MEDICAL EDUCATION RESOURCE

Minor Metabolic Pathways of Carbohydrates

Hexose Monophosphate (HMP) Shunt Pathway

The HMP shunt is an alternative metabolic route for glucose. Its role is not to produce ATP, but to generate **NADPH** and **pentose sugars**, both essential for biosynthesis and antioxidant protection.

1. Purpose of the Pathway

A. Production of NADPH

NADPH is required for:

- Fatty acid synthesis
- Cholesterol and steroid hormone synthesis
- Regeneration of reduced glutathione
- Detoxification reactions in liver (cytochrome P450 system)

B. Production of Ribose-5-Phosphate

This pentose sugar is required for:

- DNA & RNA synthesis
- ATP, NAD?, FAD, CoA synthesis

2. Tissues With High Activity

The pathway is most active in tissues that require NADPH or nucleotide precursors.

- Liver
- Adipose tissue
- Adrenal cortex
- Mammary gland
- Thyroid
- Red blood cells (primary defense against oxidative damage)

3. Phases of the Pathway

The HMP shunt consists of two distinct phases.

A. Oxidative Phase (Irreversible)

This phase oxidizes glucose-6-phosphate, producing **NADPH**, releasing **CO?**, and forming **ribulose-5-phosphate**.

Step 1: Formation of 6-phosphogluconolactone

- Enzyme: **Glucose-6-phosphate dehydrogenase (G6PD)**
- NADP? ? NADPH
- This is the **rate-limiting** and most regulated step.

Step 2: Formation of 6-phosphogluconate

- Lactonase enzyme opens the ring of 6-phosphogluconolactone.

Step 3: Formation of Ribulose-5-Phosphate and CO?

- Enzyme: **6-phosphogluconate dehydrogenase**
- Produces another **NADPH**
- Removes carbon-1 of glucose as **CO?**

B. Non-Oxidative Phase (Reversible)

This phase interconverts 3-, 4-, 5-, 6-, and 7-carbon sugars to supply either:

- **Ribose-5-phosphate** for nucleotide synthesis
- **Fructose-6-phosphate & glyceraldehyde-3-phosphate** for glycolysis
- **Glucose-6-phosphate** to restart the cycle

1. First Transketolase Reaction

- Converts xylulose-5-P and ribose-5-P into:
    - Glyceraldehyde-3-phosphate (3C)
    - Sedoheptulose-7-phosphate (7C)
- Cofactor required: **Thiamine (TPP)**

2. Transaldolase Reaction

Sedoheptulose-7-P donates a 3-carbon unit to glyceraldehyde-3-P to form:

- Fructose-6-phosphate (6C)
- Erythrose-4-phosphate (4C)

3. Second Transketolase Reaction

Xylulose-5-P donates 2 carbons to erythrose-4-P to form:

- Fructose-6-phosphate
- Glyceraldehyde-3-phosphate

4. Regeneration of Glucose-6-Phosphate

Glyceraldehyde-3-phosphate molecules combine to form fructose-6-phosphate ? converted back to glucose-6-phosphate.

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4. Carbon Rearrangement Summary

PROCESS	EXPLANATION
6 glucose molecules enter	Total 36 carbons
6 carbons removed as CO?	One carbon from each glucose (oxidative phase)
12 NADPH produced	Two per glucose oxidized
30 carbons rearranged	Converted into pentoses
5 glucose molecules regenerated	Non-oxidative recycling

One whole glucose is “sacrificed” to produce NADPH.

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5. Regulation of the Pathway

A. NADP? / NADPH ratio is the primary regulator

- High NADP? ? pathway accelerates
- High NADPH ? pathway slows down

B. Hormonal Control

- **Insulin** increases activity by inducing G6PD
- More active in the **fed state**

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6. Clinical Significance: G6PD Deficiency

RBCs rely **solely** on the HMP shunt for NADPH because they lack mitochondria.
When G6PD is deficient:

Triggers of hemolysis:

- Fava beans (favism)
- Sulfonamides
- Antimalarial drugs
- Nitrofurantoin
- Infections

Consequences:

- Oxidative injury to hemoglobin ? Heinz bodies

- RBC membrane fragility ? hemolysis
- Jaundice
- Dark urine
- Increased methemoglobin levels

Evolutionary note:

Low glutathione levels impair malaria parasite survival ? **partial protection against malaria**.

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7. Physiological Roles of the Pathway

A. Source of NADPH

- Needed for fatty acid synthesis, cholesterol synthesis, steroidogenesis
- Required for reduction of oxidized glutathione ? protects RBCs

B. Source of Ribose-5-Phosphate

- Needed for nucleotides and nucleic acids

C. Supports Detoxification

- NADPH provides reducing power for cytochrome P450 enzymes

D. Protects Against Oxidative Stress

- Especially vital in RBCs

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8. Integrated Importance

The HMP shunt does not make ATP, but it supplies the cell with **reducing power (NADPH)** and **pentose sugars**, making it crucial for:

- Anabolic processes
- Antioxidant defense
- Rapidly dividing cells
- Hormone-producing tissues

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

G6PD deficiency is the **most common inherited enzyme defect in the world**.
It directly affects the **HMP shunt pathway**, especially the **oxidative phase**, where G6PD is the **rate-limiting enzyme**.

1. Why G6PD Is Important

A. Produces NADPH

G6PD is the enzyme that starts the oxidative phase of the HMP pathway.
NADPH is needed to:

- Keep **glutathione in reduced form (GSH)**
- Protect RBC membranes and hemoglobin from **oxidative injury**
- Neutralize harmful oxidants (H?O?, free radicals)

B. Especially important in RBCs

- RBCs have **no mitochondria**
- Their **only source of NADPH** is the HMP shunt
- Without NADPH, glutathione becomes oxidized and useless
- RBCs cannot repair oxidative damage ? **hemolysis**

This is why the deficiency mainly causes **hemolytic anemia**.

2. Genetic Features

- **X-linked recessive disorder**
- Affects males more commonly
- Females can be carriers or symptomatic (lyonization)

Prevalence:

- Very common in Africa, Middle East, India, Mediterranean countries
- The distribution overlaps with **malarial endemic areas**

3. Protective Effect Against Malaria

Plasmodium species (malaria parasites) need **reduced glutathione** to survive.
In G6PD deficiency:

- Less GSH is available
- Parasites grow poorly

- Provides **partial resistance to malaria**
  (This is why the mutation persists in these populations.)

4. What Triggers Hemolysis?

People with G6PD deficiency are usually normal until exposed to **oxidative stress**.

Major triggers:

A. Foods

- **Fava beans** ? “Favism”

B. Drugs

- **Sulfonamides**
- **Antimalarials** (e.g., primaquine, chloroquine)
- **Nitrofurantoin**
- **Dapsone**
- High-dose aspirin

C. Infections

- Most common trigger
- Infection produces free radicals ? RBC damage

D. Chemicals

- Naphthalene (mothballs)

Even mild oxidative stress can destroy RBCs in severe deficiency.

5. What Happens Inside the RBC? (Pathogenesis)

Step-wise process:

1. Oxidative stress increases in the blood
2. G6PD-deficient RBC cannot produce enough NADPH
3. **Glutathione becomes oxidized** and inactive
4. Oxidants attack hemoglobin ? **Heinz body formation**
5. Heinz bodies attach to RBC membrane
6. The spleen removes these cells ? **bite cells / blister cells**
7. Sudden fall in RBC count ? **acute hemolysis**

6. Clinical Features

A. Symptoms of hemolysis

- Sudden fatigue
- Pallor
- Jaundice

- Dark brown/cola-colored urine
- Back and abdominal pain (due to hemolysis)

B. Neonatal jaundice

- Can be severe
- May require phototherapy or exchange transfusion

C. Hemolytic crisis can occur within hours after exposure to a trigger.

7. Laboratory Findings

- Hemolytic anemia
- Increased reticulocyte count
- Increased serum bilirubin
- Low haptoglobin
- **Heinz bodies** on supravital stain
- **Bite cells** on peripheral smear
- Enzyme assay: **low G6PD levels** (done in stable phase, not during acute hemolysis)

8. Management

A. Avoid triggers

- Avoid fava beans
- Avoid sulfa drugs, antimalarials, nitrofurantoin
- Avoid naphthalene balls

B. Treat hemolysis

- Stop the offending drug
- Hydration
- Treat infection
- Blood transfusion if severe

C. Neonatal care

- Phototherapy
- Exchange transfusion when required

There is **no cure**, but good avoidance and counseling prevent most episodes.

9. Key High-Yield Points for Exams

- X-linked recessive
- RBCs are especially vulnerable ? no mitochondria
- Only source of NADPH is HMP shunt

- Triggers include fava beans, sulfa drugs, antimalarials, infections
- Causes **Heinz bodies** & **bite cells**
- Provides **resistance to malaria**
- Enzyme levels must be tested **after the hemolytic episode**, not during

Glucuronic Acid Pathway (Uronic Acid Pathway)

The glucuronic acid pathway is a minor route of glucose metabolism.
Its main purpose is to produce **UDP-glucuronic acid**, a highly active form of glucuronic acid that the body uses for **detoxification and biosynthesis**.

1. Purpose of the Glucuronic Acid Pathway

A. Detoxification (Glucuronidation)

UDP-glucuronic acid attaches to toxic substances and makes them:

- **More water-soluble**
- **Easier to excrete through urine or bile**

This is essential for:

- Drug metabolism
- Bilirubin conjugation
- Steroid hormone inactivation

B. Synthesis Functions

UDP-glucuronic acid is needed for:

- **Glycosaminoglycans (GAGs)** such as:
  - Hyaluronic acid
  - Chondroitin sulfate
  - Heparan sulfate
- **Proteoglycan** formation (connective tissue strength)

2. Steps of the Pathway (Simplified)

The pathway starts from **glucose** and moves through a series of steps to produce **UDP-glucuronic acid**.

Step 1: Conversion to UDP-glucose

Glucose ? Glucose-6-phosphate ? Glucose-1-phosphate ? UDP-glucose

This prepares glucose for activation.

Step 2: Oxidation

UDP-glucose is oxidized to **UDP-glucuronic acid**.

This is the active form used for conjugation and synthesis.

Step 3: Further metabolism

UDP-glucuronic acid can enter two pathways:

- Used directly for **detoxification**
- Converted further into **L-gulonate ? L-gulonolactone**

Human Limitation

Humans **lack the enzyme L-gulonolactone oxidase**, so the pathway **cannot produce vitamin C**.
Therefore, **ascorbic acid is an essential vitamin** in humans.

(Animals that have this enzyme make their own vitamin C.)

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3. Biological Importance

? A. Bilirubin Conjugation

Bilirubin is toxic and water-insoluble.
Liver attaches **two molecules of glucuronic acid** ? forms **bilirubin diglucuronide**, which is:

- Water-soluble
- Excreted through bile

This prevents jaundice.

? B. Conjugation of Steroids and Drugs

Glucuronic acid attaches to:

- Steroid hormones (estrogen, cortisol)
- Drugs (paracetamol, morphine, chloramphenicol)
- Environmental toxins

This increases their solubility and speeds excretion.

? C. Synthesis of Glycosaminoglycans (GAGs)

GAGs form the gel-like matrix of connective tissue, skin, cartilage, and joints.

UDP-glucuronic acid is required for:

- Hyaluronic acid
- Chondroitin sulfate
- Dermatan sulfate
- Heparan sulfate

These provide:

- Lubrication
- Shock absorption
- Cell adhesion
- Structural strength

4. Clinical Correlations

A. Neonatal jaundice

Low activity of bilirubin-conjugating enzymes in newborns ? accumulation of unconjugated bilirubin.

Glucuronidation is essential to prevent:

- Kernicterus

- Severe hyperbilirubinemia

B. Drug toxicity

In conditions where glucuronidation is impaired, drugs accumulate and become toxic.

C. Vitamin C deficiency (Scurvy)

Because humans cannot synthesize vitamin C from this pathway:

- Vitamin C must be taken through diet
- Deficiency leads to scurvy (bleeding gums, poor wound healing)

5. Essential Pentosuria (Related Condition)

A rare, benign inborn error where **L-xylulose** (a sugar from this pathway) appears in urine.

Features:

- Autosomal recessive
- No symptoms
- Urine tests falsely appear “sugar-positive”
- No treatment needed

(This is often asked as a short note.)

6. Key Points to Remember

- Produces **UDP-glucuronic acid**

- Essential for **detoxification**, **bilirubin conjugation**, and **GAG synthesis**
- Humans cannot synthesize **vitamin C** due to missing enzyme
- Impairment can worsen drug toxicity and jaundice
- Essential pentosuria is related but benign

Essential Pentosuria

Essential pentosuria is a **rare, harmless, inherited metabolic condition** involving the glucuronic acid pathway.

1. Cause

- Deficiency of the enzyme **L-xylulose reductase**
- L-xylulose (a sugar from the glucuronic acid pathway) cannot be converted further
- Result ? **L-xylulose is excreted in urine**

2. Inheritance

- **Autosomal recessive**

3. Clinical significance

- Completely **benign**
- No symptoms
- No complications

- Found incidentally

4. Laboratory finding

- **Urine tests positive for “reducing sugar”**, but:
  - It is **not glucose**
  - Therefore blood sugar levels are normal
  - Important differential diagnosis for diabetes

5. Treatment

- **No treatment required**

Polyol Pathway

The polyol pathway converts **glucose ? fructose** using two steps.

1. Steps of the Polyol Pathway

Step 1: Glucose ? Sorbitol

- Enzyme: **Aldose reductase**
- Requires NADPH

Step 2: Sorbitol ? Fructose

- Enzyme: **Sorbitol dehydrogenase**
- Occurs mainly in liver, ovaries, and seminal vesicles

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2. Why the Polyol Pathway Becomes Important

Some tissues have **aldose reductase but very little sorbitol dehydrogenase**:

- **Lens of eye**
- **Retina**
- **Kidney**
- **Peripheral nerves**

In these tissues:

- Sorbitol accumulates
- Sorbitol draws water ? osmotic damage

This is a major mechanism of **diabetic complications**.

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3. Clinical importance (High-Yield)

A. Diabetic Cataract

- Excess glucose ? sorbitol ? water enters lens ? swelling ? opacity

B. Diabetic Neuropathy

- Sorbitol accumulation damages nerve axons

C. Diabetic Retinopathy

- Osmotic stress injures retinal cells

D. Diabetic Nephropathy

- Sorbitol accumulation in kidney cells triggers injury

Fructose Metabolism

Fructose is metabolized primarily in the **liver**, and bypasses the major regulatory step of glycolysis.

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1. Steps of Fructose Metabolism

Step 1: Fructose ? Fructose-1-phosphate

- Enzyme: **Fructokinase**
- Uses ATP
- Rapid phosphorylation (not regulated by insulin)

Step 2: Fructose-1-phosphate ? DHAP + Glyceraldehyde

- Enzyme: **Aldolase B**

Step 3:

- Glyceraldehyde ? Glyceraldehyde-3-phosphate
- Enters **glycolysis** or **lipogenesis**

Clinical relevance of fructose metabolism

- Rapid metabolism may increase lipogenesis ? raise triglycerides
- Excess fructose intake associated with fatty liver

Hereditary Fructose Intolerance (HFI)

A severe, potentially fatal disorder of fructose metabolism.

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1. Cause

- Deficiency of **Aldolase B**
- Fructose-1-phosphate accumulates in the liver
- This **traps phosphate**, blocks ATP production

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2. Consequences

- Severe fall in blood glucose
- Inhibition of:
  - Glycogenolysis
  - Gluconeogenesis
- Leads to **profound hypoglycemia**

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3. Symptoms

Appear when fructose, sucrose, or sorbitol is introduced in diet (weaning phase).

- Vomiting
- Sweating
- Lethargy
- Seizures
- Hypoglycemia
- Jaundice
- Hepatomegaly
- Failure to thrive

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4. Dangerous complications

- Liver failure
- Renal failure
- Death (if untreated)

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5. Diagnosis

- History of symptoms after fructose/sucrose intake
- Hypoglycemia
- Liver dysfunction
- Genetic testing for **Aldolase B mutation**

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6. Treatment

- **Strict lifelong avoidance** of:
  - Fructose
  - Sucrose
  - Sorbitol
- With avoidance ? normal life

Fructosuria (Essential Fructosuria)

A mild, benign condition involving fructose metabolism.

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1. Cause

- Deficiency of **fructokinase**

- Fructose is not phosphorylated
- It stays in free form ? excreted in urine

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2. Clinical features

- Completely **asymptomatic**
- No hypoglycemia
- No liver enlargement
- No toxicity
- Incidental finding

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3. Lab findings

- **Fructose appears in urine**
- Urine reducing test positive
- Blood glucose normal
- Distinguishes it from diabetes and HFI

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4. Treatment

- No treatment needed
- Dietary restriction unnecessary

Quickest Exam Revision

Essential pentosuria ? L-xylulose in urine, benign

Polyol pathway ? sorbitol accumulation ? diabetic complications

Fructose metabolism ? via fructokinase & Aldolase B

Hereditary fructose intolerance ? Aldolase B deficiency ? severe hypoglycemia

Fructosuria ? Fructokinase deficiency ? harmless

Galactose Metabolism

Galactose comes mainly from **lactose** in milk.
When lactose is digested in the intestine, it splits into:

- **Glucose**
- **Galactose**

Galactose is transported to the **liver**, where it is converted into glucose.

1. Steps of Galactose Metabolism

The pathway converts galactose ? glucose-1-phosphate ? glucose.

Step 1: Galactose ? Galactose-1-phosphate

- Enzyme: **Galactokinase (GALK)**
- Requires ATP
- Traps galactose inside hepatocytes

Step 2: Galactose-1-phosphate + UDP-glucose ? UDP-galactose + Glucose-1-phosphate

- Enzyme: **Galactose-1-phosphate uridyl transferase (GALT)**
- This is the **most important step**
- Creates the activated form **UDP-galactose**

Step 3: UDP-galactose ? UDP-glucose

- Enzyme: **UDP-galactose 4-epimerase (GALE)**
- Allows UDP-glucose to be reused
- This completes the **Leloir pathway**

Step 4: Glucose-1-phosphate ? Glucose-6-phosphate

- Enters **glycolysis** or **glycogen synthesis**

2. Uses of UDP-Galactose

UDP-galactose is essential for synthesizing:

- **Lactose** (in mammary gland during lactation)

- **Glycoproteins**
- **Glycolipids**
- **Proteoglycans**

Thus, galactose metabolism supports both **energy production** and **structural functions**.

3. Importance of Efficient Galactose Metabolism

If any step is blocked:

- Galactose and its metabolites accumulate
- These are **toxic**, especially in infants
- This leads to the disorder known as **galactosemia**

Galactosemia

Galactosemia refers to a group of **inherited enzyme deficiencies** in the galactose metabolic pathway.
Accumulated metabolites cause toxicity in **liver, brain, and kidney**.

There are **three types**, depending on the enzyme deficiency:

1. **Classic Galactosemia (Type I) – GALT deficiency**
2. **Galactokinase Deficiency (Type II)**
3. **Epimerase Deficiency (Type III)**

1. Classic Galactosemia (Type I)

Most severe and most important for exams

A. Cause

- Deficiency of **Galactose-1-phosphate uridyl transferase (GALT)**
- Galactose-1-phosphate accumulates in tissues ? highly toxic

B. Pathogenesis

Accumulating metabolites include:

- **Galactose-1-phosphate**
- **Galactose**
- **Galactitol** (from polyol pathway: galactose ? galactitol)

These cause:

- Liver injury
- Kidney tubular damage
- Brain dysfunction
- Lens damage (cataract)

C. Clinical Features (Infants present after milk feeding begins)

Early signs:

- Vomiting

- Diarrhea
- Poor feeding
- Lethargy
- Jaundice
- Hepatomegaly

Severe features:

- Hypoglycemia
- Failure to thrive
- Bleeding tendencies
- Sepsis (commonly *E. coli*)
- Cataract
- Progressive liver failure

D. Complications

- Liver cirrhosis
- Intellectual disability
- Kidney damage
- Ovarian failure in females

- Death if untreated

E. Investigations

- Reducing substances in urine (but not glucose)
- Elevated galactose-1-phosphate levels
- Positive newborn screening test
- Confirmed by **GALT enzyme assay**

F. Treatment

- **Immediate and lifelong removal of galactose & lactose** from diet
- Switch to lactose-free formula (soy-based)
- Treat complications like sepsis and liver dysfunction

G. Prognosis

- Early treatment prevents life-threatening complications
- Some long-term issues may persist (speech delay, learning difficulties)

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2. Galactokinase Deficiency (Type II)

Much milder

A. Cause

- Defective **galactokinase (GALK)**
- Galactose cannot be phosphorylated
- Excess galactose ? polyol pathway ? **galactitol**

B. Clinical feature

- **Infantile cataracts** (main finding)
- No liver damage
- No kidney damage
- Normal growth otherwise

C. Treatment

- Remove galactose/lactose from diet
- Prevents cataract progression

3. Epimerase Deficiency (Type III)

Two forms:

- **Benign form:** only RBC/WBC affected
- **Severe form:** resembles classic galactosemia

Features

- Ranging from symptomless to liver damage and developmental delay
- Managed similarly to GALT deficiency in severe cases

High-Yield Differences (Easy Recall)

Classic Galactosemia (GALT deficiency)

? Most severe

? Liver failure + kidney damage + sepsis

? Cataract also possible

? Treat immediately

Galactokinase deficiency (GALK)

? Only cataracts

? No liver or brain involvement

Epimerase deficiency

? Mild or severe

? Severe form mimics classic galactosemia

Ultra-Short Exam Summary

- Galactose metabolism converts galactose to glucose via GALK ? GALT ? GALE.
- Classic galactosemia = **GALT deficiency**, life-threatening.
- Galactokinase deficiency = **cataracts only**, benign.
- Remove lactose/galactose from diet in all symptomatic types.

Metabolism of Alcohol (Ethanol Metabolism)

Alcohol is mainly metabolized in the **liver**, through two major pathways.
The end goal is to convert ethanol ? acetate ? energy.

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1. Primary Pathway: Alcohol Dehydrogenase (ADH pathway)

Step 1 — Ethanol ? Acetaldehyde

- Enzyme: **Alcohol dehydrogenase (ADH)**
- Location: Cytosol
- Requires NAD? ? produces **NADH**

This step controls how fast alcohol is metabolized.

Step 2 — Acetaldehyde ? Acetate

- Enzyme: **Aldehyde dehydrogenase (ALDH)**
- Location: Mitochondria
- Also produces **NADH**

Acetaldehyde is highly toxic and responsible for:

- Facial flushing
- Hangover symptoms
- Vomiting
- Heart palpitations

People with **ALDH2 deficiency** (common in East Asians) have intense flushing after drinking.

Step 3 — Acetate ? Acetyl-CoA

- Enzyme: **Acetyl-CoA synthetase**
- Acetyl-CoA enters:
  - TCA cycle
  - Ketone body pathway
  - Fatty acid synthesis

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2. Microsomal Ethanol-Oxidizing System (MEOS)

A secondary pathway used during:

- Chronic alcohol consumption
- High alcohol levels
- Liver hypertrophy in alcoholics

Features:

- Location: **Smooth endoplasmic reticulum**
- Enzyme system: **Cytochrome P450 2E1 (CYP2E1)**
- Uses **NADPH and oxygen**
- Produces **free radicals**
  ? Contributes to **oxidative liver injury** in alcoholics.

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3. Catalase Pathway

- Minor pathway (5–10%)
- Uses hydrogen peroxide
- Occurs in peroxisomes
- Not clinically significant

4. Clinical Effects of Alcohol Metabolism

A. High NADH/NAD? Ratio

Excess NADH from ADH + ALDH leads to:

- **Lactic acidosis** (pyruvate converted to lactate)
- **Hypoglycemia** (blocks gluconeogenesis)
- **Fatty liver** (triglyceride accumulation)
- **Ketoacidosis**

B. Acetaldehyde Toxicity

- Liver inflammation
- Mitochondrial damage
- Protein adducts ? immune reactions

C. Chronic alcohol intake

- Hepatic steatosis ? hepatitis ? cirrhosis
- Induced CYP2E1 affects drug metabolism (paracetamol becomes toxic)

5. Summary

Ethanol ? Acetaldehyde ? Acetate ? Acetyl-CoA
Main pathway = ADH; Chronic use activates MEOS; High NADH causes hypoglycemia + fatty liver.

Amino Sugars

Amino sugars are **monosaccharides in which an –OH group is replaced by an –NH? group**.
They are essential components of:

- Glycoproteins
- Glycolipids
- Proteoglycans
- Cartilage
- Basement membranes

1. Common Amino Sugars

A. Glucosamine

- Derived from **fructose-6-phosphate**

- Important in:
    - Chitin
    - Hyaluronic acid
    - Heparan sulfate

B. Galactosamine

- Part of:
    - Chondroitin sulfate
    - Dermatan sulfate

C. N-Acetylated forms

- **N-acetylglucosamine (NAG)**
- **N-acetylgalactosamine (NAGal)**
  These form:
- Mucins
- GAGs
- Blood group substances

2. Biological Roles of Amino Sugars

- Provide **strength and flexibility** to connective tissues

- Form part of **cell surface receptors**
- Help in **cell adhesion**
- Needed for **joint lubrication and cartilage resilience**

3. Clinical Note

Glucosamine supplements are often used for osteoarthritis, though evidence varies.

Glycoproteins

Glycoproteins are proteins with **oligosaccharide chains (glycans)** attached to them.
They are found on:

- Cell surfaces
- Serum proteins
- Hormones
- Immunoglobulins
- Secretions (mucus, saliva)

1. Structure of Glycoproteins

A. Protein backbone

Forms the structural part.

B. Carbohydrate portion

Attached by:

- **N-linkage** (to asparagine)
- **O-linkage** (to serine/threonine)

Carbohydrates usually contain:

- Glucose
- Galactose
- Mannose
- Fucose
- N-acetylglucosamine
- N-acetylgalactosamine
- Sialic acid (NANA)

2. Functions of Glycoproteins

A. Cell Recognition & Adhesion

- Blood group antigens (A, B, O types)
- Cell–cell interaction
- Immune cell binding

B. Immune System

- Antibodies (IgG, IgM, IgA) are glycoproteins
- Complement proteins

C. Hormones & Receptors

Examples:

- FSH, LH, TSH
- Receptor proteins

D. Mucosal Protection

Mucins are glycoproteins that:

- Lubricate surfaces
- Protect against pathogens

E. Enzyme Stability

Carbohydrate chains protect proteins from degradation.

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3. Clinical Importance of Glycoproteins

A. Congenital Disorders of Glycosylation

Cause:

- Developmental delay
- Liver problems
- Neuropathy

B. Blood Group Substances

- A, B antigens = terminal sugars in glycoproteins
- Determined by glycosyltransferase activity

C. Viral Attachment

Viruses (influenza, HIV) recognize sugar chains on host glycoproteins to enter cells.

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4. Summary

Amino sugars form the building blocks.
Glycoproteins perform cell recognition, immunity, hormone activity, and protection.

Blood Group Substances (ABO Blood Group System)

Blood group substances are **carbohydrate-rich glycoproteins and glycolipids** found on the surface of red blood cells.
The **terminal sugars** determine whether a person is **A, B, AB, or O**.

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1. Basic Structure of Blood Group Antigens

All RBCs begin with a common **H-antigen backbone**.
This is made up of:

- Fucose
- Galactose
- N-acetylglucosamine

- Other linked sugars

What differentiates the groups?

Specific **glycosyltransferase enzymes** add terminal sugars:

A Group

- Enzyme adds **N-acetylgalactosamine**
- Forms **A antigen**

B Group

- Enzyme adds **Galactose**
- Forms **B antigen**

AB Group

- Both enzymes work
- A and B antigens present together

O Group

- Enzyme is inactive
- No additional sugar added
- Only **H antigen** is present

Exam point:
O group is not “empty”—it carries the basic H-antigen.

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2. Location of Blood Group Substances

Antigens are found on:

- Red blood cells
- Epithelial cells
- Secretions (saliva, gastric juice—if the person is a “secretor”)

They are part of **cell membrane glycoproteins and glycolipids**.

3. Antibodies in ABO System

Antibodies (isohemagglutinins):

- Are **IgM type**
- Naturally present due to exposure to gut bacterial antigens
- Do **not cross placenta** (important in pregnancy questions)

BLOOD GROUP	ANTIGEN ON RBC	ANTIBODY IN PLASMA
A	A antigen	Anti-B
B	B antigen	Anti-A
AB	A + B	None
O	H antigen	Anti-A & Anti-B

4. Clinical Importance

A. Blood transfusion compatibility

- Incorrect transfusion causes **acute hemolytic transfusion reaction**
- Fever, chills, hemoglobinuria, renal failure

B. Blood group & organs

- Organ transplantation requires ABO matching
- Mismatch ? rapid rejection

C. Bombay blood group (hh phenotype)

- Extremely rare
- No H antigen ? cannot form A or B antigens
- They have **anti-H antibodies**
- Can receive blood **only from another Bombay individual**

(Highly important MCQ topic)

5. Summary

Blood group substances are glycoproteins/glycolipids.
Terminal sugar determines blood group.
Antibodies are IgM.
Bombay group lacks H antigen.

Mucopolysaccharidoses (MPS)

MPS are a group of **lysosomal storage disorders** caused by deficiency of enzymes required to degrade **glycosaminoglycans (GAGs)**.

GAGs accumulate in:

- Liver
- Spleen
- Joints
- Heart valves
- Brain
- Skeleton

Leading to **progressive multi-system disease**.

---

1. What are Glycosaminoglycans (GAGs)?

Long chains of repeating sugar units:

- **Amino sugar** (N-acetylglucosamine or N-acetylgalactosamine)
- **Uronic acid** (glucuronic acid or iduronic acid)

Types of GAGs:

- Heparan sulfate
- Dermatan sulfate

- Keratan sulfate
- Chondroitin sulfate
- Hyaluronic acid

These form the structural material of connective tissue, cartilage, cornea, joints, and skin.

2. Why MPS Occur

Each MPS type is due to **deficiency of a specific lysosomal enzyme** needed to break down GAGs.
Without the enzyme:

- GAGs accumulate in lysosomes
- Cells enlarge and malfunction
- Tissues become thickened
- Progressive organ damage occurs

3. General Clinical Features of MPS

Common features across multiple types:

A. Facial changes

- Coarse facial features (“gargoyle-like facies”)
- Broad nose, thick lips, large tongue

B. Skeletal abnormalities (Dysostosis multiplex)

- Short stature
- Joint stiffness
- Enlarged skull
- Spinal deformities

C. Organ involvement

- Hepatosplenomegaly
- Cardiac valve disease

D. Eye involvement

- Corneal clouding (in some types)

E. Neurological issues

- Developmental delay (in many types)
- Behavior disturbances

F. Urinary GAGs increased

- Diagnostic feature

4. Major Types of MPS (Exam-Oriented)

1. Hurler Syndrome (MPS I H)

- Enzyme: **?-L-iduronidase deficiency**
- Accumulation: Dermatan sulfate + heparan sulfate
- Features:
    - Severe mental retardation
    - Corneal clouding
    - Hepatosplenomegaly
    - Skeletal deformities
    - Early death if untreated

2. Hunter Syndrome (MPS II)

- Enzyme: **Iduronate sulfatase deficiency**
- X-linked recessive (**only MPS that is X-linked**)
- No corneal clouding
- Similar features to Hurler but milder

3. Sanfilippo Syndrome (MPS III)

- Four enzyme defects (A–D)
- Predominantly **severe CNS involvement**
- Mild somatic features

4. Morquio Syndrome (MPS IV)

- Enzyme: N-acetylgalactosamine-6-sulfatase or ?-galactosidase
- Severe skeletal deformities
- **Normal intelligence**
- Corneal clouding present

5. Maroteaux–Lamy Syndrome (MPS VI)

- Enzyme: **Aryl sulfatase B** deficiency
- Normal intelligence
- Skeletal + cardiac involvement

6. Sly Syndrome (MPS VII)

- Enzyme: **?-glucuronidase deficiency**
- Hepatosplenomegaly
- Developmental delay
- Skeletal abnormalities

---

5. Diagnosis

- Increased urinary GAGs

- Specific enzyme assays (blood, fibroblasts)
- Genetic testing
- Imaging showing dysostosis multiplex

6. Treatment

A. Enzyme Replacement Therapy (ERT)

Available for:

- MPS I
- MPS II
- MPS IVA
- MPS VI

B. Bone Marrow Transplantation

Helps in Hurler syndrome (MPS I) if done early.

C. Supportive therapy

- Physiotherapy
- Cardiac monitoring
- Eye care
- Surgical procedures for skeletal and airway issues

7. Quick Revision Table (Concept-Based)

Hurler (MPS I) ? ?-L-iduronidase ? Corneal clouding ? Severe
Hunter (MPS II) ? Iduronate sulfatase ? No corneal clouding ? X-linked
Sanfilippo (MPS III) ? CNS dominant ? Mild somatic signs
Morquio (MPS IV) ? Skeletal abnormalities ? Normal intelligence
Maroteaux–Lamy (VI) ? Aryl sulfatase B ? No CNS issues
Sly (VII) ? ?-glucuronidase ? Variable severity

Inborn Errors Associated With Carbohydrate Metabolism

These disorders occur when **specific enzymes** in carbohydrate pathways are missing or defective.
As a result, **intermediate sugars accumulate**, becoming toxic to organs such as the liver, kidney, brain, lens, and muscle.

For easy study, they can be grouped under:

1. **Glycogen Storage Disorders (GSDs)**
2. **Fructose Metabolism Disorders**
3. **Galactose Metabolism Disorders**
4. **Pentose/Glucuronic Acid Pathway Disorders**
5. **Disorders of Pyruvate Lactate Metabolism**

Below is a clean, structured explanation of all major conditions.

---

1. Glycogen Storage Disorders (GSDs)

These arise from defects in enzymes handling **glycogen breakdown or synthesis**.

A. Von Gierke Disease (Type I)

- Enzyme defect: **Glucose-6-phosphatase**
- Liver cannot release glucose
- Features:
  - Severe fasting **hypoglycemia**
  - Lactic acidosis
  - Hyperuricemia
  - Hyperlipidemia
  - Enlarged liver (hepatomegaly)

B. Pompe Disease (Type II)

- Enzyme: **Lysosomal acid maltase (?-1,4-glucosidase)**
- GSD affecting **muscle + heart**
- Features:
  - Hypotonia
  - Cardiomegaly
  - Early death (infantile form)

C. Cori Disease (Type III)

- Enzyme: **Debranching enzyme deficiency**
- Features similar to GSD I but milder

D. Andersen Disease (Type IV)

- Enzyme: **Branching enzyme deficiency**
- Abnormal glycogen ? liver cirrhosis

E. McArdle Disease (Type V)

- Enzyme: **Muscle glycogen phosphorylase**
- Features:
  - Muscle cramps
  - Myoglobinuria after exercise
  - “Second wind phenomenon”

F. Hers Disease (Type VI)

- Enzyme: **Liver glycogen phosphorylase**
- Mild hypoglycemia + hepatomegaly

---

2. Disorders of Fructose Metabolism

A. Essential Fructosuria

- Enzyme: **Fructokinase deficiency**
- Benign
- Fructose appears in urine
- No hypoglycemia

B. Hereditary Fructose Intolerance

- Enzyme: **Aldolase B deficiency**
- **Fructose-1-phosphate accumulates**
- Features:
  - Severe hypoglycemia
  - Vomiting
  - Lethargy
  - Liver failure
- Triggered after feeding fructose/sucrose
- Requires strict fructose-free diet

---

3. Disorders of Galactose Metabolism

A. Classic Galactosemia (Type I)

- Enzyme: **Galactose-1-phosphate uridyl transferase (GALT)**
- Galactose-1-phosphate accumulates
- Features:
    - Jaundice
    - Cataracts
    - Vomiting
    - Liver failure
    - *E. coli* sepsis
- Requires lifelong lactose-free diet

B. Galactokinase Deficiency (Type II)

- Cataracts due to **galactitol** buildup
- No liver damage

C. Epimerase Deficiency (Type III)

- Mild or severe depending on form
- Severe form resembles GALT deficiency

---

4. Pentose & Glucuronic Acid Pathway Disorders

A. G6PD Deficiency

- Enzyme: **Glucose-6-phosphate dehydrogenase**
- RBCs cannot make NADPH ? oxidative damage
- Triggers:
    - Fava beans
    - Sulfa drugs
    - Antimalarials
    - Infections
- Features:
    - Hemolysis
    - Jaundice
    - Dark urine

B. Essential Pentosuria

- Enzyme: **L-xylulose reductase deficiency**
- L-xylulose in urine
- Benign, no clinical symptoms

---

5. Disorders of Pyruvate & Lactate Metabolism

A. Pyruvate Dehydrogenase Deficiency

- Pyruvate cannot enter TCA cycle
- Converts to lactate ? **lactic acidosis**
- Features:
    - Severe neurological problems
    - Developmental delay
- Treatment: ketogenic diet (bypass carbohydrates)

B. Pyruvate Carboxylase Deficiency

- Impaired gluconeogenesis
- Hypoglycemia
- Lactic acidosis
- Ketosis

---

6. Disorders of Glycolysis (Rare but Classic for Exams)

A. Hexokinase Deficiency

- Affects RBCs ? hemolytic anemia

B. Phosphofructokinase Deficiency (Tarui Disease)

- Affects muscle glycolysis

- Exercise intolerance + myoglobinuria

C. Pyruvate Kinase Deficiency

- Most common glycolytic enzyme defect causing chronic hemolytic anemia
- RBCs produce less ATP ? membrane damage

7. Disorders of Glucose Transport

GLUT1 Deficiency Syndrome

- Impaired glucose transport to brain
- Features:
  - Seizures
  - Developmental delay
- CSF glucose low
- Treatment: ketogenic diet (ketones become alternate fuel)

8. Integrated Summary (Fast Revision)

- **GSDs ? storage problems** in liver/muscle
- **Fructose intolerance ? aldolase B defect ? severe hypoglycemia**
- **Essential fructosuria ? harmless**

- **Galactosemia ? GALT defect ? liver failure + cataract**
- **G6PD deficiency ? hemolysis under oxidative stress**
- **Pyruvate disorders ? lactic acidosis + neurological issues**
- **GLUT1 defect ? low CSF glucose**

? Important Points to Remember

(Directly grounded on PDF content)

1. Polyol Pathway

- Aldose reductase converts **glucose ? sorbitol**, sorbitol dehydrogenase converts **sorbitol ? fructose**.
- Sorbitol **gets trapped inside tissues** like lens ? causes **osmotic damage ? cataract**. (PDF reference: sorbitol accumulation in lens and cataract formation)
- Polyol pathway is **active in brain**, fructose is present in **CSF**.
- Pathway is **inactive in liver**.

---

2. Essential Pentosuria

- Due to **L-xylulose reductase or xylitol dehydrogenase deficiency**.
- L-xylulose appears in urine ? **positive Benedict's test**.
- Harmless, but must be differentiated from diabetes.

---

3. Fructose Metabolism

- Fructokinase phosphorylates fructose at **1st carbon**.
- Fructose metabolism **bypasses PFK**, therefore increases glycolytic flux ? **more lipogenesis & ? triglycerides**.
- Fructose rapidly increases fatty acid synthesis and **raises LDL**.
- Fructose metabolism **depletes ATP**, increases AMP breakdown ? **? uric acid** levels.

---

4. Hereditary Fructose Intolerance (HFI)

- Caused by deficiency of **Aldolase B**.
- Fructose-1-phosphate accumulation ? inhibits **glycogen phosphorylase** ? hypoglycemia.
- Symptoms: vomiting, failure to thrive, jaundice, hepatomegaly; fatal if untreated.
- Removing fructose from diet relieves symptoms immediately.

---

5. Fructosuria

- Caused by **fructokinase deficiency**.
- Benign; fructose simply appears in urine (reducing sugar positive).

---

6. Galactose Metabolism

- Galactose is converted to UDP-galactose through **galactokinase** and **GALT**.

- UDP-galactose is needed for: lactose, GAGs, cerebrosides, glycolipids, and glycoproteins.

- Galactose tolerance test assesses **liver function** because galactose is metabolized mainly in the liver.

---

7. Galactosemia

- Galactose-1-phosphate accumulation ? cataracts (galactitol), jaundice, liver dysfunction. (PDF figure reference: Clinical features of galactosemia)

? Frequently Asked Questions (FAQs)

(Crafted from the concepts that appear in the PDF and common exam patterns)

Q1. Why does sorbitol cause cataracts in diabetes?

Because in hyperglycemia, more glucose enters the polyol pathway.
Sorbitol builds up in the lens (cannot diffuse out) ? draws water ? lens opacity.
(As shown: sorbitol accumulation damages lens)

Q2. Why is essential pentosuria not harmful?

Because L-xylulose accumulation does not damage tissues; only causes positive sugar test in urine.

Q3. Why is fructose harmful in diabetes even though it doesn't require insulin?

Fructose bypasses PFK ? rapidly increases glycolysis ? increases:

- Fatty acid synthesis

- Triglycerides

- LDL
  (All shown to be harmful and atherogenic)

Q4. Why does hereditary fructose intolerance cause severe hypoglycemia?

Fructose-1-phosphate accumulates and inhibits **glycogen phosphorylase** ? prevents glycogen breakdown.
Also blocks gluconeogenesis.

Q5. How to differentiate Hereditary Fructose Intolerance from Fructosuria?

- **HFI:** Aldolase B deficiency ? vomiting, jaundice, hepatomegaly
- **Fructosuria:** Fructokinase deficiency ? benign ? only fructose in urine

---

Q6. Why do infants with galactosemia develop cataracts?

Because unmetabolized galactose is converted to **galactitol** (via aldose reductase), which accumulates in lens causing osmotic swelling.
(Cataract feature shown in galactosemia clinical figure)

Q7. Why is galactose tolerance test used for liver function?

Galactose is metabolized **almost exclusively** in the liver; impaired metabolism suggests hepatic dysfunction.

Q8. Why is fructose found in semen?

Because fructose is produced via the polyol pathway and acts as a major energy source for sperm.

Q9. Which pathway is active in brain but inactive in liver?

Polyol pathway ? produces fructose in CSF, but liver does NOT use this pathway.

Q10. Which reducing sugars in urine indicate what disorder?

- **Fructose** ? fructosuria (benign) or HFI
- **L-xylulose** ? essential pentosuria
  (Both give positive Benedict's test)

? Clinical Points From the Chapter

1. Sorbitol-Induced Cataract (Polyol Pathway)

- In hyperglycemia, excess glucose enters the **polyol pathway** ? converted to **sorbitol**.
- Sorbitol **cannot diffuse out** of the lens ? accumulates ? osmotic swelling ? **cataract formation**.
- Same mechanism applies to **galactitol** in galactosemia.

2. Fructose as a Marker in Semen (Male Infertility Evaluation)

- Fructose is present in seminal plasma; provides energy for sperm.
- If fructose **absent in semen**, it suggests obstruction **after** seminal vesicles.
- If fructose **present**, obstruction is **before** seminal vesicles.

3. Fructose & Cardiometabolic Risk

- High fructose intake increases:
  - **Fatty acid synthesis**
  - **Serum triglycerides**
  - **LDL cholesterol**
- Increases **atherogenic risk** and worsens diabetic dyslipidemia.

---

4. Fructose ? Hyperuricemia

- Fructokinase rapidly uses ATP ? intracellular ATP **drops** ? AMP broken down ? **uric acid rises**.
- Link: fructose overload may contribute to **gout**.

---

5. Hereditary Fructose Intolerance ? Severe Hypoglycemia

- Aldolase B defect ? fructose-1-phosphate accumulates.
- This inhibits **glycogen phosphorylase** ? glycogen cannot break down ? **hypoglycemia**.
- Presents in infants when fructose / sucrose is introduced.

---

6. Jaundice & Liver Failure in HFI

- Accumulated F-1-P is hepatotoxic ? jaundice, vomiting, hepatomegaly, failure to thrive.

---

7. Fructosuria ? Benign Condition

- Fructokinase deficiency ? fructose spills in urine.
- No hypoglycemia or liver damage; only positive reducing sugar tests.

---

8. Essential Pentosuria ? False Positive Sugar Test

- L-xylulose excreted in urine ? positive Benedict’s test.
- Must differentiate from **diabetes mellitus**.

---

9. Galactosemia ? Cataract + Liver Failure

- Galactose ? galactitol (polyol pathway) ? cataracts.
- Galactose-1-phosphate accumulation causes:
  - Hepatomegaly
  - Failure to thrive
  - Vomiting

- Jaundice

- Severe cases lead to death if untreated.

---

10. Galactose Tolerance Test as a Liver Function Test

- Galactose is metabolized almost **exclusively by liver**.

- Delayed clearance of galactose ? indicates **hepatic impairment**.

---

11. Polyol Pathway Active in Brain

- Fructose appears in **CSF** because the pathway is active in brain.

- Clinical implication: sorbitol accumulation may contribute to neurotoxicity in uncontrolled diabetes.

? Clinical Problem Scenarios (Exam Pattern)

These mimic real MBBS exam/viva style “clinical problem” questions.

Problem 1: Child with Vomiting After Weaning

A 6-month-old infant develops vomiting, sweating, jaundice, and lethargy after starting fruit juices.

Diagnosis: *Hereditary Fructose Intolerance*
Cause: Aldolase B deficiency
Mechanism: F-1-P inhibits glycogenolysis ? severe hypoglycemia.
(Reference: HFI features)

Problem 2: Infantile Cataract Without Liver Symptoms

A newborn with clear liver tests but dense cataracts.

Diagnosis: *Galactokinase deficiency*
Mechanism: Galactose ? galactitol in lens ? osmotic swelling.

Problem 3: Reducing Sugar Positive but Blood Glucose Normal

Urine shows positive Benedict's test; fasting glucose normal.

Possibilities:

- Essential pentosuria (L-xylulose)
- Fructosuria (fructose)
  Differentiation:
- No systemic symptoms
- Both benign
  (Reference: pentosuria lines)

Problem 4: Diabetic Patient Developing Early Cataracts

High glucose ? high sorbitol in lens ? osmotic injury.

Diagnosis: *Diabetic cataract due to polyol pathway.*
(Reference: sorbitol leads to cataract)

Problem 5: Male Infertility Evaluation

Semen sample tested for fructose:

- **Fructose present** ? obstruction is **before** seminal vesicles

- **Fructose absent** ? obstruction **after** seminal vesicles
  (Reference: fructose in semen)

Problem 6: Hyperuricemia after High-Fructose Diet

High fructose ? ATP depletion ? excess AMP ? increased uric acid.

Clinical relevance: fructose may worsen gout or cause acute hyperuricemia.
(Reference ATP depletion ? uric acid increase)

Problem 7: Liver Function Assessment Using Sugar

If galactose blood levels remain high after ingestion ? liver cannot metabolize it.

Interpretation: hepatic impairment.
(Reference: Galactose tolerance test)

? MCQs: Minor Metabolic Pathways of Carbohydrates

> **1. Sorbitol accumulation in the lens is mainly responsible for which condition?**

A. Wilson disease
B. Diabetic cataract
C. Galactosemia liver failure
D. Wernicke encephalopathy

Answer: B. Diabetic cataract
Explanation: Polyol pathway ? sorbitol trapped in lens ? osmotic damage ? cataract.

---

2. Essential pentosuria is due to deficiency of which enzyme?

A. Aldolase B
B. Fructokinase
C. L-xylulose reductase
D. G6PD

Answer: C. L-xylulose reductase
Explanation: Leads to L-xylulose in urine ? benign condition.

---

3. Which statement correctly explains fructose metabolism in liver?

A. It depends on insulin
B. It bypasses PFK
C. It increases ATP level
D. It reduces lipogenesis

Answer: B. It bypasses PFK
Explanation: Leads to ? glycolysis flux ? ? lipogenesis & ? TAG.

---

4. High fructose intake increases uric acid because:

A. Fructose inhibits AMP deaminase
B. Fructose depletes ATP rapidly
C. Fructose increases gluconeogenesis
D. Fructose blocks ketone body production

Answer: B. Fructose depletes ATP rapidly
Explanation: Low ATP ? AMP breakdown ? ? uric acid.

---

5. A 6-month-old baby develops jaundice, vomiting, hepatomegaly after taking fruit juice. Most likely enzyme deficiency:

A. Galactokinase
B. Aldolase B
C. Fructokinase
D. Epimerase

Answer: B. Aldolase B
Explanation: Hereditary fructose intolerance; F-1-P accumulation.

---

6. Presence of fructose in semen is an indicator of:

A. Testicular failure
B. Prostate carcinoma
C. Seminal vesicle function
D. Epididymal obstruction

Answer: C. Seminal vesicle function
Explanation: Fructose is secreted by seminal vesicles.

---

7. Infantile cataracts without liver involvement is seen in:

A. Classic galactosemia
B. Galactokinase deficiency
C. HFI
D. Fructosuria

Answer: B. Galactokinase deficiency
Explanation: Due to galactitol accumulation.

---

8. A benign condition with positive Benedict's test but normal blood glucose:

A. HFI
B. Von Gierke disease
C. Essential pentosuria
D. Classic galactosemia

Answer: C. Essential pentosuria
Explanation: L-xylulose appears in urine; harmless.

---

9. Which pathway is active in brain but inactive in liver?

A. Galactose metabolism
B. Polyol pathway
C. Glycogenolysis
D. Gluconeogenesis

Answer: B. Polyol pathway
Explanation: Fructose found in CSF as pathway is active in brain but not liver.

---

10. Fructose is rapidly utilized in normal individuals because:

A. It enters pentose phosphate pathway
B. Fructokinase is inhibited by insulin
C. It bypasses glucokinase and PFK bottlenecks
D. It needs no phosphorylation

Answer: C. It bypasses glucokinase and PFK bottlenecks
Explanation: Hence rapid utilization.

---

11. Which enzyme deficiency leads to accumulation of galactose-1-phosphate?

A. Galactokinase
B. Galactose-1-phosphate uridyl transferase
C. Epimerase
D. Aldolase B

Answer: B. Galactose-1-phosphate uridyl transferase (GALT)
Explanation: Classic galactosemia (severe).

---

12. Which condition shows fructose in urine but is completely harmless?

A. HFI
B. Fructosuria
C. Galactosemia
D. Pentosuria

Answer: B. Fructosuria
Explanation: Fructokinase deficiency; benign.

---

13. Which metabolic disorder causes severe hypoglycemia due to inhibition of glycogen phosphorylase?

A. Essential pentosuria
B. Fructosuria
C. HFI
D. Galactokinase deficiency

Answer: C. HFI
Explanation: F-1-P blocks glycogen breakdown.

---

14. Which sugar is found in large quantity in seminal fluid?

A. Glucose
B. Galactose
C. Fructose
D. Mannose

Answer: C. Fructose
Explanation: Energy for sperm; secreted by seminal vesicles.

---

15. A diabetic patient develops early cataracts. The most likely accumulated substance is:

A. Mannitol
B. Sorbitol
C. Ribitol
D. Inositol

Answer: B. Sorbitol
Explanation: Sorbitol builds up in lens ? osmotic damage ? cataract.

? Viva Voce Questions – Minor Metabolic Pathways of Carbohydrates

1. What is the polyol pathway?

It is an alternative pathway where glucose is converted to **sorbitol** by aldose reductase, and sorbitol is converted to **fructose** by sorbitol dehydrogenase.

---

2. Why does sorbitol accumulate in the lens?

The lens lacks sorbitol dehydrogenase.
Sorbitol cannot exit the lens ? causes osmotic swelling ? **cataract**.

(Shown in PDF lines about sorbitol causing cataract)

---

3. In which tissues is the polyol pathway active?

- Lens
- Retina
- Kidney
- Peripheral nerves
- **Brain** (fructose found in CSF)

(Polyol pathway active in brain and not in liver)

---

4. Why is fructose commonly found in seminal plasma?

Because **seminal vesicles secrete fructose**, which is the major energy source for sperm.

---

5. Which reducing sugar is detected in essential pentosuria?

L-xylulose appears in urine due to deficiency of L-xylulose reductase.

---

6. Is essential pentosuria dangerous?

No. It is a **benign condition** but gives a positive Benedict's test, which may be confused with diabetes.

---

7. What is the first step in fructose metabolism?

Phosphorylation by **fructokinase** at carbon-1 to form fructose-1-phosphate.

---

8. Why is fructose metabolism rapid?

Because it **bypasses phosphofructokinase (PFK)**, the rate-limiting step of glycolysis.

---

9. Why does fructose increase lipogenesis?

Rapid fructolysis produces:

- Dihydroxyacetone phosphate
- Glyceraldehyde
  These increase triglyceride and fatty acid synthesis.

---

10. Why does high fructose intake raise uric acid levels?

Fructokinase consumes ATP rapidly ? ATP depletion ? AMP breakdown ? **hyperuricemia**.

---

11. What is the enzyme defect in hereditary fructose intolerance?

Aldolase B deficiency.

---

12. Why does hereditary fructose intolerance cause hypoglycemia?

Accumulated fructose-1-phosphate inhibits:

- **Glycogen phosphorylase**
- **Gluconeogenesis**

This leads to severe fasting hypoglycemia.

---

13. How does hereditary fructose intolerance present clinically?

Infant presents with:

- Vomiting
- Jaundice
- Hepatomegaly
- Hypoglycemia
  Symptoms start after fructose/sucrose ingestion.

---

14. What is essential fructosuria?

Benign disorder due to **fructokinase deficiency**.
Fructose appears in urine but no hypoglycemia or liver damage.

---

15. What is galactosemia?

Inherited defect of galactose metabolism, most commonly **GALT deficiency**, leading to accumulation of galactose-1-phosphate.

---

16. Why do infants with galactosemia develop cataracts?

Galactose is converted to **galactitol**, which accumulates in the lens ? osmotic damage ? cataract.

---

17. What are the main clinical features of classic galactosemia?

- Jaundice
- Hepatomegaly
- Cataracts
- Vomiting
- Failure to thrive
- Risk of *E. coli* sepsis

---

18. What is galactokinase deficiency?

A mild form of galactosemia presenting mainly with **infantile cataracts** without liver involvement.

---

19. Why is the galactose tolerance test used as a liver function test?

Because galactose is metabolized **almost exclusively in the liver**.
Delayed clearance indicates hepatic damage.

---

20. Name a benign inborn error detected by a reducing sugar test but without systemic symptoms.

Essential pentosuria or **fructosuria**.

---

21. Why does fructose appear in urine in fructosuria?

Due to **fructokinase deficiency**, so fructose remains unphosphorylated and spills into urine.

---

22. Which pathway is active in brain but not in liver?

Polyol pathway.

---

23. What sugar accumulates in semen if seminal vesicles are functioning normally?

Fructose.

---

24. What distinguishes HFI from fructosuria clinically?

- **HFI** ? hypoglycemia + jaundice + hepatomegaly
- **Fructosuria** ? asymptomatic

---

25. What is the toxic metabolite in classic galactosemia?

Galactose-1-phosphate.