**Basic Biochemistry lecture 4**

**Dr. Dalya Shakir Obaida / PhD Clinical Biochemistry**

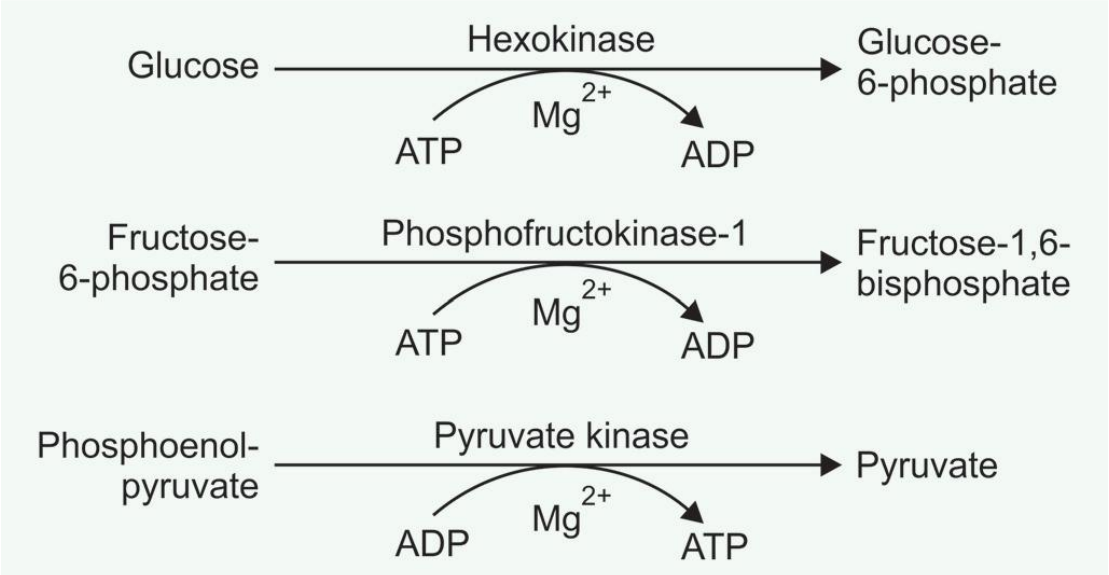
## GLUCONEOGENESIS

**Gluconeogenesis** (neoglucogenesis) is the process of the **formation of glucose** from various **non-carbohydrate sources** such as:

1) The glucogenic amino acids
2) lactate
3) glycerol, or propionate.

Gluconeogenesis takes place in the **fasting state** or on a low carbohydrate diet, particularly, in the liver and some other tissues, which are solely dependent on glucose for their energy demand. It does not take place in muscle. Gluconeogenesis thus, enables **maintenance of blood glucose** when all the dietary glucose has been absorbed and oxidized. This process is essential since blood glucose level has to be maintained, to support metabolism of the tissues that use glucose as the primary substrate such as the brain, red blood cells and lens.

Gluconeogenesis is said to be the reversal of glycolysis but truly it is not a reversal of glycolysis, since there are three irreversible reactions in the glycolytic pathway. Irreversible steps in glycolysis.



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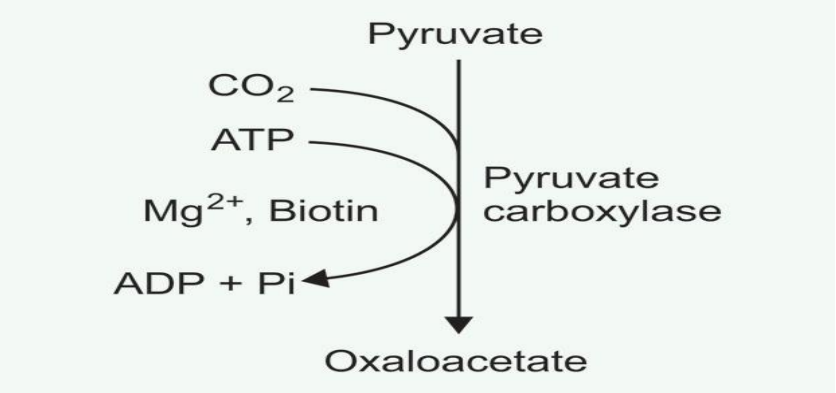
## Outline of Gluconeogenesis

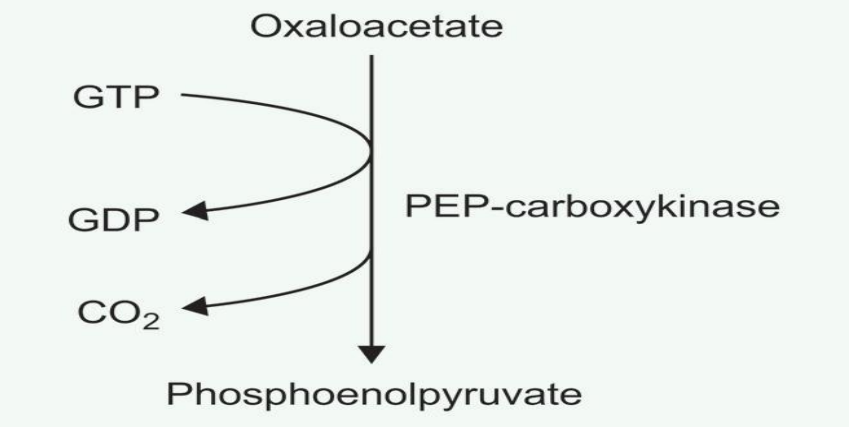
### A. Reversal of Glycolysis

It includes the following set of reactions:

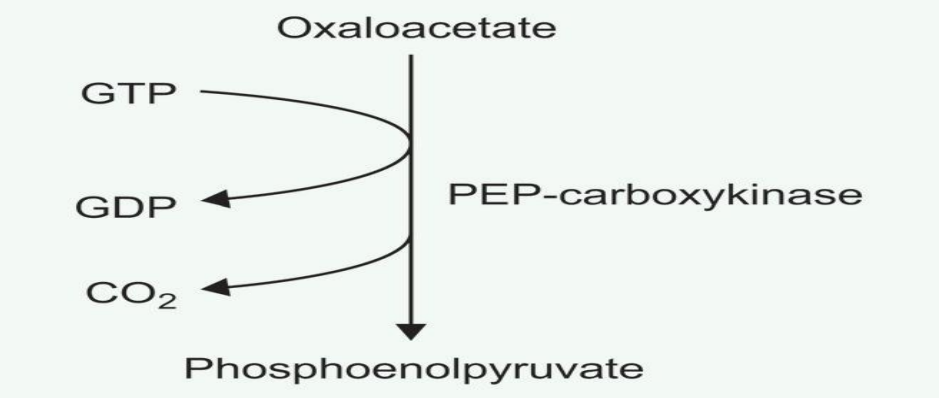
1. Conversion of pyruvate to phosphoenolpyruvate .In the reversal of the pyruvate to phosphoenolpyruvate, pyruvate is first converted to oxaloacetate by the enzyme pyruvate carboxylase, in mitochondria



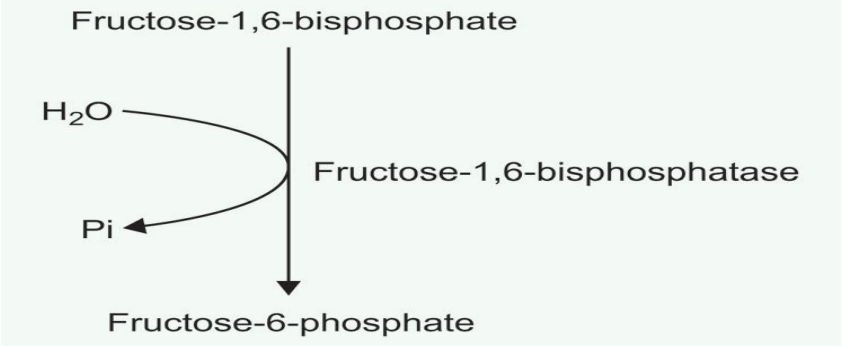

2. Conversion of pyruvate to oxaloacetate: Thereafter, malate dehydrogenase converts oxaloacetate to malate, which is freely transported across the mitochondrial membrane. Malate thus, comes out from the mitochondria to the cytosol where it is reconverted back to oxaloacetate by the same enzyme. Reactions of gluconeogenesis, thus, occur in the cytosol as well as mitochondria.



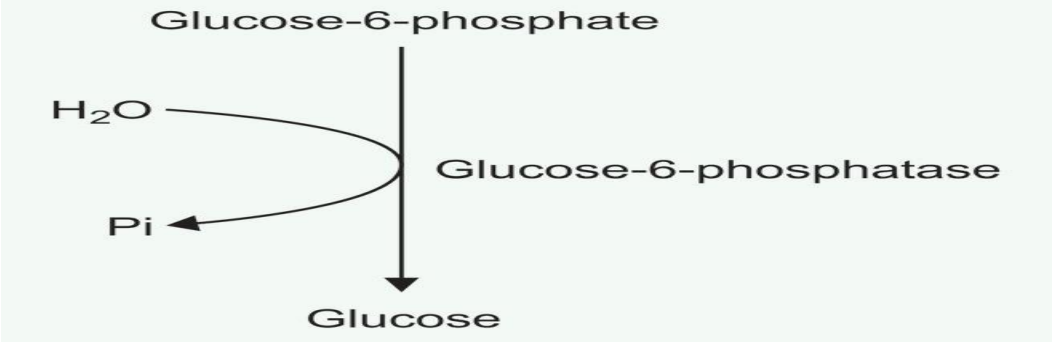
3. In the next step, oxaloacetate is converted to phosphoenolpyruvate, by the enzyme phosphoenolpyruvate carboxykinase (PEP carboxykinase.




4. Conversion of fructose-1,6-bisphosphate to fructose-6-phosphate: Fructose-1,6-bisphosphate is converted to fructose- 6-phosphate by the enzyme fructose-1,6-bisphosphatase.




1. Conversion of glucose-6-phosphate to glucose: Glucose-6-phosphate is converted to glucose by the enzyme glucose-6-phosphatase. This enzyme is not found in the muscle and adipose tissue.



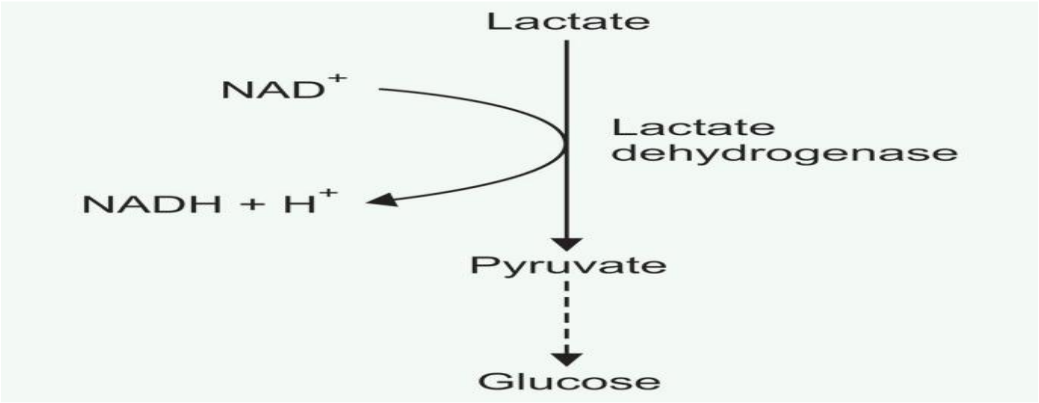
## B. Conversion of Lactate to Glucose

Lactate is produced during the process of anaerobic glycolysis. For its conversion to glucose, firstly, **lactate** is oxidized to **pyruvate**. This reaction is catalyzed by the enzyme **lactate dehydrogenase**, which requires NAD+ .Subsequently, pyruvate is converted to glucose by the **reversal of the glycolytic reactions**.

### Regulation of Gluconeogenesis

Gluconeogenesis is regulated by the enzymes:

1. pyruvate carboxylase
2. phosphoenolpyruvate carboxykinase
3. fructose-1,6-bisphosphatase
4. glucose-6-phosphatase, which catalyze the reversal of the irreversible steps of glycolysis.

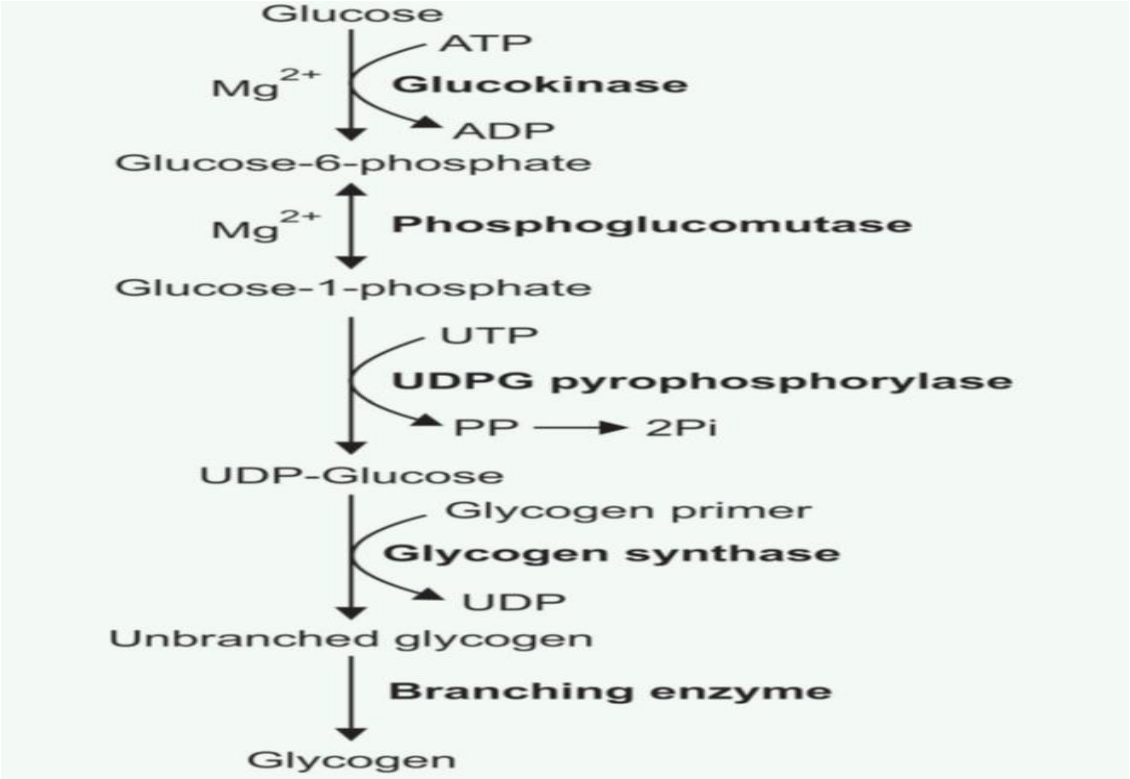



## GLYCOGENESIS

Glycogenesis (**glycogen synthesis**) is the process of the **conversion of glucose to glycogen**. Although, it is operative in several tissues, liver and muscle are the main organs for the synthesis of glycogen. Glycogenesis is stimulated by insulin. Various reactions of glycogenesis are outlined in

**Glucose** is first activated (phosphorylated) to **glucose-6-phosphate**.

In the liver, **glucokinase** converts most of the glucose into glucose-6-phosphate in the fed state. This is an inducible enzyme and has greater specificity for its substrate. In the muscle and other tissues, this reaction is catalyzed by **hexokinase**.

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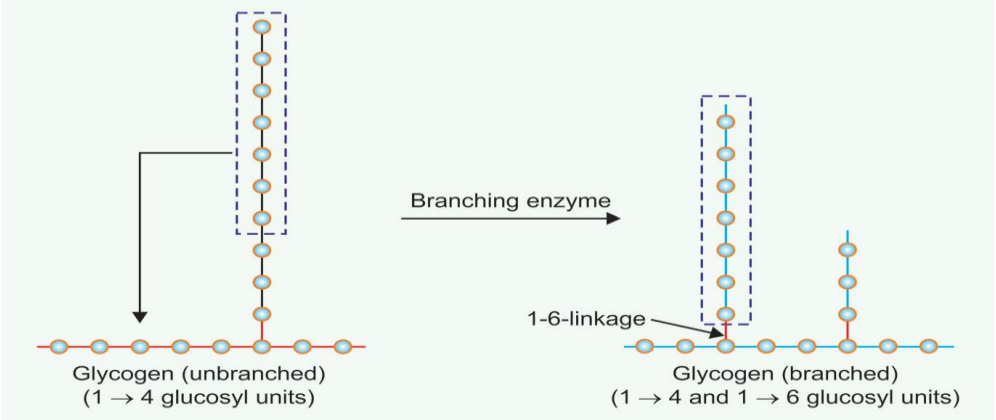
**2. Glucose-6-phosphate** is isomerized to **glucose-1- phosphate**, by the enzyme **phosphoglucomutase**.

**3. Glucose-1-phosphate** reacts with UTP and converts to **uridinediphosphate glucose** (UDP-Glu or UDPG). The reaction is

catalyzed by **UDPG pyrophosphorylase** (glucose-1-phosphate uridyltransferase). **Pyrophosphate**, so released during this process, is immediately hydrolyzed to two molecules of **inorganic phosphate** by **pyrophosphatase**.

**4.** From **UDP-Glu**, glucose is transferred to the **glycogen primer** (i.e. the preformed oligosaccharide). The enzyme glycogen synthase catalyzes this reaction. The incoming glucose is linked to the primer at the non-reducing end by a 1,4-α-glycosidic linkage and results in elongation of the pre-existing branch. This results in the formation of an **unbranched glycogen**. Both glycogen primer and UDP-Glu are substrates for glycogen synthase, which is a key enzyme of glycogenesis.

**5.** Once the straight chain containing nearly 11 glucose residues is formed, the **branching enzyme** removes a block of 7–8 glycosyl residues from the growing chain and transfers it to the neighboring chain.




**Formation of a branch point by the branching enzyme during glycogenesis**