Chapter 1

Bioenergetics and Metabolism

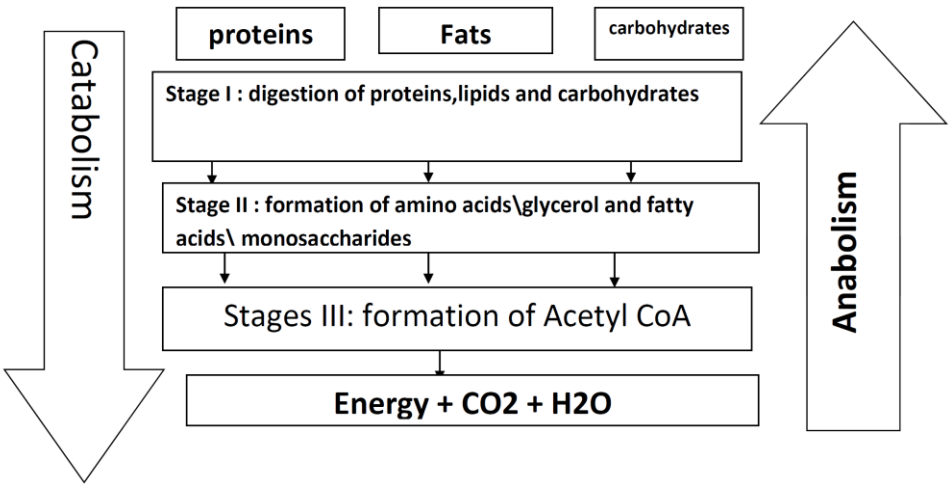
- Metabolism;

Metabolism is the reaction series of biochemical of biomolecules in living organisms. They include anabolic and catabolic reactions.

- Anabolism: Means synthesis of macromolecules from simple one. Anabolism is usually endergonic (consumes energy).

- Examples:
- Synthesis of polysaccharides from monosaccharides.
- Synthesis of triacylglycerol from glycerol and fatty acids.
- Synthesis of proteins from amino acids.

- Catabolism: Means breakdown of macromolecules into simplest components. It is usually exergonic (release energy). Catabolism of the main metabolites occurs in three stages:



- Bioenergetics:

There are two forms of energy stored in two types of bonds:
Low energy and high energy bonds.
l. Low Energy Bonds;(they give < 7.3 Kcal/mole on hydrolysis). They link food staffs:

a. **Glycosidic bond in carbohydrates.**
B. **Carboxyl-ester bond in triacylglycerol.**
c. **Peptide bond in protein.**

2. High Energy Bonds; ;(they give > 7.3 Kcal/mole on hydrolysis).

- Released energy is collected in the form of ATP in two forms:

1. Substrate level oxidative phosphorylation reactions.

2. Electron transport chain (respiratory chain) level.

1. Substrate level phosphorylation:

- **The reactions produce energy directly in the form of ATP.**
- **There are two reactions in glycolysis and one in citric acid cycle produce ATP at substrate level.**
- **Krebs' cycle:** One reaction

$$\text{Succinyl Co A} \xrightarrow{\text{thiokinase}} \text{succinate} + \text{ATP}$$

- **Glycolysis: 2 reactions**

$$\text{- Biphospoglycerate} \xrightarrow{\text{phosphoglycerate kinase}} \text{phosphoglycerate } \mathbf{+ATP}$$

$$\text{- Phosphoenol pyruvate} \xrightarrow{\text{pyruvate kinase}} \text{pyruvate} + \text{ATP}$$

2. Electron transport chain :

Definition: Electron transport chain or respiratory chain consists of series of hydrogen transfer from complexes **(more electronegative)** to give it to oxygen **(more electropositive)** to form water and **release energy** in the form (ATP).

- Diagram of The components of electron transport chain are:

$$\text{NADH} \rightarrow \text{FMN} \xrightarrow{\text{FAD}} \text{CoQ} \rightarrow \text{Cyt b} \rightarrow \text{Cytc}_1 \rightarrow \text{Cytc} \rightarrow \text{Cyta} \rightarrow \text{Cyta}_3 \rightarrow \tfrac{1}{2}\text{O}_2$$

They are present **in the form of 4 complexes, CoQ and cytochrome c.**

- Complex I: It consists of: - FMN
- NADH, H dehydrogenase
- 7FeS groups
- Many polypeptides

To transfer it to CoQ forming ($CoQH_2$) with production of one ATP.

- Complex II: It consists of: - FAD
- Succinate dehydrogenase
- 2 FeS groups.

FADH2 transfers hydrogen from succinate to CoQ to form $CoQH_2$ without production of ATP.

CoQ: is the main station between complex I and complex II

- Complex III: It consists of: - Cytochromes b & C
- One iron sulfur FeS group.

It transfers electrons from CoQH: to cytochrome c releasing four protons with production of one ATP.

- Complex IV: It consists of: - Cytochromes a-a_3 (a hemoprotein contains iron)
- 2 Copper atoms.

It transfers electrons from cytochrome c to oxygen which combines with the two protons to form water with production of 0.5ATP.

N.B.: 1- Flavoproteins are present in complex I as FMN and in complex II as FAD.
2 - Protons are pumped through complexes, I, III & IV

- Chemiosmotic theory of ATP synthesis, ATP synthase enzyme (complex V)

It consists of two subunits, F0 and F1.

- F0 subunit: Through which protons return to the mitochondrial matrix according to their concentration gradients.

- F1 subunit: Couples ADP with Pi to form ATP.

- ATP transporter (Translocater) :

Exchange of ADP to (ATP formed in respiratory chain). To avoid inhibition of ETC by the accumulated ATP.

- Regulation of respiratory chain :

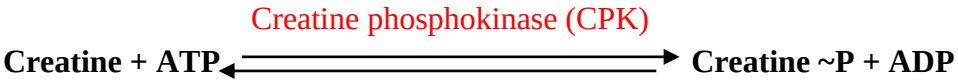
1- It is inhibited in absence of oxygen (under anaerobic condition).
2- ADP and AMP are the major control substances of E.T.C.:
E.T.C. is inhibited by excess ATP (energy in the cell) and is stimulated by ADP and highly stimulated by AMP.

- P/O ratio :

- It is the ratio between inorganic phosphate consumed to form ATP in relation to oxygen atom reduced to form water in the respiratory chain.
- In case of oxidation of NADH,H =2.5 ATPs, (formed at 3 coupling sites).
- In case of oxidation of FADH2 =1.5 ATPs, (formed at 2 coupling sites).

- Storage of energy;

Storage of energy in the form of creatine phosphate in muscles. Energy collected in the form of ATP and starts this reaction



- Uncouplers:

- Definition: They are compounds that dissociate oxidation from phosphorylation. ***they include*:**

I-physiological uncouplers

1-Calcium ions

2-Thyroxin hormone

3-Thermogenin (physiological uncoupler present in adipose tissue) it is responsible for energy is released as heat also. It is important in human babies, who cannot shiver to generate heat

II-Pharmacological uncouplers : 2,3 Dinitrophenol.

They affect ion and proton transport through the mitochondrial membrane and abolish the electrochemical gradients. They allow proton to pass through other gate named F_2. Energy is released in the form of heat.

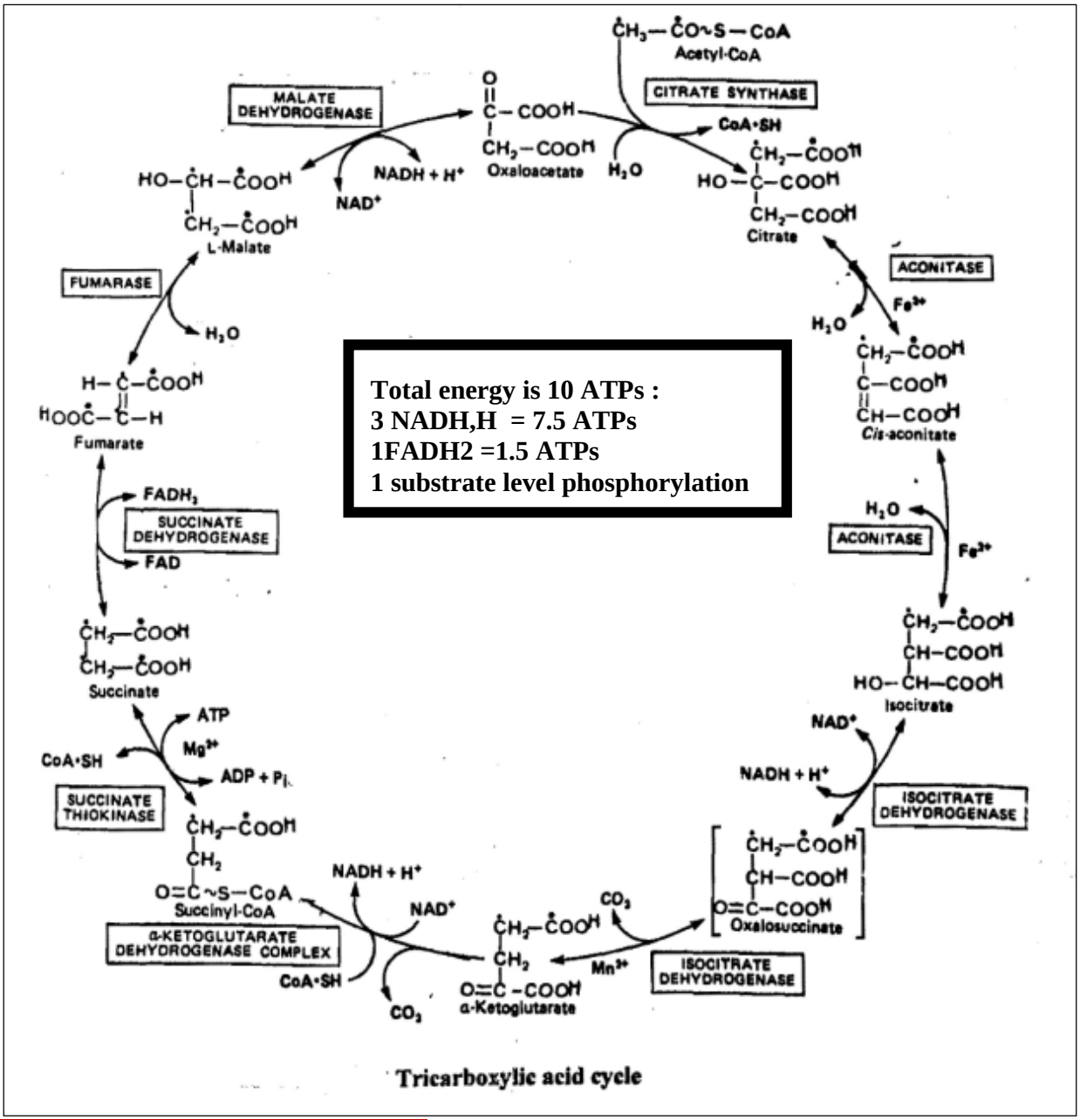
Chapter II

Tricarboxylic Acid Cycle = Citric Acid Cycle

(Kreb's Cycle)

- Definition: It is a cycle of chemical reactions for complete oxidation of active acetate (acetyl ~ SCoA) derived from carbohydrates, fats and proteins.

- Site: All components of the cycle are located free inside the **mitochondrial matrix except succinate dehydrogenase** which is present in the inner mitochondrial membrane. (complex II of respioratory chain).



Tricarboxylic acid cycle

- Importance of citric acid cycle :

I- **It is important for interconversion between carbohydrates, fats and proteins.**

II- Energy production: Oxidation of one molecule of acetyl-CoA, gives 10 ATP:

3 NADH,H in respiratory chain give 3 × 2.5 ATP = 7.5 ATPs
1 FADH2 in respiratory chain gives 1.5 ATPs
One ATP at substrate level by succinyl CoA thiokinase enzyme.

III- Important intermediates as:

1- CO_2 which is important for conversion of:

1- Pyruvate to oxaloacetate,
2- Acetyl CoA to malonyl CoA.
3- Formation of Carbamoyl phosphate needed for urea and pyrimidine synthesis.
4- Formation of carbon number 6 of purine.

2- Succinyl CoA: Which is **important for heam synthesis, ketolysis and detoxication** of compounds.

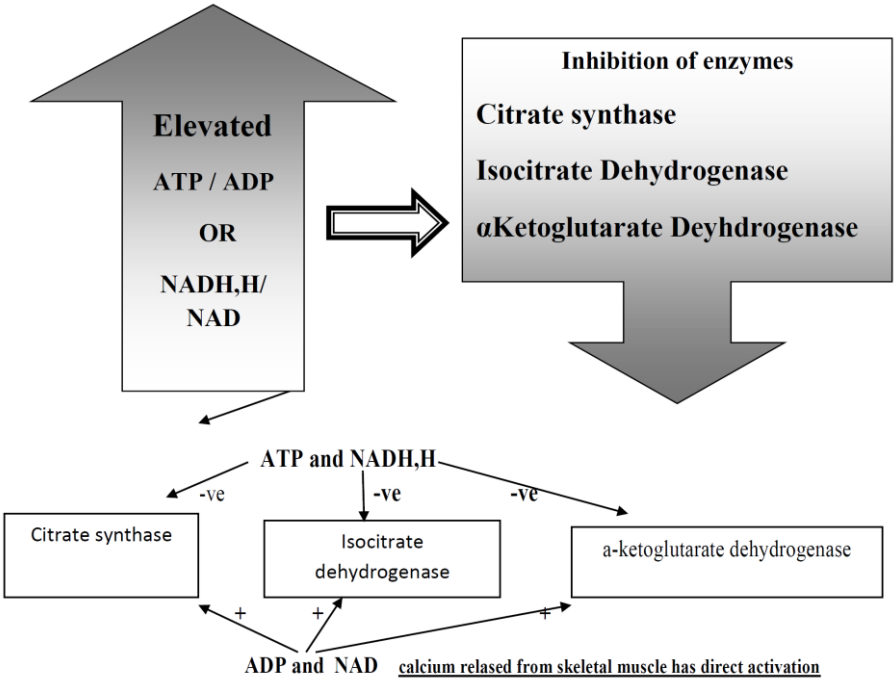
3- α-ketoglutarate: That gives Glutamate by Transamination.

4- Oxaloacetate: Which gives aspartate.

- Regulation of citric acid cycle:

1- **Increased acetyl-CoA and oxaloacetate activate** citrate synthase.
2- **Increased succinyl-CoA inhibits citrate synthase** and a-ketoglutarate dehydrogenase.
3- **Elevated ratio of NADH/NAD and ATP/ADP inhibit citrate synthase, isocitrate dehydrogenase and a-ketoglutaraie dehydrogenase**.
This occurs in the following conditions:
a-With excess ATP no need for more energy production so there is inhibition of the cycle.
b- Under anaerobic conditions when respiratory chain is inhibited and the ratio NADH/NAD is increased
4- **Elevated calcium during muscle contraction activates citrate synthase, isocitrate dehydrogenase and a-ketoglutrate dehydrogenase** to supply muscles with energy.

- Diagram of regulation of krebs'cycle



Chapter II

Carbohydrate Metabolism

- Introduction:

Intended learning outcome of this chapter are:

1. ***The important carbohydrates present in our body.***
2. ***The important pathways of glucose oxidation and energy production.***
3. ***The interconversion between different carbohydrates.***
4. ***The storage of carbohydrates as glycogen and its metabolism.***
5. ***The metabolic disorders resulting from defects in different enzymes of carbohydrate metabolism and their biomedical importance.***

- Dietary carbohydrates;

l. Monosaccharides:
They include glucose, fructose and galactose present in fruits and honey.

2. Disaccharides;
They include sucrose (in table sugar), lactose (in milk) and maltose

3. Polysaccharides;
Mainly starch in most vegetables and cereals. Cellulose in the wall of plants.

- Digestion of carbohydrates;

1. In the mouth:

$$\text{Starch} \xrightarrow{\text{Salivary Amylase}} \text{Dextrin + Maltose}$$

2. In the stomach :

HCL partially hydrolyzes carbohydrates into monosaccharides

3. In the intestine;

Pancreatic and intestinal enzymes hydrolyze, the oligo and polysaccharides into monosaccharides as follows:

- Inherited defects in digestion of carbohydrate;

1. Inherited lactase deficiency;

- In absence of lactase enzyme, lactose will not be digested and will accumulates in infant intestine and fermented by intestinal bacteria producing acids and gases.
- This will leads to distension and colic immediately after birth and is treated by lactose free milk.

2. Inherited sucrase deficiency;

In absence of sucrase enzyme, sucrose will not be digested. Also, it will lead to distension and colic. It occurs at older age.

- Absorption of monosaccharides;

1. Simple diffusion:

Fructose and pentoses are absorbed by this mechanism.

2. Facllitated transport:

Fructose, glucose and gajactose are partially absorbed by glucose transporter-5 (GLUT-5).

3. Active transport (cotransport):

It is an active process that needs energy derived from the hydrolysis of ATP. Glucose and galactose are mainly absorbed by this process, it needs Sodium glucose transporter-1 (SGLT-1).

- Inhibitors of glucose absorption:

Ouabain: it inhibits (Na^+ -K^+ pump). Phlorhizin: it inhibits glucose absorption from intestine and renal tubules.

- Fates of Absorbed Monosaccharides;

I- Glucose fate :

1- Oxidation to produce energy.
2- Converted to other sugars.
3- Building of important compounds such as glycerol-3-P and non essential amino acids.
4- Excessive glucose will be stored as glycogen in liver and muscles and as triacylglycerol in adipose tissue.
5- If blood glucose exceeds the renal threshold (180 mg/dl), , it will be excreted in urine.

II- In the liver, fructose and galactose will be converted into glucose.

- Glucose Oxidation

There are two main pathways for glucose oxidation:

1. Maior pathways:

Glycolysis followed by Kreb's Cycle The main aim of these pathways is production of energy.

2. Minor pathways:

- Hexose monophosphate pathway
- Uronic acid pathway: The aim of these pathways is formation of important metabolites (not energy production)

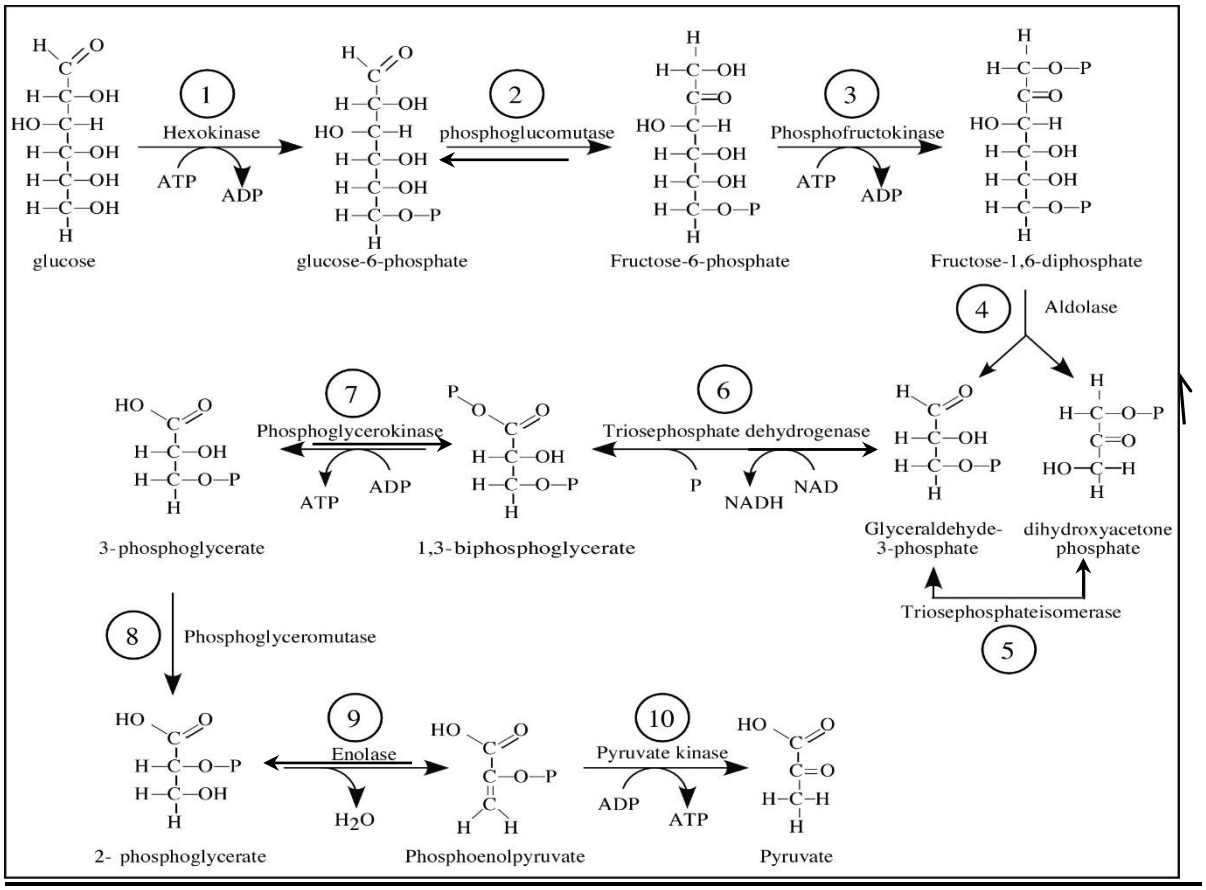
- Glycolysis = Embeden-Meyerhof Parnas Pathway

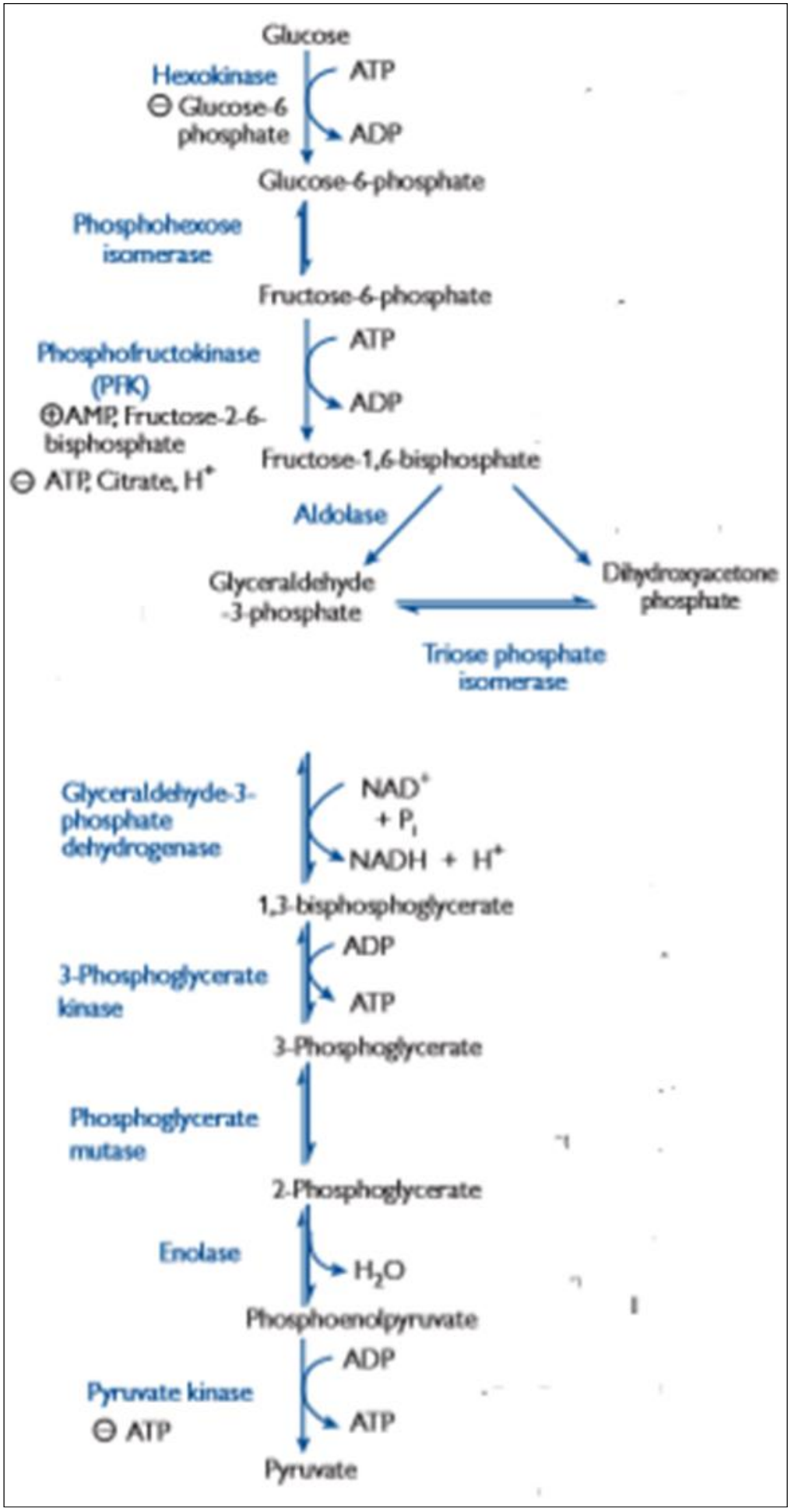
It is the oxidation of glucose into pyruvate in the presence of oxygen(under aerobic condition), and into lactate in absence of oxygen (under anaerobic condition).

- Steps:

- **Step 1:** Hexokinase or glucokinase enzyme converts Glucose into glucose-6-P to trap glucose-6 P inside the cells.
- **Step 2:** Phosphohexose isomerase converts Glucose-6-P to fructose-6 P.

- **Step 3:** Phosphofructokinase-1enzyme phosphorylate Fructose-6-P to fructose- 1,6-bisphosphate.
- **Step 4:** Aldolase-A enzyme splits Fructose-1,6-bisphosphate to two trioses:glyceraldehyde -3 P and dihydroxyacetone phosphate.
- **Step 5:** Phosphotriose isomerase converts Dihydroxyacetone phosphate to glyceraldehyde-3-P.
- **Step 6:** Glyceraldehydes-3-P dehydrogenase oxidize glyceraldehydes-3-Pto1,3-bisphosphoglycerate..
- **Step 7:** Phosphoglycerate kinase converts two molecules of 1,3-bisphosphoglycerate to 3- phosphoglycerate.
- **Step 8:** 2- phosphoglycerate mutase converts The two molecules of 3-phosphoglycerate to 2-phosphoglycerate.
- **Step 9:** Enolase enzyme dehydrates The two molecules of 2-phosphoglycerate to 2-phosphoenolpyruvate.
- **Step 10:** Pyruvate kinase enzyme converts two molecules of 2-phosphoenolpyruvate to enol pyruvate.
- **Step 11:** Enolpyruvate will be spontaneously changed into ketopyruvate.




Glucose
Hexokinase
⊖ Glucose-6 phosphate
ATP
ADP
Glucose-6-phosphate
Phosphohexose isomerase
Fructose-6-phosphate
Phosphofructokinase (PFK)
⊕AMP, Fructose-2-6-bisphosphate
⊖ ATP, Citrate, H+
ATP
ADP
Fructose-1,6-bisphosphate
Aldolase
Glyceraldehyde -3-phosphate
Dihydroxyacetone phosphate
Triose phosphate isomerase
Glyceraldehyde-3-phosphate dehydrogenase
NAD+ + Pi
NADH + H+
1,3-bisphosphoglycerate
3-Phosphoglycerate kinase
ADP
ATP
3-Phosphoglycerate
Phosphoglycerate mutase
2-Phosphoglycerate
Enolase
H2O
Phosphoenolpyruvate
Pyruvate kinase
⊖ ATP
ADP
ATP
Pyruvate

- Comment on Glycolysis:

All enzymes of Glycolysis are reversible except for 3 irreversible enzymes which are:

1- Glucokinase and\or hexokinase.
2- Phosphofructokinase.
3- Pyruvate kinase.

- Comparison between hexokinase and glucokinase:

	Hexokinase	Glucokinase
Tissue site	Extrahepatic tissues	Liver &B-cells of pancreas
Substrates	Glucose & other hexoses	Glucose only
Affinity	High affinity, so it acts under low glucose concentration	Low affinity, so it acts under high glucose concentration
Allosteric inhibition	Feed back by G-6-P	Not present
Hormonal	Not affected by hormones	Induced by insulin and repressed by anti-insulin
Feeding & fasting	No effect	Increased by feeding and in inhibited by fasting

- Total energy calculation for conversion of glucose to pyruvate:

- Energy consuming enzymes:

1- Glucokinase and \ or hexokinase = (-1 ATP)
2- Phosphofructokinase = (-1ATP)

- Total energy lost: Is -2ATPs

- Energy forming enzymes:

At substrate level two enzymes (Each Enzyme acts twice):

1- Phosphoglycerate kinase = (+1ATP) X 2 = +2ATPs
2- Pyruvate kinase = (+1ATP) X 2 = +2ATPs
3- (only aerobic) At respiratory chain one enzyme: glyceraldehydes 3 phosphate dehydrogenase produces NADH, H = 2.5 ATPs × 2ATPs = +5ATPs

- Total energy formation: Is 9 ATPs on aerobic and just 4 ATPs on anaerobic metabolism.

- Net energy gain on aerobic metabolism: Is +7 ATPs

- Net energy gain in anaerobic metabolism: Is just + 2ATPs.

- Importance of glycolysis :

1. It provides energy to every cell under aerobic and anaerobic conditions. Examples of anaerobic metabolism are **contracting muscles** (due to low oxygen supply), and **RBCs** (due to absence of mitochondria).
2. It synthesizes important compounds from glycolytic intermediates :
   - Pyruvate
   - 3 phsophoglycerate as a source of non-essential amino acid serine
   - Dihydroxyacetone as a source of Glycerol 3 phosphate for Triaceylglycerol.
3. The importance of glycolysis in red blood cells :
   - It is only source of anaerobic energy to RBCs due to absence of mitochondria. So, absence of pyruvate kinase enzymes leads to hemolytic anemia.

- It helps the reduction of methemoglobin .
- It is the source of 2,3-bisphosphoglycerate formed by reaction of Rapoport – Luebering cycle which decreases the affinity of hemoglobin to oxygen and help its delivery to tissues.

- Metabolic error of Glycolytic Enzymes:

They are enzymes deficiencies lead to hemolytic anemias:

1- Pyruvate kinase (main enzyme)
2- Phosphohexose isomerase.

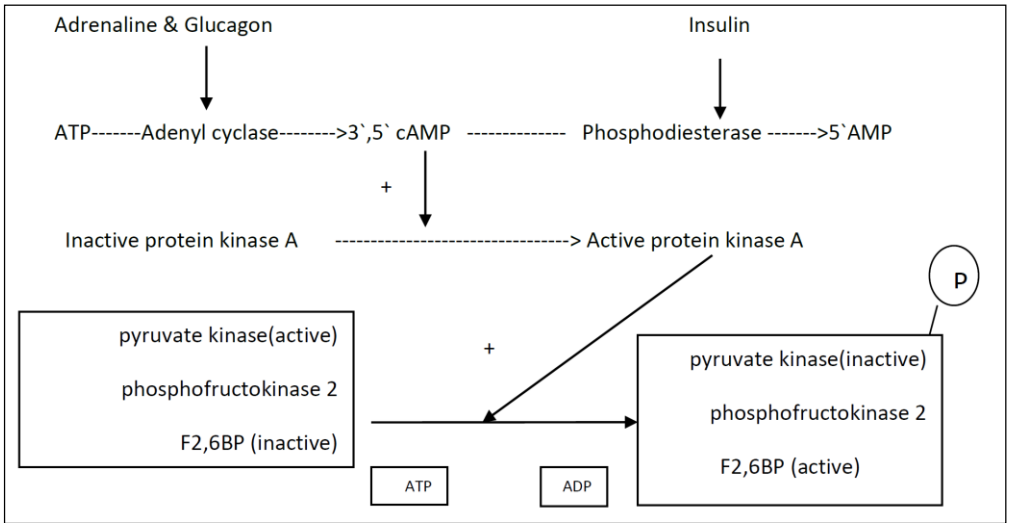
- Regulation of glycolysis

Regulationof glycolysis occurs both in vivo and in vitro.

A) In vivo:

The regulation of the 3 irreversible enzymes is lead through:

- **Allosteric regulation:**
  1. **AMP and phosphofructokinase 2**; allosterically activate phosphofructokinase-I.
  2. **F-6-P and fructose 2,6-bisphosphate (F 2.6-BP)** activate phosphofructokinase-I.
  3. **Fructose 1.6 bisphosphate (F 1.6-BP)**: Activates pyruvate kinase.
  4. **Fasting and Glucagon** suppresses the synthesis of enzymes of the three
  5. **Glucose-6-P:** It inhibits hexokinase by feedback inhibition.
  6. **Citrate:** It inhibits phosphofructokinase-1.
  7. **ATP:** Allosterically inhibits phosphofructokinase-1 and pyruvate kinase under aerobic conditions
- **Covalent modification (phosphorylation and dephosphorylation)**

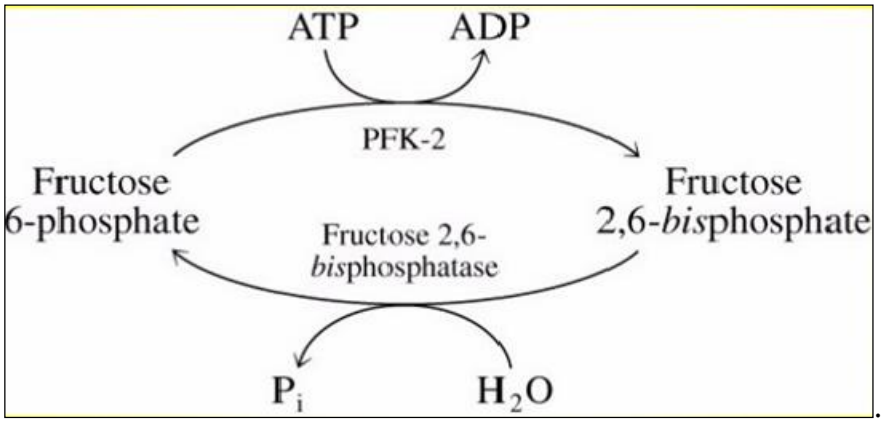


- **Regulation of transcription (change of enzyme amount):**

  Insulin induces the synthesis of the irreversible enzymes while glucagon inhibits synthesis of them.

B. In vitro regulation:

- **Fluoride inhibits enolase** enzyme by binding Mg^{++} ions. So, it is added in test tubes of blood sample taken for glucose estimation to inhibit glycolysis.
- **What is ment by phosphofructokinase-2?**
  - It is a bifunctional enzyme has two catalytic sites:
  - First function is kinase.
  - The second function acts as phosphatase .They are inversely regulated.



- Sources and fates of pyruvic acid

Sources of pyruvate	Fate of pyruvate
Glucose by glycolysis	**Oxaloacetate by carboxylation into in the mitochondria**
Glycerol-3-P by glycerol-3-Pdehydrogenase	**Oxidative decarboxylation into acetyl-CoA, in the mitochondria**
Lactate by lactate dehydrogenase enzyme.	Lactate by lactate dehydrogenase enzyme.
Alanine by transamination	**Alanine** by transamination

- Conversion of pyruvate to oxaloacetate needs:

Pyruvate carboxylase

Pyruvic acid → **Oxaloacetate**

ATP CO_2 + Biotin, Mn^{2+} **ADP + Pi**

This reaction is:

1- Activated by: -Anti-insulin (glucagon and adrenaline induce it).
- Acetyl CoA, by allosteric activation.

2- Inhibited by: Insulin suppresses its synthesis.

- Conversion Of Pyruvic Acid To Acetyl Coa:

Pyruvate is converted to acetyl CoA by **pyruvate dehydrogenase (PDH) complex: 3 enzymes and 5 coenzymes**

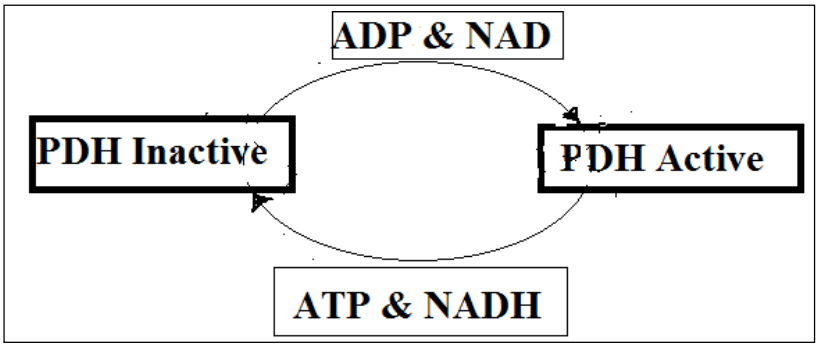
3 enzymes are:

- Pyruvate dehydrogenase, dihydrolipoyl transacetylase and dihydrolipoyl dehydrogenase.
- Five coenzymes are: NAD, FAD, COASH, Lipoic acid and TPP
- Gain of energy in this reaction is 2.5 ATPs.

- Regulation of Pyruvate dehydrogenase:

- Reaction is Activated by: Insulin, pyruvate, CoASH, NAD,ADP&Ca^{2+} and

- Inhibited allosterically by: Acetyl SCoA, NADH, ATP.



- Summary of complete oxidation of glucose under aerobic state;

- Glucose in glycolysis ⟶ 2 pyruvate (7 ATP)
- Oxidative decarboxylation of 2 pyruvic into aceryl-CoA **(2 × 2.5 = 5 ATP).**
- Oxidation of 2 acetyl CoA in Kreb's cycle (2 × 10 = 20 ATP).
- Total energy (7 + 5 + 20) = 32 ATP.

- Hexose Monophosphate Pathway (HMP)

- Pentose Phosphate Pathway:

It is a minor pathway for glucose oxidation occurring in certain tissues for production of pentose-5-P and NADPH+H*.

- Site:

Cytoplasm of: Liver, adipose tissues, lactating mammary glands,RBCs, WBCs, suprarenal glands, testis and ovaries.

- Key enzyme of HMP is Glucose-6-Phosphate dehydrogenase

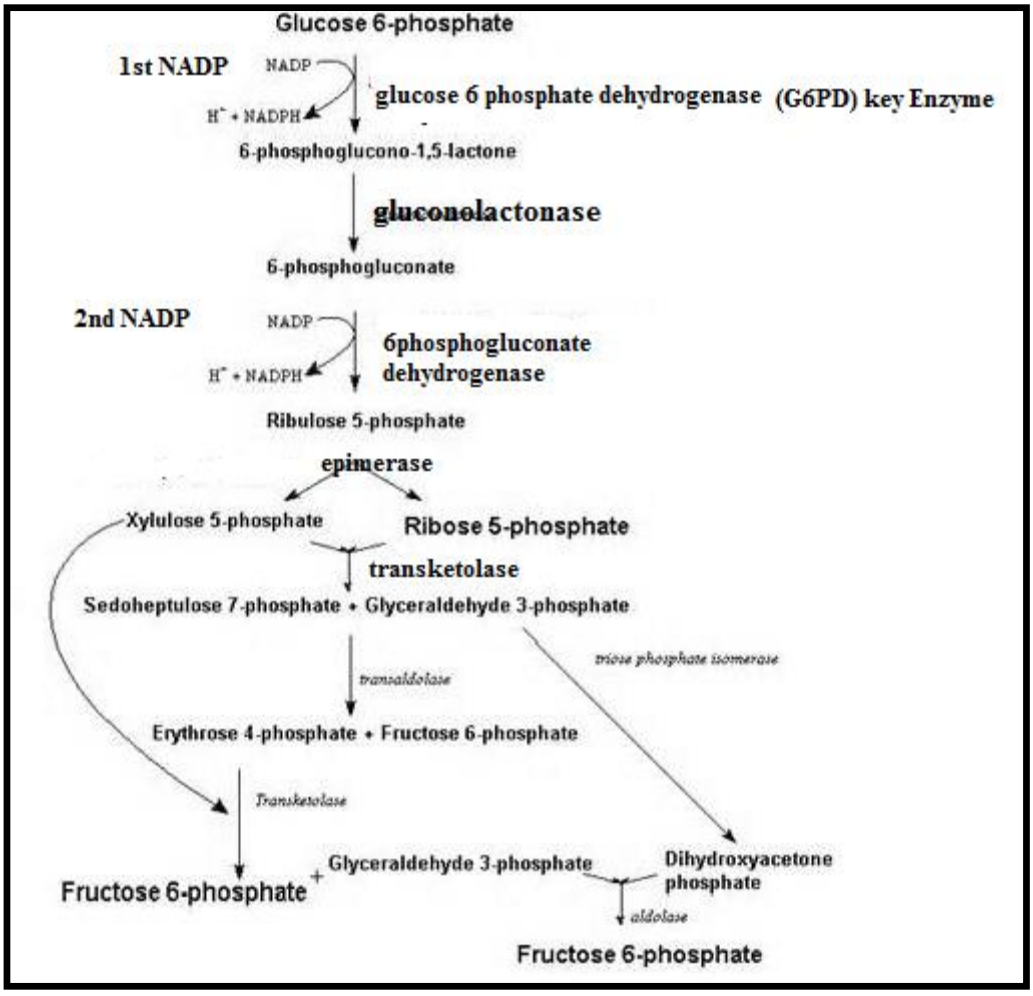
- Steps: It occurs in two major phases:

- The first is the oxidative phase (irreversible):

6 molecules of glucose-6-P are converted into 6 molecules of pentose-5-P with the release of 6 CO_2, and 12 NADPH+H

- The second is the non oxidative phase (reversible);

6 molecules of pentose-5-P are rearranged to produce 5 molecules of glueose-6-P.



- Importance of HMP:

1. Minor Pathway for glucose oxidation

2. Formation of ribose-5-P:

It is mainly used for nucleotide synthesis.

- Due to absence of pentokinase enzyme Dietary ribose is excreted in urine.

- In absence of key enzyme of HMP (Favism), Ribose-5-P could be formed in muscles and by reversal of HMP.

3. Formation of NADPH+H*:

NADPH, H is formed through:
- Glucose 6 Phosphate Dehydrogenase
- 6 Phosphogluconate Dehydrogenase

- Importance of NADPH:

a. Co-Hydroxylases:

- **Phenylalanine hydroxylase** that converts phenylalanine into tyrosine.
- **Tryptophan hydroxylase** that converts tryptophan into 5-hydroxytryptophan.
- **Hydroxylases** needed for activation of vitamin D3 into calcitriol.
- **Hydroxylases** needed for steroid hormones synthesis.

b. Co-Reductases:

Enoyl and 3-ketoacyl reductases needed for fatty acid synthesis

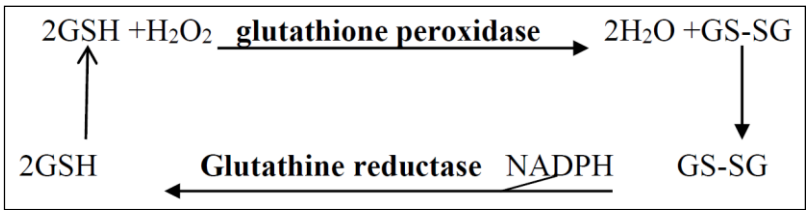
- **HMG-CoA reductase** needed for cholesterol synthesis
- **Retinal reductase** that converts retinal into retinol**.**
- **Fotate and dihydrofolate reductases** that forms tetrahydrofolate**.**
- **Glutathione reductase.**

c. Role of NADPH in phagocytic cells WBCs:

- Normally, NADPH and hypochlorous acid generate free radicals like superoxide, H_2O_2 that destroy bacterial cell membranes and kills it.
- The enzyme NADPH oxidase present in phagocytic cells consumes excessive amount of oxygen (respiratory bursts).
- **Absence of the enzyme NADPH oxidase will lead to chronic infection and granuloma formation**

d. Role of NADPH in RBCs:

- NADPH helps the removal of H_2O_2 by keeping glutathione in the reduced form (GSH) as follows:



- H_2O_2 produced during metabolism <u>is harmful</u> to RBCS because:

1- It leads to peroxidation of fatty acids present in phospholipids of cell membranes making the cells fragile and liable to hemolysis.

2- H_2O_2 oxidizes the iron of hemoglobin into methemoglobin interfering with its function as oxygen carrier.

- Regulation of HMP:

- Activation: Insulin hormone induce the synthesis of glucose-6-P dehydrogenase and 6-phosphogluconate dehydrogenases.

-Inhibition: NADPH produce feedback inhibition on glucose-6-P dehydrogenase.

- Metabolic Error in HMP: (Fav ism) ;

- It is a **x linked genetic disease**(common in males than females).
- It is caused by **deficiency of the enzyme glucose 6-phosphate dehydrogenase**.
- This will lead to **decreased production of NADPH,H^+ and reduced glutathione**.
- The cell membranes of red blood cells become fragile.
- Hemolytic attacks occur on **exposure to oxidizing agents that increase $H2O_2$ & free radical formation.**
- Free radicals are **(eating fava beans or taking drugs as primaquine or aspirin).**
- Heamolysis is a **self limited condition to the aged RBCs only**.

- Uronic acid Pathway

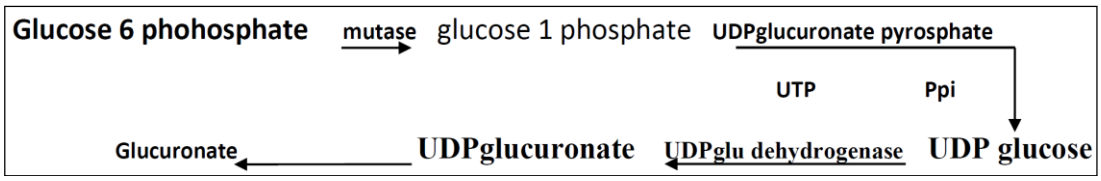
It is a pathway that converts glucose into glucuronic acid.

- Site: Cytosol of liver cells.

- Importance: Formation of active glucuronic acid (UDP-glucuronic) which is important for:

- Synthesis of heteropolysaccharides (GAGs).
- Conjugation with bilirubin and steroid hormones before excretion. Detoxication of phenolic compounds.
- It provides L-ascorbic acid in some mammalians (not in human).

- Metabolic Error in Uronic Acid Pathway;



- Essential pentosuria:

- It is a genetic disease caused by absence of the enzyme L-xylulose reductase that converts
- L-xylulose into xylitol.
- Large amont of L-xylulose appears in the urine of the patients.

- Glycogen Metabolism:

a.Glycogenesis : It is synthesis of glycogen from glucose**.**
b.Glycogenolysis : It is the breakdown of glycogen into glucose-1-phosphate.
c.Gluconeogenesis: It is synthesis of glucose or glycogen from non carbohydrate sources.

- Glycogenesis:

It is synthesis of glycogen from glucose.

- Importance of the stored glycogen:

- **Liver glycogen maintains blood glucose level during fasting less than 18 hours.**
- **Muscle glycogen provides contracting muscles with energy.**

- Sites: **Cytosol of liver and muscles.**

	Liver glycogen	Muscle glycogen
Amount	8-10% of liver weight	2 % of muscle weight
Fasting	Depleted by fasting	Little effect
Exercise	Little effect	Depleted by exercise
Insulin	Helps its formation	Helps its formation
Glucagon	Inhibits its formation	No effect (no receptors)
Adrenalin	Inhibits its formation	Inhibits its formation

- Enzymes of glycogenesis are: 1) Glycogen Synthase
2) Branching enzyme.

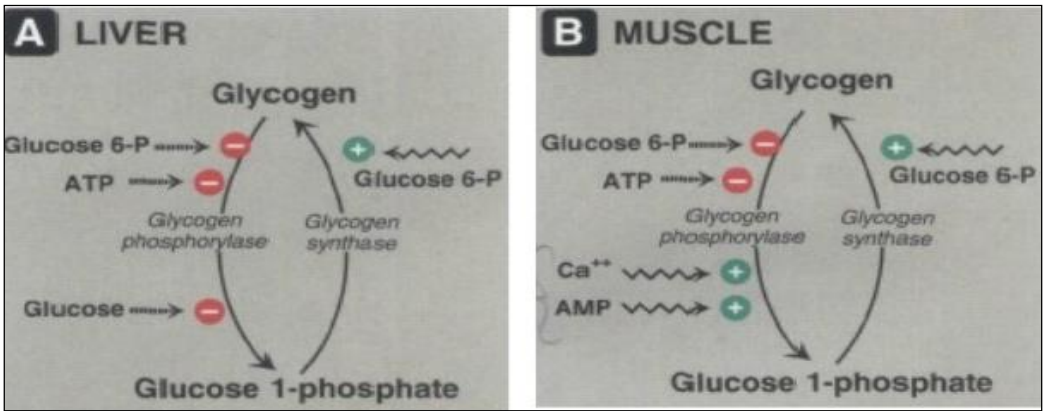
The key enzyme of glycogenesis is glycogen synthase.

- Steps of glycogenesis:

- Step 1: Glycogen synthase adds glucose to elongate the existing glycogen primer by forming α1-4 glucosidic bond. In absence of glycogen primer it adds glucose to glycogenin protein present in the liver. It also elongates the glycogen chain.

- Step 2: Branching enzyme transfers 6-8 glucose from one end to the other forming a new branch (by an a 1-6 glucosidic bond).

- Regulation of glycogen synthase by phosphorylation /dephosphorylation:



- Regulation of Glycogen Metabolism in muscles and liver.

1. Hormonal regulation:

- Glycogenesis is activated by insulin and inhibited by glucagon and adrenaline.
- The active form of glycogen synthase is dephosphorylated. It is inactivated by phosphorylation.
- This process requires active protein kinase enzyme.

2. Allosteric regulation:

Glycogen allosterically inactivates glycogen synthase, while glucose -6-P activates it.

- Glycogenolysis

It is the breakdown of glycogen into glucose-1 -phosphate.

- Sites: Cytosol of liver and muscles

- Importance glycogenolysis:

- Liver glycogen maintains blood glucose level during fasting less than 18 hours.

- Muscle glycogen provides contracting muscles with energy.

- Enzymes of Glycogenolysis:

The key enzyme of glycogenolysis is :Phosphorylase.

- **Liver phosphorylase is a monomer**
- **Muscle phosphorylase is a dimmer** each monomer contains one pyridoxal phosphate.

- Regulation in the liver and muscles

1. Hormonal regulation;

- The inactive form of phosphorylase is dephosphorylated.
- It is activated by phosphorylation of the OH group of the amino acid
- Residue in the enzyme.This process requires active *phosphorylase kinase*, which is activated by active *protein kinase A* enzyme.

2. Allosteric regulation;

Glucose-6-P and ATP allosterically inactivate phosphorylase.

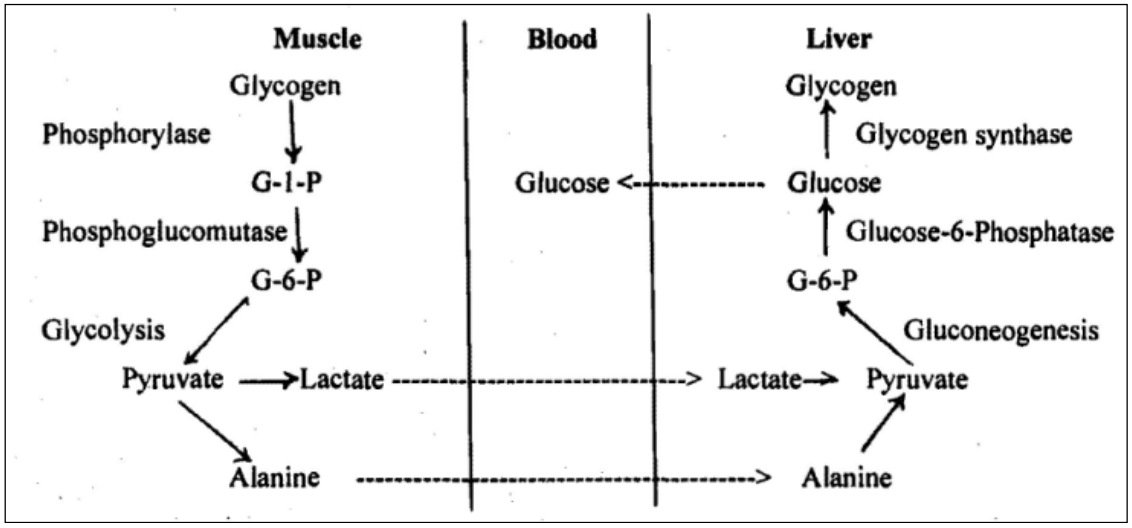
- Regulation in muscles (only):

- Effect of calcium;

Calcium released from contracting muscles produces direct activation of phosphorylase kinase (b) without phosphorylation by binding calmodulin unit of the enzyme. It also binds troponin-C protein in contracting muscles lead to more activation of phosphorylase kinase.

- Cori's Cycle and glucose alanine cycle:

- Muscle glycogen can supply glucose to blood indirectly by converting pyruvate or (alanine during starvation) into lactate during muscle contraction (anaerobic glycolysis).
- Muscle glycogen cannot provide blood glucose due to the absence of glucose 6 phosphatase enzyme.
- Both lactate (Cori cycle) and alanine (glucose alanine cycle) are converted to glucose in the liver.



- Glycogen Storage Diseases:

They are group of genetic diseases that affect glycogen metabolism. The most important are:

- Type I ;Von Gierke's disease;

It is caused by deficiency of glucose-6-phosphatase enzyme in liver. This will lead to accumulation of G-6-P and glycogen in liver. The patients suffer from hepatomegally (enlarged liver) due to glycogen accumulation, fasting hypoglycemia, hyperlipidemia due to enhanced lipolysis and hyperuricemia due to activated HMP by the excess G-6-P.

- Type V :McArdle's syndrome;

It is caused by deficiency of muscle pbosphorylase. It leads to accumulation of glycogen in muscles and failure of its conversion to glucose. The symptoms of the disease are painful muscles, muscle weakness, and cramps. Creatine phosphokinase and lactate dehydrogenase (muscle enzymes) will be elevated in serum.

- Gluconeogenesis

It is synthesis of glucose or glycogen from non carbohydrate sources.,during fasting more than 18 hours when glycogen stores are depleted.

- Sites: It occurs in cytosol of liver the kidneys .

- Importance:

1. It provides blood glucose for different tissues:

- **The Brain:**
  1- It needs Glucose a source of energy.
  2- It cannot utilize fatty acids because they are bound to albumin and cannot pass the blood brain barrier.
  3- It is the main source of oxaloacetate needed for working kreb's cycle to allow complete oxidation of acetyl SCoA derived from fatty acid oxidation.
  4- It utilizes ketone bodies after few days of fasting.
- **Skeletal muscles and RBCs**
  Glucose is the main source of energy due to the absence of mitochondria (it cannot utilize fatty acids or ketone bodies).

2. Gluconeogenesis helps the utilization of wastes as:

- Lactate produced from glycolysis in contracting muscles and RBCs.
- Glycerol-3-P derived from lipolysis.

- Enzymes of Gluconeogenesis

All the reactions are the reversal of glycolysis except those of the three irreversible reactions, which are reversed as following:

- Glucokinase and hexokinase both are reversed by glucose 6-phosphatase.
- Phosphofructokinase-I is reversed by fructose 1,6-bisphosphatase.
- Pyruvate kinase is reversed by two enzymes: Pyruvate carboxylase and phosphoenolpyruvate carboxykinase.

N.B.: All enzymes are present in the cytosol except pyruvate carboxylase, which is mitochondrial.

- Substrates for gluconeogenesis:

1. Lactate and Pyruvate;

a. Lactate is converted into pyruvate: by lactate dehydrogenase enzyme.

b. Pyruvate is converted into 2 phosphoenol pyruvate by two enzymes:

- The mitochondrial pyruvate carboxylase enzyme converts pyruvic into oxaloacetic acid.
- This reaction needs energy derived from ATP.
- Oxaloacetate by the cytosolic enzyme phosphoenolpyruvate carboxykinase is converted into phospho-enolpyruvate.
- Mitochondrial membrane is impermeable to oxaloacetate, so to be transported into cytoplasm it should be converted into malate.
- After crossing the mitochondrial membrane, malate is converted again into oxaloacetate this is called (dicarboxylic acid shuttle).

c. **Phosphoenol pyruvate** is converted into glucose: By reversal of glycolysis.

2. Glycerol-3-P:

Enzyme glycerol-3-P dehydrogenase will give dihydroxyacetone-P. By phosphotriose isomerase one molecule will give glyceraldehyde-3-P, by reversal of glycolysis they give glucose.

3. Propionyl-SCoA resulted from oxidation of odd chain fatty acid:

N.B.: Even chain fatty acid gives acetyl CoA that cannot undergoes gluconeogenesis.

4. Glucogenic amino acids:

All amino acids are glucogenic except leucine and lysine. They gives intermediates of kreb's then by reversal of glycolysis they give glucose.

- Regulation of gluconeogenesis

1. Effect of enzyme activity:

The rate of enzyme synthesis is the rate limiting step of gluconeogenesis

2. Effect of Hormones:

- Insulin suppresses the four enzymes of the irreversible reactions of gluconeogenesis.
- Glucagon induces the enzymes of the irreversible reactions.
- Growth hormone: Induces transamination of amino acids.
- Glucocorticoids: produce protein catabolism and gluconeogenesis from amino acids.

3. Effect of dietary state:

- Feeding inhibits gluconeogenesis due to stimulation of insulin.
- Fasting activates gluconeogenesis through mechanisms:

a. Stimulation of glucagon and other antiinsulin hormones.

b. Antiinsulin hormones induce lipolysis and fatty acid oxidation during fasting. This will increase the production of ATP, NADH and acetyl SCoA, all of

them inhibit pyruvate dehydrogenase and prevent the complete oxidation of pyruvate.

- Energy consumed by gluconeogenesis:

- Pyruvate carboxylase ⟶ ATP × 2 = 2 ATP
- Phosphoenol pyruvate carboxykinase ⟶ GTP × 2 = 2 ATP
- Phosphoglycerate kinase ⟶ ATP × 2 = 2 ATP
- Glyceraldehydes-3-P dehydrogenase 2 NADH ⟶ 5 ATPs
- Total energy consumed: 11 ATPs

- Galactose Metabolism

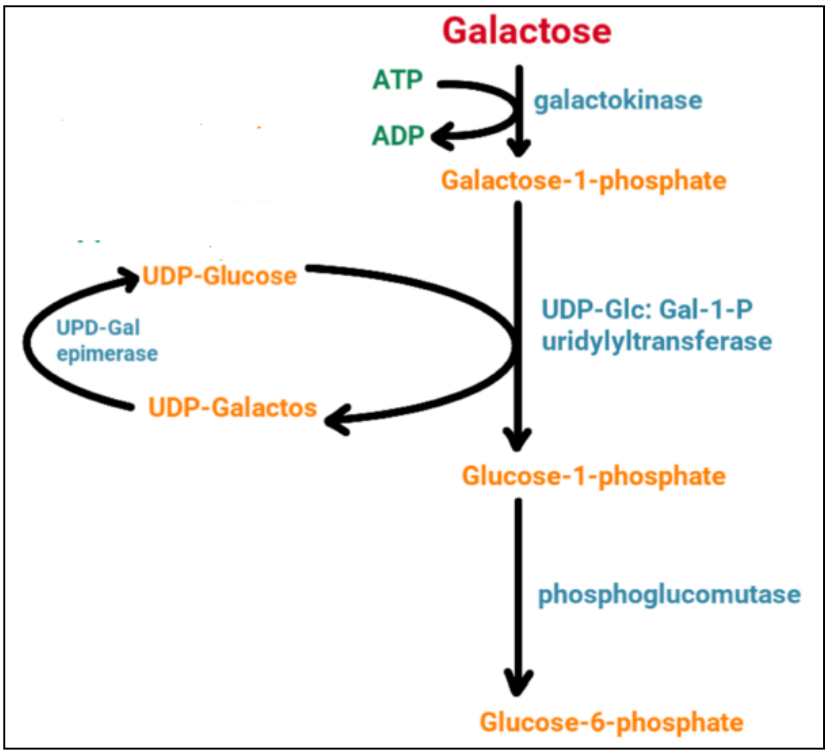
- Site: Mainly in the cytosol of liver

- Importance: Galactose is present in:

1- Lactose of milk.
2- Galactolipids.
3- Glycosaminoglycans (GAGs).

- Main enzymes of Galactose conversion to Glucose

1. Galactokinase
2. Galactose-1-P uridy transferase
3. UDP Galactose 4 Epimerase.



- Metabolic error in galactose metabolism (Galactosemia) :

Galactosemia is a genetic disease characterized by elevated galactose level in blood and urine.It is due to ***deficiency of one of the enzymes of Galactose*** metabolism.

- Manifestations:

- **Cataract** due to accumulated galactose and galactiol (reduced form of galactose) in eye lens.
- **Mental retardation** due to accumulated Galactose in the brain.
- **Liver failure** as glactose is kept in the form of Galactose 1 phosphate this leads to:
  1) Depletion of inorganic phosphate.
  2) Galactose 1 Phosphsate also,inhibits the phosphorylase and decrease ATP production.

Treatment:

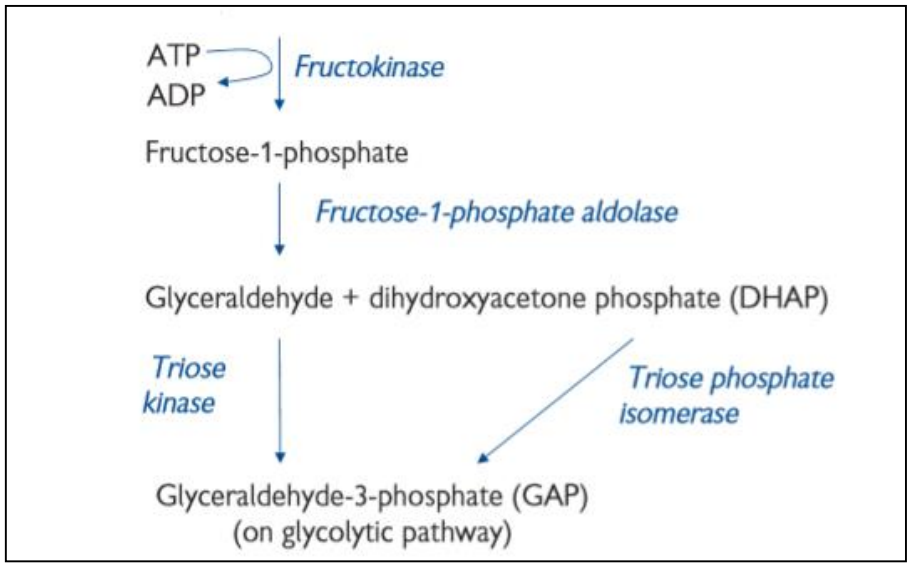
1- Galactose free diet.

2- There will be induction of other enzyme: Galactose Pyrophosphorylase enzyme to overcome the depleted enzymes.

In absence of galactose the body can synthesize its needs by converting glucose into galactose in liver cells.

- Fructose Metabolism

- Fructose has a more simple entry pathway into metabolism.
- In the liver, fructokinase converts fructose into fructose-1-phosphate
  - F1-P splits into DHAP and glyceraldehyde
  - Glyceraldehyde is converted into GAP by triose kinase
  - DHAP and GAP are both intermediates of the glycolysis pathway
- In adipose tissue, hexokinase converts fructose into fructose-6- phosphate, which can continue directly through glycolysis.



- Inborn errors in fructose metabolism;

1. Essential fructosuria: It is caused by deficiency of fructokinase enzyme. It leads to fructosemia and fructosuria.

2. Hereditary fructose intolerance: It is caused by congenital deficiency of aldolase B.

- Hypoglycemia after fructose feeding occurs by two mechanism:

1- Fructose -I-P will accumulate and allosterically inhibits the phosphorylase enzyme.

2- Also depletion of inorganic phosphate will inhibits the phosphorylase and decrease ATP production lead to liver failure.

- Blood glucose and its regulation

- Sources of blood glucose;

1. **Dietary glucose and other hexoses** are converted in the liver into glucose.
2. **Stored glycogen by the liver** by glycogenolysis during fasting less than 18 hours
3. **Glucogenic amino acids.**
4. **Glycerol-3-P** by gluconeogenesis in liver and kidneys during fasting more than 18 hours.

- Normal blood glucose levels;

- During fasting 8-12 hours : 70 - 105 mg/dl
- One hour after meal : Up to 170 mg/dl (less than renal threshold 180 mg/dl)
- Two hours after meal : 70 - 120 mg/dl

- Factors that maintain blood glucose:

They include organs and hormones:

a. Organs that maintain blood glucose:

1. Gastrointestinal tract:

- It prevents sudden elevation of blood glucose after meal as following:
- There is gradual evacuation of food from the stomach.
- There is constant rate of absorption of glucose, which is 1 g / kg B.W/ hour.
- The secretion of gastrointestinal hormones stimulates insulin secretion after meal.

2. Tissue uptake of blood glucose;

There are different glucose transporters:

1- Sodium glucose transporter-1 (SGLT-1): Present in intestine and kidneys.
2- Glucose transporter-1: Present in red blood cells.
3- Glucose transporter-2: Present in basal border of intestine, liver, kidneys and pancreas.
4- Glucose transporter-3: Present mainly in brain.
5- Glucose transporter-4: Present in heart, skeletal muscles and adipose tissue. It is an insulin dependent receptor.

ROLE OF TISSUES IN REGULATION OF BLOOD GLUCOSE	
Liver: the main regulator of glucose (glucostate)	
After meals: It increases glucose uptake. It increases different pathways of glucose oxidation. It helps the formation of other sugars from glucose. It stores excess glucose as glycogen by glycogenesis.	**During fasting:** It decreases glucose uptake. It decreases glucose oxidation. It stimulates glycogenolysis to supply blood glucose during fasting less than 18 hours. It enhances gluconeogenesis to form glucose from non-carbohydrates during fasting more than 18 hours. It helps the conversion of other hexoses into glucose.
Kidneys	
After meals: It increases glucose uptake. It increases glucose oxidation. If blood glucose exceed the maximum capacity of the kidney to reabsorb it from glomerular filtrate (renal threshold = 180mg/dl), it is excreted in urine.	**During fasting:** It decreases glucose uptake. It decreases glucose oxidation. It increases gluconeogenesis.
Muscles	
After meals: It increases glucose uptake. It increases glucose oxidation. It increases glycogenesis	**During fasting:** It decreases glucose uptake. It decreases glucose oxidation. It can supply blood glucose indirectly from alanine and lactate through Con's cycle or glucose alanine cycle
Adipose tissue	
After meals: It increases glucose uptake. It increases glucose oxidation. It increases lipogenesis	**During fasting :** It decreases glucose uptake. It decreases glucose oxidation. It increases lipolysis. Glycerol undergoes gluconeogenesis. Fatty acid will be oxidized to give acetyl-CoA, ATPs and NADH.

b. Hormones that regulate blood glucose level

1. Insulin: It is the only hypoglycemic hormone:

- It increases glucose uptake by heart, skeletal muscles and adipose tissue.
- It increases glucose oxidation by induces the three irreversible enzymes of glycolysis.
- It stimulates pyruvate dehydrogenase to complete the oxidation of glucose by
- Kreb's cycle.
- It stimulates the two dehydrogenases of HMP pathway.
- -It activates glycogen synthase so, it enhances glycogenesis.
- It inactivates glycogen phosphorylase so, it inhibits glycogenolysis.
- It inhibits gluconeogenesis by activating the irreversible enzymes of glycolysis and inhibiting those of gluconeogenesis.
- It stimulates lipogenesis and inhibits lipolysis.

2. Antiinsulin hormones:

They increase blood glucose level as following;

a. Glucagon: Its effect is on the liver:

- It increases glycogenolysis and gluconeogenesis.
- It inhibits glycolysis and glycogenesis.

b. Adrenaline: Its effect is on the liver, muscles and adipose tissue:

- It increases glycogenolysis and gluconeogenesis.
- It inhibits glycolysis and glycogenesis.
- It stimulates lipolysis in adipose tissues.

c. Glucocorticoids and Growth hormone;

- They enhance lipolysis in adipose tissues.
- They induce transaminase enzymes and gluconeogenesis from amino acids.

d. Thyroxine:

- It has some hypoglycemic and some hyperglycemic effects. The resultant is hyperglycemia.
- It increases glucose absorption from the intestine.
- It increases glucose uptake and oxidation by inducing the glucokinase enzyme.
- It stimulates insulin secretion.
- It inhibits glycogenesis.
- It activates glycogenolysis and gluconeogenesis.
- It stimulates lipolysis in adipose tissues.

- Hypoglycemia

It is the decrease of blood glucose below 45 mg/dl.

This will leads to:

- Adrenaline stimulation producing tremors, tachycardia and sweating.
- Decreased glucose supply to the brain will lead to headache, drowsiness, and if not treated it leads to coma and death.

- Types of hypoglycemia;

a. Fasting hypoglycemia;

1. **Liver diseases**: Due to decreased glycogen stores, glycogenolysis and gluconeogenesis.
2. **Chronic renal disorders**: Due to impaired gluconeogenesis and presence of glucosuria.
3. **Increased insulin level**: Due to tumor in beta cells of pancreas or overdose of insulin in diabetic patient.
4. **Decreased antiinsulin hormones**: Due to hypofunction in pituitary, thyroid or suprarenal glands 5.Hereditary metabolic diseases:
   - **Von Gierk's disease** (decreased hepatic glucose 6 phosphatase)
   - Decreased fructose-1,6-bisphosphatase.

b. Post prandial hypoglycemia;

1. **Alimentary**: Following gastrectomy and gastrojejunostomy due to rapid evacuation of the stomach. This will lead to sudden elevation of blood glucose and excessive stimulation of insulin secretion and hypoglycemia.
2. **Reactive hypoglycemia**: The normal elevation of blood glucose after meal stimulates insulin secretion lead to hypoglycemia two

hours after meal in some people, which is usually corrected by antiinsuiin hormones after short time.

3. Hereditary metabolic disorders:

Hereditary fructose intolerance: the absence of aldolase-B leads to accumulation of fructose-1-P that inhibits phosphorylase enzyme and glycogenolysis.

- Glucosuria

It is the presence of detectable amount of glucose in urine (usually above 30 mg/dl).

- Types of Glucosuria:

a. Hyperglycemic glucosuria:

It occurs when the blood glucose level exceeds the renal threshold (180 mg/dl) which is the maximum capacity of the kidneys to reabsorb glucose from the glomerular filtrate. Causes of hyperglycemic glucosuria:

- **Diabetes mellitus**: Due to imbalance between insulin and antiinsulin hormones.
- **Adrenaline glucosuria**: In cases of stress, emotion or pheochromocytoma.
- **Alimentary glucosuria**: Following gastrectomy and gastrojejunostomy due to rapid evacuation of the stomach. This will lead to increased rate of glucose absorption and sudden elevation of blood glucose.

b. Normoglycemic glucosuria:

- **Congenital renal glucosuria** (diabetes innocens): Due to congenital decrease in renal threshold.
- **Renal diseases** as nephritis.
- **Pregnancy** due to the pressure of the fetus on renal vessels.

Chapter III

Lipids Metabolism

- Forms of Dietary lipids:

Most of dietary lipids consist of:
- Triacylglycerols
- Phospholipids
- Cholesterol esters
- Fat-soluble vitamins.

- Digestion of lipids:

I-Lingual and Gastric Lipases:

Their function is not important for adult because food remains for short time in the mouth and stomach.

II- Pancreatic Lipase:

- It is the main enzyme that digest triacylglycerols.
- It hydrolyses the ester bonds at positions 1 and 3. It needs the presence of emulsify agents.
- **Emulsifying agents are:** Bile salts, phospholipids and lysophospholipids. They increases the surface area of the lipid droplets and their exposure to the enzyme.
- **Co-lipase:** It is a protein secreted by the pancreas. It helps the binding of the enzyme with the substrate.

III- Intestinal Lipase

A. Its action is intracellular. It hydrolyzes 1-monoacylglycerol after being absorbed converting it into glycerol and free fatty acids

B. Digestion of Phospholinids:

Phospholipids are hydrolyzed by the pancreatic phospholipase A_2 into lysophospholipids. Calcium ions acts as activator for the enzyme.

C. Digestion of Cholesteryl Esters':

They are hydrolyzed by pancreatic cholesteryl esterase into cholesterol and free fatty acids.

The end products of digestion of lipids:

2-monoacylglycerol, 1-monoacylglycerol, glycerol, phospholipids, lysophospholipids, cholesterol, and free fatty acids.

- Absorption of Lipids

Lipids will undergo the following within the mucosal cells;

- Long chain fatty acids **are converted to acyl-CoA,.**
- l-monoacylglycerol **is completely hydrolyzed by the intestinal lipase into glycerol and FFA..**
- 2- monoacylglycerol **is esterified by acyl-CoA into triacylglycerols.**

- Lysophospholipid **is esterified by acyl-CoA into phospholipids.**
- Cholesterol **is esterified by acyl-CoA into cholesteryl esters.**

- Formation of chylomicron:

- Chylomicron transport lipids from the intestinal mucosal cells to portal circulation.
- It is formed of triacylglycerols, phospholipids, cholesteryl esters, cholesterol and fat-soluble vitamins conjugated with proteins.
- Chylomicron, causes the turbidity of the plasma after fatty meal.
- They are cleared by the lipoprotein lipase enzyme (clearing factor).

- Metabolic defects in the digestion and absorption of lipids;

- Steatorrhea (Fatty diarrhea);

It is characterized by the presence of excess fat in stool due to the following-;

1) **Diseases of the pancreas** in cases of inflammation (pancreatitis), tumors or following pancreatectomy.
2) **Diseases of the liver and biliary system in cases of hepatitis, cholycystitis or biliary obstruction.**
3) **Diseases of the intestinal mucosal cells that lead to impaired absorption of lipids.**

- Fates of absorbed lipids:

1) **Tissue uptake**: Of triacylglycerols and chylomicrons

2) **Tissue utilization**: A– Catabolic B- Anabolic

A- Catabolic fate: Oxidation for production of energy.

B- Anabolic fate:

- Conversion to glucose.
- Formation of tissue fats:
- Formation of important biological compounds: eicosanoids, sterols, steroid hormones and others.

3) **Storage:** Lipids are stored in adipose tissues as depot fat.

4) **Secretion:** Sebaceous glands of the skin and lactating mammary glands are the main excretory form of fat.

- Metabolism of Triacylglycerol

1- Metabolism of glycerol,
2- Metabolism of fatty acids.
3- Metabolism of TAG .

- Metabolism of Glycerol

- Glycerol metabolism occurs:

1. Liver and kidneys by kinase enzyme**.**
2. In other tissues, **due to absence of glycerol- kinase**, glycerol 3-phosphate is formed from dihydroxyacetone phosphate derived from glycolysis.

- Fate of glycerol 3 phosphate:

- It is used for synthesis of triacylglycerol & phospholipids.
- It can give glucose by gluconeogenesis in liver and kidneys.

- It can give dihydroxyacetone phosphate then undergoes oxidation by glycolysis.

- Metabolism of Saturated Fatty Acids (SFA)

A- Fatty Acid Oxidation

The main pathway of fatty acid oxidation is the β -oxidation, other uncommon pathways are the α and ω-oxidation**.**

B- β-Oxidation of Fatty Acids:

- **Importance:**

It is the main source of energy during starvation and in carbohydrate deficiency. Active acetate produced is oxidized in Kreb's cycle.

- **Site:**

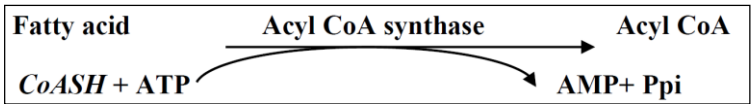
β-oxidation occurs in the liver, kidneys, lungs, heart, muscles and adipose tissues. The enzymes of β-oxidation are present in the mitochondrial matrix next to citric acid cycle and respiratory chain.

- **Steps:**

1- Fatty acids activation (synthesis of acyl -CoA).
2- Fatty acids transport through inner mitochondrial membrane.
3- β-oxidized of fatty acid in the mitochondrial matrix.

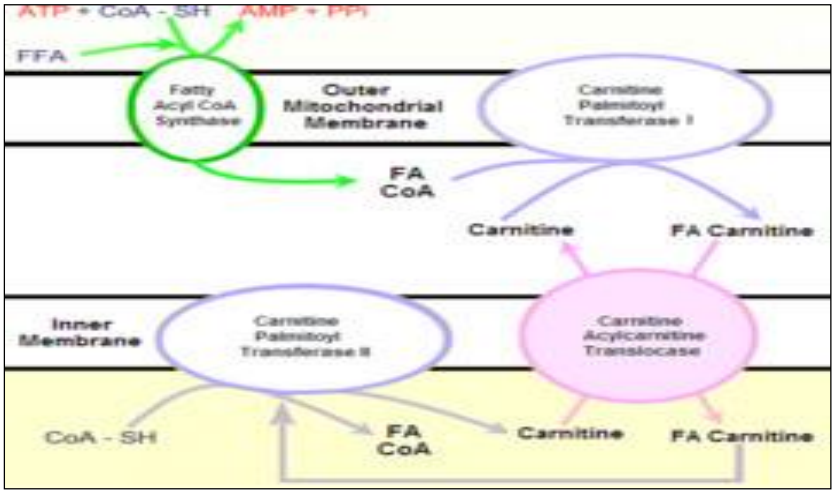
1- Fatty acids activation (synthesis of acyl-CoA):

1. Activation of fatty acids (Synthesis of acyl CoA) occurs in the outer membrane space

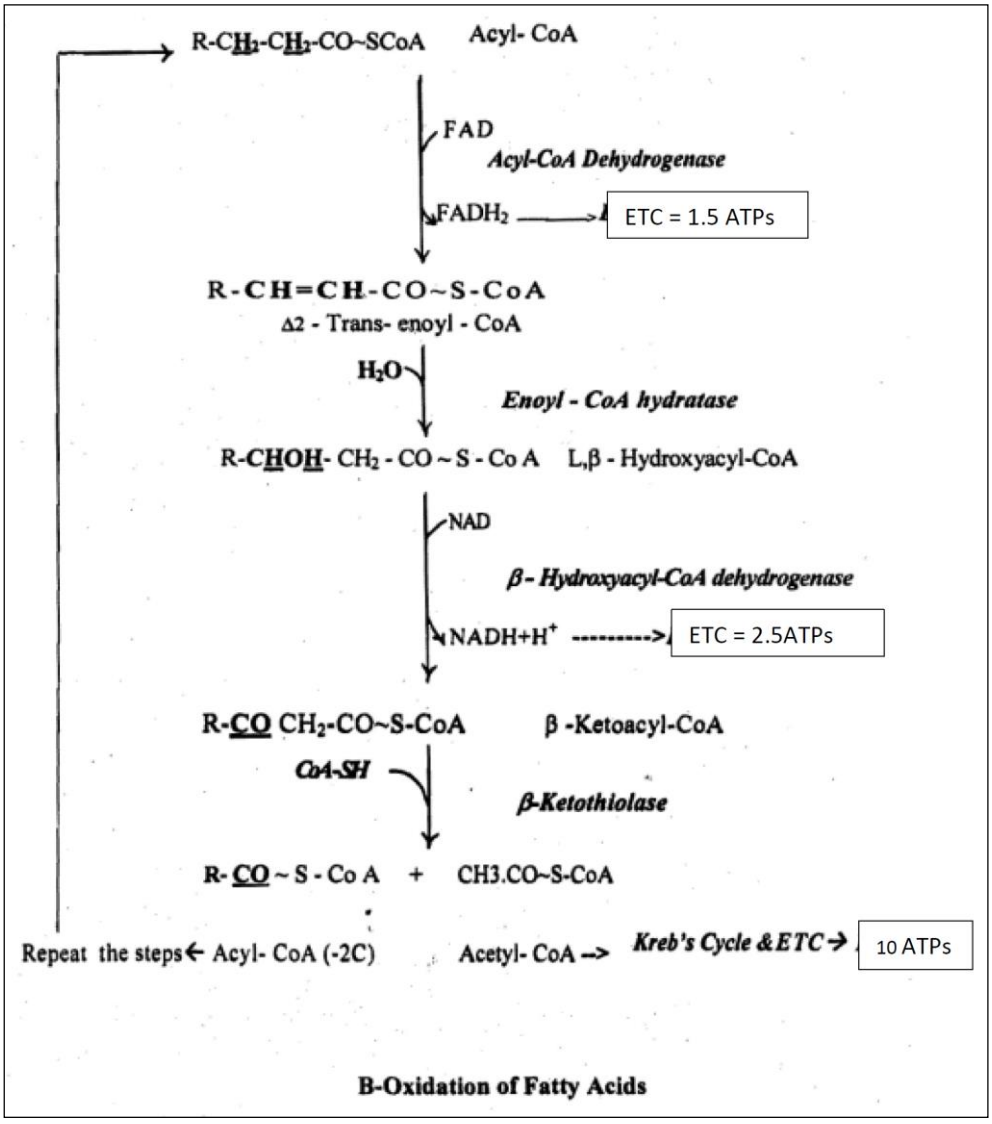


2. Transport of fatty acid across mitochondrial membrane (carnitine shuttle)

- Short chain fatty acyl-CoA can pass through the inner mitochondrial membrane.
- Long-chain acyl-CoA requires the presence of a carrier called carnitine (β-hydroxy -γ- trimethyl ammonium butyrate).



Steps of β-oxidation:



3- Oxidation of Acyl-CoA;

- Fatty acid oxidation occurs in the mitochondrial matrix.
- It is a multicyclic process, in each cycle two carbons are removed as active acetate (acetyl-CoA)
- Reduced coenzymes (FADH2 and NADH, H+) are produced.

Energy Produced from β-Oxidation of fatty acids:

- Palmitic acid contains 16 carbons. It undergoes 7 cycles of β -oxidation resulting in the production of 8 molecules of active acetate, 7 FADH2 and 7 NADH,H^+.

The number of ATP produced by 7 cycles of p oxidation could be calculated as following:

- 7 $FADH_2$ ⟶ Respiratory chain = 7 × 1.5 ATP = 10.5 ATP
- 7 $NADH+H^+$ ⟶ Respiratory chain = 7 × 2.5 ATP = 17.5 ATP
- 8 Active Acetate ⟶ Kreb's cycle = 8 × 10 ATP = 80 ATP

- 80 ATP + 17.5 ATP + 10.5 ATP = 108 ATP
- 2~ P (used for Acyl CoA synthetase) = - 2 ATP

Total energy gained = 106 ATP

- Regulation of Fatty Acid (FA) Oxidation:

1- Effect of hormones, feeding and fasting ;

- **Carbohydrate feeding** stimulates insulin secretion. It inhibits lipolysis and the release of FFA from adipose tissues and decreases FA oxidation.
- **Fasting** stimulates the secretion of anti insulin hormones that stimulate lipolysis and increase fatty acids oxidation.

2- ATP/ADP ratios

The increase of ATP/ADP ratio produces inhibition of the ETC. This will lead to accumulation of NADH and FADH2 inhibiting of the dehydrogenases of β-oxidation.

3- Malonyl-CoA:

It inhibits carnitine palmitoyl-transferase I enzyme so, it decreases fatty acid transport through mitochondrial membrane.

- Peroxisomal system of modified β oxidation of fatty acids:

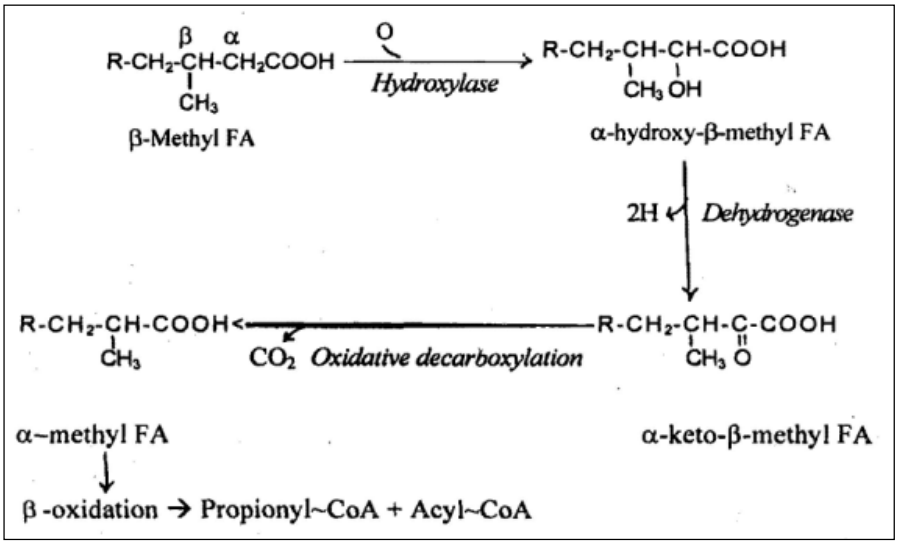
It is important to shorten very long chain fatty acids (more than 20 carbons) .It ends with fatty acids with 8 carbons in length.

- Metabolic Errors of Fatty Acid Oxidation;

They may be due to deficiency of carnitine, CPT-1, CPT-II.

II- α -OXIDATION OF FATTY ACIDS

It is a pathway for oxidation of fatty acids *(phytanic acid),* that have a methyl group in the β- carbon blocking the P oxidation. It occurs in microsome of brain tissues.



- Refsum's Disease

- It is a congenital deficiency disease of the enzymes of α - oxidation.
- It leads to accumulation of phytanic acid in nervous system.
- Complications of the disease are deafness, blindness, and polyneuritis.

- ω OXIDATION OF FATTY ACIDS

- It is a minor pathway for fatty acid oxidation in liver microsome.
- It is catalyzed by cytochrome P450 hydroxylase that oxidizes the terminal CH3 group.
- It then undergoes β- oxidation from both ends.

- Fatty Acid Synthesis

Two systems are present for fatty acid synthesis:

1- De novo system of fatty acids synthesis (Cytosolic system).
2- Fatty Acid Elongation system (Microsomal system).

- De novo synthesis of fatty acids:

- Importance: Conversion of excess acetyl- CoA derived from carbohydrates into fatty acids.

- Site: It is present in the cytosol of liver, adipose tissues, mammary glands, kidneys, lungs and brain.

- Steps: Synthesis of palmitic acid requires the following:

1- 8 molecule of Acetyl-CoA: Which are mainly derived from glucose oxidation due to the availability of oxaloacetate and Citrate.

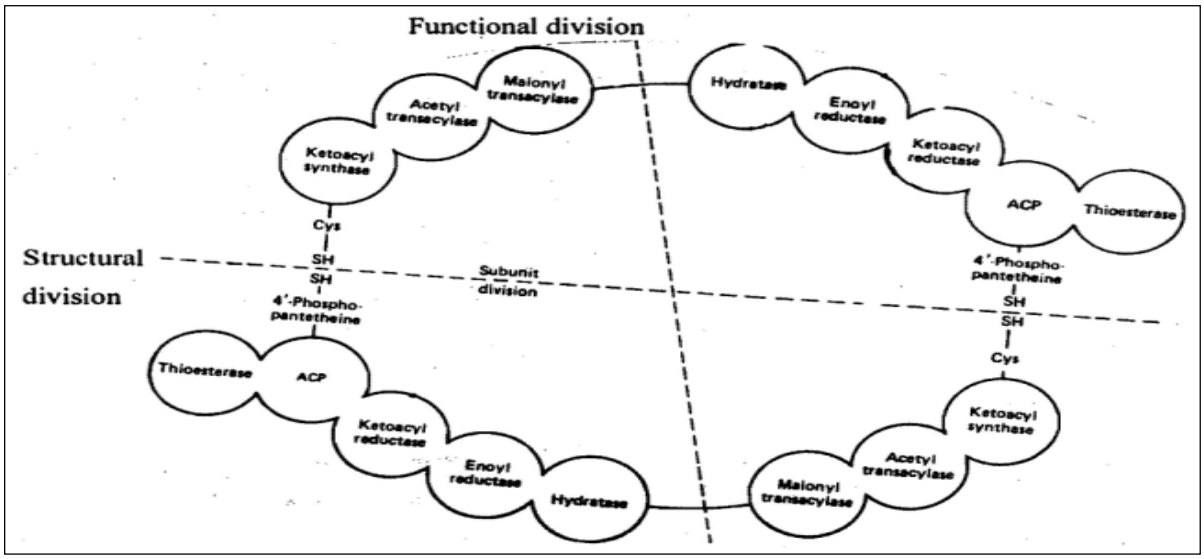
2- NADPH derived from:

- The two dehydrogenases of Hexose monophosphate pathway (HMP).
- Cytosolic isocitrate dehydrogenase enzyme.
- Malic Enzyme:

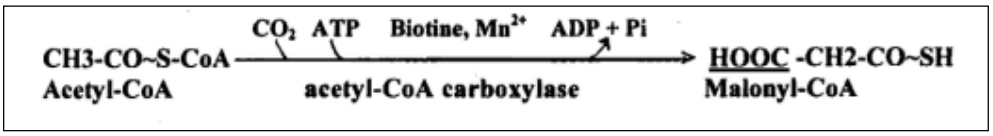
$$\text{Malate} + \text{NADP} \xrightarrow{\text{Malic Enzyme}} \text{Pyruvate} + CO_2 + \text{NADPH} + H^+$$

3- Fatty acid synthase enzymes (multienzyme complex):

- The enzymes of fatty acid synthesis are linked together in the form of multienzyme complex. They are present in the form of two identical polypeptide chains (dimmer) arranged in opposite directions. Each monomer consists of seven enzymes.
- Two SH groups in each monomer act a carriers for the acyl groups during fatty acid synthesis. One SH is derived from 4-phosphopantetheine.The second is that of the amino acid cysteine present in ketoacyl synthase enzyme.



1. **The first step is the conversion of 7 molecules of acetyl-CoA to 7 molecules of malonyl-CoA by acetyl-CoA carboxylase enzyme.**



- Role of glucose in fatty acid synthesis:

- Glucose by glycolysis gives pyruvate,

1- It is converted into active acetate in the mitochondria and form oxaloacetate to form Citrate.

2- In the cytosol, ATP-citrate lyase enzyme hydrolyzes Citrate into oxaloacetate and acetyl-CoA for fatty acid synthesis.

3- Glucose give dihydroxyacetone –P, which will be converted to glycerol -3-P and will be esterified with FA to remove its inhibitory effect on acetyl-CoA carboxylase.

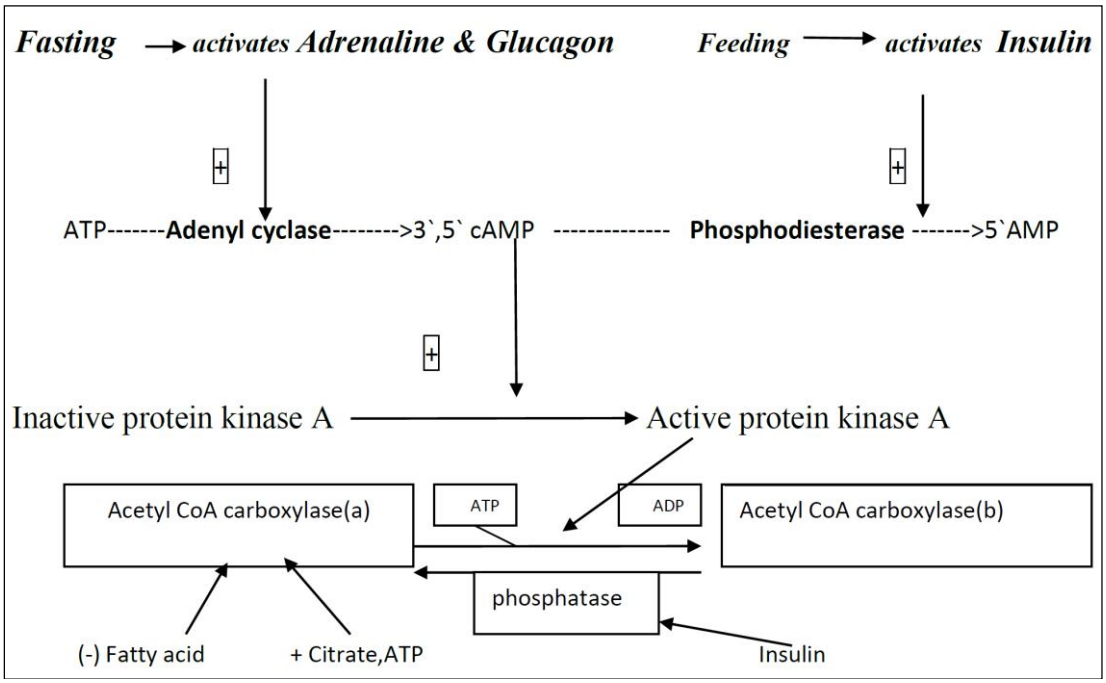
- Glucose by HMP provides NADPH needed for fatty acid synthesis in the cytosol.

- Regulation of Fatty Acid Synthesis

- Acetyl - CoA carboxylase **is the key enzyme of fatty acid synthesis.**
- **It is present in two forms, an active dephosphorylated form and inactive phosphorylated form.**

- Regulation of Fatty acid synthase by phosphorylation / dephosphorylation.

Feeding and insulin induces synthesis of enzymes .Citrate causes allosteric activation of enzymes .ATP activates enzymes. free long chain fatty acid inhibits the enzyme.



II- Microsomal System For Chain Elongation

- Importance: Elongation of C10 saturated and unsaturated acyl - CoA to provide C24 fatty acids needed for formation of cerebroside essential for the myelination process in brain.

- Site: It is highly active in the brain microsome.

- Needs: It needs malonyl- CoA for the elongation process and NADPH, as a source of hydrogen.

- Metabolism of Unsaturated Fattv Acids (USFA)

Unsaturated fatty acids are classified into two main groups:

1- Monoenoic acids:

They have one double bond e.g. palmitoleic (ω7, 16:1), oleic (ω 9, 18:1)

II- Polyenoic (polyethenoid) acids:

They have more than one double bond and called polyunsaturated fatty acids (PUFA). They are classified according to:

1. The number of double bonds **into: Diethenoids (Linoleic acid, ω 6:18:2),** triethenoids (Linolenic acid, ω3 : 18 : 3), Tetraethenoids **(Arachidonic acid, ω 6:20:4).**
2. Linoleic acid **and** Linolenic acid **are essential.**
3. <u>The position of double bond into:</u> **ω3 (linolenic), ω6, (linoleic and arachidonic).**

- Biosynthesis of Unsaturated fatty acids (UFA);

Importance of PUFA:

1- Formation of phospholipids that enter in the structure of cell membranes, and has many important functions.

2- Also formation of cholesterol esters and different eicosanoids .

- Tissue Fat and Depot Fat Metabolism

A. Tissue fat:

- It is the fat that enters in tissue structure and is not affected by the dietary state so, it is called constant element.
- It is formed of phospholipids, cholesterol, glycolipid.
- It is rich in unsaturated fatty acids.

B. Depot fat:

- Depot fat is the fat stored in fat cells of adipose tissue. Its amount is variable depending on the dietary state so, it is called the variable element. It increases by over feeding of carbohydrates and fats and decreases by fasting. It is composed mainly of triacylglycerol.
- **The amount of depot fats is controlled by the rate of its synthesis (lipogenesis) and its oxidation (lipolysis).**

I- Lipogenesis;

It is the synthesis of triacylglycerol. **steps:**

<u>1- Synthesis of Acyl-CoA:</u>

There are two sources for acyl-CoA in adipose tissues:

a- De novo synthesis from active acetate by fatty acid multienzyme complex.
b- Hydrolysis of triacylglycerol present in chylomicrons and very low density lipoproteins by lipoprotein lipase enzyme.

2- Synthesis of Glycerol - 3 - phosphate;

Glycerol-3-phosphate is derived from dihydroxyacetone phosphate from glycolysis. **lipogenesis occur only during carbohydrate feeding as in adipose tissue there is no glycerol kinase enzyme.**

3- Esterification of acyl-CoA with glycerol-3-phosphate;

Catalyzed by the acyl-transferase enzyme.

Regulation of lipogenesis:

1- **Feeding** leads to increased Insulin secretion that stimulates lipogenesis as follows:
2- **Insulin** stimulates glycolysis that leads to the formation of:
1- Dihydroxyacetone phosphate which is converted into glycerol 3-phosphate.
2- Pyruvate that forms acetyl-CoA and oxaloacetate needed for synthesis and transfer of fatty acid.
3- Insulin activates HMP to provide NADPH + H^+ used for fatty acid synthesis.
4- Insulin enhances the synthesis of lipoprotein lipase enzyme of adipose tissues.

II-Lipolysis

The hydrolysis of triacylglycerols present in adipose tissue occurs by the enzyme hormone sensitive lipase. It hydrolyzes triacylglycerol (TAG) into glycerol and free fatty acid (FFA).

Regulation of lipolysis;

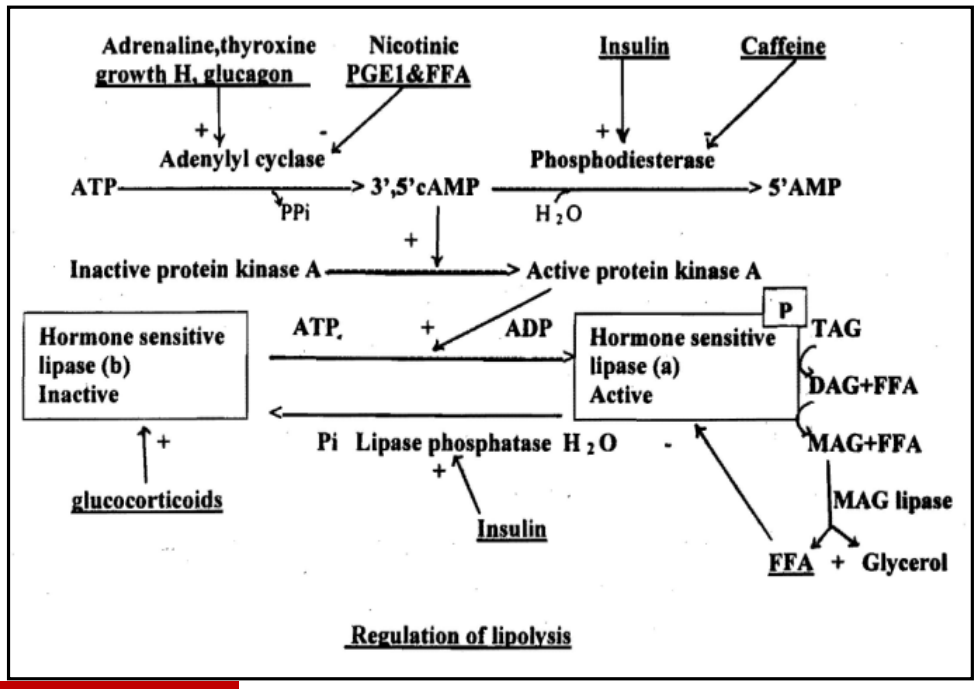
- Hormone sensitive lipase is the key enzyme of lipolysis. It is present in an active phosphorylated form (a) and an inactive dephosphorylated form (b).
- Its activation requires the presence of active protein kinase enzyme, which is activated by cAMP.

Fasting, hypoglycemia and stress;

Increase the secretion of antiinsulin hormones (adrenaline, glucagon, growth hormone and thyroxine) that activate adenylyl cyclase, increasing the cAMP level & lipolysis.

- **Glucocorticoids:** It induces the synthesis of hormone sensitive lipase.
- **Feeding:** Leads to increased insulin secretion which inhibits lipolysis by:
  - It lowers cAMP by stimulating phosphodiesterase and inhibiting adenylyl cyclase. This will inhibit the phosphorylation of hormone sensitive lipase.
  - It activates lipase phosphatase that dephosphorylates the enzyme.
  - It stimulates lipogenesis (see before).
- **Caffeine:** It increases cAMP and lipolysis by inhibiting phosphodiesterase.
- **PGE1 and nicotinic acid:** Decrease lipolysis by inhibiting adenylyl cyclase.

FFA: Produces feedback inhibition on adenylyl cyclase and hormone sensitive lipase



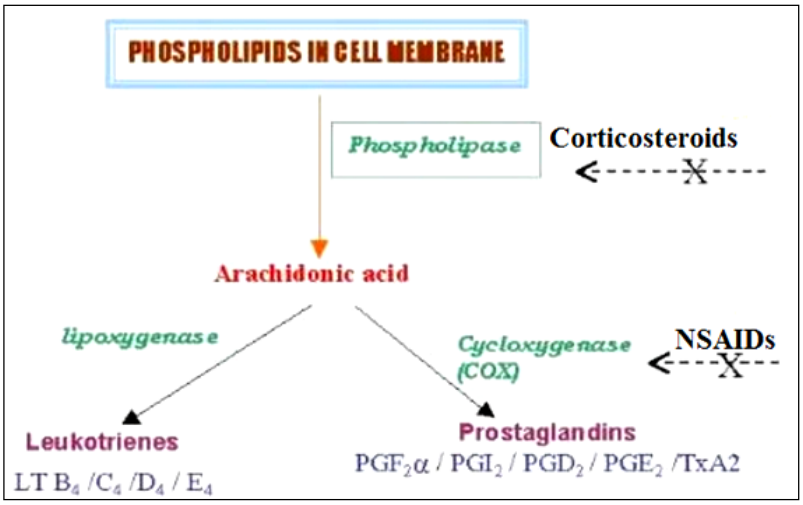
- Metabolism of Eicosanoids

- Eicosanoids are physiologically active compounds derived from C20 PUFA (eicosa means 20).
- They are derived from Arachidonic acid.
- **Arachidonic acid** is released from phospholipids of cell membrane by the enzyme **phospholipase A2**.
- Eicosanoids are classified into two main groups, Prostanoids and leukotrienes.
  - **Prostanoids** includes (prostaglandins, prostacyclin and thromboxan)
  - **Leukotrienes** include leukotrienes and lipoxins.

- Eicosanoids are formed by two main pathways;

A- Cyclo-oxygenase pathway;

- It is catalyzed by prostaglandin synthase.
- It has two enzyme activities (**cyclooxygenase and peroxidase)**. **prostaglandin synthase** forms (PGE and PGF).
  - **Prostacyclin synthase** forms prostacyclins (PGI) .



- **Thromboxane synthase** forms thromboxanes (TX). According to the number of double bonds present each type is classified into three subgroups(PGE1, PGF1, TXAI); (PGE2, PGF2, PGI2 ,TXA2) and (PGE3, PGF3, TXA3).

B- The lipoxygenase pathway:

- **Leukotrienes (LT) and lipoxins (LX)** are formed by this pathway. According to the number of double bonds present, there are LTA3, LTA4 and LTA5.
- **Functions of Eicosanoids;**

I-Prostaglandins;

- **PGE relaxes the smooth muscles of bronchi** and produces **vasodilatation** of blood vessels. They play a role in inflammatory reactions by mediating vasodilatation, fever and pain
- They could be used in the treatment of bronchial asthma and hypertension.
- It induces smooth muscles contraction in the wall of bronchi and blood vessels.
- they stimulate uterine contraction and help the induction of labor
- **They increase cAMP in certain endocrine glands as pituitary, thyroid, and suprarenals** leading to increased hormonal secretion.
- They decrease cAMP in stomach lead to decreased secretion of gastric HCL .

II-Prostacyclins:

- PGI2 are formed by the endothelial cells lining the blood vessels.
- They produce vasodilatation.
- They inhibit platelet aggregation by increasing cAMP in platelets.

III-Thromboxancs;

- They are formed by platelets (thrombocytes) and help thrombus formation and control of bleeding decreasing cAMP in platelets.
- They produce vasoconstriction of blood vessels.
- They promote platelet aggregation**.**

IV-Leukotrienes;

- They are formed by leukocytes and they help the migration of polymorphnuclear leukocyte to the sites of inflammation.
- They are responsible for, broncho-spasm, vasodilatation of blood vessels and the drop of blood'pressure.
- They are released during severe allergic reaction (anaphylactic shock).

- Inhibitors of prostaglandin synthesis;

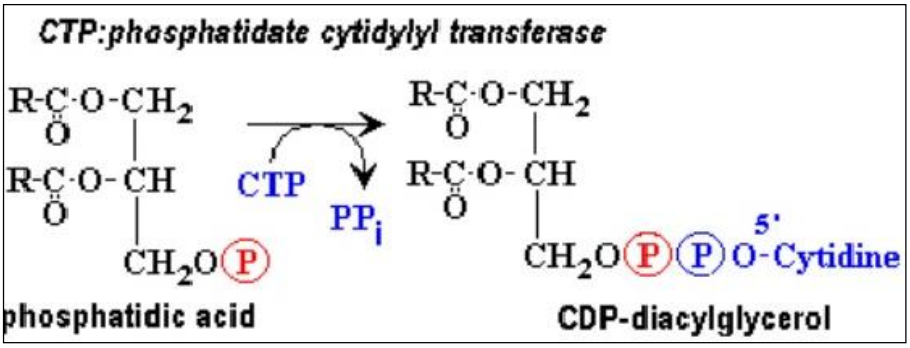
1. **Non Steroid Anti Inflammatory Drugs: like aspirin and brufen,** inhibit the *cyclooxygenase*. so they relieve the symptoms of inflammation.
   Aspirin **decreases the formation of thromboxane** in platelets and prevents thrombus formation.
2. **Steroidal anti-inflammatory drugs: As cortisone** inhibits phospholipase A2 and prevents the release of arachidonic acid from phospholipids
   They inhibit both cyclooxygenase and lipoxygenase pathways of eicosanoid synthesis. So, They are used in the treatment of severe inflammations, anaphylactic shock and to relief bronchial asthma.

- Phospholipids Metabolism

Phospholipids are classified according to the alcohol they contain into: phosphoglycerides (contain glycerol) and sphingoliplds (contain sphingomylin),

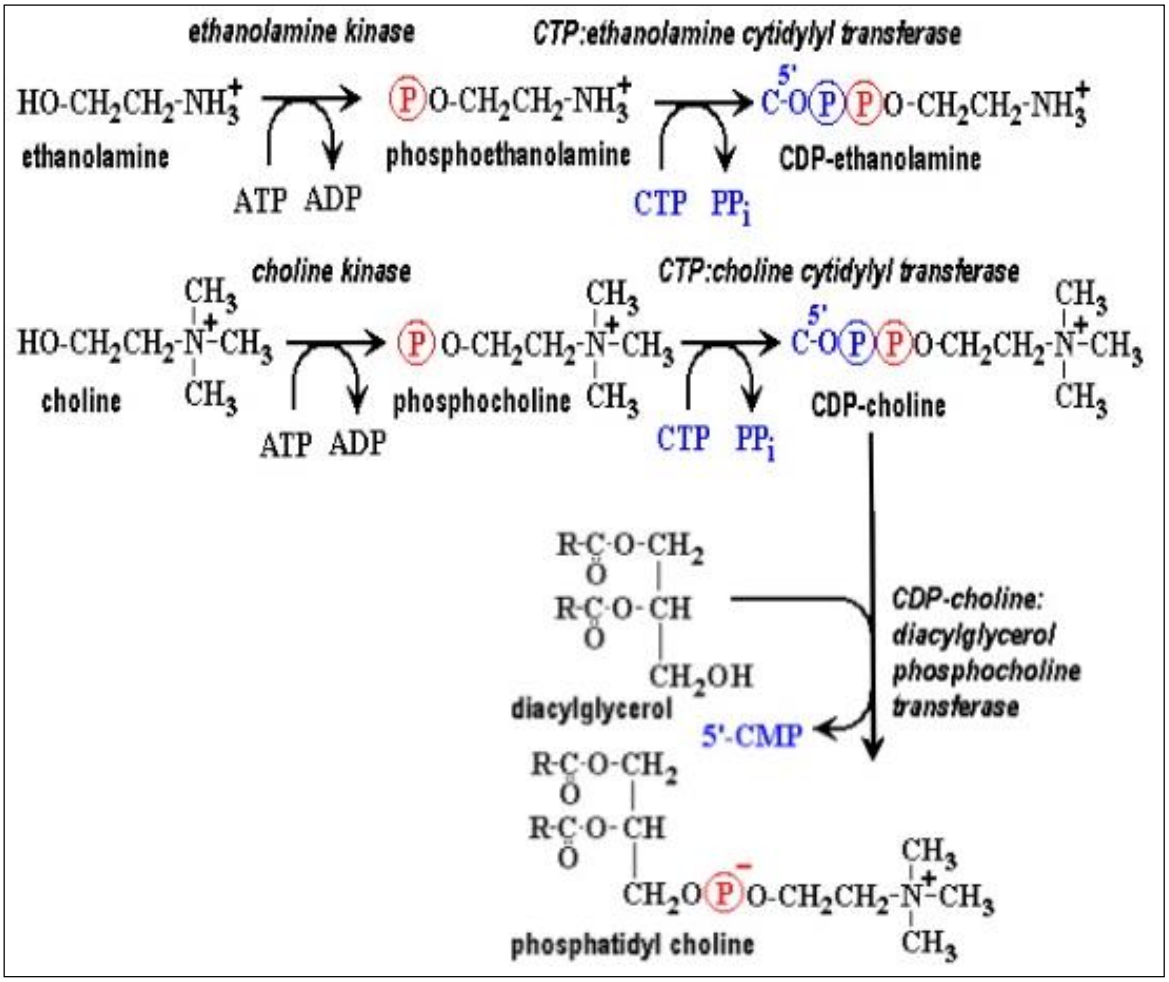
A- Phosphoglycerides include:

1- Phoaphatldic acid
2- Phosphatidyl – serine
3- Phosphatidyl - ethanolamino (cephalln)
4- Phosphatidyl - cholinc (lecithin)
5- Phosphatidyl - inositol (lipositol)



They are formed from phosphatidic acid (1,2- Diacylglycerol -3-phosphate) by conjugation with different bases to form the different types of phospholipids.

Synthesis of phosphatidyl Ethanolamine and phosphatidyl Choline



B. Catabolism of phosphoglycerides

1- They are hydrolyzed by phospholipases A1, A2, B, and C enzymes

2- Lecithin-Cholesterol Acyl Transferase (LCAT)

$$\text{Lecithin + Cholesterol} \xrightarrow{\text{LCAT}} \text{Lysolecithin + Cholersterol Ester}$$

- Importance of Phospholipids

1-They enter in the structure of cell membranes.

2-Phospholipids contain nonpolar group (fatty acid) and polar group (phosphate & bases), this gives them hydrotropic property important for:

- Emulsiflcation of dietary fats to help their digestion and absorpton.
- They prevents the formation of cholesterol stones in biliary system.

3-They enter in the structure of plasma lipoproteins which help the transfer of different types of lipids in plasma.

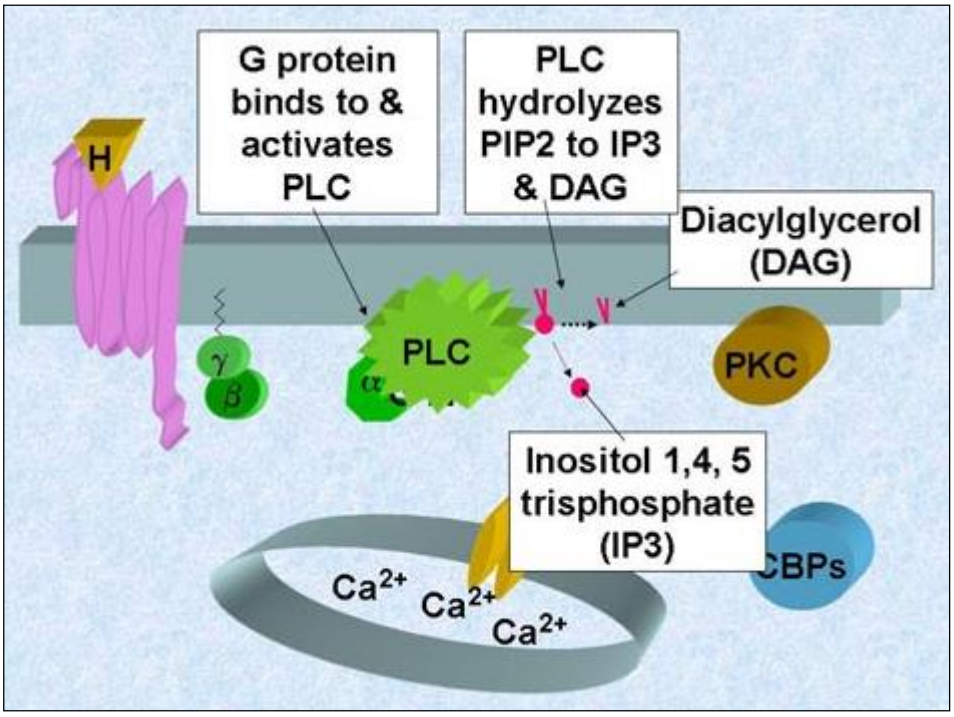
4-Dipalmitoyl-lecithin acts as lung surfactant, to prevent the collapse of pulmonary alveoli their deficieny in premature infants lead to respiratory distress syndrome.

5-They enter in the formation of platelet activating factor needed for blood clotting.

6-They are the main source of arachidonic acid that form the different eicosanoids.

7-They act as second messengers of hormone action:

- The binding of hormones with their receptors produces activation of G proteins that activates phospholipase C enzyme.
- Phospholipase C hydrolyses phosphatidyl-inositol - 4,5 - bisphosphate (PIP2) into inositol-triphosphate (IPS) and diacylglycerols (DAG).
- Both act as hormone second messengers.
- IP3 releases intracellular calcium from its stores .
- DAG activates protein kinase that lead to phosphorylation of cellular proteins enzymes.



H: hormone PLC :phospholipase C PKC:Protein Kinase C

- Sphinsolipids

They includes;

- Sphingomyelin: It consists of sphingosine , fatty acid and phosphocholine.
- Glycolipids: Glucocerebrosides, galactocerebrosides and Gangliosides. They consist of sphingosine , fatty acid and carbohydrates
- Sulfolipid. Consists of sphingosine , fatty acid and galactose 3 sulfate.

- Synthesis of Sphingolipids:

1. The first step of synthesis of sphingolipids is the formation of ceramide (sphingosine + fatty acid).
2. Ceramide + glucose = Glucocerebrosides
3. Galactocerebrosides + sulfate = Sulfolipids.

- Sphingosine is synthesized from palmitoyl- CoA and the amino acid serine.

- **Ceramide + Phosphatidylcholine** ⟶ Sphingomyelin + Diacylglycerol
- **Ceramide + UDP-galactose** ⟶ Galactocerebroside ⟶ Sulfolipids
- **Ceramide + UDP-glucose** ⟶ Glucocerebrosides ⟶ Gangliosides

C- Catabolism of sphingolipids;

Group of lysosomal hydrolase enzymes are responsible of sphingolipids catabolism.

- Sphingolipidosis:

- They are group of **lipid storage diseases** caused by deficiency of sphingolipid catabolic enzymes/Complex lipids will accumulate in different tissues, producing hepatomegaly (liver enlargement), neurological disorders and mental retardation.
- **Examples:**

1- Gaucher's Disease: Due to deficiency of the enzyme p- Glucosidase lead to accumulation of glucocerebrosides.

2- Niemann-Pick Disease: Due to deficiency of sphingomyelinase enzyme lead to accumulation of sphingomyelin.

- Cholesterol Metabolism

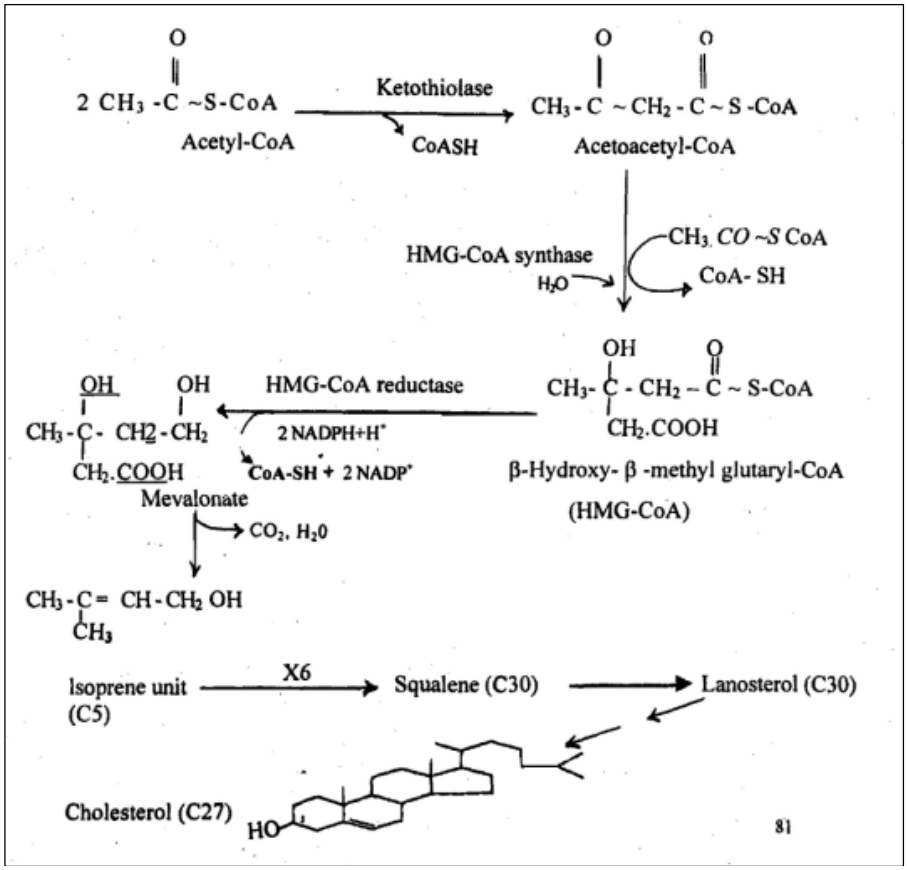
- Sources of cholesterol:

Dietary sources: Brain, liver, kidney, red meat and egg yolk. -Endogenous-sources: Active~acetate (acetyl-CoA).

- Cholesterol synthesis;

- Site :

1. Every cell can form its own cholesterol.
2. Plasma cholesterol is formed by the liver. The enzymes of cholesterol synthesis are present in the microsome and cytosol of the cells.



- Regulation of Cholesterol Synthesis:

Regulation of key enzyme (HMG CoA reductase)

1. Carbohydrate feeding and insulin decrease cAMP level and increase the activity of HMG - CoA reductase
2. Fasting and glucagon decrease its activity.
3. Feed back inhibition: both mevalonate and cholesterol inhibit HMG-CoA reductase.

Regulation: It occurs through covalent modification (phosphorylation-→inactive form) and (dephosphorylation -→ active form of the enzyme)

- Importance of Cholesterol:

1-It is a component of **cell membranes**.

2-It enters in the formation of **plasma lipoproteins.**

3-Cholesterol is the **precursor of Vitamin D3**

4-It is the **precursor of the different sex hormones** (male and female sex hormones), and steroid hormones (corticoids).

5-It is the **source of bile acids and salts**.

- Bile Acids and Bile Salts Metabolism

- The key enzyme of bile acid synthesis is 7 α - hydroxylase.
- It is stimulated by thyroid hormones and vitamin C and feedback inhibited by bile salts.

- Primary bile acids (cholic and chenodeoxy cholic acids).

- They are synthesized in the liver by hydroxylase enzyme.
- It acts at carbons 7 & 12.

- Secondary bile acids (deoxycholic and lithocholic acids).

- They are formed in the intestine by intestinal bacteria.
- Intestinal bacteria remove the OH at C7 from primary bile acids by 7 dehydratase enzyme.

- Synthesis of Bile salts :

Bile acids + (sodium or Potassium salt) + (glycine or taurine) will form bile salts

- Importance of bile salts:

1-Emulification of dietary fat to help their digestion.
2- Formation of micelle to help the absorption of digested lipids.
3-A mean for cholesterol excretion (50% as bile salts and 50% as cholesterol).
4-They prevent cholesterol precipitation in biliary system and formation of biliary stones.
5-They have choleretic effect that help more bile excretion.

- Plasma Cholesterol;

1-The total plasma cholesterol ranges form 100 - 200 mg/dl.
2-Cholesterol is carried mainly in the form of Cholesteryl esters.
3-⅔ of plasma cholesterol is carried on low density lipoproteins (LDL) risk cholesterol and ⅓ on high density lipoproteins (HDL) safe cholesterol.
4-The ratio LDL/HDL (atherogenic index) if more than 4/1 it indicates high incidence to develop atherosclerosis and its complications as hypertension and coronary heart disease.

- Causes of Hypercholesterolemia (cholesterol above 200 me/dl):.

1-Diet rich in carbohydrates
Due to increased availability of acetyl-CoA.

2- Diabetes mellitus: Due to:

- Increased lipolysis and decreased lipoprotein lipase enzyme
- Decreased clearance of plasma lipoproteins.

3-Hypothyroidism:
Due to decreased conversion of cholesterol to bile acids)

4-Obstructive jaundice:
Due to decreased excretion of cholesterol.

5-Coffee drinking and cigarette smoking:
Due to increased lipolysis.

6-Familial hypercholesterolemia
Due to defect in LDL receptors on cell membrane of extrahepatic tissues.

- Causes of Hypocholesterolemia): (cholesterol level below 50 mg/dl):

1-Diet poor in carbohydrate and fats.

2-Starvation
Due to decreased activity of HMG -CoA reductase by antiinsulin hormones.

3-Liver diseases
Due to decreased synthesis of cholesterol and LCAT enzyme that helps its esterification.

4-Hyperthyroidism

Due to increase formation of bile salts from cholesterol.

5-Chronic infections as tuberculosis.

6-Severe anemia.

- Ketone Bodies Metabolism:

- **Ketogenesis:** It means the synthesis of ketone bodies in liver mitochondria.
- **Ketolysis**: It is the break down of ketone bodies in mitochondria of extrahepatic tissues.
- **Ketosis:** It is the increased level of ketogenesis than ketolysis and increased excretion of ketone bodies in urine (ketonuria).

N.B. Acetyl CoA derived from carbohydrates won't form ketone bodies. This because carbohydrates can give oxaloacetate and allows the oxidation of acetyl-CoA by citric acid cycle. Importance of Ketone Bodies;

1-Ketogenesis

- Definition: It is the synthesis of ketone bodies from acetyl-CoA (active acetate).

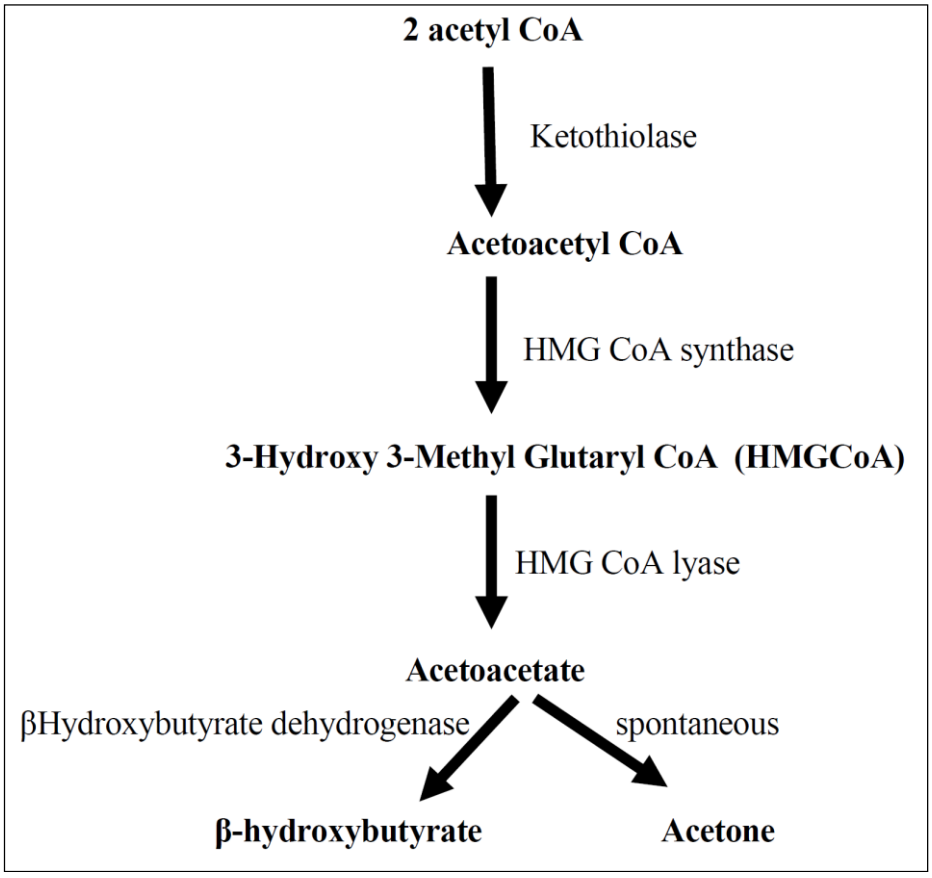
- Overview:

- Ketogenesis is a preparatory step for oxidation of fatty acids in extrahepatic tissues during starvation because they are oxidized more rapid than fatty acids.
- Also, ketone bodies could be oxidized by brain (5 to 6 days after starvation) that cannot oxidize fatty acids.

- Site:

It occurs in the mitochondria of liver due to the presence of the enzymes, synthase and HMG-CoA lyase.

- Pathway of Ketogenesis



- Factors that increase ketogenesis;

1-Starvation due to hypersecretion of anti-insulin hormones.

2-Diet rich in fats and poor in carbohydrates due to decreased availability of oxaloacetate.

3-Diabetes mellitus lead to impaired glucose oxidation and increased fatty acid oxidation.

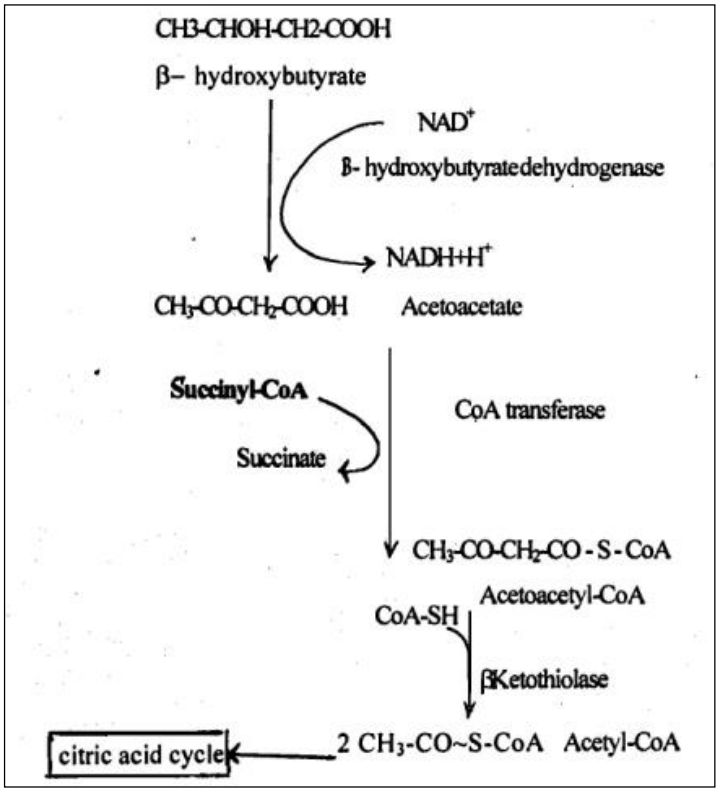
- Ketolysis

- Definition: Ketolysis means oxidation of ketone bodies.

- Site:

- It occurs in the mitochondria of extra hepatic tissues due to the presence of succinyl- CoA - acetoacetate-CoA transferase enzyme. Steps;

- β-hydroxybutyrate is converted to acetoacetate, then acetoacetate is activated and divided into 2 molecules of acetyl-CoA that complete oxidation in Krebs cycle.



- Relation between ketolysis and citric acid cycle;

1-Succinyl-CoA produced by citric acid cycle is used for the activation of acetoacetate.

2-Acetyl-CoA produced by ketolysis complete its oxidation by citric acid cycle.

- Importance of ketolvsis

It is the main source of energy in extrahepatic tissues during starvation and low carbohydrate supply.

- Ketosis:

Ketosis is the increased level of ketone bodies in blood (Ketonemia) (mainly acetoacetate and β - hydroxybutyrate) and increased their excretion in urine (ketonuria),

It is due to increased rate of ketogenesis than that of ketolysis. The normal concentration of ketone bodies in blood is about 1 mg/dl.

- Causes of Ketosis:

1-Prolonged starvation due to increased anti-insulin hormones, that increase the rate of lipolysis and FA oxidation.

2-High fat and low carbohydrates diet that lead to elevated acetyl CoA and decreased availability of oxaloacetate needed for their oxidation through kreb's cycle.

3-Severe uncontrolled diabetes mellitus.

- Complication of Ketosis

1-**Acidosis** due to accumulation of acetoacetate and p- hydroxybutyrate. They are buffered by bicarbonate system lead to a decrease in alkali reserve.

2-**Osmotic diuresis** will occur and Ketone bodies are excreted as sodium and potassium salts.

3-It leads to **electrolytes imbalance**.

4-It leads to **dehydraton**.

5-Finally **coma** occurs that may be fatal.

- Treatment of Ketosis;

Treat the cause:

1-**Intravenous glucose and insulin** infusion in case of **diabetics.**

2-**Intravenous glucose** infusion in case of fasting or **starvation.**

3-**Correct acidosis**: By giving bicarbonate salts.

4-**Correct dehydration**: By fluids

5-**Correct electrolyte imbalance** by sodium and potassium in case of hypokalemia

- Ketogenic Substances;

These are substances that give active acetate without oxaloacetate:

1-Fatty acids and ketogenic amino acids.

2-Diabetes mellitus due to decreased glucose oxidation and oxaloacetate.

3-Starvation due to increased anti-insulin hormones that stimulate lipolysis, and FA oxidation.

- Anti-Ketogenic Substances;

These are substances, that give pyruvate and oxaloacetate that help the oxidation of active acetate by kreb's cycle.

- Carbohydrates, glycerol and glucogenic amino acids.
- Insulin: Stimulates glucose oxidation and lipogenesis and inhibits lipolysis .

- Plasma Lipoproteins

- Sources of plasma lipids;

- Dietary sources.
- Lipid synthesized in the liver.
- Lipids derived by lipolysis in adipose tissues.

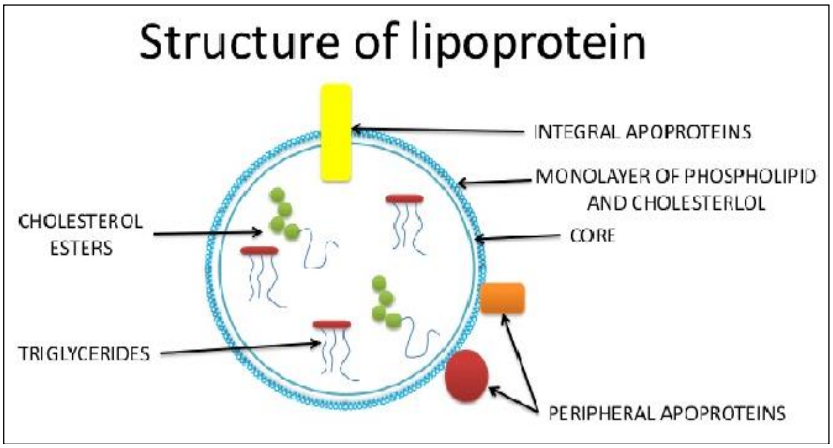
- Structure of Plasma Lipoproteins

Plasma lipoproteins consist of:

1-**Outer layer** A protein part called (apolipoproteins) .

2-**In the middle part:** polar lipids (phospholipids and non-esterified free cholesterol), and proteins.

3-**At the core**:The non-polar lipids (triacylglycerols and cholesteryl-esters) are present.



1- Apolipoproteins:

It is present in two forms:

- **Peripheral protein**: Attached to the surface of lipoprotein and can be easily separated from it.
- **Integral protein**: Inserted in the lipoprotein and cannot be separated from it.

- Functions of the apoproteins:

1-They help the transfer of lipids in the aqueous phase of plasma.
They include certain enzymes as lecthicin cholesterol acyl transferase (LCAT).

2-They act as activator for enzymes (**apo C** II activates lipoprotein lipase and **apo A** actives LCAT present in HDL lipoprotein).

3-They are important for the recognition and uptake of plasma lipoproteins by specific receptors.

4-Apo-D helps the exchange of cholesterol ester and triacylglycerol between plasma lipoproteins.

There are two main methods for Separation of plasma lipoproteins:

Electrophoresis and ultracentrifiigation.

- Products of separation include:

- Chylomicrons (non mobile fraction)
- Very low density Upoproteins (VLDL)
- Intermediate density lipoproteins (IDL)
- Low density lipoproteins (LDL)
- High density lipoproteins (HDL)
- Free fatty acids-albumin complex.

I. Metabolism of Chylomicrons;

- Importance;

- Chylomicrons transport the absorbed dietary lipids from the intestine to lymphatics then to blood.
- They are formed by intestinal mucosal cells

- Components :

- Apoproteins Apo A & Apo B-48.(Apo B-48 represents expression of 48% of apo B gene).
- **Nascent chylomicrons** are released from intestinal cells into intestinal lacteals to the thoracic duct then to blood stream.
- d- Nascent chylomicrons are converted into mature chylomicrons by receiving apoproteins C and E from HDL
- 2-Hydrolysis of TAG of chylomicron;

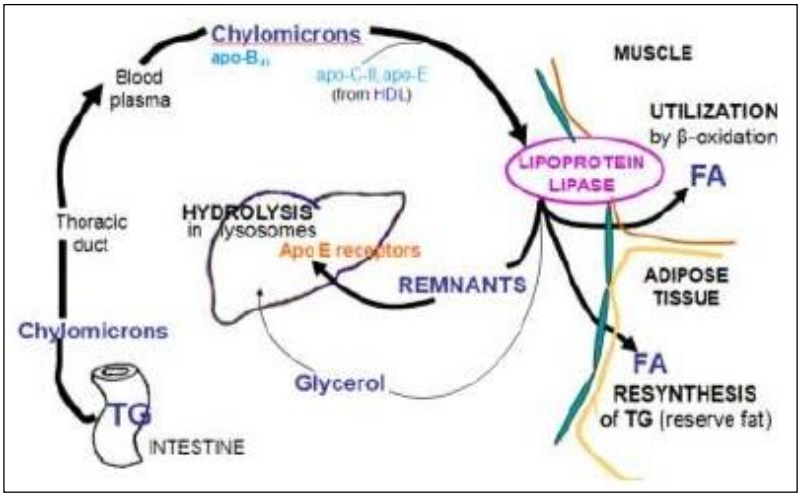
- Role of The enzyme lipoprotein lipase

- It is attached to the endothelial lining of the blood capillaries of different tissues.
- The enzyme hydrolyzes triacylglycerols into glycerol and free fatty acids. Glycerol is taken by the liver due to the presence of glycerol kinase enzyme.
- Free fatty acids either enter the tissues or are transported by plasma albumin to the liver.
- Lipoprotein lipase, enzyme is called the clearing factor because it clears the plasma turbidity produced by chylomicrons after fatty meals.
- Insulin enhances the synthesis of the enzyme, while heparin and apo C -// increase its activity.

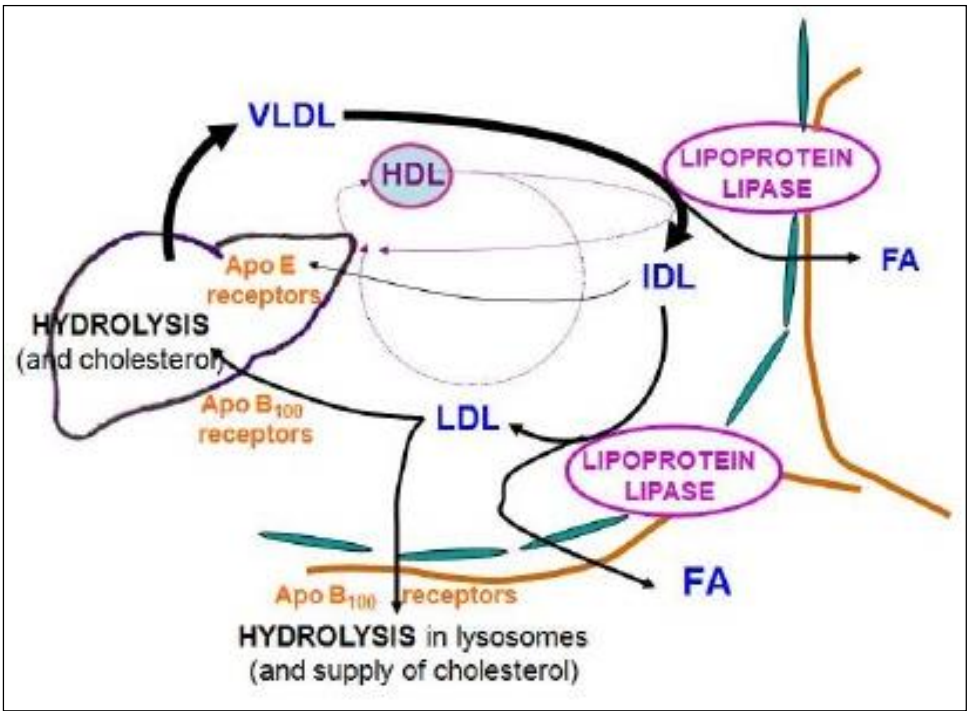
- Formation of chylomicron remnants;

- After hydrolysis of most TAG contents, chylomicron is converted into chylomicron remnant by transferring apo C and apo A to HDL. Also, part of TAG is transferred to HDL in exchange with cholesteryl esters by the effect of cholesteryl ester transfer protein (apo D).
- The chylomicron remnants have lower content of TAG and higher percent of cholesterol, cholesteryl esters and phospholipids. It enters the liver through specific receptors for apo E. In liver cells.

- Diagram for Metabolism of chylomicron



II. Metabolism of VLDL, IDL and LDL:



- Importance and synthesis:

- VLDL is formed in the liver to transport lipids (mainly TAG) from liver to extrahepatic tissues.
- It is synthesized by the following steps:

1- Synthesis of VLDL:

- **Nascent VLDL** is formed by liver and it has high TAG contents and also contain cholesterol and phospholipid and the apo protein B-100.
- **Mature VLDL:** VLDL receives apo C and E from HDL, in the blood.

2- Hydrolvsis of TAG content of VLDL;

Lipoprotein lipase enzyme hydrolyzes most of the TAG contents of VLDL into glycerol and free fatty acids.

3- (VLDL remnants): Formation of intermediate density lipoproteins (IDL)

IDL is formed after the hydrolysis of TAG and return of apo C to HDL.

4- Formation of low density lipoprotein (LDL);

- It is formed by the return of Apo E to HDL.
- Part of TAG is transferred to HDL in exchange with cholesteryl esters. by cholesteryl ester transfer protein (apo D).

- Fate of LDL;

- LDL is the main source of cholesterol to extrahepatic tissues.
- Its uptake is througha specific apo B-100 receptors present, in both extrahepatic tissues (30%) and liver (70%).
- *Thyroid hormones help the formation of LDL receptors. So, hypercholesterolemia occurs in cases of hypothyroidism*.

III. Metabolism of HDL

- Importance of HDL:

- HDL are important for removal of cholesterol form the tissues to the liver (reverse cholesterol transport) so, high levels of HDL protect against atherosclerosis.
- LCAT is activated by apo A.
- Cholesterol esters enter at the center of the particle separating the phospholipid bilayer apart giving HDL spherical shape.

- Synthesis of HDL particles:

It is formed by liver and small intestine in the form of disc shape particles

- It consists of:

1-Phospholipid bilayer.
2-Free cholesterol and apoproteins (A, C, E & D).
3-Enzyme lecithin cholesterol acyl transferase (LCAT).

- Importance of HDL:

1-HDL supplies different apoproteins (C & E), to chylomicrons and VLDL.
2-Apo D helps the transfer of cholesteryl esters to chylomicron remnants and LDL in exchange with triacylglycerols.

- Fate of HDL:

- HDL are taken by liver cells by endocytosis.
- Cholesterol esters are hydrolyzed and free cholesterol is either reused in the synthesis of lipoproteins, or become converted into bile acids and secreted in bile.

IV- Metabolism of Plasma Free Fatty Acids:

- The sources of free fatty acids are either lipolysis in adipose tissues or chylomicrons and VLDL after hydrolysis by lipoprotein lipase. Free fatty acids (FFA) are transported carried on plasma albumin. Their levels increase in cases of enhanced lipolysis e.g. fasting and diabetes mellitus or overfeeding of fats.

- Atherosclerosis

- It is a disease caused by the deposition of lipids, mainly cholesterol in the arterial walls. The ratio between LDL/HDL is called atherogenic index. If it is above 4 there is increased risk for atherosclerosis.

- Mechanism of development of atherosclerosis (atheroma):

1-**Oxidation of LDL particles** by different oxygen free radicals leads to their modification .

2-**Uptake by macrophages** transforming these cells into foam cells.

3-**Foam cells will penetrate the arterial walls** and stimulate the release of growth factors from endothelial cells'.

4-**Proliferation of smooth muscles** in the walls of blood vessels and formation of plaque (atheroma).

5-**Complications of atherosclerosis** including narrowing of blood vessels that predisposes to hypertension, vascular thrombosis and myocardial infarction.

6-**Decrease of the risk by: Intake of antioxidants** vitamins (A, C and E) and selenium, can decrease the risk of atherosclerosis.

- Errors of Plasma Lipoproteins Metabolism:

(Dyslipoproteinemia)

A- Hyperlipoproteinemia;

1. Primaryhyperlipoproteinemia:

- Type I:

- Caused by congenital deficiency of plasma lipoprotein lipase enzyme.
- This will affect the catabolism of chylomicrons and VLDL, so their plasma levels increase.

- Type II:

Familial Hypercholesterolemia:

- It is due to genetic defect in LDL receptors.
- The uptake of LDL by different tissues will decrease leading to marked increase in plasma LDL cholesterol.

- Patients develop atherosclerosis and its complications at young ages.

2. Secondary Hyperlipoproteinemia:

It is due to the presence of disease that affect lipid metabolism:

1- Diabetes mellitus

2- Obstructive jaundice

3- Hypothyroidism

4- Obesity

B- Hypolipoproteinemia;

1- Abetalipoproteinemia:

- It is due failure of synthesis of apo-B.

- This leads to defective and decreased formation of chylomicrons, VLDL and LDL.

2- Hypoalphalipoproteinema;

- It is due failure of synthesis of apo-A. This leads to decreased formation of HDL.
- Patients develop atherosclerosis and its complications at young ages.

3- Deficiency of LCAT;

This will produces marked decrease in cholesterol esters and elevated disk shape HDL.

- Fatty Liver:

Fatty liver means accumulation of excessive TAG in liver (up to 40% of its weight). This leads to liver enlargement and fat will produce pressure atrophy on liver cells leading to hepatic dysfunction and, later on liver cirrhosis.

- Causes of Fatty Liver;

1- Over feeding of fats:

The uptake of excessive amount of fat by liver cells will exceed the capacity to mobilize it in the form of VLDL.

2-Over feeding of Carbohydrates:

Excessive carbohydrates will be stored as glycogen then by lipogenesis as TAG.

3- Over mobilization of fat from adipose tissues (increased lipolysis);

As in cases of diabetes mellitus lead to flow of excessive amount of fat to the liver.

4- Decreased fatty acids oxidation;

This occurs in the following conditions:

A- Deficiency of pantothenic acid needed for synthesis of coenzyme A (CoASH).

B- Deficiency in the enzymes needed to transport FA across mitochondrial membrane.

C- Deficiency in carnitine or in methyl donor needed for its synthesis.

5- Deficiency of lipotropic factors needed for mobilization of fat from the liver;

- These are factors needed for synthesis of lipoproteins that help the mobilization of fat from the liver.

- They include factors needed for proteins and phospholipids synthesis.

a. Factors that affect protein synthesis:

- Decreased essential ami no acids.
- Hereditary abeta or hypobetalipoproteinemia.
- Liver toxins as CCU, chloroform, arsenic and phosphorus decreasing protein synthesis

b. Factors that affect phospholipids synthesis:

- Decreased essential fatty acids.
- Decreased inositol and choline.
- Decreased methyl donors and vitamins needed for choline synthesis.
- Excessive intake of nicotinic acid produces depletion of methyl donors as it is excreted in urine as n-methylnicotinamide.

6- Alcoholism: Ethyl alcohol may be oxidized to acetate which produces increase in lipogenesis

- LIPOTROPIC FACTORS

- Definition:

- They are substances that help the mobilization of fat from the liver.
- They are needed for the synthesis of plasma lipoproteins.
- They are used to treat patients with fatty liver.

- Substances needed for synthesis of proteins include:

Essential amino acids needed for synthesis of proteins.

- Substances needed for oxidation of fatty acids:

- Pantothenic acid needed for synthesis of CoASH that activates fatty acid before oxidation.
- Carnitine that help fatty acid transport across mitochondrial membrane.

- Substances needed for synthesis of phospholipids Include;

a- Essential fatty acids (PUFA).
b- Inositol and choline
c- Methyl donors or compounds needed for synthesis of methyl group of cmitine and choline, they includes:

- Methionine.
- Glycine betaine (trimethylglycine).
- Folic acid and vitamin B_{12} needed for synthesis of methyl group.

- ROLE OF LIVER IN LIPID METABOLISM

Liver has the following important roles in lipid metabolism:

1- Uptake of absorbed lipids.
2- Synthesis of fatty acids and TAG.
3- Ketogenesis.
4- Oxidation of FA to supply energy.
5- Gluconeogenesis from glycero] and odd chain fatty acids
6- Synthesis and catabolism of phospholipids.
7- Synthesis of plasma cholesterol.
8- Conversion of cholesterol to 7-dehydrocholesterol.
9- Formation of bile salts.

Synthesis of plasma lipoproteins (VLDL, HDL).

Chapter IV:

Protein Metabolism

- Proteins are required for life of human being. They supply us with the essential amino acids needed for normal growth.
- The requirements of proteins are not so much for anyone.
- **It is only 0.8 g\kg body weight \ day.** This requirement increases in case of growing infants, during pregnancy and convalescence of diseases.

- Sources of proteins are:

1) Exogenous :

a) Animal proteins: Meat, milk, fish and eggs.

b) Plant proteins: Cereals and nuts.

2) Endogenous

From catabolism of tissue proteins.

- Digestion of proteins

It is known that proteins are anitgenitic (they can cause immunologic response if pass to blood directly) .The digestion of proteins prevents its antigenicity and helps its utilization.

- In the mouth: No digestion.

- In the stomach:

a) Pepsin enzyme digests proteins.It is secreted as inactive then it is activated by HCL pepsin is an endopeptidase leads to denaturation of proteins.

b) Rennin: It is important in infants.It causes coagulation of proteins of milk.

- In the intestine:

Different enzymes are secreted from the intestine to digest proteins:

- Pancreatic enzymes:

- **Pancreatic endopeptidase**: Trypsin ,Chymotrypsin hydrolyse proteins to form small peptides.
- **Pancreatic carboxypeptidases:** And intestinal aminopeptidases are the end of protein digestion.

- Absorption of amino acids:

- Most of naturally occurring amino acids are in the form of L- form.
- It is an active process it needs either ***Sodium amino acid carrier or γ glutamyl cycle.***

- Classifications of amino acids

There are different classifications of Proteins.

1) According to the biological value: **They are either**

- High biological value:

They are easily digested and contain all essential amino acids.

- Low biological value:

They are deficient in or more of the essential amino acids.

- Essential amino acids: They are not synthesized on our bodies.
They include: Lysine, valine, leucine, tryptophan, mehtionine and phenylalanine.

- Semi essential amino acids: They are synthesized in our bodies in sufficient amounts for adults but not for children.
They include: Histidine and arginine.

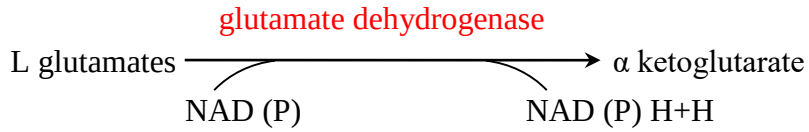
- Non essential amino acids: The body can synthesize them in sufficient amounts for growth of both adults and children.
They include: glycine,alanine,serine and cystiene.

- Deamination of amino acids:

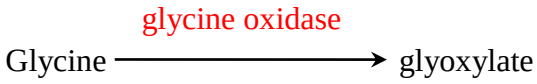
(Enumerate) ***1) Oxidative Deamination.***
2) Transamination
3) Transdeamination
4) Non oxidative Deamination

1) Oxidative Deamination;

1. L-glutamate dehydrogenase



2. Glycine Oxidase



3. L-Amino acid oxidase with coenzyme FMN, forms imino acid and then α keto acid

2) Transamination:

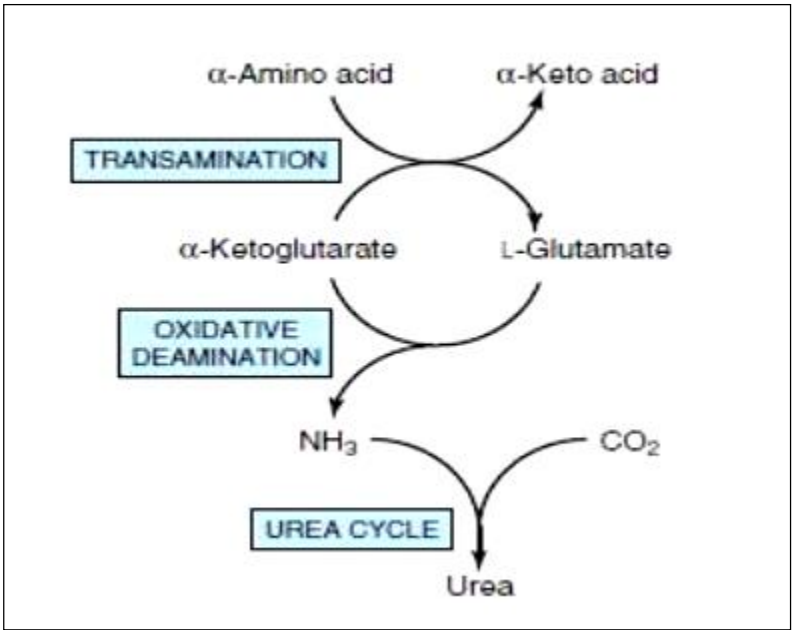
It is the transfer of amino group from amino acid to α keto acid, it needs (PLP/vit B6).

A) Alanine transaminase *ALT or (GPT)*

B) Aspartate transaminase *AST or (GOT)*

3) Transdeamination

It is the main mechanism of Deamination in the body: It is a combined method of transamination and oxidative deamination.



4) Specific methods of deaminations;

- ***Glycine cleavage system (glycine ⟶ CO_2 + NH_3)***
- ***Serine dehydrates (serine ⟶ Pyruvic acid + NH_3)***
- ***Cysteine desulfhydrase (cysteine ⟶ Pyruvic acid + NH_3)***
- ***Histidase (hisidine ⟶ Urocanic)***

Metabolism of Ammonia

- Sources of ammonia:

Deamination of amino acids derived from tissues or protein intake.

- Fate of ammonia:

1) Synthesis of:

- Non essential amino acid.
- Purine and pyrimidines.
- Synthesis of amino sugars.

2) Catabolic pathway:

- **In the liver**: It is converted to urea or to lesser extent glutamine.
- **In the brain and extra hepatic tissues:** It combines ammonia with glutamic acid forming glutamine.
- **In the kidneys:** Urea and ammonia are excreted in urine.

- Fates of amino acids:

1. **Pure ketogenic** amino acids; **leucine** is the only one.
2. **Mixed glucogenic and ketogenic** are; **phenylalanine, tyrosine, trytophan and lysine.**
3. **Other amino acids** are **Glucogenic**.
   They produce Pyruvate or intermediates of citric acid cycle, so they can give glucose.

- Urea cycle:

- It is the main mechanism for excretion of ammonia in the body.
- Pathway of urea synthesis occurs the liver: 1st 2 reactions occur in mitochondria and then in the cytosol.
- ***Key enzyme: Carbamoyl Phosphate Synthase I* (CPS I)**

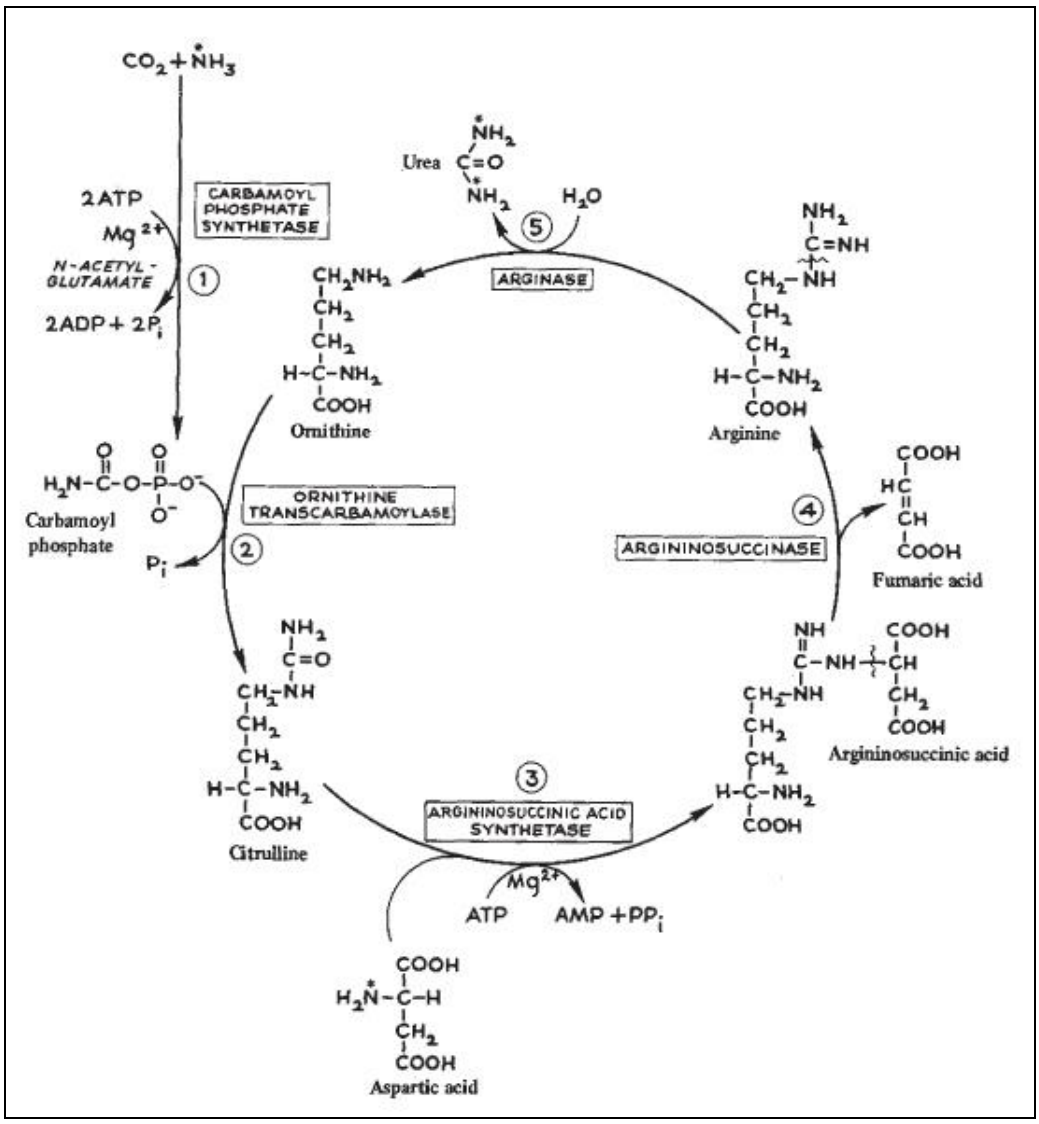
***Carbamoyl Phosphate Synthase I* (CPS I)**	***Carbamoyl Phosphate Synthase I* (CPS II)**
Liver mitochondria	***Cytosol of cells***
Urea synthesis	***Pyrimidine Synthesis***

- Enzymes present in the mitochondria are:

1-Carbmoyl Phosphate Synthase I
2- Ornithine Transcarbmoylase .

- Enzymes present in the cytosol are:

1- Argininosuccinate synthase.
2- Argininosuccinase
3- Arginase



- Regulation:

(Feeding of proteins and increased N-acetyl glutamate) increase the activity of the key enzyme.

- Hyperammonemia:

It is a condition in which ammonia increases in blood and this is due to many causes:

1. ***Liver failure***
2. ***Renal failure***
3. ***Genetic causes***

- Clinincal picture of hyperammonemia:

- Infants with hyperammonemia are complaining of: Blurring of vision, lethargy, slurred speech, hypothermia, seizures and coma.
- Plama ammonia:150 mmol\L or higher is an indicator of urea cycle disease.

- Genetic causes include:

1- Hyperammonemia type 1: It is a familial disorder due to deficiency of **carbmoyl phosphate synthase I.**

2- Hyperammonemia type 2: It is x linked disease due to deficiency of **ornithine transcarbmoylase**.

3- Citrullinemia deficiency of **argininosuccinate synthase.**

4- Argininosuccinateacidemia due to deficiency of **argininosuccinase**

5- Hyperargininemia due to deficiency of **arginase.**

UREA CYCLE DISORDERS

S.No	Disorder	Enzyme involved
1.	Hyperammonemia type I	Carbamoyl phosphate synthase I
2.	Hyperammonemia type II	Ornithine transcarbamoylase
3.	Citrllinemia	Arginosuccinate synthase
4.	Arginosuccinicaciduria	Arginosuccinase
5.	Hyperargininemia	Arginase

- Complications of hyperammonemia:

1- It leads to disturbed sleep rhythm and irritability due to ***decrease of αketoglutarate (normally αketoglutarate enters in Kreb's cycle but in hyperammonemia it is converted to glutamate and then to glutamine with decrease of Krebs cycle and energy).***

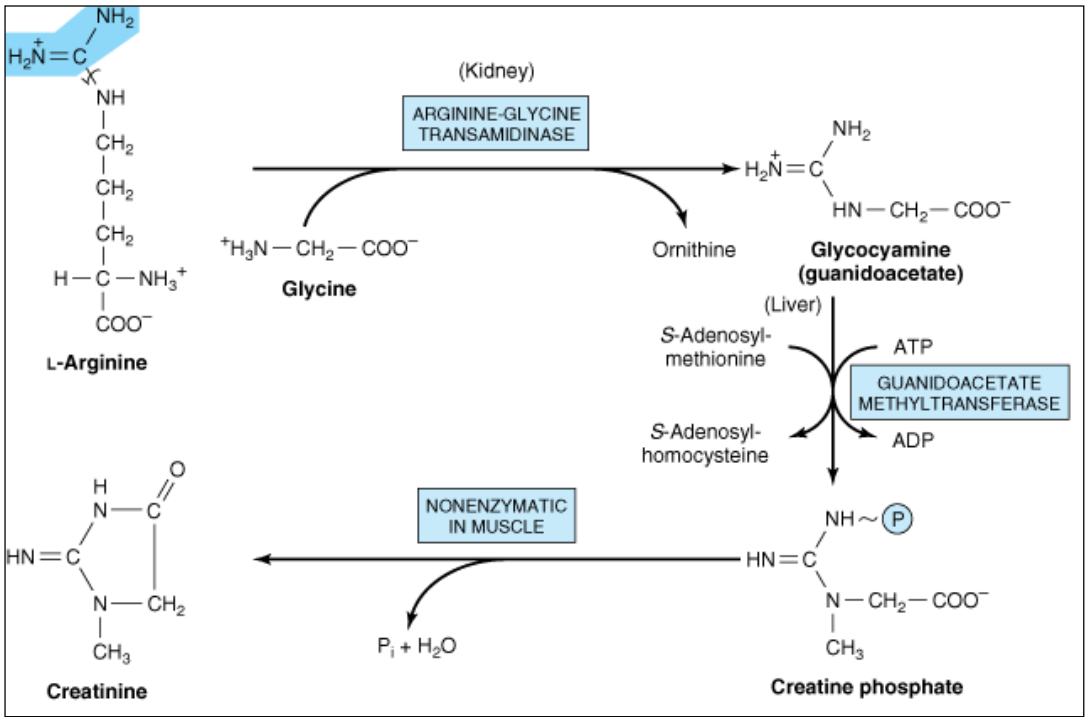
2- ***Increased ammonia leads to encephalitis and alkalosis***

- Treatment of hyperammonemia

1) Decrease protein intake
2) Dialysis to reduce plasma ammonia.
3) Na phenyl acetate and Na benzoate to combine with glycine and glutamic acid to form hippuric acid (glycine and glutamic amino acids catabolism constitute main bulk of ammonia)
4) Diet must be fortified with arginine, as it becomes essential.

- Creatine metabolism

- *Creatine phosphate is the **storage form of energy in muscles**.*
- *It is formed in the kidney liver and muscles.*



- *Creatine supplies ATPs under anaerobic metabolism of the muscles.*
- **Androgen hormone increases creatine** *in muscles and is the cause of increase muscle bulk in males than females.*
- **Normal level of creratine in serum; (0.4 - 1.4 mg/dL)**

- Causes of creatinurea:

- Physiological:

1) Childhood (due to deficiency of androgen)
2) After labor (due to decrease of uterine muscle bulk*).*

- Pathological:

1) Myopathies
2) Starvatoion
3) Hypogonadism
4) Diabetes mellitus
5) Vitamin E deficiency.

Nitrogen Balance

It is the difference between the nitrogen intake and nitrogen excretion. There are 3 forms of nitrogen balance.

1. **Positive nitrogen balance**:
   it occurs when the intake of proetins is more than its excretion. The best example during childhood, adolescence and convalescence period s
2. **Negative nitrogen balance** :
   It occurs when the intake is less than excretion or there is a disease leads to marked loss of proteins as diabetes ,chronic infection, thyrotoxicosis and chronic blood loss.
3. **Nitrogen equilibrium** :
   It occurs with a balanced normal adult when the intake is equal to excretion.

Metabolism of individual amino acid:

- Glycine:

- It is the shortest amino acid.

Glycine is glucogenic as it gives serine

Glycine is a nonessential amino acid:being synthesized from different sources.

- Sources of glycine;

1) From Serine by hydroxymethyl transferase.

Serine —(hydroxymethyltransferase)→ **Glycine**

2) From threonine by aldolase.

Threonine —(threonine aldolase)→ **Glycine + acetaldehyde**

3) ByReversal of glycine cleavage system.

4) Transamination of glyoxylate.

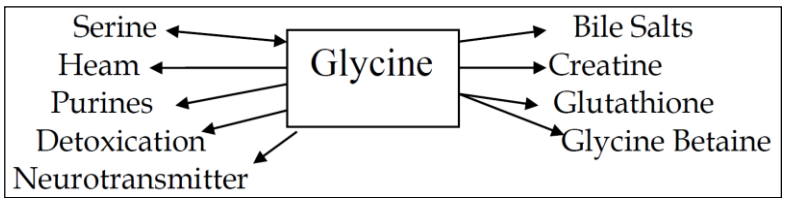
Glycine —(Transaminase)→ **glyoxylate**

- Importance (Important derivatives) of glycine:

It participates in the following compounds:

- **Serine**: By hydroxymethyltransferase
- **Heam synthesis**: Glycine with succinyl CoA
- **Bile salts**: With cholic acid
- **Glutathione:** With glutamic and cystiene
- **Glycine Betain:** It is the methylation product of glycin
- **Creatine:** Glycine and arginine.
- **Purines:** It participates in the purine ring synthesis
- **Detoxication:**
  - **Collagen formation.**
  - **Neurotransmitter** (it acts as a neurotransmitter in brain stem and spinal cord).

- Diagram of different fates of Glycine



- Metabolic errors of glycine metabolism:

1) Primary Hyperoxalurea;

It is due to deficiency of decarboxylation of glyoxalate,there is excess oxalate in urine.The condition leads to formation of urinary stones.

2) Hyperglycinemia;

It is an increase in glycine level in blood due to failure of the enzymes to utilize glycine.

3) Glycinurea;

It is due to failure of kidneys to reabsorb glycine back to blood.

- Serine:

- Nonessential

Being synthesized from glycine by hydroxymethyltransferase.

- Glucogenic:

It gives Pyruvate by serine dehydratase.

- Importance of serine

1) It gives the site for covalent modification of enzymes.
2) It gives *glycine.*
3) Synthesis of *cystiene*

- Importance of serine in lipidmetabolism

1) It synthesize phosphoglycerides (phosphatidyl serine,phosphatidyl thanolamine and phosphatidyl choline)
2) It synthesizes sulfolipids
3) It synthesizes sphingomyeline.

- Alanine:

- It is a Nonessential and glucogenic amino acid.

- It gives Pyruvate by transamination.Glutamate Pyruvate Transaminase its other name is (Alanine Transaminase, ALT).

- Cystiene:

- It is a nonessential amino acid.It is formed from homocystiene and serine

- It is glucogenic amino acid.

- It gives Pyruvate by cystiene desulfhydrase.

- Importance of cystiene:

1) ***Synthesis of bile salts (sodium taurocholate and potassium taurocholate) from its by product taurine.***
2) ***Synthesis of glutathione = (cystiene + glycine + glutamic)***

- Importance of glutathione:

A) Absorption of amino acids.

B) *It acts as* ***antioxidant*** *for removal of H_2O_2 in RBCs.*

C) Detoxication *of compounds*

D) Coenzyme of insulin glutathione transhydrogenase.

3) ***(SH) group of cystiene gives:***

a) *Active site(catalytic site) of many enzymes.*

b) *It gives cystine for synthesis of* ***immunlglobulin*** *and* ***insulin****.*

C) *H_2S enters in the formation of Phosphoadenosine phosphosulfate* ***(PAPS)(****active sulfur donor)for formation of GAGS ,sulfolipids and detoxication of aromatic amino acid*

4) ***Decarboxylation of cystiene gives thioethanolamine,which enter in synthesis of (CoASH) and Acyl Carrier Protein used in fatty acid synthesis.***

- Metabolic errors of cysteine:

1) ***Cystinurea:*** *A genetic defect in renal reabsorption of cystiene and* ***diamino acids including (lysine,arginine and ornithine)****with excessive excretion of these acids in urine and formation of* ***cystiene stones.***

2) ***Cystinosis:*** *It is a genetic disease with* ***generalized aminoaciduria****. there is deposition of cystiene in tissues .Usually there is early death of infants due to renal failure.*

- Threonine:

- ***It is an essential, glucogenic as it gives butyric acid by transamination,propionylCoA and Succinyl CoA which gives oxaloacetate in Kreb's cycle.***
- Importance of threonine;it gives glycine (by threonine aldolase).

- Arginine:

- ***It is*** *Semi essential*, glucogenic gives (ornithine then α ketoglutarate)
- Importance of arginine;it gives ***urea, creatine and nitricoxide and spermine and spermidine.***

- Lysine ***Essential, ketogenic*** (it gives acetoacetyl CoA)

It is important for *collagen and elastin synthesis. hydroxylysine for collagen*

- Branched chain amino acids(Valine,leucine and isoleucine)

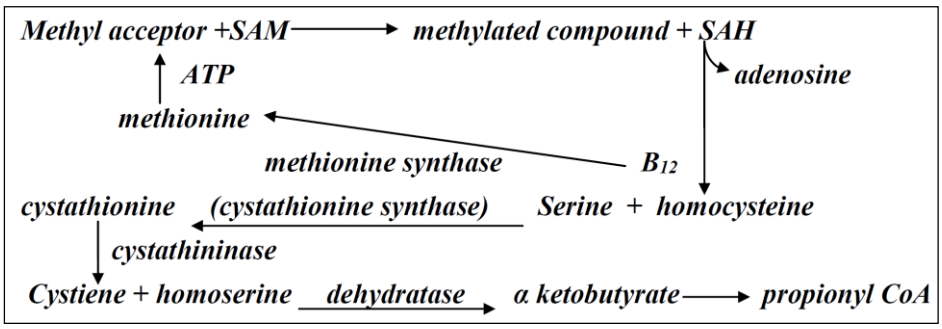
- ***Essential, catabolized by transaminase and ketoacid decaroxylase***
- ***Valine (glucogenic , produces succinyl CoA)***
- ***Leucine (ketogenic gives, acetyl and acetoacete)***
- ***Isoleucine(mixed glucogenic and ketogenic gives,propionylCoA and acetyl CoA).***

**Maple syrup disease:

It is due to deficiency of (α ketoacid decarboxylase) leading to accumulation of branched α ketoacids in tissues and urine ,urine has the odor of maple, there is mental retardation.

- Methionine:

It is essential and glucogenic *(it gives homocystiene then homoserine then αketobutyrate,prpionyl COA and succinyl CoA)*.



- Importance of methionine;

- *It enters in the structure of* ***cysteine***
- *It acts as a* ***methyl donor***

*N.B.****other methyl donors are (folic acid ,vitamin B12 and glycine betaine)***

- Methyl acceptor:

- ***Guanido acetate +methyl ⟶ Creatine***
- ***ethanolamine +methyl ⟶ Choline***
- ***Norepinephrine +methyl ⟶ Epinephrine***
- ***N- acetyl sseritonine+methyl ⟶ Melatonin***
- ***Carnosine + methyl ⟶ Anserine***

***Metabolic error of methionine and homocysteine

1- Homocystinurea

It *is excretion of large amounts of homocysteine in urine*

- Type 1: *It is due to deficiency of* ***cystathionine synthase*** *and excretion of large amounts of methionine, SAM and homocystiene in urine.cysteine becomes essential.Vascular thrombosis is a complication of the disease.*

- Other types of Homocystinurea *result from deficiency of methionine synthase or vit B_{12} and folic acid.*

- 2-cystathioninurea: *It is due to deficiency of cystathioninase enzyme with excretion of large amounts of cystathionine in urine treatment by diet low in methionine and more vit B6 and vit B_{12}.*

- Aspartic acid Non essential, glucogenic (by transamination gives oxaloacetate)

Important derivatives: 1- Purines
2- Pyrimidines
3- β –Alanine by decarboxylation.
4- Asparagine,needed for protein synthesis.

- Glutamic acid Non essemtial, glucogenic (by transamination gives glutaric acid).

- It is formed by catabolism of glutamate family (arginie,praline and histidine).

- Importance of glutamic acid:

1- Synthesis of arginine and praline.
2- Synthesis of glutathione.
3- Synthesis of GABA.

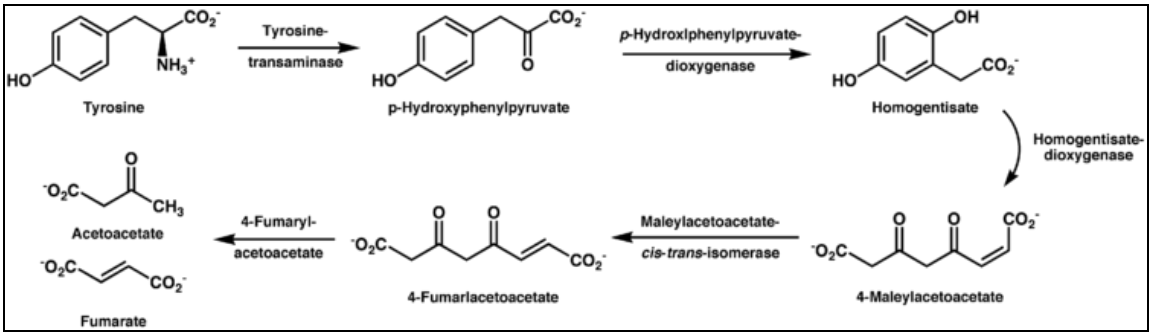
4- Synthesisof glutamine (removal of ammonia, synthesis of Pyrimidines and detoxification).

- Glutamine:

Important for: 1) Detoxication of ammonia
2) Purine synthesis
3) Pyrimidine synthesis
4) Synthesis of amino sugars.

- Tyrosine:

- Phenylalanine is an essential amino acid.Tyrosine is synthesized from phenylalanine.
- They are mixed ketogenic giving acetoacetate and glucogenic giving fumarate.



- Phenylketonurea:

It is genetic autosomal recessive disease due to deficiency of *phenylalanine hydroxylase* leading to increase of phenylalanine and its conversion to phenylpyruvate, phenyllactate and phenylacetate . All metabolites are excreted in urine.

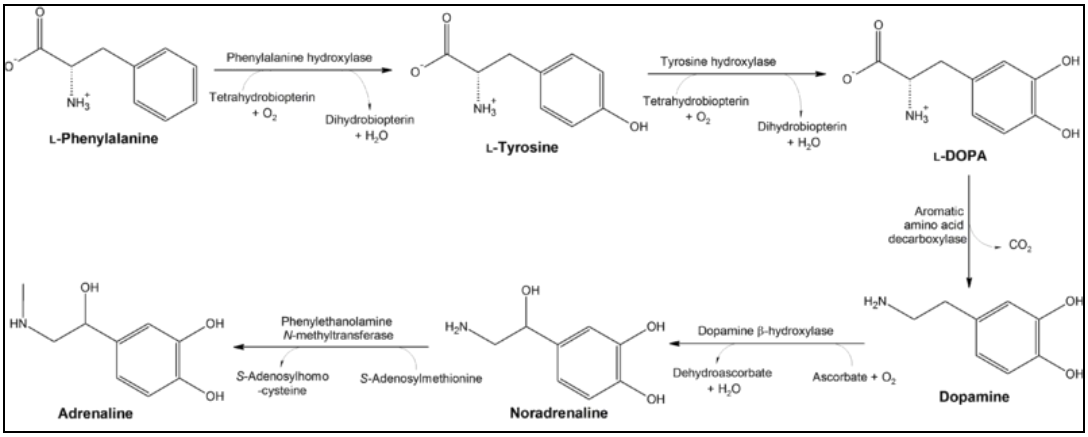
- Complications of tyrosine deficiency:

Mental retardation and seizures due to decrease in tyrosine and decrease of its neurotransmitter derivatives .

- Treatment: *By phenylalanine free diet, milk formula must be fortified with tyrosine.*

- Derivatives of tyrosine

1) Adrenaline and nor-adrenaline



2) Thyroxine

3) Melanin

- Metabolic error of tyrosine

1) Tyrosinemia *due to deficiency of catabolic enzymes of tyrosine metabolism as fumaryl acetoacetate or tyrosine transaminase.there is mental retardation.*

2) Alkaptonurea: *Deficiency of homogentisic acid oxidase and homogenitisic acid accumulates in tissues and give the black color of urine.*

3) Albinism *due to deficiency of tyrosinase enzyme and decrease of melanin pigment.*

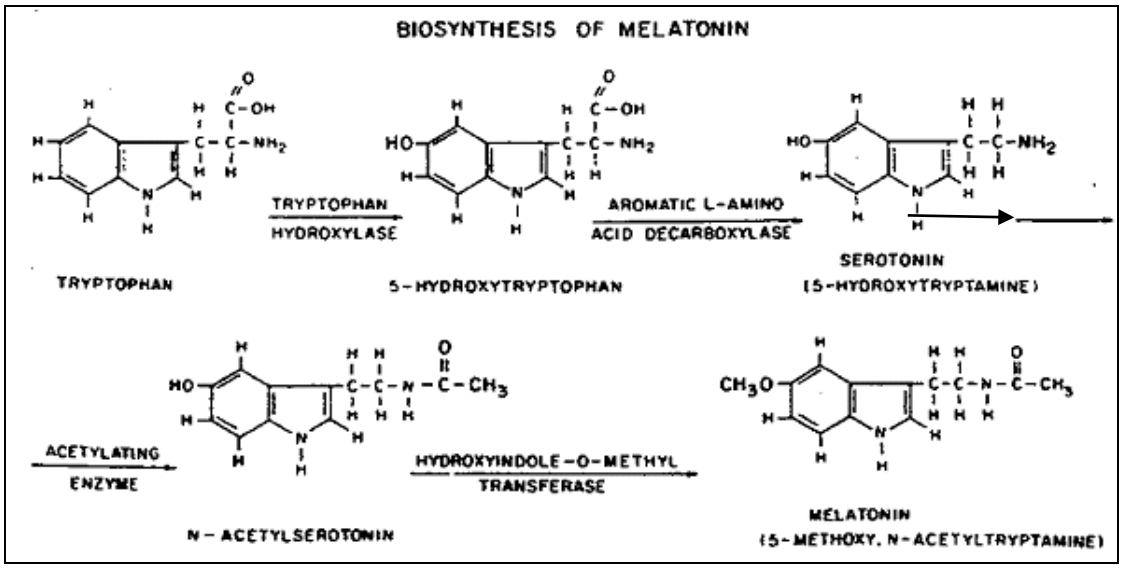
Neonatal tyrosinemia is due to deficiency of P- hydroxyphenylpyruvate hydroxylase

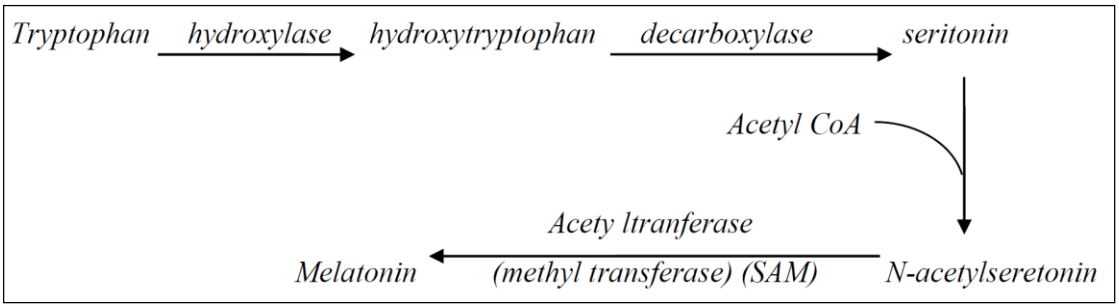
Tyrosine ⟶ DOPA ⟶ DOPAmine ⟶ Nor epinephrine ⟶ Epinephrine

- Tryptophan:

- *Essential, mixed glucogenic and ketogenic(Alanine and acetoacetyl CoA).*
- *Important derivatives:*
  1) *Niacin major catabolic pathway*
  2) *Serotonin formed in GIT and catabolized by MAO enzyme*
  3) *Melatonin is an antioxidant affects the sleep rythm*
  4) *Indole and skatole in intestine by bacteria*

- Pathway of conversion of tryptophan to melatonin;





- Metabolic disorders of Tryptophan

1) ***Hatnup disease****: There is a defect in intestinal absorption of tryptophan and renal reabsorption of tryptophan leading to decrease in its level in blood and mental retardation, Pellagra like symptoms skin rash .*

2) ***Vitmin B_6 deficiency***: *Leading to decrease conversion of tryptophan to kynurinine and also decrease in synthesis of Niacin. Excretion of xanthurenic acid in urine.*

- Histidine:

- *It is a Semi-essentialamino acid.*
- *It is glucogenic as it gives glutamic acid.*
- *<u>Important derivatives</u>:*
  1) *Histamine- (vasodilator)*
  2) *Anserine and carnosine (muscle buffers)*
  3) *Ergothionine:it is the betaine of thiolhistidine (it acts as an antioxidant).*

- Metabolic errors of histidine metabolism

1) ***Histidinemia***: *Defect in histidase with elevated histidine level in blood and urine and delayed speech.*
2) ***Urocanic acidurea***: *Deficiency in urocanase and elevation in urine.*
3) ***Folic acid deficiency***: *Increase of FIGLU in urine.it is diagnostic for folic acid deficiency.*

Proline *Nonessential, glucogenic (gives glutamic acid) important with hydroxyproline for synthesis of collagen. Hydroxyproline gives pyruvate and glyoxylate*

Both proline and hydroxyproline stabilize collagen structure

Amino acids give acetyl CoA :leucine and isoleucine

Amino acids give acetoacetate leucine lysine tyrosine tryptophan and phenylalanine

Amino acids give succinyl CoA methionine isoleucine valine threonine

Amino acids give ketoglutarate glutamate proline histidine arginine

Interconversion of carbohydrates lipids and proteins

- Interconversion between carbohydrates and lipids:

Carbohydrates provide:

1) Glycerol 3 phosphate
2) Acetylcoa for fatty acid synthesis, then estrification of glycerol and fatty acids to form triacylglycerol.

- Interconversion between lipids and carbohydrates:

During starvation: Lipids are hydrolysed to glycerol which give dihydroxiacetone (used for gluconeogenesis)and propionyl CoA(used for gluconeogenesis).

- Interconversion between carbohydrates and proteins:

Carbohydrates give non essential a.a. as serine,Alanine,glutamic acid and aspartic acid.

- Interconversion between proteins and carbohydrates:

Gluvogenic amino acids give glucose by different pathways

- Interconversion between proteins and lipids:

Ketogenic amino acids give either acetyl or acetoacetylCoA.

- Interconversion between lipids and proteins:

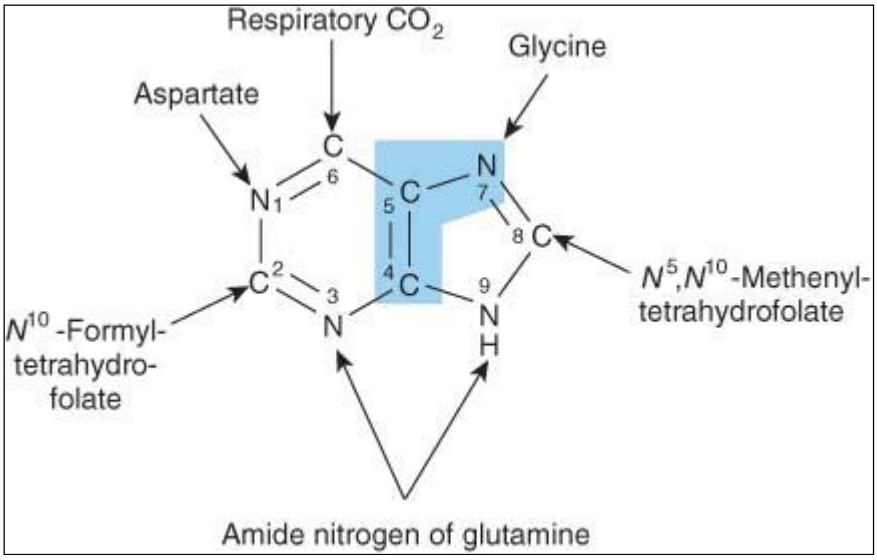
Lipids give glycerol 3P for synthesis of carbohydrates, then carbohydrates give non essential amino acids.

Chapter V Purines&Pyrimidines

Biosynthesis of Purines

- Purine synthesis occurs either by DeNovo pathway in all tissues or salvage pathway in RBCs, lymphocytes and brain cells.
- Salvage pathway occurs through adding phosphate and ribose (Adenine phosphoribosyl transferase or HGPRTASE for guanine and hypoxanthine
- Salvage pathway may occur for adenosine by adding phosphate through kinase enzyme.
  1- De novo
  2- Salvage system.
- Every cell can perform ***de-novo system except the brain and RBCs.***
- Folate is important for C2 and C4 of purine ring folate antagonists as methotrexate inhibit purine synthsis and cell division.so they are used as treatment of cancer.

- Diagram for Different sources of purine atoms:



Key enzyme is phosphoribosyl pyrophosphate synthase (PRPP Synthase)

- Steps of purine nucleotide biosynthesis:

1-Ribose 5 phosphate derived from HMP by ***PRPP Synthase*** is converted to 5 phosphoribosyl 1- pyropophate

2-amide group of glutamine is added by ***PRPP- glutamyl amidotransferase.***

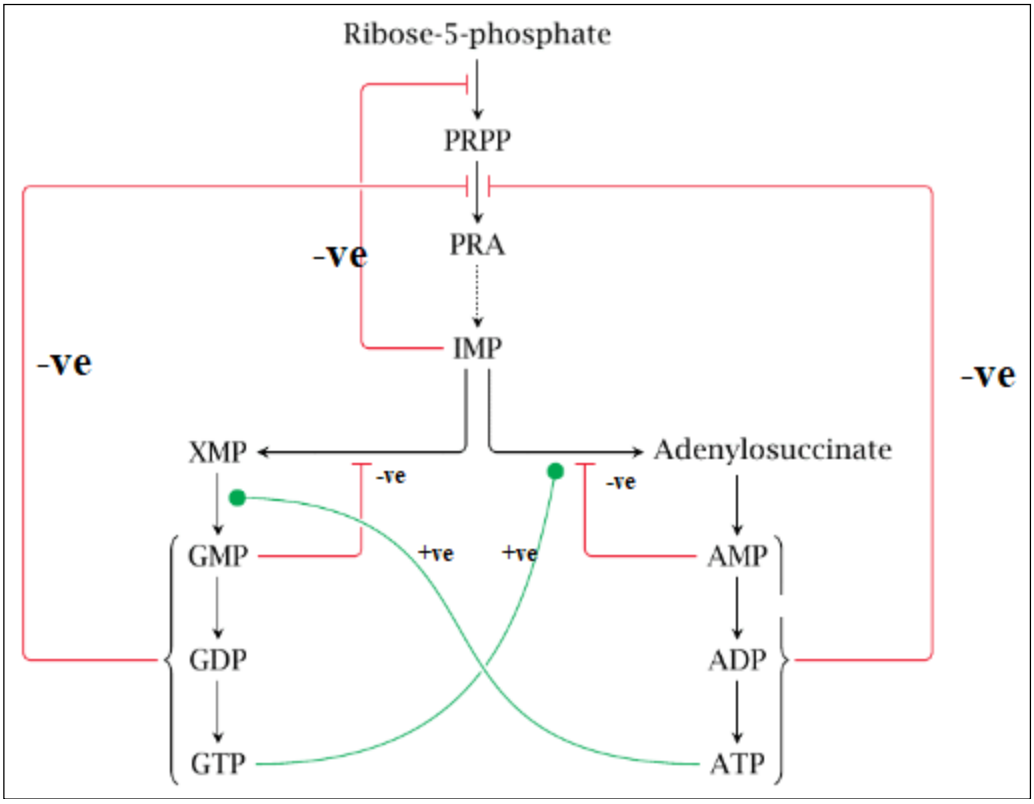
The first nucleotide formed is Inosine monophosphate (hypoxanthine ribose phosphate)

IMP —(aspartic)→ XMP → GMP

IMP → AS → AMP

Synthesis of deoxyribose of DNA: The enzyme requires protein factor: Thioredoxin and NADPH .

- Diagram for Regulation of purine synthesis



Gout and hyperuricemia

Causes of gout may be metabolic or renal causes.

a. Metabolic hyperuricemia

There are many causes of hyperuricemia:

- Primary metabolic (hyperuricemia) gout

It occurs since birth due to inherited enzyme deficiency.

Causes:

1- Increased activity of PRPP Synthase.
2- Partial deficiency in activity of HGPRTASE.
3- Complete deficiency of HGPRTASE (Lysh Nyhan syndrome)
4- VonGeirke's disease (due to deficiency of Glucose 6- phosphatase in the liver, Glucose-6-phosphate increases and converted to ribose-5-phosphate activating PRPP Synthase enzyme with formation of excess purines more than needed for the body, leading to catabolism of these purines forming excess uric acid.

- Secondary metabolic gout:

It occurs many years after birth due to transient causes

Causes of secondary metabolic (hyperuricemia) gout:

1- Leukemia
2- Over protein intake.
3- Treatment of cancers.

b. Renal gout:

- Causes of renal gout:

- Primary causes of renal gout:

Primary defect of excretion of uric acid.

- Secondary causes of renal gout:

1- Nephritis.

2- Certain drugs reduce excretion of uric acid.

- Treatment of gout:

1- Reduce protein intake and use other forms of proteins like milk and eggs.

2- Alkalinzation of urine to dissolve uric acid in the form of urates.

3- Use of Allopurinol as a drug of choice to reduce synthesis of uric acid by competitive inhibition of xanthine oxidase enzyme .

- Hypouricemia

- It is a genetic disease with deficiency of uric acid due to deficiency of:
- ***Xanthine Oxidase Enzyme, Adenosine Deaminase Enzyme Or Purine Nucleoside Phosphorylase Enzyme***
- There is deficiency of purine synthesis and decrease activity of B and T lymphocytes and mental retardation and early death.

Pyrimidine synthesis

- **Synthesized by DeNovo or Salvage pathway**
- **Key enzymeof de nove: carbamoyl phosphate synthesase II(CPS II)** it takes **nitrogen from glutamine** it is a **cytosolic enzyme**,it **does not need N acetylglutamine**.
- **It differs from (CPSI** of urea synthesis take its source nitrogen from ammonia,it is mitochondrial enzyme)
- All enzymes are cytosolic except dihydro-orotate dehydrogenase

orotic acidurea

due to deficiency of orotate phosphoribosyltransferase or orotodyldecarboxylase

- Catabolism of pyrimidine

3 steps: (reduction – hydrolysis - reduction)

* ***Cytosine and uracil*** give (B alanine and CO_2 NH_3)

* ***Thymine*** give (B aminoisobutyric acid and CO_2 and NH_3).

Chapter VI
Vitamins

Fat Soluble Vitamins:

Fat soluble vitamins are A,D,E and K

VITAMIN A (anti xero-ophthalmia)

Vitamin A is an alcohol (retinol) which insoluble in fats and fat solvents and insoluble in water. Vitamin A is a derivative of the carotenoids, which contain beta ionone ring. The provitamin is converted in the liver (in man) or the intestine (in lower animals) by the enzyme carotenase and alcohol dehydrogenase.

Sources : Carotenes (provitamin A) is present in carrots, lettuce, sweet potato, spinach, apricots .Cod liver oils is very rich source of vitamin A.

Vitamin A is present only in animal tissues e.g. liver , lung, kidney, egg yolk, milk and butter.

B carotenes gives 2β ionone rings give 2 vitamin A,

α or γ carotenes give 1β ionone give 1 vitamin A

Functions of Vitamin A

1) Vitamin A and vision : there are two types of receptors called rods and cones present in the retina:

- Rods the retinal light receptors responsible for night vision contain the photosensitive pigment rhodopsin .
- Cones : are the retinal light receptors containing the photosensitive pigment (iodopsin or visual violet) and are responsible for day vision. On exposure to light, these pigments undergo changes account for coloured vision.

In good exposure to light, rhodopsin is converted to the colourless protein (opsin) + trans-retinal.

This photochemical change is associated with the initiation of nerve impulse which finally propagates along the optic nerve.Good vision in dim light requires rapid regeneration of rhodopsin, which in turn requires a good supply of vitamin A. Thus, in vitamin A deficiency we get **night blindness (nyctalopia).**

Rhodopsin Cycle (Wald's Visual Cycle

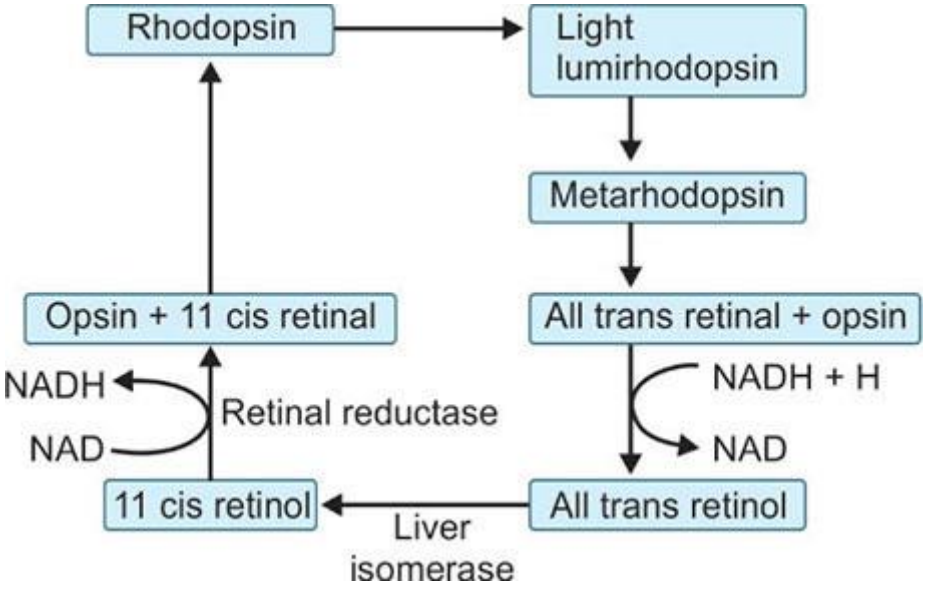
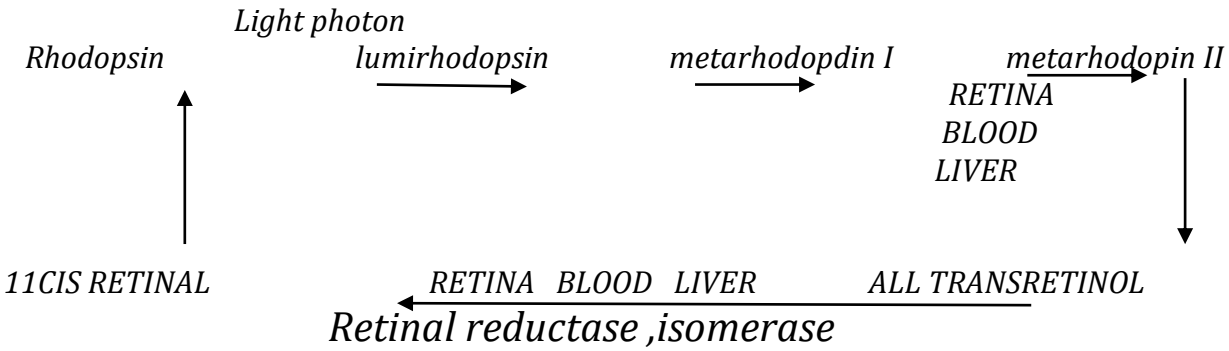
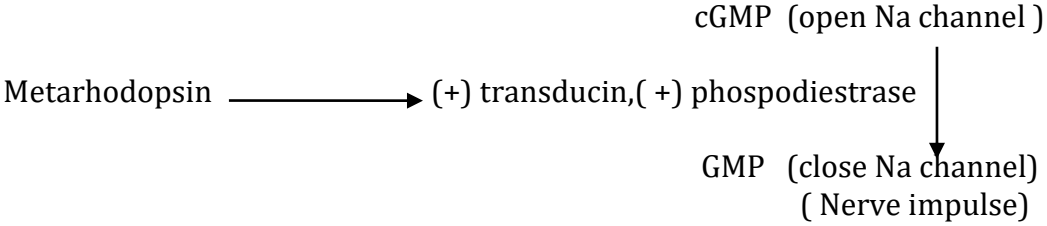


Diagram of Rhodopsin Cycle



Photochemical changes in the retina translated to visual impulse



2) development of healthy connective tissues synthesis of glycoprotein and C.T. bones and teeth.
3)maintenance of healthy epithelium
4)Vit A prevents high molecular weight KERATIN from respiratory and urinary systems
5) antioxidant vitamin (CEA) protect against hazards of oxidants of metabolism.
6)normal growth and differentiation of cells. Retinoic acid is important for gene expression and cell growth and bind specific receptor for DNA.

Deficiency manifestaitons of vitamin A
hyperkeratinization of epithelial tissues leads to 1) **Dryness of the eyes (xero-ophthalmia)** 2)repeated chest infection 3)repeated urinary infections 4) **night blindness (nyctaopia).** 5) rough skin 6)hyperkeratinization of the cornea

Vitamin D

Sources

Cholesterol ⟶ ***7- dehydrocholesterol*** ***UV*** ⟶ ***(VITAMIN D3)***
Cholecalciferol

(LIVER)
(25 – α HYDROXYLASE)

25 (oH)vit D 3
(Kidney)

1 hydroxylase
24 hydroxylase

24,25 (OH)2 vit D3 — ***(Inactive)***
1,25 (OH) 2 vitD3 — ***active***

Regulation of calcitriol level: PTH activates 1α hydroxylase, elevated calcitriol level causes feed back on 1α Hydroxylase and stimulation of 24 hydroxylase.

Importance of vit D3

1)effect on intestine ;

a)*it increases calcium absorption from intestine*

Vitamin D (CALCITRIOL) is ***considered as a hormone*** *it stimulates the nucleus to increase synthesis of m RNA responsible for calcium binding protein(CBP) increasing calcium absorption.*

b)*it also increases phosphorus absorption from intestine*

2)effect on kidneys *it increases calcium and phosphorus reabsorption from kidneys*

3)effects on bones *it increases calcium and phosphorus in bones*

Vitamin D deficiency in young is rickets and in adults is osteomalacia

Rickets

Causes of rickets

1. Malnutrition
2. Unexposure to sunlight
3. Deficiency of 1 hydroxylase in kidneys
4. Congenital deficiency of the receptor of vitamin D 3 in tissues.

Manifestations of rickets

1-Delayed eruption of bones and teeth with deformities of skull
2- Deformities in chest
3- Deformities in pelvis
4-deformities in vertebral column
5- Deformities in lower limbs

Rickets is a disease diagnosed through laboratory and radiological findings

Laboratory finding in case of Rickets:

Early changes in Rickets

Calcium is normal and phosphorus is low , high alkaline phosphatase enzyme. This is due to over activity of Parathyroid hormone.

Late changes in Rickets

Calcium is low and phosphorus is low. high alkaline phosphatase enzyme.

Osteomalcia

It is reduction of calcium level in adults mainly in females due to:

1. Repeated pregnancy and lactation.
2. Steatorhea.
3. Patients with renal failure may develop osteomalcia due to decrease of α1 hydroxylase enzyme,needed for activation of vitamin D3.

VITAMIN E

*Its main function is **antioxidant** vitamin.*

*****It protects PUFA in the membranes from free radicals** (ROS).SO, increase of PUFA increases the needs of vitamin E.*

***Vitamin E deficiency leasds to vitamin A deficiency ,as it protects vitamin A from free radicals and oxidizing agents.*

***trace element **SELENIUM acts as potent antioxidant** (as it activates glutathione reductase)*

So the requirement of vitamin E decreases in presence of selenium

***Deficiency of vitamin E leads to**;*

1- increase fragility of RBCs
2- vascular thrombosis
3- liver necrosis

Vitamin K(antiheamorrhage vitamin)

Vitamin K is fat soluble vitamin (k1 and k2) vitamin k 3 is a synthetic water soluble vitamin

Functions

1)It is important for **carboxylation of glutamic acid proteins of clotting factors 2,7,9 and 10 and activation of blood cloting**

2) It is important for **carboxylation of glutamic acid in osteocalcin leading to bone formation**

Vitamin K is synthesized by intestinal bacteria so it deficiency is rare

Vitamin K deficiency leads to heamorrhage

Deficiency of vitamin K occurs with

1) sterility of intestine by prolonged antibiotics
2) liver diseases (leads to dysfunction of the vitamin)
3) biliary obstruction and steatorrhea due to impaired absorption of vitamin **carboxylation of glutamate changes vitamin K to vitamin K epoxide, reactivation of vitamin K needs epoxide reductase**

dicumarol and warfarin (act as anticoagulant) they are structurely similar to vitamin K compete with vitamin K on epoxide reductase enzyme .

Water soluble vitamins

Water soluble vitamins are :B complex and C

Vitamin C (L-Ascorbic acid) antiscurvy vitamin

*It is the end product of its **catabolism is oxalic acid***

Good sources are orange and guava.

Functions.
1- acts as ***hydrogen carrier***
2- coenzyme ***keeping SH group of enzymes.***
3- ***antioxidant vitamin***
4- cofactor of ***steroidogenesis and collagen***
*5-****activates folic acid***
6- ***importance of Vitamin C for heam synthesis*** *;1)it helps iron absorption*
2) It activates folic acid by dihydrofolate reductase 3) It keeps the integrity of connective tissue and blood So deficiency of vitamin C may lead to ***any type of anemia***
Deficiency manifestations ***(scurvy)*** manifested by bleeding gums, loosening of teeth and heamorrhagic spots under the skin and anemia(three types may occur).In children impaired bone growth and teeth eruption may occur.

Vitamin	Major Dietary Sources	Some Major Functions in the Body	Possible Symptoms of Deficiency or Extreme Excess
Water-Soluble Vitamins			
Vitamin B_1 (thiamine)	Pork, legumes, peanuts, whole grains	Coenzyme used in removing CO_2 from organic compounds	Beriberi (nerve disorders, emaciation, anemia)
Vitamin B_2 (riboflavin)	Dairy products, meats, enriched grains, vegetables	Component of coenzymes FAD and FMN	Skin lesions such as cracks at corners of mouth
Niacin	Nuts, meats, grains	Component of coenzymes NAD^+ and $NADP^+$	Skin and gastrointestinal lesions, nervous disorders Flushing of face and hands, liver damage
Vitamin B_6 (pyridoxine)	Meats, vegetables, whole grains	Coenzyme used in amino acid metabolism	Irritability, convulsions, muscular twitching, anemia Unstable gait, numb feet, poor coordination
Pantothenic acid	Most foods: meats, dairy products, whole grains, etc.	Component of coenzyme A	Fatigue, numbness, tingling of hands and feet
Folic acid (folacin)	Green vegetables, oranges, nuts, legumes, whole grains (also made by colon bacteria)	Coenzyme in nucleic acid and amino acid metabolism	Anemia, gastrointestinal problems May mask deficiency of vitamin B_{12}
Vitamin B_{12}	Meats, eggs, dairy products	Coenzyme in nucleic acid metabolism; needed for maturation of red blood cells	Anemia, nervous system disorders
Biotin	Legumes, other vegetables, meats	Coenzyme in synthesis of fat, glycogen, and amino acids	Scaly skin inflammation, neuro-muscular disorders