Glycolysis

Definition: Oxidation of glucose or glycogen to pyruvate and lactate is called **glycolysis.**

- It is the only pathway that is taking place in all the cells of the body.

- Erythrocytes and nervous tissues drive its energy mainly from glycolysis.

- Glycolysis occurs in the cytosol of all cells of the body.

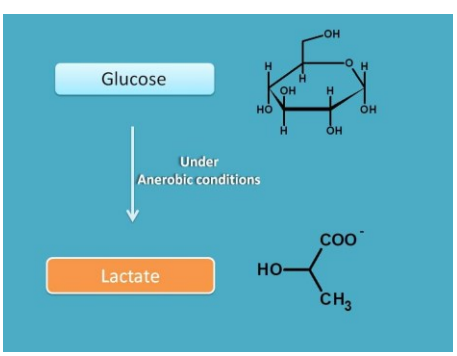
There are two phases of glycolysis:

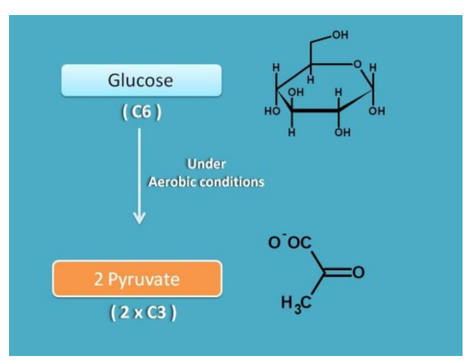
1- Aerobic phase (with oxygen): This series of ten reactions is called **aerobic glycolysis** because oxygen is required to reoxidize the NADH formed during the oxidation of glyceraldehydes – 3 – phosphate. Aerobic glycolysis sets the stage for the oxidative phosphorylation of pyruvate to acetyl CoA, a major fuel of the citric acid cycle.

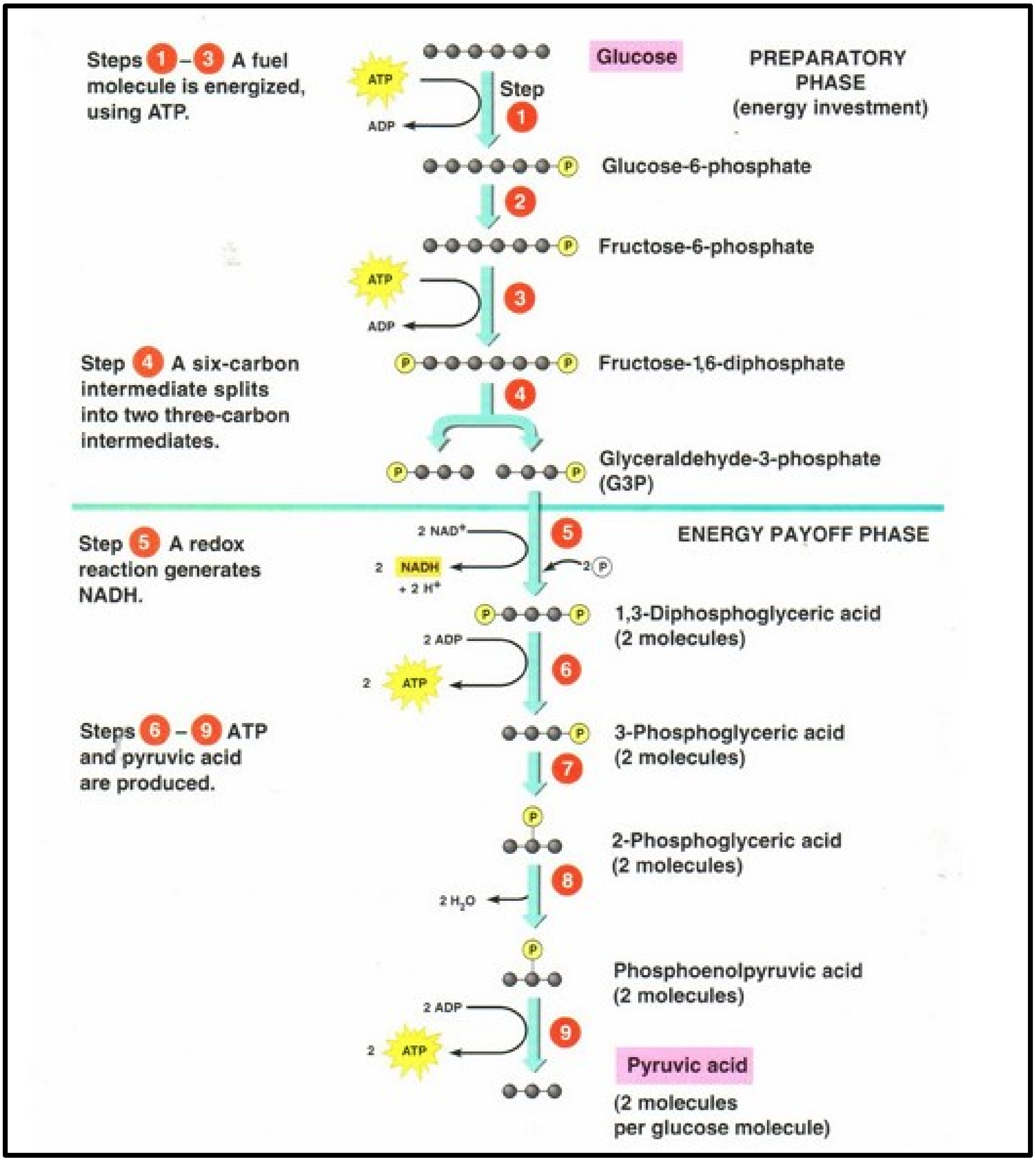
Glucose ($C_6H_{12}O_6$) + Oxygen (O_2) → Carbon-dioxide (CO_2) + Water (H_2O) + Energy (ATP) + product

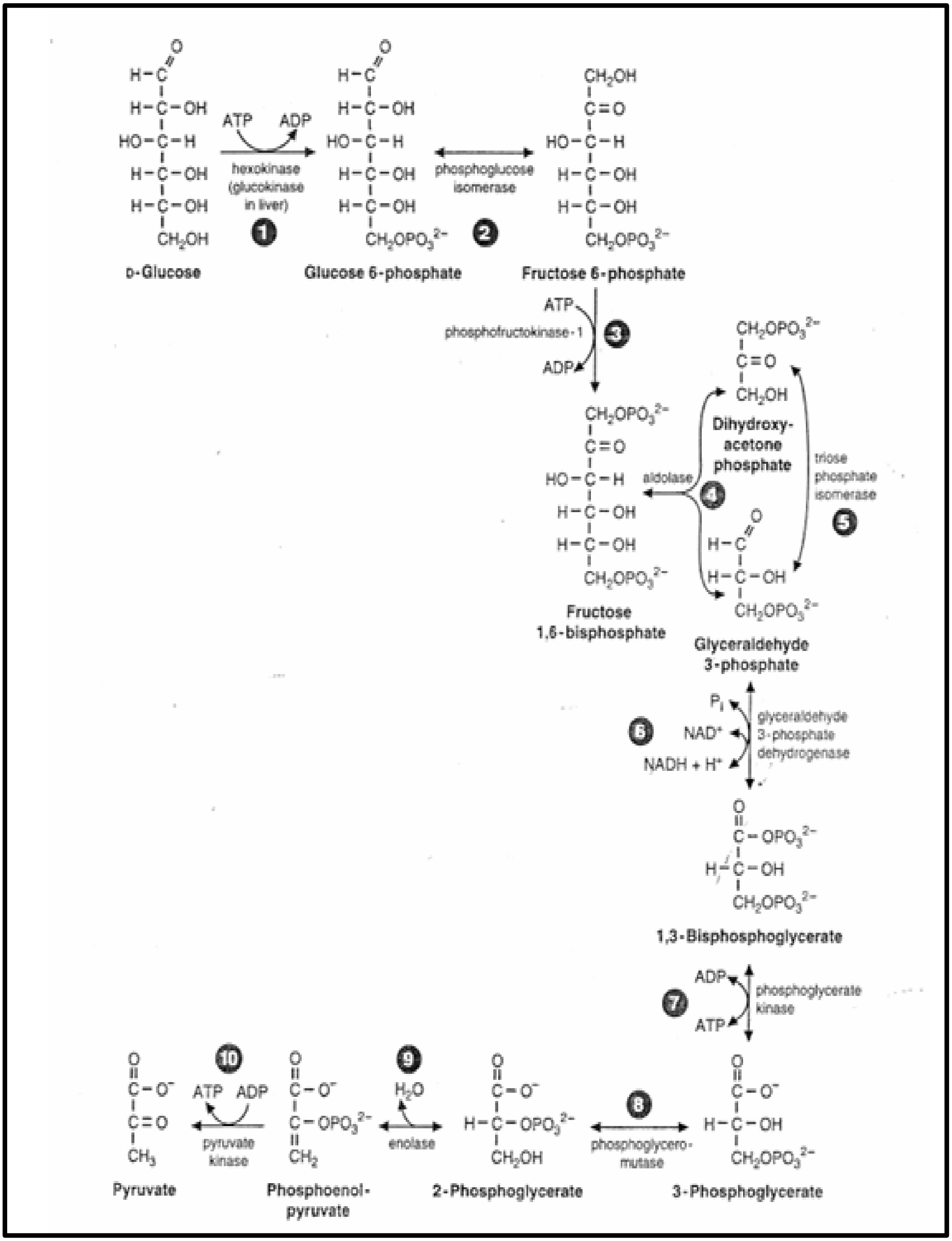
2- Anaerobic phase (without oxygen): Glucose can be converted to pyruvate which is reduced by NADH to form lactate. This conversion of glucose to lactate is called anaerobic pathway because it can occur without the participation of oxygen. Anaerobic glycolysis allows the continued production of ATP in tissues that lack mitochondria, like red blood cells, or in cells deprived of sufficient oxygen.

The anaerobic phase of glucose metabolism occurs whether O2 is present or not.






Steps 1 – 3 A fuel molecule is energized, using ATP.
ATP
ADP
Step 1
Glucose
PREPARATORY PHASE (energy investment)
Glucose-6-phosphate
2
Fructose-6-phosphate
ATP
ADP
3
Step 4 A six-carbon intermediate splits into two three-carbon intermediates.
Fructose-1,6-diphosphate
4
Glyceraldehyde-3-phosphate (G3P)
Step 5 A redox reaction generates NADH.
2 NAD+
2 NADH + 2 H+
5
2 P
ENERGY PAYOFF PHASE
1,3-Diphosphoglyceric acid (2 molecules)
2 ADP
2 ATP
6
Steps 6 – 9 ATP and pyruvic acid are produced.
3-Phosphoglyceric acid (2 molecules)
7
2-Phosphoglyceric acid (2 molecules)
2 H2O
8
Phosphoenolpyruvic acid (2 molecules)
2 ADP
2 ATP
9
Pyruvic acid
(2 molecules per glucose molecule)


ATP
ADP
hexokinase (glucokinase in liver)
1
phosphoglucose isomerase
2
D-Glucose
Glucose 6-phosphate
Fructose 6-phosphate
ATP
phosphofructokinase-1
3
ADP
Dihydroxy-acetone phosphate
triose phosphate isomerase
5
aldolase
4
Fructose 1,6-bisphosphate
Glyceraldehyde 3-phosphate
P_i
NAD^+
$NADH + H^+$
6
glyceraldehyde 3-phosphate dehydrogenase
1,3-Bisphosphoglycerate
ADP
ATP
7
phosphoglycerate kinase
10
ATP ADP
pyruvate kinase
9
H_2O
enolase
8
phosphoglycero-mutase
Pyruvate
Phosphoenol-pyruvate
2-Phosphoglycerate
3-Phosphoglycerate

Reactions of glycolysis:

1- Phosphorylation of glucose: glucose is converted to glucose – 6 – phosphate in a reaction that uses ATP and produce ADP. The reaction is catalyzed by specific enzyme (glucokinase) in liver cells and by non – specific (hexokinase) in liver and extra hepatic tissues. Both of these enzymes are subject to regulatory mechanisms.

Hexokinase	Glucokinase
1-Non – specific, can phosphorylate any of the hexoses.	**1**- specific, can phosphorylated glucose only.
2- Found almost in all tissues.	**2**- Found only in liver.
3- Found in fetal as well as in adult liver.	**3**- Found in adult liver, not in foetal liver.
4- More stable.	**4**- Physiologically more labile.
5- Allosteric inhibition by G-6-P.	**5**- Not inhibited by G-6-P.
6-Km is low = 0.1mM, hence high affinity for glucose.	**6**- Km is high = 10Mm, low affinity for glucose.
7-Not very much influenced by diabetic state or fasting.	**7**-Depressed in fasting and in diabetes. Glucokinase is deficient in patients of DM.
8- No change with glucose feeding.	**8**- Increased by feeding of glucose after fasting.
9- Inhibited by glucocorticoids and GH, insulin doesn't affect it.	**9**- Inhibited by glucocorticoids and GH. Synthesis is induced by insulin.
10- Main function to make available glucose to tissues for oxidation at lower blood glucose level.	**10- Main function is to clear glucose from blood after meals and at blood levels greater than 100 mg/dl.**

2- Isomerization of glucose-6- phosphate to fructose–6 – phosphate.

3- Phosphorylation of fructose – 6 – phosphate to fructose 1,6 – bis – phosphate: This reaction is phosphorylated by ATP by the enzyme phosphofructokinase – 1 (PFK-1) is the most important control point and the rate – limiting step of glycolysis. This enzyme is activated by AMP and F-2, 6 – P and inhibited by ATP and citrate.

4- Cleavage of fructose 1, 6 – bisphosphate, to form the triose phosphate: glyceraldehyde 3 – phosphate and dihydroxyacetone phosphate (DHAP).

5- Isomerization of DHAP and formation of glyceraldehydes-3-P.

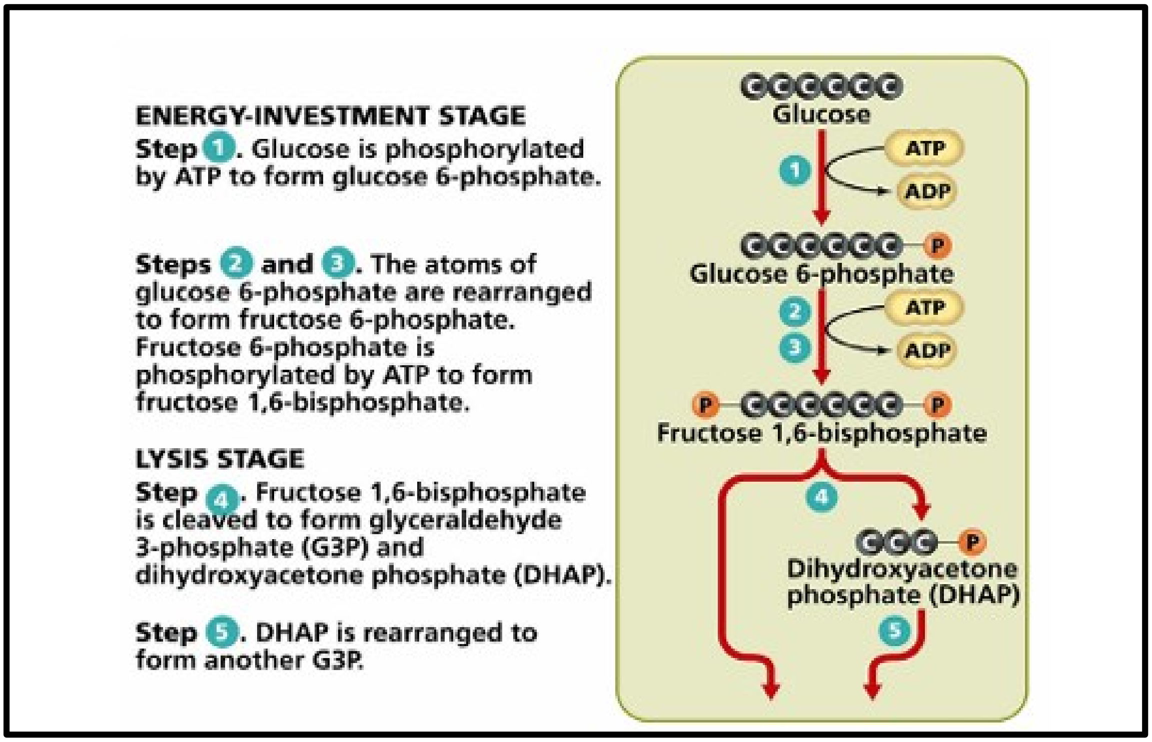
6- Oxidation of glyceraldehydes – 3 – phosphate to 1, 3 – Bisphosphoglycerate.

7- Synthesis of 3-phospoglycerate producing ATP

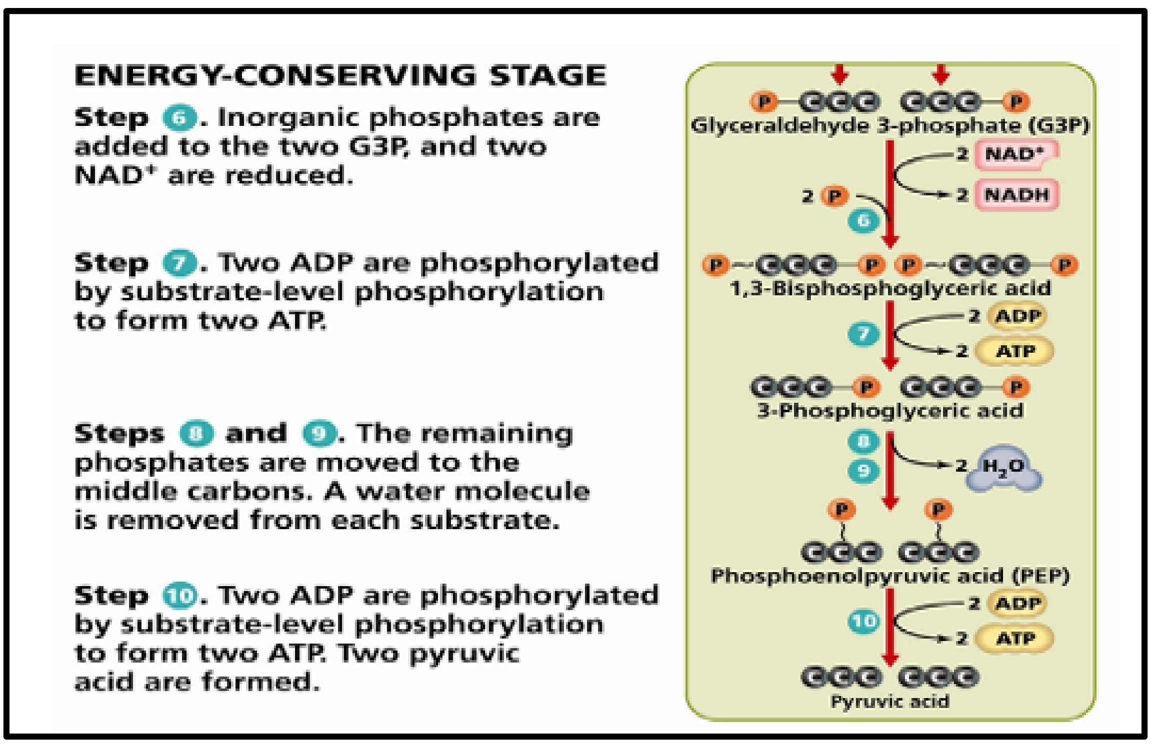
8- Shift of the phosphate group from carbon 3 to carbon 2 and form 2-phosphoglycerate.

9- Dehydration of 2 – phosphoglycerate and form (PEP) phosphoenol pyruvate.

10- Formation of pyruvate producing ATP: The conversion of PEP to pyruvate is catalyzed by pyruvate kinase, the third irreversible reaction of glycolysis, pyruvate kinase is activated by F-1,6-p and inhibited by alanine and by phosphorylation in the liver during fasting.



Steps of using energy in glycolysis



Steps of produce energy in glycolysis

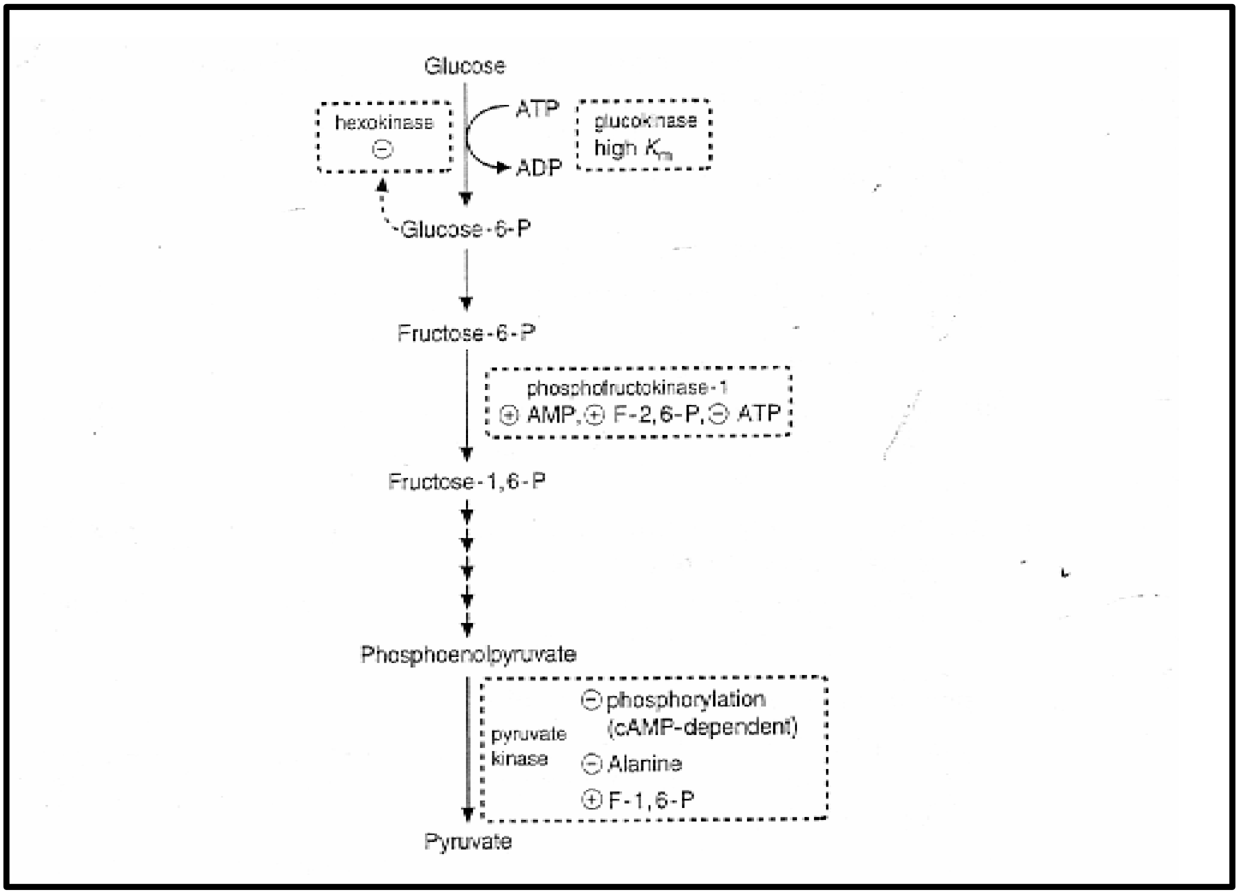
There are three key enzymes in TCA cycle:

Shown in figure below:

1) Hexokinase **(step 1)**

2) Phosphofructokinase **(step 3)**

3) Pyruvate kinase **(step 10)**



Key enzymes of glycolysis pathway

Energy yield per glucose molecule oxidation :

A-In Glycolysis in presence of O_2 (Aerobic phase)

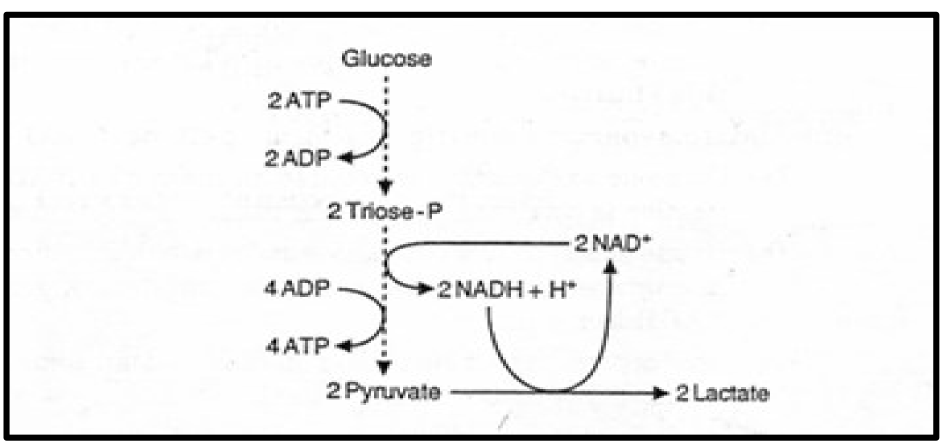
Energy yield per glucose molecule oxidation

A – In Glycolysis in presence of O_2 (Aerobic phase).

Reaction Catalyzed by	ATP production
(phosphorylation)	
1- Hexokinase/Glucokinase reaction	- 1 ATP
2- Phosphofructokinase	- 1 ATP
(Oxidation of 2 NADH in electron transport chain)	
3- Glyceraldehyde - 3 - P dehydrogenase	+ 6 ATP
(Substrate level phosphorylation)	
4- Phosphoglycerate kinase	+ 2 ATP
5- Pyruvate kinase	+ 2 ATP
*** (1 NADH → 3 ATP) Net gain**	= 10 – 2
	= 8 ATP

B-*In Glycolysis in the absence of O_2* (Anaerobic phase) This is achieved by re-oxidation of NADH by conversion of pyruvate to lactate (without producing ATP) by the enzyme lactate dehydrogenase.

(Net gain / 2NADH = 6ATP)



Clinical Importance of anaerobic glycolysis:

• Tissues that function under hypoxic circumstances will produce lactic acid from glucose oxidation, producing local acidosis. If lactate production is more it can produce metabolic acidosis.

• Whether O2 is present or not, glycolysis in erythrocytes always terminates in pyruvate and lactate.

• Vigorously contracting skeletal muscle will produce relative anaerobiosis and glycolysis will produce lactic acid.

• Inhibitor of Lactate Dehydrogenase (LDH) is Oxamate: it competitively inhibits lactate dehydrogenase and prevents the reoxidation of NADH. The Biomedical Importance of Glycolysis

• This pathway is meant for provision of energy.

• It has importance in skeletal muscle as glycolysis provides ATP even in absence of O2. • Muscle can survive anoxic episodes.

• Insulin favors glycolysis by activating the three key glycolytic enzymes.

• Glucagon and glucocorticoid inhibit glycolysis and favor gluconeogenesis

Heart muscle: as compared to skeletal muscle, heart muscle is adapted for aerobic performance. It has relatively poor glycolytic activity and poor survival under conditions of ischemia.

• Role in cancer therapy: In fast- growing cancer cells, rate of glycolysis is very high. Producing more pyruvic acid than TCA cycle can handle. Accumulation of pyruvic acids leads to excessive formation of lactic acid producing local lactic acidosis.

• Hemolytic anemia: inherited enzyme deficiencies like hexokinase deficiency and pyruvate kinase deficiency in glycolytic pathway enzymes, can produce hemolytic anemia.