Lecture 2 **Dr. Maytham Ahmed**

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 is larger and more dense than LDL but has a similar composition, 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).

Lipoprotein metabolism

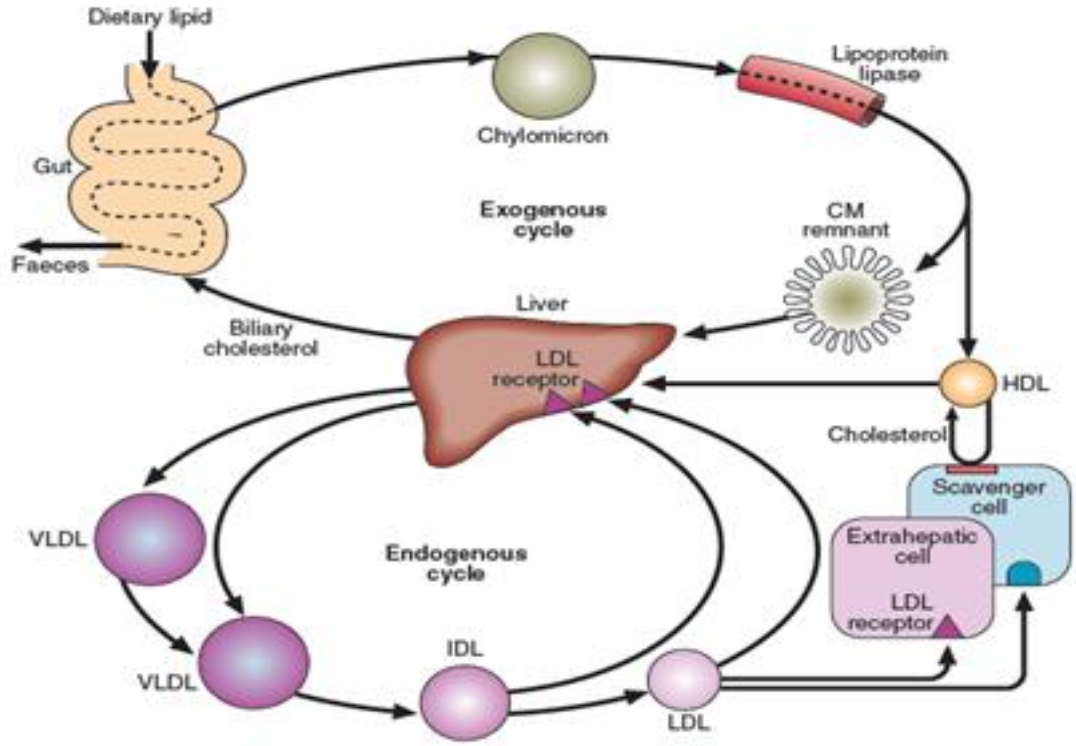

Figure (1) Lipoprotein metabolism

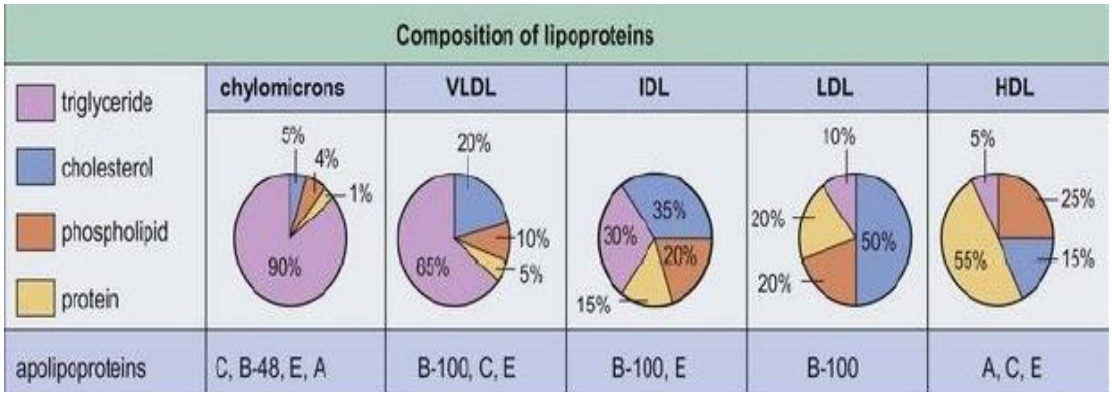

Figure (2) Composition of lipoproteins

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 contains the smallest densest particles and **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 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.

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. ciclosporin and chlorinated hydrocarbons.

Predominant hypertriglyceridaemia

Alcohol excess, obesity, diabetes mellitus and metabolic syndrome, certain drugs, e.g. estrogens, b-blockers (without intrinsic sympathomimetic activity), thiazide diuretics, acitretin, protease inhibitors, some neuroleptics and glucocorticoids, chronic kidney disease, some glycogen storage diseases, e.g. von Gierke's type I, systemic lupus erythematosus, paraproteinaemia.

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 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.**