



# **College of Pharmacy**

## **Fifth Stage**

### **Clinical Chemistry**

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**Lecture 9**

**Disorders of Lipid Metabolism**

## Disorders of Lipid Metabolism

### Lipids and Lipoproteins

The major lipids present in the plasma are **fatty acids**, **triglycerides (TG)**, **cholesterol** and **phospholipids**. Other lipid-soluble substances, present in much smaller amounts but of considerable physiological importance, include **steroid hormones** and **fat soluble vitamins**.

**Triglycerides:** consist of glycerol esterified with three long-chain fatty acids. Triglyceride is present in **dietary fat**, and **can be synthesized in the liver** and **adipose tissue** to provide a source of stored energy; this can be mobilized when required, for example during starvation. Triglycerides containing both saturated and unsaturated fatty acids are important components of cell membranes.

**Cholesterol** is also important in membrane structure and is the precursor of steroid hormones and bile acids. Cholesterol is **present in dietary fat**, and **can be synthesized in the liver**. Cholesterol can be excreted in the bile either per se, or after metabolism to bile acids.

**Phospholipids** are compounds similar to the triglycerides but with one fatty acid residue replaced by phosphate and a nitrogenous base.

Because they are **not water soluble**, **lipids** are **transported in the plasma in association with proteins**. **Albumin** is the principal **carrier of free fatty acids (FFAs)**; the other lipids circulate in complexes known as **lipoproteins**. These consist of a non-polar core of triglyceride and cholesteryl esters surrounded by a surface layer of phospholipids, cholesterol and **proteins known as apolipoproteins**. The latter are important both structurally and in the metabolism of lipoproteins.

## Classification of Lipoproteins

Lipoproteins are **classified on the basis of their densities** as demonstrated by their **ultra-centrifugal separation**. Density increases from **chylomicrons (CM, of lowest density)** through lipoproteins of very low density (VLDL), intermediate density (IDL) and low density (LDL), to **high density lipoproteins (HDL)**. **Lipoprotein (a), or Lp (a), is an atypical lipoprotein of unknown function**. It has a similar composition to LDL except that it contains in addition one molecule of apo (a) for every molecule of apo B-100. Apo (a) shows considerable **homology with plasminogen**. An elevated concentration of **Lp (a) appears to be an independent risk factor for coronary heart disease (CHD)**. It is markedly **more atherogenic than LDL**.

## Lipoprotein Metabolism

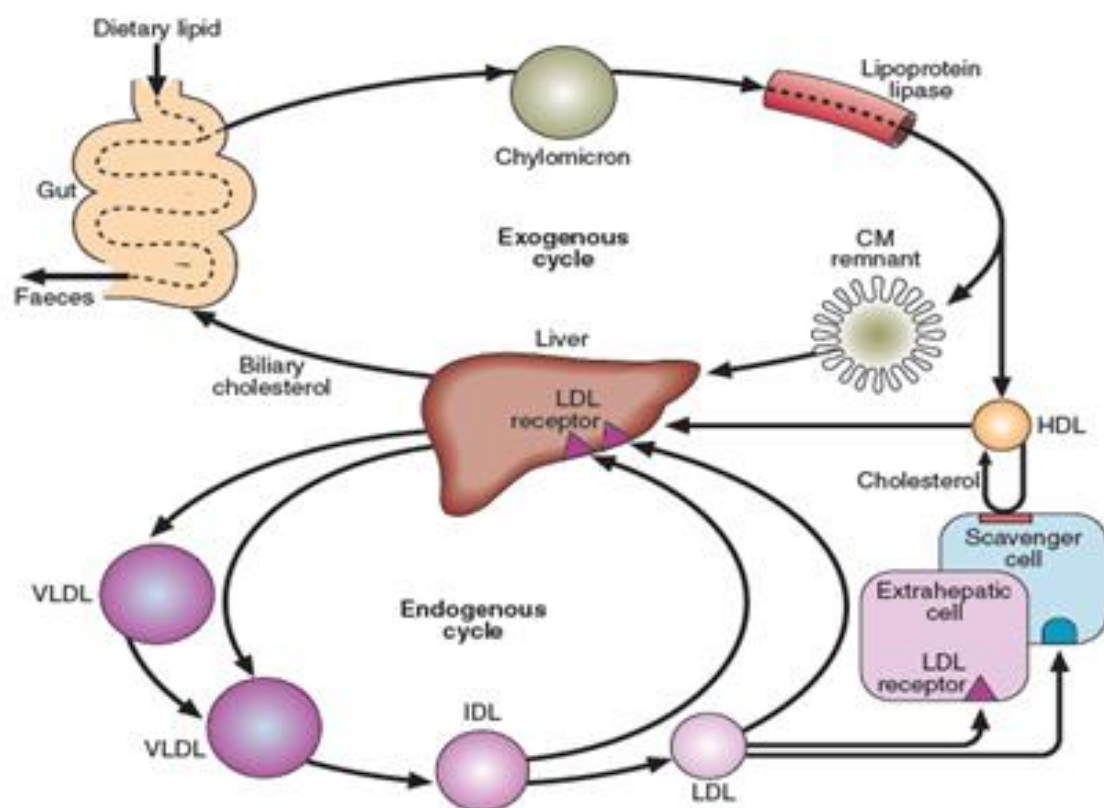
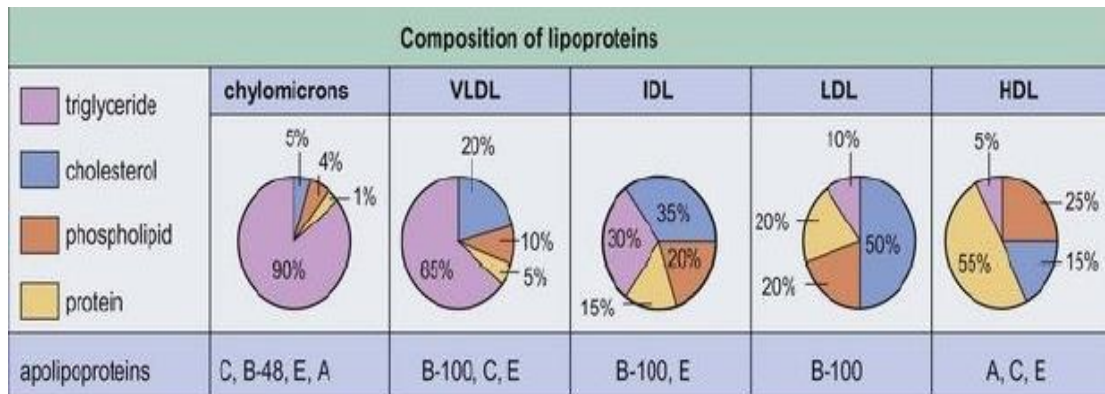


Figure (1) Lipoprotein metabolism



**Figure (2) Composition of lipoproteins**

**Table (1) Classification and characteristics of lipoproteins**

Classification and characteristics of lipoproteins					
Lipoprotein	Density (g/mL)	Mean diameter (nm)	Electrophoretic mobility	Source	Principal function
CM	<0.95	500	remains at origin	intestine	transport of exogenous triglyceride
VLDL	0.96–1.006	43	pre-β	liver	transport of endogenous triglyceride
IDL	1.007–1.019	27	'broad β'	catabolism of VLDL	precursor of LDL
LDL	1.02–1.063	22	β	catabolism of VLDL, via IDL	cholesterol transport
HDL	1.064–1.21	8	α	liver, intestine; catabolism of CM and VLDL	reverse cholesterol transport

- **HDL** the **smallest in size** and **densest** particles with **lowest** content of **lipid**.
- **Chylomicrons** have a **high** content of **lipid** , are **large** and **least dense**.
- Lipoproteins transport absorbed dietary fat and endogenously synthesized cholesterol and TG.

### **The Essential Features of Lipoprotein Metabolism**

- **Exogenous pathway**---lipids from food. Dietary triglycerides are transported in **chylomicrons** to tissues where they can be used as an energy source or stored. Dietary cholesterol reaches the liver in **chylomicron remnants**.

- **Endogenous pathway** ---lipids synthesized by the liver. Endogenous triglycerides, synthesized in the liver, are transported in **VLDL** and are also available to tissues as an energy source or for storage. Cholesterol synthesized in the liver is transported to tissues in **LDL, derived from VLDL**.

- **Reverse cholesterol transport**---return of cholesterol from tissues to liver. The **HDL** acquire cholesterol from peripheral cells and other lipoproteins and this is esterified by lecithin–cholesterol acyltransferase (LCAT) converted to cholesteryl ester, cholesteryl esters are transferred to remnant particles, which are taken up by the liver, whence the cholesterol is excreted.

**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. Lipoproteins may accumulate in the plasma due to overproduction and/or deficient removal. Fredrickson, Levy and Lees first defined the hyperlipidaemias in a **classification system based on which plasma lipoprotein concentrations were increased**, as explained in Table (2)

**Table (2) 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.

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. The Fredrickson type can change as a result of dietary or drug intervention.

**Hyperlipidemias** are classified as either **primary**, comprising a group of **genetically** determined disorders, or **secondary**, in which the abnormalities are the result of an **acquired** condition.

### **Primary and Secondary Hyperlipidemias**

A more descriptive classification is used for the **primary hyperlipidaemias**, as follows:

- 1- Chylomicron syndrome
- 2- Familial hypercholesterolaemia (FH)
- 3- Familial defective apoB3500
- 4- Familial combined hyperlipidaemia (FCH)
- 5- Familial hypertriglyceridaemia
- 6- Type III hyperlipoproteinaemia
- 7- Polygenic hypercholesterolaemia
- 8- Hyperalphalipoproteinaemia

### **Secondary hyperlipidaemias**

#### **- Predominant hypercholesterolaemia**

Hypothyroidism, nephrotic syndrome, cholestasis, e.g. primary biliary cirrhosis, certain drugs or toxins, e.g. cyclosporine 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.

**Other lipid abnormalities** include hypoalphalipoproteinaemia (Low plasma HDL concentration), abetalipoproteinaemia (LDL deficiency) and lecithin-cholesterol acyltransferase (LCAT) Deficiency.

### Lipids and Cardiovascular Diseases

Elevated plasma concentrations of lipids, particularly cholesterol, are causally related to the pathogenesis of **atherosclerosis**, the process responsible for the majority of cardiovascular diseases (coronary, cerebrovascular and peripheral vascular disease). Elevated plasma cholesterol concentrations are a major risk factor for CHD. While there is an undoubted association between plasma cholesterol concentration (and, in particular, **LDL cholesterol (bad)** and an **increased risk of CHD**, there is an **inverse correlation between HDL cholesterol (good) and CHD risk**. **Hypertriglyceridemia** is also a **risk factor for CHD** which are particularly associated with type 2 diabetes mellitus.

Triglyceride, total cholesterol, LDL and HDL cholesterol concentrations can **easily be measured in the laboratory**.

The **LDL cholesterol** can be calculated using the formula:

$$\text{LDL CHOL} = \text{TOTAL CHOL} - \left( \text{HDL CHOL} + \frac{\text{TRIG}}{2.2} \right)$$

This formula is invalid if the triglyceride concentration exceeds 4.5 mmol/L.

## **Lipid Lowering Therapy**

The help of a dietitian is invariably useful in treating dyslipidaemias. Decrease total fat intake, with an increase in monounsaturated fat. Low saturated fat/reduced cholesterol diets are instigated. Five daily portions of fruit and vegetables are advisable. Decrease alcohol intake. Increased intake of plant sterols and stanols may lead to competition for cholesterol intestinal absorption, thereby reducing the plasma cholesterol concentration. Ideally, patients should aim to achieve their recommended body mass index. **If diet and lifestyle measures fail, drug therapy may be indicated.**