Inherited Metabolic Disorders of Carbohydrate Metabolism

Glycogen Storage Disease
Figure 1. The glycogen structure showing the glycosidic bonds

- liver stores glycogen that provides 75% of glucose needed (mostly by RBC and brain) during first 24 hours of food deprivation

- muscle stores glycogen for its own needs; lack of G-6-Pase prevents formation and secretion of glucose for use by other tissues

- highly branched structure to increase solubility; provides many more sites for removal of glucose units that are phosphorylated by glycogen phosphorylase
Glycogen Storage Diseases (Glycogenoses)

- Glycogen storage diseases are a group of inherited conditions characterized by tissue deposits of glycogen that are abnormal in amount or structure.

- Glycogen is found principally in liver and muscle, and is synthesized from glucose by different enzymes from those which mediate glycogenolysis.
Glycogen metabolism. The enzymes promoting glycogen synthesis are different from those involved in glycogenolysis.
### Table 26.17 Listing of the More Common Glycogen Storage Diseases, Tissues Affected, and Clinical Symptoms

<table>
<thead>
<tr>
<th>Glycogen Storage Disease and Enzyme Defect</th>
<th>Tissue(s) Affected</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I</strong></td>
<td></td>
<td></td>
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<tr>
<td>Glucose-6-phosphatase deficiency</td>
<td>Liver, kidney, small intestine</td>
<td>Hypoglycemia, hepatomegaly, lactic acidosis, hyperlipidemia, hyperuricemia, poor growth, and osteoporosis</td>
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<tr>
<td><strong>Type II</strong></td>
<td></td>
<td></td>
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<tr>
<td>Lysosomal acid alpha-glucosidase deficiency</td>
<td>Most tissues</td>
<td>Cardiomegaly in infants, hypotonia</td>
</tr>
<tr>
<td><strong>Type III</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycogen debranching enzyme</td>
<td>Liver and muscle</td>
<td>Hepatomegaly, variable hypoglycemia; similar to type I</td>
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<tr>
<td><strong>Type IV</strong></td>
<td></td>
<td></td>
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<tr>
<td>Branching enzyme</td>
<td>Liver, leukocytes, and fibroblasts</td>
<td>Progressive cirrhosis with hepatosplenomegaly, failure to thrive, and ascites</td>
</tr>
<tr>
<td><strong>Type V</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle phosphorylase deficiency</td>
<td>Muscle</td>
<td>Easy fatigability, painful cramps after strenuous exercise, myoglobinuria</td>
</tr>
<tr>
<td><strong>Type VI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver phosphorylase defect</td>
<td>Liver, leukocytes</td>
<td>Mild hepatomegaly, mild hypoglycemia and hyperlipidemia, growth retardation</td>
</tr>
<tr>
<td><strong>Type VII</strong></td>
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<td></td>
</tr>
<tr>
<td>Muscle phosphofructokinase deficiency</td>
<td>Muscle</td>
<td>Easy fatigability, painful cramps after strenuous exercise, myoglobinuria, degenerative brain disease</td>
</tr>
<tr>
<td><strong>Type IX</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defect in 1 of the 4 subunits of phosphorylase kinase</td>
<td>Liver and muscle</td>
<td>Mild hepatomegaly, mild hypoglycemia and hyperlipidemia, growth retardation</td>
</tr>
</tbody>
</table>
• Type I glycogenosis (von Gierke's disease) is caused by a deficiency in glucose-6-phosphatase, which results in impaired glucose release from glycogen and thus hypoglycaemia.
Features of Glycogen Storage Diseases

• Lactate metabolism is also impaired as it is converted to glucose via glucose-6-phosphate in the Cori cycle, metabolic acidosis is a clinical feature.
Substrates for Gluconeogenesis: Lactate, pyruvate, glycerol, propionny-CoA and certain Amino Acids but never FAT!!

• The Cori cycle involves the utilization of lactate, produced by glycolysis in non-hepatic tissues, (such as muscle and erythrocytes) as a carbon source for hepatic gluconeogenesis. In this way the liver can convert the anaerobic byproduct of glycolysis, lactate, back into more glucose for reuse by non-hepatic tissues. Note that the gluconeogenic leg of the cycle (on its own) is a net consumer of energy, costing the body 4 moles of ATP more than are produced during glycolysis. Therefore, the cycle cannot be sustained indefinitely.
Features of Glycogen Storage Diseases

• Hyperuricaemia is also seen, partly due to increased metabolism of glucose-6-phosphate via the pentose phosphate pathway, forming ribose-5-phosphate and purines (the catabolism of purines occurs through a common pathway leading to uric acid formation).
Features of Glycogen Storage Diseases

- In glycogen synthase deficiency, which is extremely rare, very little glucose is converted to glycogen, although conversion to lactate does occur, with hyperglycaemia and hyperlactataemia being features of this deficiency.
Figure 3. Pathway of glycogen synthesis (glycogenogenesis)
Glycogen Storage Diseases

• In general, Glycogen Storage Diseases (GSD)
  – Deficiencies of enzymes that regulate the synthesis or degradation of glycogen (8 types)
    – Most related to deficient activity in conversion of glycogen to glucose-6-phosphate (GSD I), which impairs gluconeogenesis and glycogenolysis
  – Results in abnormal glycogen deposition in liver and muscle or both
Glycogen Storage Diseases

- Glycogen Storage Disease Type 1 (GSD I)
  - Most commonly diagnosed
  - Deficiency of enzyme glucose-6-phosphatase resulting in hypoglycemia
  - Low blood glucose results in short periods of fasting (2-4 hours)
  - Elevations in lipids, lactate, uric acid (see the next figure)
  - Chronic lactic acidosis, poor growth
  - Osteoporotic bones, delayed bone age
FIGURE 28.9 Metabolic Pathway Affected in Glycogen Storage Disease Type I

- Glycogen
  - UDP-glucose
    - Glucose-1-phosphate
      - Glucose-6-phosphate
        - Nucleotides
          - Uric Acid
        - Glucose
          - Glucose-6-Phosphatase
            - Hepatocyte
        - Glucose-6-phosphate
          - Pyruvate
            - Lactate
          - Acetyl CoA
        - Triglyceride
          - Cholesterol

- Glucose
  - UDP-glucose
Glycogen Storage Diseases

• Nutrition Therapy for Glycogen Storage Diseases
  – Nutrition Intervention

• CHO: complex sources (cornstarch), about 60-70% of the total caloric intake

• Protein: lean sources, 10-15% of total kcal

• Fat: less than 30%, dietary saturated fats should be limited
GLYCOGEN STORAGE DISEASES

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type</th>
<th>Enzyme Deficiency</th>
<th>Organ Location</th>
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<tbody>
<tr>
<td>von Gierke disease</td>
<td>I</td>
<td>glucose-6-phosphatase</td>
<td>liver</td>
</tr>
<tr>
<td>McArdle disease</td>
<td>V</td>
<td>glycogen phosphorylase</td>
<td>muscle</td>
</tr>
</tbody>
</table>

Type I: Von Gierke Disease

Hypoglycemia due to defect of the final step of gluconeogenesis
Decreased mobilization of glycogen produces hepatomegaly.

Type V: McArdle Disease

Skeletal muscle affected, but liver enzyme is normal
No hypoglycemia - muscle glycogen does not produce glucose
Temporary weakness and cramping of muscle after exercise
No rise in blood lactate during strenuous exercise
Muscle contains a high level of glycogen
• **Glycogenosis type I – Girke’s disease.** Girke’s disease cause deficit of glucose-6-phosphatase. This enzyme provides 90 % of glucose which disengages in liver from glycogen. It play central role in normal glucose homeostasis. Glucose which disengages attached to disintegration of glycogen or is derivated in process of gluconeogenesis obligatory goes over stage of glucose-6-phosphate. Enzyme glucose-6-phosphatase tears away a phosphate group from glucose. There free glucose is formed it goes out in blood. Attached to Girke’s disease stage of tearing phosphate group is blocked. There are no free glucose hypoglycemia occur. Hypoglycemia arises. Attached to Girke’s disease glycogen is deponed in liver and kidneys.
• **Type II glycogenosis – Pompe’s disease.** Illness is related to deficit of lysosomal enzyme – sour maltase, or \( \alpha-1,4\)-glucosidase. This enzyme slits glycogene to glucose in digestive vacuoles. Attached to it’s deficit glycogen accumulates at first in lysosomes and then in cytosole of hepatocytes and myocytes.

• **Type III glycogenosis – Cori’s disease, Forbs’ disease.** This illness is named limitdecstrinosis. In it’s base lies a deficit of amylo-1,6-glucosidase. Degradation of glycogen pauses in sites of branching. Glycogen accumulates in liver and muscles. Cure is diet with big proteins maintenance.

• **Type IV glycogenosis – Anderson’s disease.** It is called by deficit of amilo-1,4,1,6-transglucosidase (branching enzyme). As result of this There is derivated anomalous glycogen with very long branches and rare points of branching. It is not exposed to degradation and accumulates in liver, heart, kidneys, spleen, lymphatic nods, skeletal muscles.
• **Type V glycogenosis – McArdel’s disease.** It’s cause is deficit of phosphorilase of myocytes. Typical pain displays in muscles after physical loading. Glycogene does not slit only in muscles. Here it accumulates. In liver mobilization of glycogen comes normal.

• **Type VI glycogenosis – Hers’ disease.** Illness arises as result of insufficiency of hepatic phosphorilase complex. Glycogen accumulates in liver. Typical sign is hepatomegalia.

• **Type VII glycogenosis.** Illness essence is in oppression of muscle phosphofrutokinase. Symptoms are similar to McArdles disease.
Glucose-6-phosphate dehydrogenase deficiency

This is an X-linked defect in the first, irreversible step of the pentose phosphate pathway.

![Chemical Reaction Diagram]

Glucose-6-phosphate dehydrogenase

Glucose-6-phosphate → 6-phosphogluconolactone

NADP ↔ NADPH + H

A decrease in NADPH production makes red blood cells membranes vulnerable to oxidative stress, leading to haemolysis.

The most common manifestations are early neonatal unconjugated jaundice and acute haemolytic anaemia. However most individuals with the deficiency are clinically asymptomatic.

The haemolytic crises are usually in response to an exogenous trigger such as certain drugs (e.g. antimalarials), food (broad beans) or an infection. Female heterozygotes may have symptoms but the severity varies due to non-random X chromosome inactivation.

The highest frequency is in those of Mediterranean, Asian or African origin.

The diagnosis is by measurement of the enzyme activity in erythrocytes either by a qualitative test similar to the Beutler test or by quantitation.

However the test is not reliable in detecting female heterozygotes and if required molecular testing is the preferred method.
- Beutler Test

Whole blood and a reaction mixture (UDP-glucose, galactose-1-phosphate, NADP) is spotted onto filter paper at:

- 0 minutes, after 60 minutes incubation & after 120 min incubation

Normal transferase activity results in the production of NADPH, which is fluorescent under UV light.

No fluorescence indicates galactose-1-phosphate uridyltransferase deficiency.

False negative results may occur if the patient has had a blood transfusion up to 6 weeks before the sample was taken. False positive results may occur if the patient has glucose-6-phosphate dehydrogenase deficiency as the endogenous activity of this enzyme is used to generate NADPH.