Chapter 1

Glycogen Storage Diseases

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Basic biochemistry

- Glucose is the principle substrate of energy metabolism in humans.
- The ultimate fate of glucose depends on body needs; thus glucose may be:
  - Oxidized to give energy or
  - Stored as glycogen (muscles, liver) or
  - Converted to triglycerides, amino acids and proteins.
• Glycogen is a glucose polymer joined in straight chains by alpha 1,4 linkages and branched at intervals of 4 to 6 residues by alpha 1,6 linkages. It forms a tree like molecule and can have a molecular weight of many millions. Glycogen is the storage form of glucose and is found in abundance in the liver, muscles and kidneys.
Glycogen polymer
* Glycolysis:
  - The oxidation of glucose to pyruvate with generation of ATP for energy (2 moles of ATP per glucose molecule).
  - Takes place in the cytoplasm of the cell.
  - May also occur in the absence of O2, in which case pyruvate is converted to lactate.
Glycogenesis:
- The conversion of excess glucose to glycogen for storage.
- Begins with the phosphorylation of glucose to glucose-6-phosphate, which is then isomerized to glucose-1-phosphate and added to a glycogen primer, uridine diphosphoglucose (UDPG).
- Catalyzed by glycogen synthetase, which exists in 2 forms; an active (D or dependent) form and an inactive (L or independent) form.
**Glycogenolysis:**
- The degradation of glycogen to glucose.
- A phosphorylase enzyme splits the alpha 1,4 linkage releasing glucose-1-phosphate, a debranching enzyme then splits the alpha 1,6 linkage.
- The phosphorylase enzyme has two forms; an inactive form (phosphorylase b) and an active form (phosphorylase a). Conversion to the active form is catalyzed by phosphorylase b kinase.
• The glucose-1-phosphate can then be isomerized to glucose-6-phosphate and either enter glycolysis or be hydrolysed to free glucose.
• The latter step is catalyzed by a glucose-6 phosphatase enzyme and facilitated by a translocase that transports glucose-6-phosphate across the microsomal membrane.
Glycogenolysis

Glycogen

GLYCOGEN PHOSPHORYLASE

Glucose-1-P

PHOSPHOGLUCOMUTASE

Glucose-6-P

GLUCOSE-6-PHOSPHATASE
(liver and kidney only)

Glycolysis

Pyruvate

PYRUVATE DEHYDROGENASE

Acetyl CoA

LACTATE DEHYDROGENASE

Lactate

CO₂
Regulation of glycogen metabolism

- Cyclic AMP activates a cAMP-dependent protein kinase which in turn activates both phosphorylase b kinase (to promote glycogenolysis) and glycogen synthetase kinase (to promote glycogenesis) thus keeping a state of balance in glycogen turnover.

- Adrenaline and glucagon activate glycogenolysis and inhibit glycogenesis, while insulin does the opposite.
Definition of GSD and their pathophysiology

• A group of inherited disorders caused by a defect in glycogen metabolism characterized by impaired conversion of glycogen to free glucose resulting in the accumulation of normal and abnormal glycogen in tissues.

• Disruption of glycogen metabolism also affects other biochemical pathways as the body seeks alternative fuel sources.

• Accumulation of abnormal metabolic by-products can damage other organs.
The system for glycogen metabolism relies on a complex system of enzymes. These enzymes are responsible for creating glycogen from glucose, transporting the glycogen to and from storage areas within cells, and extracting glucose as needed. Both creating and tearing down the glycogen macromolecule are multistep processes requiring a different enzyme at each step. If one of these enzymes is defective and fails to complete its step, the process halts.
Glycogen Storage Disorders

Type Ia (von Gierke's disease), type Ib, type Ic, type Id.
Type II (Pompe's disease).
Type III (Forbes-Cori disease).
Type IV (Andersen's disease).
Type V (McArdle's disease).
Type VI (Hers' disease).
Type VII (Tarui's disease).
Type IX (Liver phosphorylase kinase deficiency).
Type XI (Fanconi-Bickel syndrome).
Type 0 (Lewis' disease).

**Type I glycogen storage disorder is the most common.**
About one quarter of people who have glycogen storage disorder have type I. Type VIII and type X are now classified with type VI.
Causes

Glycogen-storage disease Ib is caused by deficiency of glucose-6-phosphate translocase, which is responsible for importing glucose-6-phosphate from the cytosol to the interior of the microsome, thus bringing substrate into contact with enzyme. To date, allelic variation in this disorder has not been explored.
Clinical Presentation

Initial symptoms of neonatal hypoglycemia occur shortly after birth in patients with glycogen-storage disease type I (GSD I). Symptoms include the following:

- Tremors
- Irritability
- Cyanosis
- Seizures
- Apnea
- Coma
### Table 21.1 Glycogen-storage diseases

<table>
<thead>
<tr>
<th>Type</th>
<th>Defective enzyme</th>
<th>Organ affected</th>
<th>Glycogen in the affected organ</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Glucose 6-phosphatase or transport system</td>
<td>Liver and kidney</td>
<td>Increased amount; normal structure.</td>
<td>Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia. Cardiorespiratory failure causes death, usually before age 2.</td>
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<tr>
<td>Von Gierke disease</td>
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<tr>
<td>II</td>
<td>α-1,4-Glucosidase (lysosomal)</td>
<td>All organs</td>
<td>Massive increase in amount; normal structure.</td>
<td></td>
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<tr>
<td>Pompe disease</td>
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<tr>
<td>III</td>
<td>Amylo-1,6-glucosidase (debranching enzyme)</td>
<td>Muscle and liver</td>
<td>Increased amount; short outer branches.</td>
<td>Like type I, but milder course.</td>
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<tr>
<td>Cori disease</td>
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<tr>
<td>IV</td>
<td>Branching enzyme (α-1,4 → α-1,6)</td>
<td>Liver and spleen</td>
<td>Normal amount; very long outer branches.</td>
<td>Progressive cirrhosis of the liver. Liver failure causes death, usually before age 2. Limited ability to perform strenuous exercise because of painful muscle cramps. Otherwise patient is normal and well developed. Like type I, but milder course.</td>
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<tr>
<td>Andersen disease</td>
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<tr>
<td>V</td>
<td>Phosphorylase</td>
<td>Muscle</td>
<td>Moderately increased amount; normal structure.</td>
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<tr>
<td>McArdle disease</td>
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</tr>
<tr>
<td>VI</td>
<td>Phosphorylase</td>
<td>Liver</td>
<td>Increased amount.</td>
<td>Like type I, but milder course.</td>
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<td>Hers disease</td>
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</tr>
<tr>
<td>VII</td>
<td>Phosphofructokinase</td>
<td>Muscle</td>
<td>Increased amount; normal structure.</td>
<td>Like type V.</td>
</tr>
<tr>
<td>VIII</td>
<td>Phosphorylase kinase</td>
<td>Liver</td>
<td>Increased amount; normal structure.</td>
<td>Mild liver enlargement. Mild hypoglycemia.</td>
</tr>
</tbody>
</table>

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