Biochemistry

Lec.(1) **Dr.shaimaa S.mutlak**

Lipid metabolism and disorder

Major Concepts:

A. Study the lipids present in plasma.

B. Study the Metabolism of lipids present in plasma ,adipose tissue and role of 'Brown' adipose tissue.

→ **Lipids play a critical role in almost all aspects of biological life :–**

1. they are structural components in cells.
2. Involved in metabolic and hormonal pathways.

PLASMA LIPIDS

1- In mammals, principal Lipids that have metabolic significance are as follows:

- Tri acyl glycerol (TG): Also called Neutral fats (NF)
- Phospholipids
- Steroids: Chief of which is cholesterol.
- Fatty acids: Long-chain and short-chain (free FA).

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 esterified 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.

2-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 triglyceride concentrations rise after a meal, unlike that of plasma cholesterol.

3-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 had an important structural role in cell membranes, and the phosphate group confers solubility on nonpolar lipids and cholesterol in lipoproteins**.**

4-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.

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.

2- Extraction of plasma lipids with a suitable Lipid solvent and subsequent separation of the extract into various classes of lipids shows the presence of:

- Tri acyl glycerol (TG)
- Phospholipids (PL) approximately in
- Cholesterol and equal quantities
- A much smaller fraction of non-esterified long chain fatty acid (NEFA) or free-fatty acid (FFA), which constitutes less than 5 per cent of total FA present in plasma.

3- NEFA is now known to be metabolically most active of the plasma lipids and 1/2 life being approximately 2 to 3 minutes.

4- Plasma lipids at any time may be considered to represent the net balance between production, utilization and storage.

Lipid fraction Plasma level in mg/100 ml

Total lipids	360-820
Triacyl glycerol (TG)	80-180
Total phospholipids (PL)	125-390
• Phosphatidyl choline (Lecithin)	50-200
• Phosphatidyl ethanolamine (cephalin)	50-130
• Sphingomyelins	15-35
Total cholesterol	150-250
Free cholesterol (nonesterified)	25-105
Free fatty acids or nonesterified FA (NEFA)	6-16

TRANSPORTATION OF PLASMA LIPIDS:

► Principal lipid, triacyl glycerol (TG), is hydrophobic material. To transport them in blood in an aqueous medium poses a problem, which is solved by associating the more insoluble lipids with more "Polar" ones, such as phospholipids, cholesterol and combining with a specific, protein molecule (called as 'apo-proteins').

► Thus, the hydrophobic and insoluble triacyl glycerol (TG) is converted by above combination into a hydrophilic and "soluble" Lipoprotein "complex". Thus: TG derived from intestinal absorption of fats is transported in the blood as a lipoprotein complex called chylomicrons. Chylomicrons are small microscopic particles of fats, about 1μ in diameter and are responsible for transport of exogenous (TG) in the blood.

• Similarly, TG that are synthesised in Liver cells are converted to lipoprotein particles, called very low density lipoproteins (VLDL) and thrown into the circulation. VLDL is mainly concerned with transport of endogenous TG.

• Fatty acids released from adipose tissue by hydrolysis of TG are thrown in the circulation as free fatty acid (FFA). They are carried in non-esterified state in plasma, hence also called NEFA. In circulation, FFA/NEFA combines with albumin and are carried as albumin-FFA complex. Some 25 to 30 mols of FFA are present in combination with one mol. of albumin.

SEPARATION OF PLASMA LIPIDS

(a) Ultracentrifugation

Pure fat is less dense than water. As the proportion of lipid to protein in lipoprotein complex increases, the density of the molecule decreases. This property has been utilized in separation of plasma lipids, the various lipoprotein fractions, by ultracentrifugation.

(b) Electrophoresis

Lipoproteins may be separated also according to their electrophoretic properties and identified more accurately using immunoelectrophoresis. **Fredrickson and others (1967)** identified lipoproteins into **4 groups** by electrophoresis as follows:

• **HDL:** Moves fastest and occupies position of α globulin-called α ***lipoproteins***

• **LDL:** β-**lipoproteins**

• **VLDL:** ***(Pre-β or α2 lipoproteins)*** and

• **Chylomicrons:** Slowest moving and remains near the origin.

METABOLISM OF ADIPOSE TISSUE:

The lipids in the body physiologically exist in **two forms:**

1- "Element constant" or structural lipids and

2- "Element variable": stored lipids (Depot fats).

1- Composition of Element Constant

Cytoplasm and cell membranes of all organs are composed of **element constant**, so that their fat content does not diminish in starvation. Element constant is composed chiefly of :-

Phospholipids (PL), along with smaller amounts of other lipids, including cholesterol. It is independent of previous feeding. It remains an integral part of cell protoplasm and is essential for its life.

2- **Composition of Element Variable**

— The lipids which are stored in the body in excess of above. The amount fluctuates and it is composed mainly of triacyl glycerol (TG), also called as neutral fats (NF). Thus, depot fat is chiefly composed of glycerides of various fatty acids and usually contains 75 per cent of oleic acid, 20 per cent of palmitic acid and 5 per cent of stearic acid. Traces of lecithin and cholesterol as well as a little amount of Polyunsaturated FA are also present. The depot fat is called "adipose tissue", they are intracellular fats which remain inside the cells of adipose tissue.

— **Dynamic state of adipose tissue:** Adipose tissue is not just a static lump of fats; it is in **dynamic state**; breakdown of fats and synthesis take place all the time.

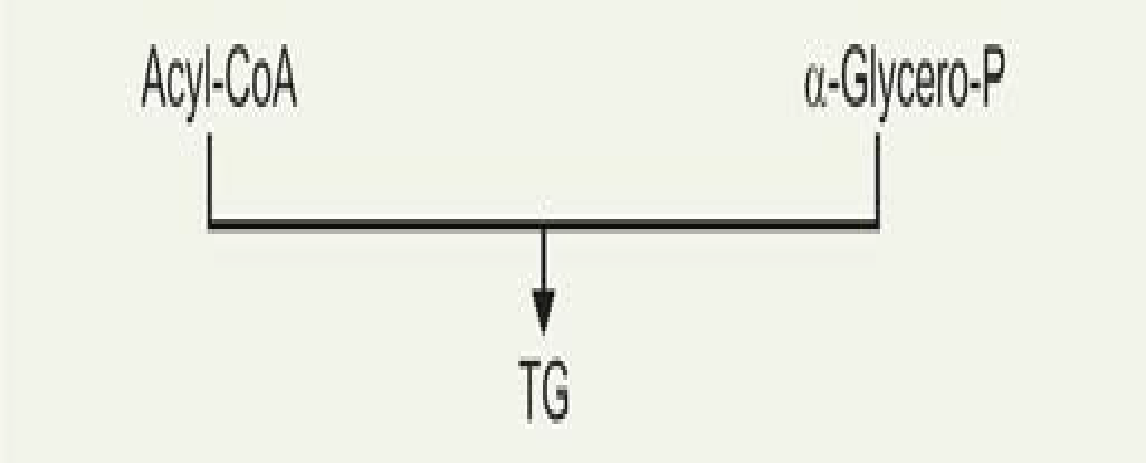
— **METABOLISM**

—— TG stores in the body are continually undergoing (a) Esterification (synthesis) and (b) Lipolysis (breakdown). These two processes are not the forward and reverse processes of the same reaction. They are entirely different pathways involving different reactants and enzymes. Many of the nutritional, metabolic and hormonal factors regulate either of these two mechanisms, i.e. esterification and lipolysis. Resultant of these two processes determine the magnitude of free fatty acid pool in adipose tissue and this, in turn, will determine the level of free fatty acid (FFA) circulating in the blood.

— **I. Esterification (Synthesis of TG)**

In adipose tissue, for TG synthesis, two substrates are required:

— • Acyl-CoA and α-Glycerol-P



Sources of Acyl-CoA

Sources of FFA in blood are:

1- Dietary,
2- Synthesis of FA (palmitic acid) from acetyl-CoA 'de novo' synthesis (extramitochondrial). Further elongation to form other fatty acids in microsomes.
3- Acyl-CoA obtained from lipolysis taking place in adipose tissue **(FFA-Pool No. 1)**.
4- FFA obtained from lipolysis of TG of circulating chylomicrons and VLDL by lipoprotein lipase enzyme present in capillary wall **(FFA-Pool No.2)**, which are taken up by adipose tissue.

Source of α-Glycerol-P

Mainly two:

1- Conversion of glycerol to α-Glycero-P by the enzyme Glycerokinase in presence of ATP.
2- The other source is from glucose oxidation. Dihydroxyacetone-P is converted to α-Glycero-P.

Note:

The enzyme glycerokinase is practically absent in adipose tissue. If any glycerokinase is present, it has very low activity. Hence, glycerol produced by lipolysis in adipose tissue cannot be utilised for provision of α-Glycero-P and thus, glycerol passes into the blood, from where it is taken up by liver, kidney and othertissues which possess glycerokinase and is utilised for gluconeogenesis. Thus, for provision of α-Glycero-P in adipose tissue for TG synthesis, the tissue is dependent on a supply of glucose and glycolysis.

II. Lipolysis (Breakdown of TG)

TG in adipose tissue undergoes hydrolysis by a **hormone-sensitive TG lipase enzyme** to form free fatty acids and glycerol.