Lipid Disorder (Dyslipidemia)

PLASMA LIPOPROTEINS & HYPERLIPIDEMIA

Lipid Importance:

Lipids are ubiquitous in the body tissue and play a vital role in virtually all aspects of life.

(1) hormones or hormone precursors,

(2) aiding in digestion,

(3) providing a source of metabolic fuel and energy storage,

(4) acting as functional and structural components in cell membranes, and

(5) forming insulation to allow nerve conduction or to prevent heat loss.

BASIC BIOCHEMISTRY

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.

Fatty acids can esterify with glycerol to form triglycerides or be non-esterifi ed (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.

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.

2- 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 hysiologically important steroids, including bile acids and steroid hormones.

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.

3-LIPOPROTEINS

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

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.

Lipoproteins can be classified into five main groups. 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:

i- Chylomicrons are the largest and least dense lipoproteins and transport exogenous lipid from the intestine to all cells.

ii- Very low-density lipoproteins (VLDLs) transport endogenous lipid from the liver to cells.

iii- 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:

iv- Low-density lipoproteins (LDL) are formed from VLDLs and carry cholesterol.

v- 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 HDL2 and HDL3.

In some cases of hyperlipidemia, 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 a (HDL), pre-b (VLDL), b (LDL) and chylomicron.

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

LDL cholesterol(mmol/L) = total cholesterol – HDL cholesterol- [triglyceride]/2.2 4

There has been recent interest in the subdivision of LDL particles into small dense LDL2 and LDL3, which appear to be more atherogenic and more easily oxidized than the larger LDL1 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 apoA1 and apoA2)is the major group associated with HDL particles. The apoB series (apoB100) is predominantly found with LDL particles and is the ligand for the LDL receptor. Low-density lipoprotein has one molecule of apoB100 per particle. Some reports have suggested that the plasma apoA1 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.

Disorder 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 .

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.

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.

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 un cleared chylomicron particles occurs. Lipid stigmata include eruptive xanthomata, hepatosplenomegaly and lipaemia retinalis .

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

Apolipoprotein C2 deficiency is also inherited as an autosomal recessive condition affecting about 1 in1 000 000 people. The gene for apoC2 is located on chromosome 19 and mutations resulting in low plasma concentrations have been found.

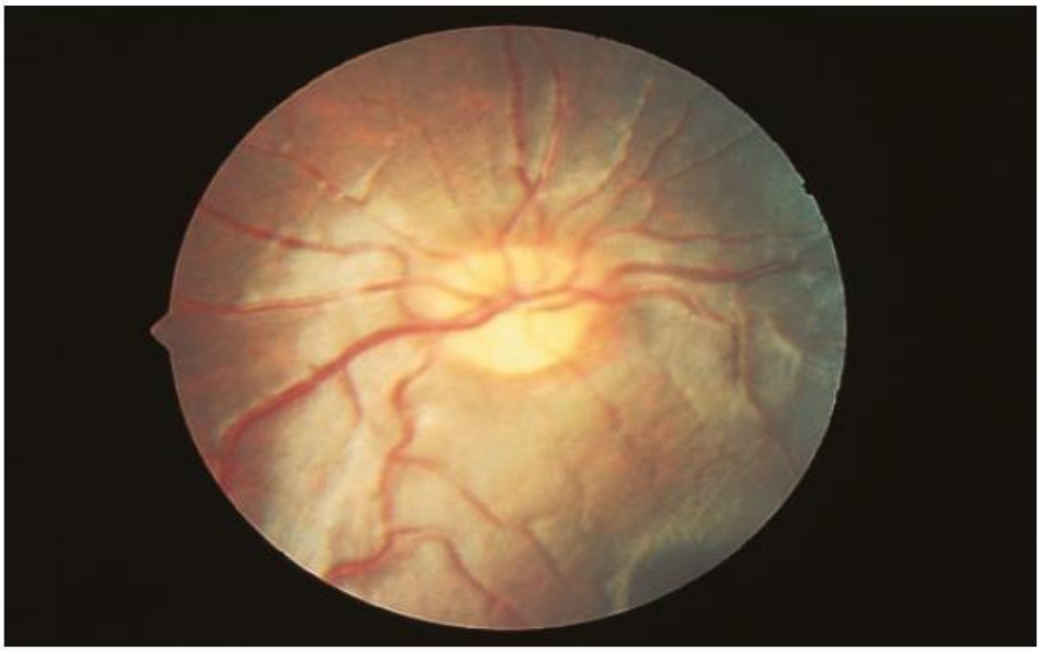

Figure 13.10 Lipaemia retinalis in a patient with lipoprotein lipase deficiency. Reproduced with kind permission from Nyhan WL and Barshop BA. *Atlas of*

Familial hypercholesterolaemia (FH)

This condition is usually inherited as an autosomal dominant trait . The inheritance of one mutant gene that encodes for the LDL receptor affects about 1 in every 500 , 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.

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. 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 . Premature cardiovascular disease is often observed, along with premature corneal arci .Using the Fredrickson's classification, this condition has also been termed familial type IIa.

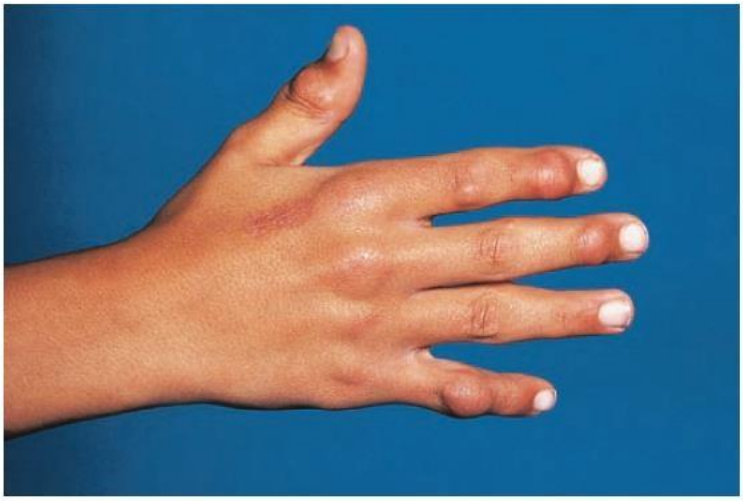

Figure 13.11 Tendinous xanthomas in familial hypercholesterolaemia. Reproduced with kind permission from Nyhan WL and Barshop BA *Atlas of*

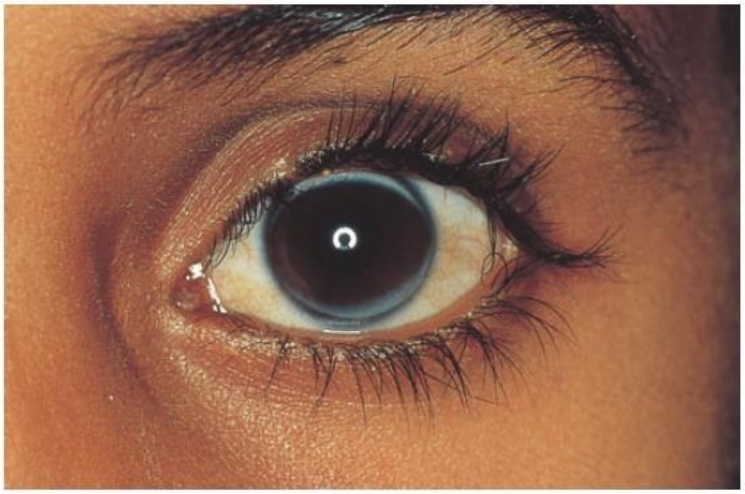

Figure 13.12 Corneal arcus in familial hypercholesterolaemia. Reproduced with kind

Familial Combined Hyperlipidaemia

In familial combined hyperlipidaemia (FCH), the plasma lipids may 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.

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 lipidlowering drugs such as the fibrates or w-3 fatty acids, are used to treat the condition.

Type III hyperlipoproteinaemia

This condition is 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 β-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).

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.

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 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.

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

Secondary hyperlipidaemias .

there are many secondary causes of hyperlipidaemia.

Secondary causes 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.

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, β-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

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.

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

Primary
Familial hypoalphalipoproteinaemia
$ApoA_1$ 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, probucol, β-blockers (without intrinsic sympathomimetic activity), progestogens, anabolic steroids, bexarotene