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.

Absorption of Carbohydrates

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

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.

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).

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).

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**

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**

---

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

---

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

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 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

---

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 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

---

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 (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.

---

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**.

---

3. Phosphoglucomutase

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

---

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.

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 **?-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.

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.

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 ?-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 ?-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

• 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 ?-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. ?-1,4
B. ?-1,6
C. ?-1,4
D. ?-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. Ca²?–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?

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

---

7. What type of linkage does branching enzyme form?

?-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.

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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