

Major Metabolic Pathways of Glucose

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Digestion of Carbohydrates

- Dietary carbohydrates include starch, glycogen, sucrose, and lactose.
- Digestion starts in the **mouth** by salivary α -amylase but stops in the stomach due to acidity.
- **Pancreatic α -amylase** in the small intestine breaks α -1,4 linkages $\rightarrow$ 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 $\rightarrow$ 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 β -cells, kidney.
 - Facilitated diffusion (uniport).
 - High K_m β 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 β 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 β -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).

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
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- Gluconeogenesis
 - Hyperglycemic hormones: glucagon, steroids, epinephrine, GH, ACTH, thyroxine.
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Factors Decreasing Blood Glucose

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

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**
-

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.

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 O₂ delivery capacity
- Fetal hemoglobin (HbF) binds 2,3-BPG poorly ? higher O₂ 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
-

3. Pyruvate ? Oxaloacetate

Enzyme: **Pyruvate carboxylase**

Requires **biotin**.

Functions

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

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
-

5. Pyruvate ? Ethanol

Occurs in **yeast and bacteria**

Enzyme: pyruvate decarboxylase ? alcohol dehydrogenase

(Not in humans)

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 CO₂
 - 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
-

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

Enzyme: **Phosphohexose isomerase**

6. Glucose-6-phosphate ? Glucose

Enzyme: **Glucose-6-phosphatase**

- Present in liver, kidney, and intestine
 - **Absent in muscle**, so muscle cannot release free glucose
-

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

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**

4. Glucose Returns to Muscle

- Produced glucose is sent back to muscle → enters glycolysis → forms pyruvate again
- Cycle continues

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

Comparison with Cori's Cycle

FEATURE	GLUCOSE–ALANINE CYCLE	CORI'S CYCLE
Transported substance	Alanine	Lactate
What is removed from muscle?	Ammonia (NH₃)	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.
-

2. Debranching Enzyme System

Two enzymatic activities:

i. Transferase Activity

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

ii. α -1,6-Glucosidase Activity

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

3. Phosphoglucomutase

- Converts **glucose-1-phosphate** $\leftrightarrow$ **glucose-6-phosphate**.
-

4. Fate of Glucose-6-Phosphate

Liver

- Contains **glucose-6-phosphatase** $\rightarrow$ releases free glucose into blood.

Muscle

- **Lacks glucose-6-phosphatase** $\rightarrow$ retains G6P for glycolysis and ATP production.
-

Energetics

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

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 **α-1,4 linkages**.
-

4. Branching Enzyme

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

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.

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.
-

Type II – Pompe Disease

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

Type III – Cori Disease

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

Type IV – Andersen Disease

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

Type V – McArdle Disease

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

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

Type VI – Hers Disease

- Enzyme: **Liver phosphorylase deficiency**
 - Features:
 - Mild fasting hypoglycemia
 - Hepatomegaly
-

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 α -1,4 chains; branching enzyme makes α -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 **α -1,4 linkages**; branching enzyme forms **α -1,6 linkages**.
- Glycogen phosphorylase removes glucose as **glucose-1-phosphate** (not free glucose).
- Debranching enzyme has **two activities**: transferase + α -1,6-glucosidase.
- Muscle lacks **glucose-6-phosphatase**, so it cannot release free glucose into blood.
- Glycogen metabolism is regulated by **phosphorylation**:
 - Glycogen phosphorylase $\uparrow$ active when phosphorylated
 - Glycogen synthase $\uparrow$ active when dephosphorylated

- 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.

FAQs

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

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

2. What is the main purpose of liver glycogen?

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

3. Why is branching important in glycogen?

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

4. Which enzyme requires vitamin B6 (PLP)?

Glycogen phosphorylase.

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

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

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

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

7. What stimulates glycogen breakdown during exercise?

- **AMP** (low energy)
 - **Ca²⁺–calmodulin** (muscle contraction)
 - **Epinephrine**
-

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).

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.

10. Which GSD causes cardiomyopathy in infants?

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

11. Which GSD shows the “second wind phenomenon”?

McArdle disease (Type V) — muscle phosphorylase deficiency.

12. Why does von Gierke disease cause lactic acidosis?

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

13. Which GSD involves a defect in branching?

Andersen disease (Type IV) — branching enzyme deficiency.

14. Which enzyme is essential for initiating glycogen synthesis?

Glycogenin, which serves as the primer.

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
-

2. Glycogen phosphorylase requires which cofactor?

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

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

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

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

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

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

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

6. Branching enzyme forms which type of linkage?

- A. α -1,4
 - B. α -1,6
 - C. β -1,4
 - D. β -1,6
-

7. cAMP activates glycogenolysis by:

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

8. PLP-deficiency will primarily affect activity of:

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

9. Which hormone stimulates glycogen breakdown in muscle?

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

10. "Limit dextrins" accumulate in which GSD?

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

11. Massive hepatomegaly + severe fasting hypoglycemia suggests:

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

12. Cardiomegaly and early death in infancy occur in:

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

13. Exercise intolerance with "second wind phenomenon" is typical of:

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

14. Branching enzyme deficiency is seen in:

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

15. Liver phosphorylase deficiency causes:

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

16. Glycogen synthase is active when:

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

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

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

18. Glucose yield from glycogen breakdown during glycolysis is:

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

19. Which GSD is due to acid maltase deficiency?

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

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

- A. Ca^{2+} -calmodulin
 - B. Glucagon
 - C. Epinephrine only
 - D. Insulin
-

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.

2. What is the function of muscle glycogen?

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

3. What is the first product of glycogen breakdown?

Glucose-1-phosphate.

4. Which cofactor is required for glycogen phosphorylase?

Pyridoxal phosphate (PLP).

5. Why doesn't muscle contribute glucose to blood?

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

6. What enzyme removes branch-point glucose?

α-1,6-glucosidase activity of the debranching enzyme.

7. What type of linkage does branching enzyme form?

α-1,6 linkage.

8. Which enzyme is the regulatory enzyme of glycogenesis?

Glycogen synthase.

9. Which enzyme initiates glycogen synthesis?

Glycogenin.

10. When is glycogen phosphorylase active?

When **phosphorylated**.

11. When is glycogen synthase active?

When **dephosphorylated**.

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

Stimulates **glycogenolysis**; inhibits glycogenesis.

13. Which hormone activates glycogen breakdown in muscle?

Epinephrine.

14. Which hormone activates glycogen breakdown in liver?

Glucagon (and epinephrine).

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

3 ATP per glucose.

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

Limit dextrins.

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

Glucose-6-phosphatase deficiency.

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

Because glucose cannot be released from G6P.

19. Which glycogen storage disease affects the heart predominantly?

Pompe disease (Type II).

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

Exercise intolerance with second-wind phenomenon.

21. Which GSD involves a defect in branching enzyme?

Andersen disease (Type IV).

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

Liver phosphorylase deficiency causing mild hypoglycemia.

23. Why is glycogen branched?

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

24. What activates muscle glycogenolysis during contraction?

Ca²⁺-calmodulin complex.

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

α -1,4 = linear chain

α -1,6 = branch point