MEDICAL EDUCATION RESOURCE

# Major Metabolic Pathways of Glucose

## Major Metabolic Pathways of Glucose

### Digestion of Carbohydrates

• Dietary carbohydrates include starch, glycogen, sucrose, and lactose.
• Digestion starts in the **mouth** by salivary ?-amylase but stops in the stomach due to acidity.
• **Pancreatic ?-amylase** in the small intestine breaks ?-1,4 linkages ? maltose, isomaltose, dextrins.
• **Brush border enzymes**—sucrase, maltase, isomaltase, lactase—convert disaccharides to monosaccharides.

**Clinical point: Lactose intolerance**

• Caused by lactase deficiency.
• Leads to lactose accumulation ? irritation, flatulence, diarrhea.
• May be congenital or acquired.

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### Absorption of Carbohydrates

• Only **monosaccharides** are absorbed.
• Absorption rate: **galactose > glucose > fructose**.

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## Glucose Transporters (GLUT & SGLUT Systems)

### 1. SGLUT-1 (Sodium-Dependent Glucose Transporter-1)

• Located on the intestinal mucosal side.
• Transports **glucose + sodium** (secondary active transport).
• Sodium pump indirectly provides energy.
• Defect causes **glucose-galactose malabsorption**.

### 2. SGLUT-2

• Present in kidney proximal tubule.
• Defect results in **congenital renal glycosuria**.

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### 3. GLUT-2

• Found in intestine (blood side), liver, pancreatic ?-cells, kidney.
• Facilitated diffusion (uniport).
• High Km ? acts as **glucose sensor** and helps regulate insulin release.

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### 4. GLUT-4

• Located in skeletal muscle and adipose tissue.
• **Insulin-dependent** transporter.
• Reduced membrane GLUT-4 in Type 2 DM ? insulin resistance.

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### 5. GLUT-1

• Present in RBCs, brain, kidney, colon, retina, placenta.
• Maintains basal glucose uptake.

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### 6. GLUT-3

• Located in neurons.
• High affinity ? ensures continuous glucose supply to brain.

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### 7. GLUT-5

• Found in small intestine, testis, and sperm.
• **Fructose transporter**.

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### 8. GLUT-7

• Located on the liver ER membrane.
• Moves glucose from ER lumen ? cytoplasm.

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### Absorption Summary

• Glucose & galactose: **SGLUT-1** (active).
• Fructose: **GLUT-5** (facilitated).
• Exit into blood: **GLUT-2**.

## Regulation of Blood Sugar

According to a document from your file *vasu biochem.pdf*, blood glucose is maintained within narrow limits because the brain, RBCs, and renal medulla require a continuous glucose supply.

## Post-Prandial Regulation (High Insulin)

When a meal is taken:
• Glucose is absorbed into blood ? blood glucose rises.
• **Insulin secretion increases** from pancreatic ?-cells.
• Insulin promotes:
– Glucose uptake in extrahepatic tissues (via GLUT-4)
– Glycogen synthesis
– Lipogenesis

High glucose ? high insulin ? lowering of blood sugar by:
• Tissue utilization
• Glycogen formation
• Fat synthesis
(Shown in Fig. 24.2B).

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## Fasting State Regulation (High Glucagon)

About 2–2.5 hours after a meal, glucose falls toward fasting levels.

Maintained by:
• **Hepatic glycogenolysis** for ~3 hours
• Later by **gluconeogenesis**

In fasting:
• Glucagon is high.
• Adipose tissue releases free fatty acids as alternate fuel (Fig. 24.2A).

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## Factors Increasing Blood Glucose

(Box 24.1)
• Intestinal absorption
• Glycogenolysis

• Gluconeogenesis
• Hyperglycemic hormones: glucagon, steroids, epinephrine, GH, ACTH, thyroxine.

### Factors Decreasing Blood Glucose

• Glucose utilization in tissues
• Glycogen synthesis
• Lipogenesis
• Insulin (hypoglycemic hormone).

## Embden–Meyerhof Pathway (Glycolysis)

### Definition

Glycolysis is the sequence of reactions where **one molecule of glucose** is converted into **two molecules of pyruvate (aerobic)** or **two molecules of lactate (anaerobic)** with the production of ATP and NADH.

## Location

Occurs entirely in the **cytoplasm** of all cells.

## Physiological Importance

• Only pathway that occurs in **all human tissues**.
• Primary and only ATP source for **RBCs**.
• Major ATP source during **strenuous exercise**.
• Provides intermediates for **amino acid and glycerol** synthesis.
• Several reversible steps are shared with **gluconeogenesis**.

## Steps of Glycolysis

## Phase 1 – Energy Investment Phase (Uses 2 ATP)

**Step 1: Glucose ? Glucose-6-phosphate**

Enzyme: **Hexokinase / Glucokinase**
Irreversible; traps glucose inside the cell.

**Step 2: Glucose-6-phosphate ? Fructose-6-phosphate**

Enzyme: **Phosphohexose isomerase**

**Step 3: Fructose-6-phosphate ? Fructose-1,6-bisphosphate**

Enzyme: **PFK-1 (Rate-limiting step)**
Irreversible.

**Step 4: Fructose-1,6-bisphosphate ? DHAP + Glyceraldehyde-3-phosphate**

Enzyme: **Aldolase**

**Step 5: DHAP ? Glyceraldehyde-3-phosphate**

Enzyme: **Triose phosphate isomerase**

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## Phase 2 – Energy Generation Phase (Produces 4 ATP + 2 NADH)

**Step 6: Glyceraldehyde-3-phosphate ? 1,3-Bisphosphoglycerate**

Enzyme: **G3P dehydrogenase**
Generates **NADH**.

**Step 7: 1,3-BPG ? 3-Phosphoglycerate**

Enzyme: **Phosphoglycerate kinase**
Produces **ATP** (substrate-level phosphorylation).

**Step 8: 3-Phosphoglycerate ? 2-Phosphoglycerate**

Enzyme: **Phosphoglycerate mutase**

**Step 9: 2-Phosphoglycerate ? Phosphoenolpyruvate (PEP)**

Enzyme: **Enolase**

**Step 10: PEP ? Pyruvate**

Enzyme: **Pyruvate kinase**
Produces **ATP**.
Irreversible.

## Irreversible Steps (Regulatory Steps)

1. Hexokinase / Glucokinase
2. Phosphofructokinase-1 (PFK-1)
3. Pyruvate kinase

## Energy Yield

### Aerobic Glycolysis

• Net gain: **2 ATP** and **2 NADH**
• Total ATP yield (after ETC reoxidation): **7 ATP per glucose**

### Anaerobic Glycolysis

• Pyruvate ? Lactate
• Net gain: **2 ATP**
• NADH is reoxidized to NAD? by lactate dehydrogenase.

## Regulation of Glycolysis

### 1. Hexokinase / Glucokinase

• Hexokinase: inhibited by **glucose-6-phosphate**
• Glucokinase: active when blood glucose is high; induced by **insulin**

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### 2. Phosphofructokinase-1 (PFK-1)

**Most important control point**

• Activated by: **AMP, Fructose-2,6-bisphosphate**
• Inhibited by: **ATP, citrate**

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### 3. Pyruvate Kinase

• Activated when energy demand is high
• Inhibited when ATP is abundant
• Also regulated by **phosphorylation/dephosphorylation** depending on hormonal status

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## Fructose-2,6-Bisphosphate Regulation

• Formed by **PFK-2**
• Most powerful activator of **PFK-1**
• High glucose ? ?F-2,6-BP ? ?glycolysis
• Low glucose ? ?F-2,6-BP ? ?glycolysis

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## Hormonal Influence

• **Insulin** stimulates glycolysis (increases key enzyme activities).
• **Glucagon** inhibits glycolysis (via cAMP ? enzyme phosphorylation).
• Counterregulatory hormones (epinephrine, cortisol) also reduce glycolytic flux when needed.

## Cori’s Cycle

Cori’s Cycle explains how **lactate produced in muscles and RBCs** is recycled by the liver to maintain blood glucose.

### Process

• During anaerobic glycolysis (exercise, hypoxia), **pyruvate ? lactate**.
• Lactate enters blood and is carried to the **liver**.
• Liver converts lactate ? **pyruvate ? glucose** via gluconeogenesis.
• Newly formed glucose is released back into blood and reused by muscle.

### Purpose

• Prevents lactic acidosis.
• Supplies glucose during prolonged exercise.
• Allows continued glycolysis in tissues lacking mitochondria (RBCs).

### Clinical Relevance

• Excessive lactate production ? lactic acidosis (shock, sepsis, hypoxia).
• Essential for RBC metabolism since they rely only on glycolysis.

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## Rapaport–Leubering Cycle (BPG Shunt)

This pathway operates **exclusively in RBCs** to regulate oxygen delivery.

### Key Steps

• 1,3-Bisphosphoglycerate is diverted from glycolysis ? forms **2,3-BPG**.
• 2,3-BPG binds to **deoxygenated hemoglobin**, decreasing its affinity for oxygen.

### Functions of 2,3-BPG

• Enhances **oxygen unloading** to tissues.
• Shifts oxygen–hemoglobin dissociation curve **to the right**.

### When 2,3-BPG Increases

• High altitude
• Chronic hypoxia
• Anemia

**When 2,3-BPG Decreases**

• Stored blood ? reduced O? delivery capacity
• Fetal hemoglobin (HbF) binds 2,3-BPG poorly ? higher O? affinity

## Fate of Pyruvate

Pyruvate is the central metabolic junction connecting glycolysis with multiple pathways.

### 1. Aerobic Conditions (Mitochondria)

**Pyruvate ? Acetyl-CoA**
Enzyme: **Pyruvate dehydrogenase complex (PDH)**
Requires thiamine, lipoic acid, CoA, FAD, NAD?.

**Uses of Acetyl-CoA**

• Enters **TCA cycle**
• Fatty acid synthesis
• Ketone body synthesis (liver)

**PDH Deficiency**

• Lactic acidosis
• Neurological defects
• Treated with thiamine supplementation

### 2. Anaerobic Conditions (Cytoplasm)

**Pyruvate ? Lactate**
Enzyme: **Lactate dehydrogenase**

Purpose: regenerate **NAD?** for glycolysis.

**Where it occurs**

• RBCs
• Exercising muscle
• Hypoxic tissues

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### 3. Pyruvate ? Oxaloacetate

Enzyme: **Pyruvate carboxylase**
Requires **biotin**.

**Functions**

• First step of **gluconeogenesis**
• Replenishes TCA intermediates (anaplerosis)

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### 4. Pyruvate ? Alanine

Enzyme: **Alanine transaminase (ALT)**

**Purpose**

• Part of **glucose–alanine cycle** between muscle and liver
• Transports amino nitrogen to the liver for urea synthesis

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### 5. Pyruvate ? Ethanol

Occurs in **yeast and bacteria**
Enzyme: pyruvate decarboxylase ? alcohol dehydrogenase
(Not in humans)

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## Important Points to Remember

• Cori’s cycle conserves glucose during anaerobic conditions.
• 2,3-BPG regulates oxygen delivery by modifying hemoglobin affinity.
• Pyruvate connects glycolysis with TCA, gluconeogenesis, amino acid metabolism, and lactate formation.
• PDH is inhibited by ATP, NADH, and acetyl-CoA; activated by ADP and pyruvate.
• Lactate production allows glycolysis to continue without oxygen.
• Oxaloacetate formation is essential during fasting for gluconeogenesis.

## Gluconeogenesis

### Definition

Gluconeogenesis is the process of synthesizing **glucose from non-carbohydrate precursors** such as lactate, glucogenic amino acids, glycerol, and propionyl-CoA.

### Site

• Mainly in the **liver**
• Partly in the **renal cortex**
• Reactions occur in **both mitochondria and cytosol**

### Key Enzymes (Bypass Enzymes)

These replace the irreversible steps of glycolysis:

1. **Pyruvate carboxylase**
2. **PEP carboxykinase (PEPCK)**

3. **Fructose-1,6-bisphosphatase**

4. **Glucose-6-phosphatase**

## Steps of Gluconeogenesis

### 1. Pyruvate ? Oxaloacetate

Enzyme: **Pyruvate carboxylase**
• Occurs in mitochondria
• Requires **ATP** and **biotin**
• Activated by **acetyl-CoA**

Oxaloacetate must move to cytosol via:
• **Malate shuttle**, or
• **Aspartate shuttle**

### 2. Oxaloacetate ? Phosphoenolpyruvate (PEP)

Enzyme: **PEP carboxykinase (PEPCK)**
• Uses **GTP**
• Removes CO?
• First major bypass of glycolysis

### 3. Reversible Glycolytic Steps

PEP ? Fructose-1,6-bisphosphate using steps 8, 7, 6, 5, and 4 of glycolysis (all reversible).

### 4. Fructose-1,6-bisphosphate ? Fructose-6-phosphate

Enzyme: **Fructose-1,6-bisphosphatase**

• Major regulatory step of gluconeogenesis

• Inhibited by AMP and fructose-2,6-bisphosphate

• Activated during fasting

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### 5. Fructose-6-phosphate ? Glucose-6-phosphate

Enzyme: **Phosphohexose isomerase**

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### 6. Glucose-6-phosphate ? Glucose

Enzyme: **Glucose-6-phosphatase**

• Present in liver, kidney, and intestine

• **Absent in muscle**, so muscle cannot release free glucose

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## Substrates for Gluconeogenesis

### 1. Lactate

• From muscle and RBCs

• Converted to pyruvate ? enters pathway

• Part of **Cori’s cycle**

### 2. Glucogenic Amino Acids

• Alanine, glutamate, aspartate, etc.

• Alanine is the **major** substrate (glucose–alanine cycle)

• Increased proteolysis in starvation or uncontrolled diabetes

### 3. Glycerol

• From triglyceride breakdown
• Converted to DHAP in the liver

**4. Propionyl-CoA**

• From **odd-chain fatty acids**
• Converted to succinyl-CoA
• Minor source

**Important:** Even-chain fatty acids **cannot** form glucose.

## Energy Requirement

To form **one glucose molecule**, gluconeogenesis uses:

• **6 ATP equivalents**
– 2 ATP (pyruvate ? oxaloacetate)
– 2 GTP (oxaloacetate ? PEP)
– 2 ATP (3-phosphoglycerate ? 1,3-BPG)

## Regulation of Gluconeogenesis

Gluconeogenesis and glycolysis are **reciprocally regulated**.

### Stimulators

• Glucagon
• Cortisol
• Epinephrine
• Acetyl-CoA

### Inhibitors

• Insulin
• High AMP

• High fructose-2,6-bisphosphate

**Key Regulation Points**

**1. Pyruvate Carboxylase**

• Activated by **acetyl-CoA**

**2. PEPCK**

• Induced by fasting hormones (glucagon, cortisol)

• Inhibited by insulin

**3. Fructose-1,6-bisphosphatase**

• Inhibited by AMP

• Inhibited by fructose-2,6-bisphosphate

**4. Glucose-6-phosphatase**

• Active only in tissues capable of releasing glucose

## Significance

• Maintains blood glucose during fasting, starvation, and exercise

• Essential for tissues requiring glucose (brain, RBCs, kidney medulla)

• Prevents hypoglycemia when glycogen stores are depleted

• Complements Cori's cycle and glucose–alanine cycle

## Rapid Revision Points

• Occurs in liver and partly kidney

• Not a simple reversal of glycolysis

• Four bypass enzymes overcome irreversible steps

• Alanine and lactate are major substrates

• Requires 6 ATP per glucose

• Insulin inhibits; glucagon stimulates

• Muscle lacks glucose-6-phosphatase ? cannot contribute to blood glucose

Notes downloaded from **Medmentoredu** 

# Glucose–Alanine Cycle

## Concept

The glucose–alanine cycle transfers **amino nitrogen** from muscle to liver and returns **glucose** back to muscle.
It connects **protein catabolism in muscle** with **gluconeogenesis in liver**.

## Where it occurs

• **Muscle** ? production of alanine
• **Liver** ? conversion of alanine to glucose
• Cycle repeats during fasting, exercise, and muscle protein breakdown

## Steps of the Cycle

### 1. In Muscle

• During exercise or fasting, muscle proteolysis releases amino acids.
• Pyruvate (from glycolysis) accepts amino group from glutamate via **ALT (alanine transaminase)**.
• This produces **alanine**.
• Alanine is released into bloodstream.

### 2. Transport to Liver

• Alanine circulates from muscle to liver.
• This safely transports **ammonia** in a nontoxic form.

### 3. In Liver

• Alanine ? Pyruvate via ALT
• Amino group enters **urea cycle** ? converted to **urea** for excretion
• Pyruvate enters **gluconeogenesis** ? forms **glucose**

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### 4. Glucose Returns to Muscle

• Produced glucose is sent back to muscle ? enters glycolysis ? forms pyruvate again
• Cycle continues

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## Purpose of Glucose–Alanine Cycle

• Removes **ammonia** safely from muscle
• Provides **glucose** to muscle during exercise and fasting
• Supports **gluconeogenesis** in liver
• Helps maintain **blood glucose** when glycogen stores are depleted
• Prevents buildup of pyruvate and lactate in muscle

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## Comparison with Cori's Cycle

| FEATURE | GLUCOSE–ALANINE CYCLE | CORI'S CYCLE |
|---|---|---|
| Transported substance | **Alanine** | **Lactate** |
| What is removed from muscle? | **Ammonia (NH?)** | **Lactic acid** |
| Liver uses for gluconeogenesis? | Pyruvate from alanine | Pyruvate from lactate |

| FEATURE | GLUCOSE–ALANINE CYCLE | CORI'S CYCLE |
|---|---|---|
| Additional effect | Detoxifies ammonia | Prevents lactic acidosis |

## Clinical Relevance

• Elevated ALT indicates muscle or liver injury (cycle enzyme).
• Increased in **fasting**, **trauma**, **burns**, **sepsis**, due to increased muscle proteolysis.
• Important in maintaining glucose in prolonged starvation or uncontrolled diabetes.

## Rapid Revision Points

• Transfers nitrogen from muscle ? liver.
• Alanine carries both **nitrogen** and **carbon skeleton**.
• Liver converts alanine ? glucose; glucose returns to muscle.
• ALT is key enzyme in both tissues.
• Helps prevent hyperammonemia and provides fuel during fasting.

## Glycogenolysis (Breakdown of Glycogen)

Glycogenolysis is the breakdown of glycogen into glucose units.
All enzymes involved are **cytoplasmic**.

### 1. Glycogen Phosphorylase

• Removes glucose units as **glucose-1-phosphate** (phosphorolysis).
• Acts only on **?-1,4 linkages**.
• Stops 3–4 residues before a branch point.

• Requires **pyridoxal phosphate (PLP)** as cofactor.

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## 2. Debranching Enzyme System

Two enzymatic activities:

**i. Transferase Activity**

• Transfers block of **3 glucose residues** to another chain.

**ii. ?-1,6-Glucosidase Activity**

• Cleaves the remaining **?-1,6-linked glucose**, releasing **free glucose**.

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## 3. Phosphoglucomutase

• Converts **glucose-1-phosphate ? glucose-6-phosphate**.

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## 4. Fate of Glucose-6-Phosphate

**Liver**

• Contains **glucose-6-phosphatase** ? releases free glucose into blood.

**Muscle**

• **Lacks glucose-6-phosphatase** ? retains G6P for glycolysis and ATP production.

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## Energetics

• From glycogen-derived glucose: **3 ATP** (no ATP required for Step 1 of glycolysis).
• From free glucose: **2 ATP**.

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### Regulation

**Muscle**

• Activated by **AMP** and **Ca²?–calmodulin**, and by **epinephrine**.
• Glucagon has **no effect**.

**Liver**

• Controlled mainly by **glucagon** and **epinephrine** (via cAMP cascade).

## Glycogen Synthesis (Glycogenesis)

Glycogenesis is **not** the reverse of glycogenolysis; it has distinct enzymes.

### 1. Glycogen Primer & Glycogenin

• Core protein = **glycogenin**, attaches first glucose and forms an oligosaccharide of 7 glucose units per monomer.

### 2. UDP-Glucose Formation

• Glucose-1-P + UTP ? **UDP-glucose**
(Activation step)

### 3. Glycogen Synthase

• Adds glucose from UDP-glucose to **non-reducing ends** of glycogen via **?-1,4 linkages**.

### 4. Branching Enzyme

• Amylo-[1,4]?[1,6]-transglucosidase creates **?-1,6 branches**.
• Transfers block of **6–8 glucose residues** to form a branch.

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### Regulation of Glycogenesis

• Glycogen synthase is **active when dephosphorylated**.
• Glucose-6-P activates dephosphorylated glycogen synthase.
• Hormonal regulation via **cAMP**, affecting both synthase & phosphorylase reciprocally.

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## Glycogen Storage Diseases (GSDs)

(Based on the clinical sections of the glycogen metabolism chapter)

GSDs are inherited disorders caused by enzyme defects in glycogen metabolism.
Below is the **high-yield clinically relevant list** following standard classification.

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### Type I – Von Gierke Disease

• Enzyme: **Glucose-6-phosphatase deficiency**
• Affected tissue: Liver, kidney
• Features:
– Severe fasting hypoglycemia
– Lactic acidosis
– Hyperuricemia
– Hepatomegaly
• Reason: Impaired release of glucose from liver.

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## Type II – Pompe Disease

• Enzyme: **Lysosomal ?-1,4-glucosidase (acid maltase)**
• Generalized, including cardiac muscle
• Features:
– Cardiomegaly
– Heart failure in infancy
– Muscle hypotonia

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## Type III – Cori Disease

• Enzyme: **Debranching enzyme deficiency**
• Accumulation of **limit dextrins**
• Features:
– Mild hypoglycemia
– Hepatomegaly
– Muscle weakness

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## Type IV – Andersen Disease

• Enzyme: **Branching enzyme deficiency**
• Very long, unbranched glycogen ? **liver fibrosis**
• Features:
– Cirrhosis
– Failure to thrive
– Death in childhood

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## Type V – McArdle Disease

• Enzyme: **Muscle glycogen phosphorylase deficiency**
• Features:

– Exercise intolerance
– Muscle cramps
– “Second wind” phenomenon
– Myoglobinuria

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### Type VI – Hers Disease

• Enzyme: **Liver phosphorylase deficiency**
• Features:
– Mild fasting hypoglycemia
– Hepatomegaly

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## Important Points to Remember

• Liver glycogen maintains blood glucose; muscle glycogen fuels contraction.
• Glycogen phosphorylase removes G1P; debranching enzyme removes branch residues.
• Muscle cannot release glucose due to absence of glucose-6-phosphatase.
• Glycogen synthase builds ?-1,4 chains; branching enzyme makes ?-1,6 linkages.
• Glycogen metabolism is reciprocally regulated by cAMP.
• GSDs involve specific enzyme defects ? characteristic presentations.

## Important Points to Remember

• Liver glycogen maintains **blood glucose** during fasting; muscle glycogen supplies **local energy** only.
• Glycogen synthase forms **?-1,4 linkages**; branching enzyme forms **?-1,6 linkages**.
• Glycogen phosphorylase removes glucose as **glucose-1-phosphate** (not free glucose).
• Debranching enzyme has **two activities**: transferase + ?-1,6-glucosidase.
• Muscle lacks **glucose-6-phosphatase**, so it cannot release free glucose into blood.
• Glycogen metabolism is regulated by **phosphorylation**:
– Glycogen phosphorylase ? active when phosphorylated
– Glycogen synthase ? active when dephosphorylated

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• cAMP stimulates glycogen breakdown via **phosphorylase activation**.
• PLP (vitamin B6) is a cofactor for **glycogen phosphorylase**.
• Glycogenesis and glycogenolysis are **reciprocally regulated**.
• In glycogenolysis, glycolysis yields **3 ATP** per glucose (because hexokinase step is bypassed).
• Most GSDs are **autosomal recessive** disorders.
• Pompe disease is the only GSD involving a **lysosomal enzyme**.
• McArdle disease presents with **exercise intolerance** and **second-wind phenomenon**.
• Von Gierke disease causes **severe hypoglycemia**, lactic acidosis, hyperuricemia, hepatomegaly.

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## FAQs

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**1. Why does muscle glycogen not contribute to blood glucose?**

Because muscle lacks **glucose-6-phosphatase**, so G6P cannot be converted into free glucose.

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**2. What is the main purpose of liver glycogen?**

To maintain **blood glucose** between meals and during early fasting.

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**3. Why is branching important in glycogen?**

Branching increases **solubility**, **storage efficiency**, and allows **faster synthesis and breakdown**.

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**4. Which enzyme requires vitamin B6 (PLP)?**

**Glycogen phosphorylase**.

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**5. What happens to the glucose released from ?-1,6 linkages?**

Debranching enzyme releases it as **free glucose**, not G1P.

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**6. Why is glycogenesis not simply the reverse of glycogenolysis?**

Different enzymes catalyze the forward and reverse pathways; several steps are **irreversible**.

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**7. What stimulates glycogen breakdown during exercise?**

• **AMP** (low energy)
• **Ca²?–calmodulin** (muscle contraction)
• **Epinephrine**

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**8. How does glucagon affect glycogen metabolism?**

In liver:
• Increases **cAMP** ? activates phosphorylase ? promotes glycogenolysis
• Inhibits glycogenesis
It has **no effect on muscle** (muscle lacks glucagon receptors).

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**9. Why is glycogen used instead of fat for quick energy?**

Glycogen can be rapidly converted to glucose **anaerobically**, while fat oxidation requires oxygen and is slower.

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**10. Which GSD causes cardiomyopathy in infants?**

**Pompe disease (Type II)** — deficiency of lysosomal acid maltase.

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**11. Which GSD shows the "second wind phenomenon"?**

**McArdle disease (Type V)** — muscle phosphorylase deficiency.

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**12. Why does von Gierke disease cause lactic acidosis?**

Blocked glucose-6-phosphatase causes glucose-6-phosphate to be shunted into **glycolysis ? lactate**.

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**13. Which GSD involves a defect in branching?**

**Andersen disease (Type IV)** — branching enzyme deficiency.

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**14. Which enzyme is essential for initiating glycogen synthesis?**

**Glycogenin**, which serves as the primer.

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**15. Why is hypoglycemia mild in Hers disease?**

Because **gluconeogenesis is intact** even though liver phosphorylase is deficient.

## MCQs

**1. The first product released during glycogenolysis is:**

A. Glucose
B. Glucose-1-phosphate
C. Glucose-6-phosphate
D. Free glucose only from branches

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**2. Glycogen phosphorylase requires which cofactor?**

A. Biotin
B. Thiamine
C. Pyridoxal phosphate (PLP)
D. FAD

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**3. Debranching enzyme releases the branch-point glucose as:**

A. Glucose-1-phosphate
B. UDP-glucose
C. Free glucose
D. Fructose-6-phosphate

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**4. Muscle cannot release glucose into the blood because it lacks:**

A. Phosphoglucomutase
B. Glucose-6-phosphatase
C. Glycogen synthase
D. Debranching enzyme

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**5. The rate-limiting enzyme of glycogen synthesis is:**

A. Glycogen phosphorylase
B. Branching enzyme
C. Glycogen synthase
D. Glucokinase

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**6. Branching enzyme forms which type of linkage?**

A. ?-1,4
B. ?-1,6
C. ?-1,4
D. ?-1,6

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**7. cAMP activates glycogenolysis by:**

A. Dephosphorylating phosphorylase kinase
B. Phosphorylating glycogen phosphorylase
C. Inhibiting glycogen synthase only
D. Activating branching enzyme

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**8. PLP-deficiency will primarily affect activity of:**

A. Glycogen synthase
B. UDP-glucose pyrophosphorylase
C. Glycogen phosphorylase
D. Glucose-6-phosphatase

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**9. Which hormone stimulates glycogen breakdown in muscle?**

A. Glucagon
B. Epinephrine
C. Cortisol
D. Thyroxine

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**10. “Limit dextrins” accumulate in which GSD?**

A. Pompe
B. Cori
C. Andersen
D. McArdle

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**11. Massive hepatomegaly + severe fasting hypoglycemia suggests:**

A. McArdle disease
B. Pompe disease
C. Von Gierke disease
D. Andersen disease

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**12. Cardiomegaly and early death in infancy occur in:**

A. Hers disease
B. Pompe disease
C. Cori disease
D. McArdle disease

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**13. Exercise intolerance with “second wind phenomenon” is typical of:**

A. Type I
B. Type III
C. Type V
D. Type IV

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**14. Branching enzyme deficiency is seen in:**

A. Andersen disease
B. Cori disease
C. Von Gierke disease
D. McArdle disease

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**15. Liver phosphorylase deficiency causes:**

A. Von Gierke disease
B. Hers disease
C. McArdle disease
D. Pompe disease

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**16. Glycogen synthase is active when:**

A. Phosphorylated
B. Ubiquitinated
C. Dephosphorylated
D. Bound to AMP

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**17. Which enzyme initiates glycogen synthesis (primer formation)?**

A. Glycogenin
B. Glycogen synthase
C. Branching enzyme
D. UDP-glucose pyrophosphorylase

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**18. Glucose yield from glycogen breakdown during glycolysis is:**

A. 0 ATP
B. 1 ATP
C. 2 ATP
D. 3 ATP

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**19. Which GSD is due to acid maltase deficiency?**

A. Type I
B. Type II
C. Type III
D. Type VI

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**20. Glycogen breakdown in muscle during contraction is directly stimulated by:**

A. Ca²?–calmodulin
B. Glucagon
C. Epinephrine only
D. Insulin

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## Answer Key

1-B
2-C
3-C
4-B
5-C
6-B
7-B
8-C
9-B
10-B
11-C
12-B
13-C
14-A
15-B
16-C
17-A
18-D
19-B

## Viva Voce

**1. What is the primary function of liver glycogen?**

To maintain **blood glucose** during fasting.

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**2. What is the function of muscle glycogen?**

To provide **rapid local ATP** for muscle contraction.

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**3. What is the first product of glycogen breakdown?**

**Glucose-1-phosphate**.

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**4. Which cofactor is required for glycogen phosphorylase?**

**Pyridoxal phosphate (PLP)**.

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**5. Why doesn’t muscle contribute glucose to blood?**

Because muscle **lacks glucose-6-phosphatase**.

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**6. What enzyme removes branch-point glucose?**

**?-1,6-glucosidase** activity of the debranching enzyme.

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**7. What type of linkage does branching enzyme form?**

**?-1,6 linkage**.

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**8. Which enzyme is the regulatory enzyme of glycogenesis?**

Notes downloaded from **Medmentoredu** | Page 32

**Glycogen synthase**.

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**9. Which enzyme initiates glycogen synthesis?**

**Glycogenin**.

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**10. When is glycogen phosphorylase active?**

When **phosphorylated**.

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**11. When is glycogen synthase active?**

When **dephosphorylated**.

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**12. What is the effect of cAMP on glycogen metabolism?**

Stimulates **glycogenolysis**; inhibits glycogenesis.

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**13. Which hormone activates glycogen breakdown in muscle?**

**Epinephrine**.

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**14. Which hormone activates glycogen breakdown in liver?**

**Glucagon** (and epinephrine).

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**15. What is the ATP yield when glycogen-derived glucose undergoes glycolysis?**

**3 ATP** per glucose.

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**16. What accumulates in Cori disease (Type III)?**

**Limit dextrins**.

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**17. What is the enzyme defect in Von Gierke disease?**

**Glucose-6-phosphatase deficiency**.

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**18. Why is severe hypoglycemia seen in Von Gierke disease?**

Because glucose cannot be released from G6P.

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**19. Which glycogen storage disease affects the heart predominantly?**

**Pompe disease (Type II)**.

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**20. What is the hallmark feature of McArdle disease (Type V)?**

**Exercise intolerance with second-wind phenomenon**.

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**21. Which GSD involves a defect in branching enzyme?**

**Andersen disease (Type IV)**.

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**22. What is the characteristic of Hers disease (Type VI)?**

**Liver phosphorylase deficiency** causing mild hypoglycemia.

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**23. Why is glycogen branched?**

To increase **solubility** and allow **rapid synthesis & degradation**.

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**24. What activates muscle glycogenolysis during contraction?**

**Ca²?–calmodulin complex**.

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**25. What is the difference between ?-1,4 and ?-1,6 linkages?**

?-1,4 = linear chain
?-1,6 = branch point