Glycogen Metabolism:
1- Glycogen is a storage form of Glc. It provides Glc. Once needed by the body, so it acts as a source of it.
2- Glycogen structure is highly branched very large polymer of Glc linked by $\alpha$-1,4 glycosidic linkage and branches by $\alpha$-1,6 glycosidic bonds at about every 10 residues. It is found in the Cytosol as granules.
3- Major sites of storage are muscle and liver.
   (Concentration is higher in the liver than in the muscle, but the amount is larger in the muscle).
   Liver – releases Glc. From glycogen into blood
   Muscle- No release of Glc from Glycogen but uses glycogen for its own energy needs.
4- Duration of liver glycogen storage is $\approx 12$ hrs. (i.e. enough for about 12 hours) then gluconeogenesis starts.

Glycogenesis (Glycogen synthesis)
1- Synthesis of uridine diphosphate glucose (UDP-Glc), the precursor of glycogen.

\[
\text{Glc-1-P} \xrightarrow{\text{mutase}} \text{Glc-1-P} + \text{UTP} \xrightarrow{\text{pyrophosphorylase}} \text{UDP-Glc} + \text{PPi} + \text{H}_2\text{O} \\
\text{Pyrophosphatase} \rightarrow 2 \text{Pi}
\]
2- Synthesis of glycogen molecule:
   a- Formation of the amylose chains.
      The synthesis of new glycogen requires the presence of existing glycogen chains and Glc residue from UDP-Glc. The Glc residues are added (successively) to the C-4 terminus of an existing glycogen chain in α-1,4 glycosidic linkages.

\[
\text{UDP-Glc} + \text{glycogen (n residues)} \rightarrow \text{UDP} + \text{glycogen (n+1 residues)}
\]

Glycogen synthase

This reaction is the rate-limiting step in Glycogen synthesis.

b- Formation of branched chains and further growth.
   1- Segments of amylose chain are transferred onto the C-6 OH group of neighboring chains forming α-1,6 linkages.
      \(\star\) this is done by the branching enzyme glucosyl – 4:6 transferase.

   2- Seven (7) – residue segments of amylase terminal chains are transferred to a C-6 OH group of a glucosyl residue that is 4 residues away from an existing branch. A terminal branch must be at least eleven residues in length before a segment is transferred from it.

   3- Genetic defect in the branching enzyme leads to Type IV glycogen storage disease (Anderson disease).
      Infants born with this disease suffer cirrhosis and failure of the liver and hepatosplenomegaly.
      Most affected infants die by 2 years of age.
Glycogenolysis
(glycogen degradation or use)

1- Phosphorlytic cleavage of the terminal \(\alpha\)-1,4 glycosidic bond.

This cleavage reaction, which is the rate-limiting step in glycogenolysis, gives Glc-1-P and a glycogen chain that is smaller by one glucose unit.

\[
\text{Glycogen (n residue)} + \text{Pi} \xrightarrow{\text{Glycogen phosphorylase}} \text{Glycogen (n-1 residue)} + \text{Glc 1P}
\]

Glycogen phosphorylase – dimeric enzyme and needs pyridoxal phosphate as a coenzyme.

Genetic defect of Glycogen phosphorylase:
  a- Type V glycogen storage disease (McArdle disease) in muscles. Patients suffer from skeletal muscle cramps and show low blood lactate level during exercise.
  b- Type VI glycogen storage disease (Her’s disease) in liver. Patients suffer hepatomegaly, hypoglycemia acidosis and growth retardation.

2- Removal of branch chains:
   This is catalysed by the “debranching enzyme system”, it has 2 enzymatic activities:
   a- 1,4\(\xrightarrow{\text{1,4 glucantransferase (glucosyl transferase)}}\) 1,4 glucantransferase (glucosyl transferase)
      In this step, 3 Glc-residues from a branch are transferred onto a chain terminus, leaving a single residue on C-6.
   b- \(\alpha\)-1,6 glucosidase (amylo-6-glucosidase).
      In this step, a single residue on C-6 is removed to give a free glucose molecule.
      In lysosomes, another enzyme, \(\alpha\)-1,4 glucosidase is involved in debranching.
Disorders due to genetic defect in debranching enzymes:

a- Type II glycogen storage disease (Pompe’s disease):
Defect in α-1,4 glucosidase of lysosomes

Glycogen accumulates → General nervous system problems, enlarged heart and later failure of heart and lung.

b- Type III glycogen storage disease (Cori-Forbes disease):
Defect in debranching enzyme system, also heart and lung problems → stunted growth (growth stop), enlarged liver, hypoglycemia and acidosis.

Glycogen storage disease: caused by genetic deficiencies of certain enzymes of glycogen metabolism → accumulation of glycogen and/or inability to use that glycogen as a fuel source.

Recently more than 10 glycogen storage diseases have been found out, most common ones are Type I, Type III, Type IV of which Type I incidence is about 1/20,000 person.

Regulation of glycogen metabolism:
A- Hormonal
In liver
- Glucagon (stimulates glycogenolysis, reduces glycogenesis)
- Insulin (stimulates glycogenesis)

In muscle
- Epinephrin (promotes glycogenolysis, inhibits glycogenesis)
- Insulin (stimulates glycogenesis, reduces glycogenolysis)
☆ Glucagon/insulin ratio is important in regulating Gly metabolism
☆ Insulin is an anabolic hormone

B- Level of cAMP (a.k.a. ¹ covalent modification, i.e. phosphorylation)

Adequate level → Glycogenolysis is increased
High

Low level → Glycogenesis is increased

¹ a.k.a = also known as
**Effect of epinephrine and/or glucagon:**

$\text{epinephrin}$

$\text{Adenylate cyclase (Ia)} \rightarrow \text{adenylate cyclase (a)}$

$\text{ATP} \rightarrow \text{cAMP}$

$\text{Phospho diesterase}$

$\text{Protein kinase (Ia)} \rightarrow \text{protein kinase (a)}$

$\star \text{Ia} = \text{Inactive}$  
$\text{a} = \text{active}$

**After the activation of protein kinase, there are 2 pathways:**

1.

$\text{Protein kinase (a)}$

$\text{Glycogen synthase I} \rightarrow \text{Glycogen synthase D}$

(Active)  
(Inactive)

Dephosphorylated  
Phosphorylated

**Glycogenesis Stops**

$\text{UDP-Glc} \rightarrow \text{Glycogen}$

2.

$\text{Protein kinase (a)}$

$\text{Phosphorylase kinase} \rightarrow \text{phosphorylase kinase}$

(inactive)  
(active)

$\text{Ca}^{2+}$

$\text{Phosphorylase b} \rightarrow \text{phosphorylase a}$

(inactive)  
(active)

This reaction can be reversed  
By phosphatase enzyme

**Glycogenolysis Starts**

$\text{Glycogen} \rightarrow \text{Glc-6-P}$
This regulation is called **Cascade** regulation of Glycogen synthase activity and Glycogen phosphorylase activity (Glycogenesis and Glycogenolysis).

 فإذا **Cascade** = Type of an amplification system, where one molecule or few of circulating hormones like Epinephrin or glucagon can activate another molecule(s) to produce a larger number of cAMP which cause activation of protein kinase and so on...
<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Features</th>
<th>Glycogen in the affected organ</th>
<th>Organ affected</th>
<th>Defective enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Mild hepatomegaly, normal liver enlargement, like Type V, but milier course.</td>
<td>Massively increased amount; normal structure.</td>
<td>Liver</td>
<td>Type I glucose 6-phosphatase or Type I glucokinase</td>
</tr>
<tr>
<td>II</td>
<td>Pompe disease</td>
<td>Massively increased amount; normal structure.</td>
<td>Muscle</td>
<td>Type II glucocerebrosidase</td>
</tr>
<tr>
<td>III</td>
<td>Cori disease</td>
<td>Massively increased amount; very long outer branches.</td>
<td>All organs</td>
<td>Type III-α-glucosidase or Type III-α-glucosidase</td>
</tr>
<tr>
<td>IV</td>
<td>Andersen disease</td>
<td>Massively increased amount; normal structure.</td>
<td>Liver and spleen</td>
<td>Type IV-α-glucosidase</td>
</tr>
<tr>
<td>V</td>
<td>McArdle disease</td>
<td>Massively increased amount; normal structure.</td>
<td>Muscle</td>
<td>Type V 4-α-glucosidase</td>
</tr>
<tr>
<td>VI</td>
<td>Hers disease</td>
<td>Increased amount; normal structure.</td>
<td>Liver and skin</td>
<td>Type VI β-glucocerebrosidase</td>
</tr>
<tr>
<td>VII</td>
<td>Type VII</td>
<td>Increased amount; normal structure.</td>
<td>Muscle</td>
<td>Type VII-α-glucosidase</td>
</tr>
<tr>
<td>VIII</td>
<td>Type VIII</td>
<td>Increased amount; normal structure.</td>
<td>Muscle</td>
<td>Type VIII-α-glucosidase</td>
</tr>
</tbody>
</table>

Note: Types I through VII are inherited as autosomal recessives. Type VIII is X-linked.