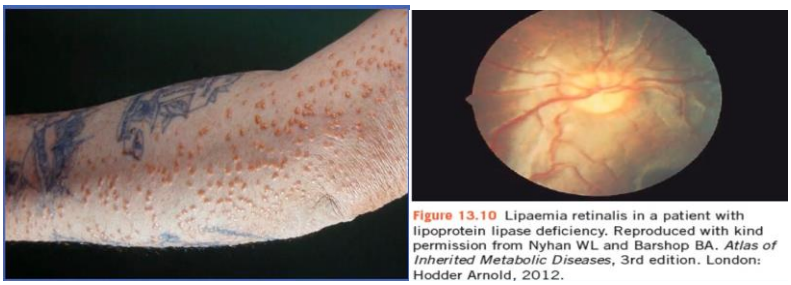

Figure 13.10 Lipaemia retinalis in a patient with lipoprotein lipase deficiency. Reproduced with kind permission from Nyhan WL and Barshop BA. *Atlas of Inherited Metabolic Diseases*, 3rd edition. London: Hodder Arnold, 2012.

Other variants of the chylomicron syndrome include circulating inhibitors of lipoprotein lipase and deficiency of its physiological activator apoC2.

Apolipoproteins C2 deficiency is also inherited as an autosomal recessive condition affecting about 1 in I 000 000 people. The gene for apoC2 is located on chromosome 19 and mutations resulting in low plasma concentrations have been found.

Treatment of the chylomicron syndrome involves a low-fat diet, aiming for less than 20g 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 apoC2 deficiency, fresh plasma may temporarily restore plasma apoC2 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 apoC2 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.

2. 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 hypercholesterolemia (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 family history of either

- **an elevated plasma cholesterol concentration of more than 7.5 mmol/L in first-degree or second-degree relative or**
- **myocardial infarction below the age of 50 years in first-degree relative or below the age of 60 years in a second-degree relative.**

❖ **Premature cardiovascular disease is often observed, along with premature corneal arci .**

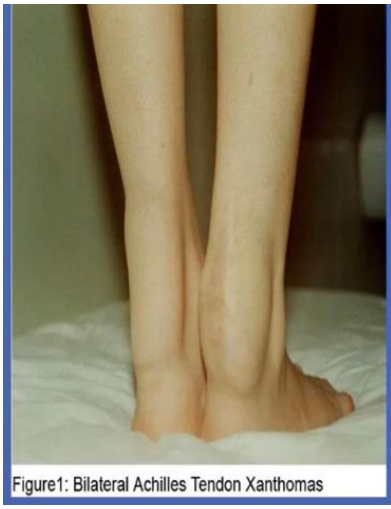

Figure1: Bilateral Achilles Tendon Xanthomas

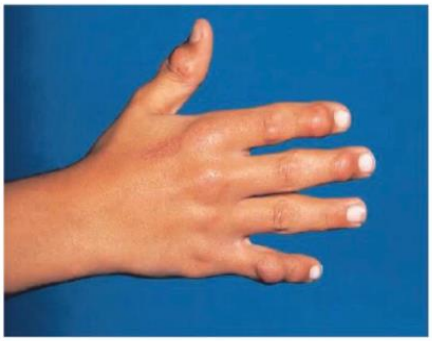

Figure 13.11 Tendinous xanthomas in familial hypercholesterolaemia. Reproduced with kind permission from Nyhan WL and Barshop BA. *Atlas of Inherited Metabolic Diseases*, 3rd edition. London: Hodder Arnold. 2012.

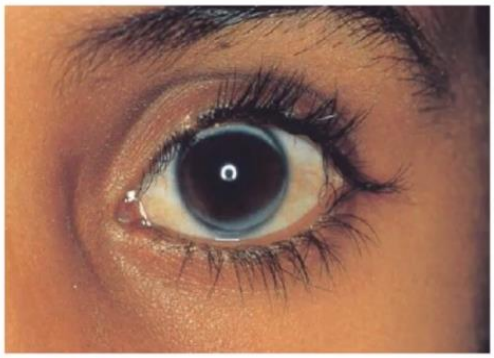

Figure 13.12 Corneal arcus in familial hypercholesterolaemia. Reproduced with kind permission from Nyhan WL and Barshop BA. *Atlas of Inherited Metabolic Diseases*, 3rd edition. London: Hodder Arnold. 2012.

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

Plasma HDL cholesterol concentration can vary in different individuals although low concentrations may increase the likelihood of cardiovascular disease.

The diagnosis may not be so clear cut in patients without the lipid stigmata, 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 (3- hydroxy-3-methylglutaryl CoA: this enzyme catalyzes the rate limiting step in cholesterol synthesis), that is, the statins.

3. Familial defective apoB3500

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 disease. The treatment is similar to that for heterozygote FH. The apoB gene is located upon chromosome 2.

4. Familial combined hyperlipidaemia

In familial combined hyperlipidaemia (FCH), the plasma lipids may elevate plasma cholesterol concentrations often being between 6mmol/L and 9mmol/L and plasma triglyceride between 2mmol/L and 6mmol/L .

The Fredrickson's phenotype seen in this condition includes IIa, IIb and IV. Familial combined hyperlipidaemia may be inherited as an autosomal dominant trait (although others suggest that there may be segregation of more than one gene).

About 0.5 per cent (1/200) of the European population is affected, and there is an increased incidence of coronary artery disease in family member.

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 hypertriglyceridemia (V phenotype) , (the IIa and IIb phenotype are not usually found in familial hypertriglyceridemia, although are in FCH

5. Familial hypertriglyceridemia

Familial hypertriglyceridemia 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 over production 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.

6. 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 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 such as the statins.

7. 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 cardio protective, and individuals displaying this should be reassured.

8. 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.

Secondary causes of hyperlipidemia include

1. **obesity ,**
2. **type 2 diabetes mellitus,**
3. **hypothyroidism,**
4. **chronic kidney disease,**
5. **cholestasis and certain drugs.**

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

Drug	Cho	Tg	HDL	LDL
Statins	↓↓↓	↓	↑	↓↓↓
Fibrates	↓/–	↓↓↓	↑↑	↓/–
Bile salt-sequestrating agents	↓	↑/–	↑	↓
Ezetimibe	↓↓	↓	↑	↓↓
Nicotinic acid	↓↓	↓↓↓	↑↑↑	↓↓
ω-3 fats	↓/–	↓↓	↑/–	↓/–

Cho, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Tg, triglyceride.
↓, reduced; –, no major change; ↑, raised.