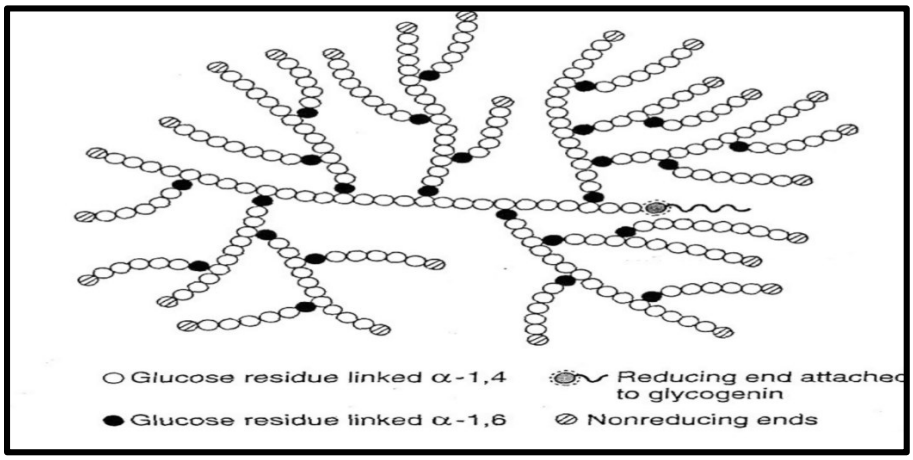
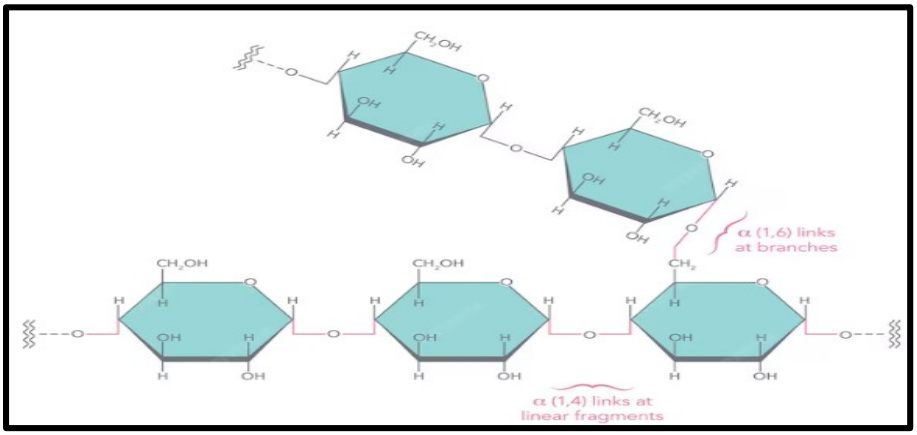
Glycogenesis

Glycogen: is the storage form of glucose, which is stored in animal body especially in **liver and muscles**. It is mobilized to glucose whenever body tissue requires.

Glycogen is a branched polymer of glucose that contains a minor amount of phosphate and glucosamine. In the linear chains, the glucose residues are connected by **α-1,4-glycosidic linkages** while **α-1,6 glycosidic bonds** create the branch points. Branches within normal glycogen are distributed at even intervals resulting in a structure with spherical shape. The source and function of phosphate and glucosamine in human glycogen are unclear.





The glycogen particle consists of up to 55.000 glucose residues. In skeletal muscle, glycogen particles have a size of 10–44 nm in diameter while in the liver measure approximately 110–290 nm. Glycogen can be identified by electron microscopy inside the cells.

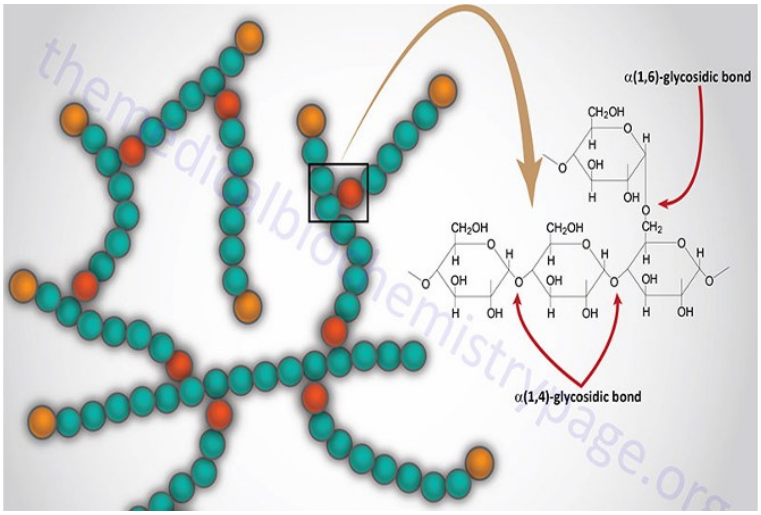
Glycogen is a large branched polymer consist of D– glucose residue.

Notes:

1. The linkages between glucose residues are α-1-4 except at branch points where the linkage is α-1, 6. Branching is more frequent in the interior of the molecule and less frequent at the periphery, the average being an α-1-6 branch every (8-10) residues.

2. One glucose unit, located at the reducing end of each glycogen molecule, is attached to the protein glycogenin.

3. The glycogen molecule branches like a tree and has many non-reducing ends at which addition and release of glucose residues occur during synthesis and degradation, respectively.



Role of liver glycogen

1- It is the only immediately available reserve store of blood glucose.

2- A high liver glycogen level protects the liver cells against the harmful effects of many poisons and chemicals e.g., CCl4, ethyl alcohol, arsenic, various bacterial toxins.

3- Certain forms of detoxication, e.g., conjugation with glucuronic acid, and acetylation reactions, are directly influenced by the liver glycogen level.

4- The rate of deamination of amino acids in the liver is depressed as the glycogen level rises, so that amino acids are preserved longer in that form and so remain available for protein synthesis in the tissues.

5- Similarly, a high level of liver glycogen depresses the rate of ketone bodies formation.

The causes of storage glucose as glycogen

Possible reasons:

1-Being **insoluble** it exerts no osmotic pressure, and so does not disturb the intracellular fluid content and doesn't diffuse from its storage sites.

2-It has a **higher energy level** than a corresponding weight of glucose (though energy has to be expended to make it from glucose).

3-It is **readily broken down** under the influence of hormones and enzymes:

• Into glucose in liver **(to maintain blood glucose level)**.

• Into lower intermediates in skeletal muscle and other tissues for energy.

Biomedical importance of glycogen

1-Liver glycogen is largely concerned with storage and supply of glucose -1-P which is converted to glucose, for maintenance of blood glucose, particularly in between meals.

2-Muscle glycogen on the other hand, is to act as readily available source of intermediates of glycolysis for provision of energy within the muscle itself. Muscle glycogen cannot directly contribute to blood glucose level.

3-Inherited deficiency of enzymes in the pathway of glycogen metabolism produces certain inherited disorders called as "Glycogen storage diseases" (GSDs).

*** Glycogenesis and glycogenolysis are finely controlled at substrate level, by end-products and hormones.**

*** When glycogenesis occurs, glycogenolysis does not take place and vice versa.**

Glycogen synthesis (Glycogenesis)

1- It is the formation of glycogen from glucose. Principally it occurs in **liver and skeletal muscles**, but it can occur in every tissue to some extent. Glycogenesis requires energy supplied by ATP.

2- It occurs in the **cytosol of cells** (except RBCs) especially in **liver & muscles**

3- UDP-glucose (Uridine diphosphate glucose) is the precursor for glycogen synthesis.

Sources of glucose:

A-For liver glycogen:

1. Blood glucose (Diet)

2. Other hexoses: fructose and galactose

3. Non-carbohydrate sources: "gluconeogenesis", e. g. amino acids, glycerol and lactate during fed state.

B-For muscle glycogen: blood glucose only.

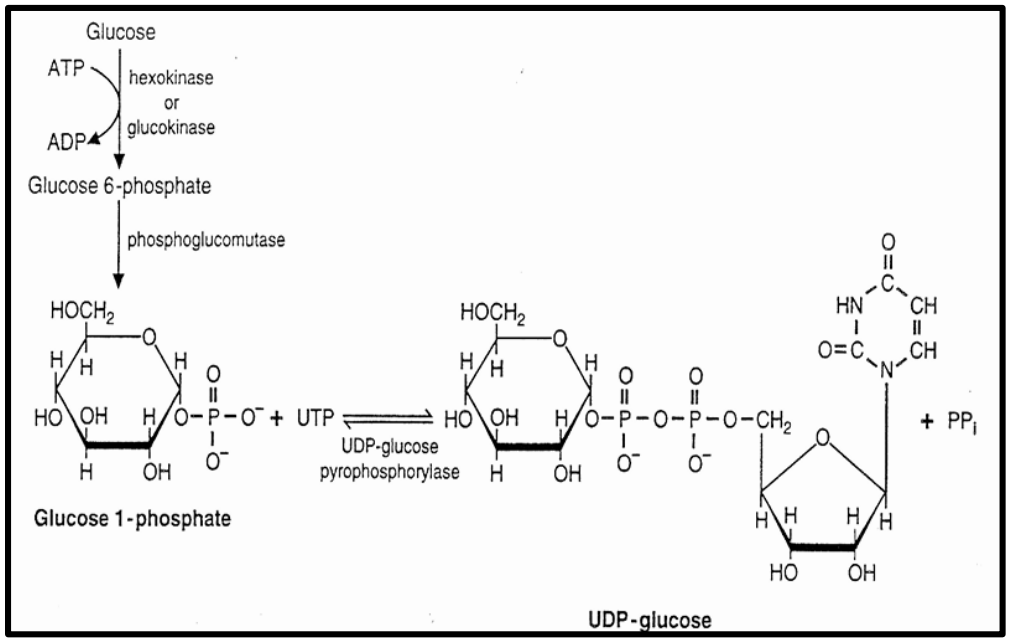
Steps of glycogenesis

1. Synthesis of UDP-glucose

a. Glucose enters cells and is phosphorylated to glucose 6-phosphate by hexokinase (or by glucokinase in the liver). ATP provides the phosphate group.

b. Phosphoglucomutase converts glucose 6-phosphate to glucose 1-phosphate.

c. Glucose 1-phosphate reacts with UTP, forming UDP-glucose in a reaction catalyzed by UDP- glucose pyrophosphorylase. Inorganic pyrophosphate (PPi) is released in this reaction. PPi is cleaved by a pyrophosphatase to 2 Pi. This removal of product helps to drive the process in the direction of glycogen synthesis.



2-Action of glycogen synthase.

a. Glycogen synthase is the key regulatory enzyme for glycogen synthesis. It transfers glucose residues from UDP-glucose to the nonreducing ends of a glycogen primer. UDP is released and reconverted to UTP by reaction with ATP.

b. The primers, which are attached to glycogenin, are glycogen molecules that were partially degraded in liver during fasting or in muscle and liver during exercise.

3. Formation of branches

a. When a chain contains (11 or more glucose residues), an oligomer (6-8 residues) in length, is removed from the nonreducing end of the chain. It is reattached via an α-1, 6 linkage to a glucose residue within an α-l, 4-Iinked chain.

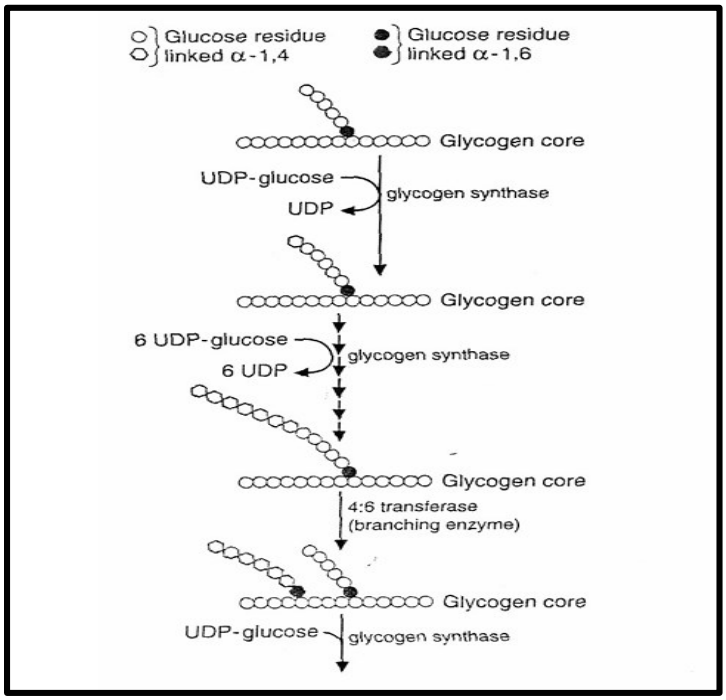
b. These branches are formed by the branching enzyme, a glucosyl 4:6 transferase that breaks an α-1, 4 bond and forms an α-1, 6 bond.

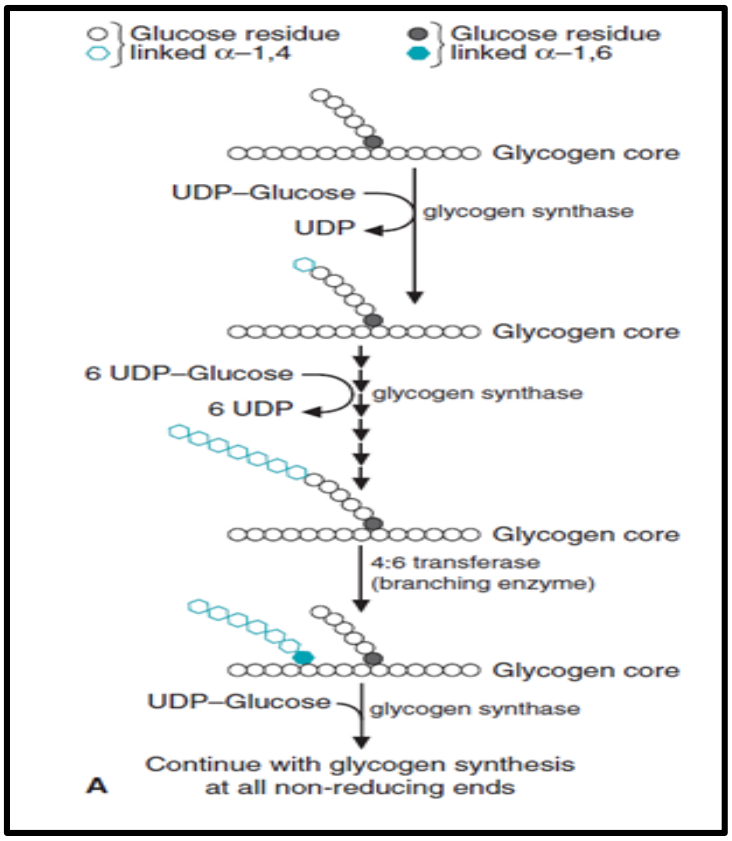
c. The new branch points are at least 4 residues and an average of (7-11 residues) from previously existing branch points.

4. Growth of glycogen chains

a. Glycogen synthase continues to add glucose residues to the nonreducing ends of newly formed branches as well as to the ends of the original chains.

b. As the chains continue to grow, additional branches are produced by the branching enzyme.


Glucose residue linked α-1,4
Glucose residue linked α-1,6
Glycogen core
UDP-glucose
UDP
glycogen synthase
Glycogen core
6 UDP-glucose
6 UDP
glycogen synthase
Glycogen core
4:6 transferase (branching enzyme)
Glycogen core
UDP-glucose
glycogen synthase


Glucose residue linked α–1,4
Glucose residue linked α–1,6
Glycogen core
UDP–Glucose
UDP
glycogen synthase
Glycogen core
6 UDP–Glucose
6 UDP
glycogen synthase
Glycogen core
4:6 transferase (branching enzyme)
Glycogen core
UDP–Glucose
glycogen synthase
Continue with glycogen synthesis at all non-reducing ends
A

Stimulation of Glycogenesis

1- Insulin: Stimulate glycogen synthesis in liver and muscle.

2- Glucocorticoids: effect seen 2-3 hours after administration.

• Enhances gluconeogenesis and glycogen synthesis in liver.

• Increases activity of protein phosphatase -1.

• Increases synthesis of the enzyme "glycogen synthase".

3- Glucose: high substrate concentration increases synthesis.

Inhibition of glycogenesis

1- Increased concentration of glycogen inhibits Glycogenesis "feedback inhibition".

2- Increased concentration of cyclic – AMP which affects protein phosphatase-1