MEDICAL EDUCATION RESOURCE

Metabolism of Fatty Acids

Metabolism of Fatty Acids

Fatty acid metabolism begins with **digestion and absorption of dietary lipids**, followed by **transport**, **oxidation**, and **energy production**.

? Digestion of Fats

Dietary fats are mainly:

- **Triacylglycerols (TAG)**
- Phospholipids
- Cholesterol esters
- Fat-soluble vitamins

They are **hydrophobic**, so digestion requires **emulsification**.

1. Emulsification in the Small Intestine

Performed by **bile salts** from the liver.

Functions:

- Break large fat droplets into small micelles
- Increase surface area for enzymes

- Keep lipids suspended in watery environment

No major digestion occurs in stomach except **gastric lipase**, which is minor.

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2. Pancreatic Enzymes for Fat Digestion

A. Pancreatic Lipase

- Acts on **TAG ? 2-monoacylglycerol + free fatty acids**
- Requires **colipase** for activation
- Inhibited by bile salts unless colipase binds

B. Phospholipase A?

- Converts **phospholipids ? lysophospholipids + fatty acid**

C. Cholesterol Esterase

- Converts **cholesterol esters ? free cholesterol + fatty acid**

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3. Formation of Mixed Micelles

Micelles contain:

- 2-monoacylglycerol
- Free fatty acids

- Lysophospholipids
- Cholesterol
- Bile salts

Micelles deliver lipids to **enterocytes** (brush border).

? Absorption of Fats

1. Transport into Intestinal Cells

- Micelles fuse with the brush border
- Lipids enter by diffusion
- Bile salts remain in lumen ? later reabsorbed in ileum (enterohepatic circulation)

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2. Re-esterification Inside Enterocytes

Inside the cell:

- FA + CoA ? **Fatty acyl-CoA**
- 2-monoglycerol + fatty acyl-CoA ? **TAG**
- Lysophospholipids ? phospholipids
- Cholesterol ? cholesterol esters

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3. Chylomicron Formation

TAG + cholesterol + phospholipids + apoB-48 ? **Chylomicrons**

Enter:

- Lymphatics (lacteals) ? thoracic duct ? systemic circulation

? ?-Oxidation of Fatty Acids

?-oxidation is the **mitochondrial pathway** that breaks down fatty acids to produce:

- **Acetyl-CoA**
- **NADH**
- **FADH?**

These products enter TCA cycle and electron transport chain.

1. Activation of Fatty Acids

Before entering mitochondria:

- **Fatty acid + CoA ? Fatty acyl-CoA**
- Enzyme: **Acyl-CoA synthetase**
- Occurs in cytosol
- Requires **ATP ? AMP + PPi** (equivalent to 2 ATP)

2. Transport into Mitochondria (Carnitine Shuttle)

Long-chain fatty acids require transport.

A. Carnitine Palmitoyl Transferase I (CPT-I)

- Located on outer mitochondrial membrane
- Converts **fatty acyl-CoA ? acyl-carnitine**

B. Carnitine–Acylcarnitine Translocase

- Moves acyl-carnitine into matrix

C. Carnitine Palmitoyl Transferase II (CPT-II)

- Regenerates **fatty acyl-CoA** inside mitochondria

Inhibition:

- CPT-I inhibited by **malonyl-CoA** (key control step)

3. Steps of ?-Oxidation (One Cycle)

Each cycle removes **2 carbons** from the fatty acid.

Step 1: Oxidation

Fatty acyl-CoA ? trans-?²-enoyl-CoA
Produces **FADH?**

Step 2: Hydration

Enoyl-CoA ? Hydroxyacyl-CoA

Step 3: Oxidation

Hydroxyacyl-CoA ? Ketoacyl-CoA
Produces **NADH**

Step 4: Thiolysis

Ketoacyl-CoA ?

- **Acetyl-CoA**
- **Fatty acyl-CoA (shorter by 2C)**

Cycle repeats until all carbons are released as acetyl-CoA.

? Energy Yield from ?-Oxidation

Example: **Palmitic acid (16C)**

- 7 cycles of ?-oxidation
- 8 Acetyl-CoA
- 7 NADH
- 7 FADH?

Total ATP ? **106 ATP** per palmitate.

(Without memorizing the number, understand pattern: more carbons ? more ATP.)

? Regulation of ?-Oxidation

1. CPT-I inhibition by malonyl-CoA

Prevents simultaneous:

- FA synthesis
- FA oxidation

2. Availability of NAD? / FAD

Needed for oxidation steps.

3. Hormonal control

- **Insulin ?** ?-oxidation
- **Glucagon ?** ?-oxidation

? Clinical Correlations

1. Carnitine Deficiency

- Muscle weakness
- Hypoglycemia
- Increased long-chain fatty acids in blood
  Occurs in:
- Malnutrition
- Liver disease
- Hemodialysis
- Genetic transporter defects

2. CPT-II Deficiency

- Muscle pain on exercise
- Myoglobinuria
- Rhabdomyolysis
  FA oxidation blocked.

3. Medium-chain acyl-CoA dehydrogenase (MCAD) Deficiency

- Hypoketotic hypoglycemia
- Vomiting
- Lethargy
- Sudden infant death (SIDS association)
  Occurs after fasting.

4. Refsum Disease

- Defect in ?-oxidation
- Phytanic acid accumulation
- Retinitis pigmentosa, neuropathy

(Important when discussing special FA pathways)

? Energetics of ?-Oxidation

The energy yield depends on the number of carbons in the fatty acid.

Example: Palmitic Acid (16 carbons)

It undergoes **7 cycles** of ?-oxidation.

Products from ?-oxidation

- **7 FADH?**
- **7 NADH**
- **8 Acetyl-CoA**

ATP yield

- Each FADH? ? **1.5 ATP** ? 7 × 1.5 = **10.5 ATP**
- Each NADH ? **2.5 ATP** ? 7 × 2.5 = **17.5 ATP**
- Each Acetyl-CoA ? **10 ATP** in TCA ? 8 × 10 = **80 ATP**

Total = 108 ATP

Minus **2 ATP** used during activation ? **Net = 106 ATP**

(This is the value usually quoted in exams.)

? General Rule for Even-Chain Fatty Acids

For a saturated fatty acid with **n carbons**:

- Number of cycles = (n/2) ? 1

- Number of Acetyl-CoA = n/2
- Total ATP = [(Number of cycles × 4 ATP) + (Number of Acetyl-CoA × 10 ATP)] ? 2 (Using modern ATP values)

? Oxidation of Odd-Chain Fatty Acids

Odd-chain fatty acids are found mainly in:

- Dairy fats
- Ruminant animals
- Some plant fats

?-oxidation proceeds normally until the last cycle.

End products:

- Multiple **Acetyl-CoA (2-carbon units)**
- One **Propionyl-CoA (3-carbon unit)**

Conversion of Propionyl-CoA to Succinyl-CoA

1. **Propionyl-CoA ? Methylmalonyl-CoA**
    - Enzyme: Propionyl-CoA carboxylase
    - Requires **Biotin**

2. **Methylmalonyl-CoA ? Succinyl-CoA**
    - Enzyme: Methylmalonyl-CoA mutase
    - Requires **Vitamin B?? (cobalamin)**
3. **Succinyl-CoA enters TCA cycle**

Clinical Correlation

- Vitamin **B?? deficiency** ? methylmalonic acidemia, methylmalonic aciduria
- Causes neurological damage

? ?-Oxidation of Fatty Acids

?-oxidation occurs when ?-oxidation **cannot** proceed due to a methyl group at the ?-carbon.

Main substrate:

Phytanic acid (branched-chain fatty acid from dairy products)

Why ?-oxidation fails:

A methyl group at ?-carbon blocks dehydrogenation.

Steps of ?-Oxidation

- Hydroxylation at the **?-carbon**
- Removal of 1 carbon ? forms **pristanic acid**

- Pristanic acid enters **?-oxidation**

Occurs mainly in **peroxisomes**.

Clinical Correlation – Refsum Disease

- Defect in **phytanoyl-CoA ?-hydroxylase**
- Leads to accumulation of **phytanic acid**

Features:

- Retinitis pigmentosa
- Peripheral neuropathy
- Ataxia
- Hearing loss

Treatment:

- Avoid dairy + chlorophyll-rich foods
- Plasmapheresis in severe cases

? ?-Oxidation of Fatty Acids

?-oxidation occurs when ?-oxidation is impaired or overloaded.

Site:

Endoplasmic reticulum (mostly liver & kidney)

Process:

- Oxidation begins at the **?-carbon** (terminal carbon)
- Produces **dicarboxylic acids**
- These dicarboxylic acids can undergo **?-oxidation** in peroxisomes

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Clinical Importance

- When ?-oxidation is defective (e.g., **MCAD deficiency**), the body increases ?-oxidation.
- **Dicarboxylic acids appear in urine** ? important diagnostic clue.

? Summary for Quick Revision

?-Oxidation: mitochondrial, produces Acetyl-CoA, NADH, FADH?
Odd-Chain FA: produce Propionyl-CoA ? Succinyl-CoA (requires B??)
?-Oxidation: handles branched-chain fatty acids (phytanic acid)
?-Oxidation: ER pathway ? produces dicarboxylic acids, active when ?-oxidation is blocked

? Organic Acidurias

Organic acidurias are **inborn errors of metabolism** involving defects in the breakdown of amino acids and odd-chain fatty acids.
They result in the accumulation of **organic acids** in blood and urine ? **metabolic acidosis**, **ketosis**, **hypoglycemia**, and **neurological dysfunction**.

These disorders often present in early infancy with serious symptoms after feeds.

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1. Methylmalonic Acidemia (MMA)

Cause

- Deficiency of **methylmalonyl-CoA mutase**
- Or deficiency of **Vitamin B??**

Biochemical Defect

Propionyl-CoA ? methylmalonyl-CoA ? **(blocked)** ? succinyl-CoA
Methylmalonic acid accumulates.

Clinical Features

- Severe metabolic acidosis
- Ketosis
- Hyperammonemia
- Lethargy, hypotonia
- Developmental delay

Key Note

B?? deficiency in infants mimics MMA.

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2. Propionic Acidemia

Cause

- Deficiency of **propionyl-CoA carboxylase**

Accumulation

- Propionic acid
- Methylcitrate

Clinical Features

- Recurrent vomiting
- Metabolic acidosis
- Hyperammonemia
- Neutropenia

Treatment

- Low-protein diet
- Biotin supplementation

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3. Multiple Carboxylase Deficiency

Includes:

- **Holocarboxylase synthetase deficiency**
- **Biotinidase deficiency**

Defect

Biotin cannot be used ? impaired carboxylation reactions.

Features

- Dermatitis
- Alopecia
- Acidosis
- Seizures

Treatment

- Biotin supplementation dramatically improves symptoms.

? De Novo Synthesis of Fatty Acids

Occurs mainly in:

- **Liver**
- Lactating mammary gland
- Adipose tissue

Occurs in the **cytosol**.

1. Starting Material

- **Acetyl-CoA**
- Obtained from mitochondria but transported as **citrate** (citrate shuttle)

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2. Conversion of Acetyl-CoA ? Malonyl-CoA

Enzyme: Acetyl-CoA Carboxylase (ACC)

- Rate-limiting enzyme
- Requires **biotin**
- Reaction: Acetyl-CoA + CO? ? **Malonyl-CoA**

Regulation of ACC

- **Activated by:** Insulin, citrate
- **Inhibited by:** Glucagon, epinephrine, AMP-activated protein kinase, palmitoyl-CoA

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3. Fatty Acid Synthase (FAS) Complex

A large multi-enzyme protein.

What FAS does

- Sequentially adds **2-carbon units** from malonyl-CoA
- Produces **palmitate (16C)** as primary end product

Cofactor required

- **NADPH**
  (from HMP shunt and malic enzyme)

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4. Steps in Fatty Acid Synthesis

Each cycle includes:

1. **Condensation**
2. **Reduction** (uses NADPH)
3. **Dehydration**
4. **Reduction** (uses NADPH)

Cycle repeats until 16 carbons are reached.

Summary of De Novo FA Synthesis

- Location: Cytosol
- Need: Acetyl-CoA, malonyl-CoA, NADPH
- Enzyme: FAS synthesizes **palmitic acid (16:0)**

- Hormone: Insulin stimulates the entire pathway

? Elongation of Fatty Acids

Occurs mainly in:

- **Smooth endoplasmic reticulum (SER)**
- **Mitochondria**

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1. ER Elongation

- Uses **malonyl-CoA** as carbon donor
- Adds 2C per cycle
- Produces long-chain fatty acids (>16C)

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2. Mitochondrial Elongation

- Uses **acetyl-CoA** as carbon donor
- Mainly elongates medium-chain FA
- Mechanism resembles ?-oxidation in reverse (but uses NADPH)

? Desaturation (Bonus – Needed for completeness)

Although not asked, this always comes with elongation in exams.

Enzymes: Desaturases

Present in ER.

Humans lack certain desaturases

- Cannot introduce double bonds beyond **C9**
- Hence **linoleic and ?-linolenic acids** are **essential fatty acids**

? Synthesis of Triglycerides (Triacylglycerols)

Occurs mainly in:

- Liver
- Adipose tissue
- Intestine

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1. Starting Materials

- **Glycerol-3-phosphate**
- **Fatty acyl-CoA**

Sources of Glycerol-3-Phosphate

- Liver: glycerol kinase or glycolysis
- Adipose tissue: **only from glycolysis** (due to lack of glycerol kinase)

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2. Steps of TAG Synthesis

Step 1

Glycerol-3-phosphate + fatty acyl-CoA ?
Lysophosphatidic acid

Step 2

Addition of another fatty acid ?
Phosphatidic acid

Step 3

Dephosphorylation ?
Diacylglycerol (DAG)

Step 4

Addition of 3rd fatty acid ?
Triacylglycerol (TAG)

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3. Fate of TAGs

In Liver

- Packaged into **VLDL**
- Released into blood

In Adipose Tissue

- Stored as fat droplets
- Mobilized during fasting by **hormone-sensitive lipase**

? Clinical Correlations

1. B?? deficiency

? Methylmalonic acidemia
? Neurological defects

2. Propionic acidemia

? Recurrent acidosis, hyperammonemia

3. Fatty liver

? Excess TAG synthesis
? Occurs in alcohol, diabetes, obesity, starvation

4. Essential FA deficiency

? Dermatitis
? Poor wound healing
? Growth retardation

5. MCAD deficiency

? Increased ?-oxidation ? dicarboxylic acids in urine

? Metabolism of Adipose Tissue

Adipose tissue is the **major storage site** for triglycerides (fat).
Its metabolism is controlled by **insulin**, **glucagon**, **catecholamines**, and overall nutritional status.

Adipocytes perform two key functions:

1. **Lipid storage (fed state)**
2. **Lipid mobilization (fasting state)**

? 1. Lipid Storage in Adipose Tissue (Fed State)

Activated in:

- After meals
- When insulin levels are high

Sources of Fatty Acids for Storage

1. **Dietary TAGs**
   Delivered as **chylomicrons** and **VLDL**.
2. **De novo lipogenesis (from liver)**
   Liver converts carbohydrates ? fatty acids ? VLDL ? adipose tissue.

Step-by-Step Storage Process

Step 1 — Lipoprotein Lipase (LPL) Activity

- Insulin **stimulates LPL** on capillary walls of adipose tissue.
- LPL hydrolyzes TAGs in:
  - Chylomicrons
  - VLDL
    ? releases **free fatty acids (FFAs)** + glycerol.

Step 2 — Uptake

- FFAs enter adipocytes.
- Glycerol cannot be used (no glycerol kinase in adipose tissue).

Step 3 — Glycerol-3-Phosphate Formation

- Glycerol-3-P is formed **from glycolysis**:
  Glucose ? DHAP ? glycerol-3-phosphate
- Requires insulin because insulin ? glucose uptake in adipocytes.

Step 4 — TAG Synthesis

Fatty acyl-CoA + glycerol-3-P ? TAGs
TAGs are stored as lipid droplets.

Key Hormone Regulation

- **Insulin promotes fat storage:**
  - ? LPL
  - ? Glucose uptake
  - ? TAG synthesis
  - ? Hormone-Sensitive Lipase
  - ? Lipogenesis

? 2. Lipid Mobilization (Fasting State)

When fasting or during stress, adipose tissue releases **fatty acids** for energy.

Triggered by:

- Low insulin
- High glucagon
- Catecholamines (epinephrine/noradrenaline)

The key enzyme responsible is **Hormone-Sensitive Lipase (HSL)**.

? Hormone-Sensitive Lipase (HSL)

HSL is the **rate-limiting enzyme for lipolysis** in adipose tissue.

? 1. Function

HSL breaks down stored TAGs into:

- Free fatty acids (FFA)
- Glycerol

Process:
TAG ? DAG ? MAG ? FA + glycerol
(HSL acts mainly on TAG and DAG)

? 2. Regulation of HSL

Activated by (fasting state):

- **Glucagon**

- **Epinephrine**
- **Norepinephrine**
- **ACTH**

Mechanism:

- Hormones ? ? cAMP ? activates **protein kinase A** ? **phosphorylates HSL** ? HSL becomes active.

Inhibited by (fed state):

- **Insulin**

Mechanism:

- Insulin ? ? cAMP ? activates phosphodiesterase ? dephosphorylates HSL ? **inactive**.
- Insulin also inhibits breakdown of TAGs by stimulating **phosphoprotein phosphatase**.

? 3. Fate of Lipolysis Products

A. Free Fatty Acids

- Released into blood
- Carried by **albumin**
- Used by:

- Liver
- Muscle
- Heart

Fuel source during fasting.

B. Glycerol

- Transported to **liver**
- Converted to:
  - **Glucose (via gluconeogenesis)**
  - **TAG synthesis**

? 3. Brown vs White Adipose Tissue (Exam Question)

White Adipose Tissue (WAT)

- Main storage depot
- Large single lipid droplet
- Few mitochondria
- Stores TAG for long-term energy

Brown Adipose Tissue (BAT)

- Many mitochondria

- Rich blood supply
- Contains **uncoupling protein-1 (UCP-1)**
- Generates heat (non-shivering thermogenesis)
- Prominent in newborns

? 4. Clinical Correlations

1. Obesity

- Excess TAG accumulation in adipocytes
- Insulin resistance increases due to adipokines

2. Diabetes Mellitus

- High HSL activity due to low insulin ? ? lipolysis
- Leads to ? FFAs ? ? ketogenesis ? diabetic ketoacidosis

3. Lipodystrophy

- Abnormal or absent adipose tissue
- Causes insulin resistance and fatty liver

4. Hormone-Sensitive Lipase Defect (rare)

- Causes impaired lipolysis

- Leads to enlarged adipocytes and fasting intolerance

? 5. Summary (Ultra-Short)

- **Insulin ? storage** (activates LPL, inhibits HSL)
- **Glucagon/epinephrine ? mobilization** (activate HSL via cAMP)
- HSL = key enzyme for TAG breakdown
- FFAs go to tissues for oxidation
- Glycerol goes to liver for gluconeogenesis

? Liver–Adipose Tissue Axis

The liver and adipose tissue work together to maintain **energy balance**, **lipid homeostasis**, and **glucose metabolism**.
They constantly exchange signals and metabolites depending on the fed or fasting state.

Think of them as two major metabolic partners regulating storage and release of fat.

? 1. Fed State (High Insulin)

In Adipose Tissue

- Insulin ? glucose uptake
- Glucose ? glycerol-3-phosphate

- FFA from chylomicrons/VLDL ? TAG synthesis
- **Hormone-sensitive lipase inhibited** ? ? lipolysis

In Liver

- Glucose ? acetyl-CoA ? **de novo FA synthesis**
- FA + glycerol ? TAG
- TAG ? **VLDL** ? exported to adipose tissue

Connection:
Adipose tissue stores the TAGs that liver produces.
Liver depends on adipose LPL (activated by insulin) for FFA uptake.

? 2. Fasting State (Low Insulin, High Glucagon)

In Adipose Tissue

- **HSL activated** ? TAG breakdown
- FFA released into blood (bound to albumin)
- Glycerol sent to liver ? gluconeogenesis

In Liver

- FFA undergo **?-oxidation** ? acetyl-CoA ? ATP
- Excess acetyl-CoA ? **ketogenesis**

- Glycerol ? glucose

Connection:
Adipose tissue supplies FFAs and glycerol ? liver produces glucose and ketone bodies ? used by muscle/brain.

? 3. Dysfunction of Liver–Adipose Axis

When this axis is disturbed (by obesity, insulin resistance), the liver receives more FFAs than it can handle ? **fatty liver**, **hypertriglyceridemia**, **metabolic syndrome**.

? Obesity

Obesity is a **chronic metabolic disease** with increased adipose mass and altered endocrine function of fat tissue.

Types:

- **Hypertrophic obesity** ? enlarged adipocytes (adult type)
- **Hyperplastic obesity** ? increased number of adipocytes (childhood type)

? 1. Adipose tissue as an endocrine organ

Adipose tissue secretes **adipokines**:

A. Leptin

- Signals satiety to hypothalamus
- Obesity ? **leptin resistance**

- Result: persistent hunger + reduced energy expenditure

B. Adiponectin

- Anti-inflammatory
- Enhances insulin sensitivity
- Obesity ? ? adiponectin ? insulin resistance

C. TNF-?, IL-6

- Promote inflammation
- Induce insulin resistance
- Contribute to metabolic syndrome

D. Resistin

- Promotes insulin resistance

? 2. Metabolic Consequences of Obesity

- **Insulin resistance**
- **Type 2 diabetes mellitus**
- **Dyslipidemia** (? TAG, ? HDL)
- **Hypertension**

- **Non-alcoholic fatty liver disease (NAFLD)**
- **Atherosclerosis**

? 3. Causes of Obesity

- Excess caloric intake
- Sedentary lifestyle
- Genetic predisposition
- Sleep deprivation
- Hypothyroidism
- Medications (steroids, antipsychotics)

? 4. Brown vs White Fat (High-yield)

White adipose tissue

- Energy storage
- Endocrine organ
- Large single droplet

Brown adipose tissue

- Thermogenesis (via UCP-1)
- Many mitochondria
- Prominent in infants

? Fatty Liver (Hepatic Steatosis)

Fatty liver occurs when triglycerides accumulate in hepatocytes because **inflow > outflow**.

Types:

- **Non-alcoholic fatty liver disease (NAFLD)**
- **Alcoholic fatty liver disease**

? 1. Causes of Fatty Liver

A. Increased Fat Delivery to Liver

- Obesity
- High-fat diet
- Increased lipolysis (uncontrolled diabetes, fasting)

B. Increased Lipogenesis

- High carbohydrate intake
- Excess insulin

- Fructose-rich diet
- Hyperinsulinemia activates ACC and FAS ? ? fatty acid synthesis

C. Decreased Fat Export

- ? VLDL synthesis
- Choline deficiency
- Protein malnutrition

D. Alcohol

- NADH accumulation
- Inhibits ?-oxidation
- Promotes fat deposition

? 2. Mechanism of Fatty Liver (Why liver fills with fat?)

Step 1: ? FFA supply from adipose tissue

Step 2: ? Fatty acid synthesis in liver (de novo lipogenesis)

Step 3: ? ?-oxidation (due to high NADH in alcohol or insulin resistance)

Step 4: ? VLDL secretion

? TAG accumulation in hepatocytes

? 3. Clinical Features

Fatty liver is often asymptomatic.
When severe:

- Hepatomegaly
- Right upper quadrant discomfort
- Elevated liver enzymes (ALT > AST in NAFLD)
- ALT < AST in alcoholic liver disease

? 4. Complications

- Steatohepatitis (NASH)
- Fibrosis
- Cirrhosis
- Hepatocellular carcinoma

? 5. Reversible vs Irreversible

- Early fatty liver is **reversible** with weight loss and metabolic control.
- Progression to NASH and fibrosis becomes partly irreversible.

? Integrated Summary

Liver–Adipose Axis:

- Fed state ? adipose stores fat, liver makes VLDL
- Fasted state ? adipose releases FFAs, liver oxidizes them ? ketones

Obesity:

- Enlarged adipose tissue ? releases inflammatory adipokines ? insulin resistance

Fatty Liver:

- Excess FFA delivery + high insulin + low FA oxidation ? TAG buildup in liver

? Lipotropic Factors

Lipotropic factors are **substances that prevent fat accumulation in the liver**.
They enhance **export of fat as VLDL** or increase oxidation of fatty acids.

Major Lipotropic Factors

1. Choline

- Required to synthesize **phosphatidylcholine (lecithin)**
- Lecithin is essential for **VLDL formation**
- Without choline ? ? VLDL ? fatty liver

2. Methionine

- Source of methyl groups ? needed for choline synthesis
- Deficiency ? impaired VLDL production ? fatty liver

3. Vitamin B?? & Folic Acid

- Participate in methyl group transfers
- Help in methionine synthesis ? indirectly maintain choline levels

4. Inositol

- Component of phospholipids
- Supports membrane integrity and fat mobilization

5. Polyunsaturated Fatty Acids

- Improve VLDL secretion
- Prevent fat accumulation in hepatocytes

Clinical relevance

- **Choline deficiency** ? hepatic steatosis
- High fructose diet **? lipogenesis**, worsening fatty liver unless lipotropic factors are adequate

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? Ketone Bodies

Ketone bodies are **water-soluble fuels** produced from excess acetyl-CoA when carbohydrate availability is low.

Three ketone bodies:

1. **Acetoacetate**

2. **?-hydroxybutyrate**
3. **Acetone** (volatile, exhaled; fruity breath smell)

? Ketogenesis

Ketogenesis is the process of **ketone body synthesis in the liver**, occurring in the **mitochondria** of hepatocytes.

Occurs in:

- Prolonged fasting
- Starvation
- Low-carbohydrate intake
- Uncontrolled diabetes mellitus
- High FFA oxidation

Mechanism (Stepwise)

1. Excess Fatty Acid Oxidation

? massive production of **acetyl-CoA**

2. Oxaloacetate diverted to gluconeogenesis

- TCA cycle slows
- Acetyl-CoA accumulates

3. Acetyl-CoA ? Acetoacetyl-CoA

4. Acetoacetyl-CoA ? HMG-CoA

Enzyme: **HMG-CoA synthase** (rate-limiting)

5. HMG-CoA ? Acetoacetate

Enzyme: **HMG-CoA lyase**

6. Acetoacetate ?

- **?-Hydroxybutyrate** (via NADH-dependent enzyme)
- **Acetone** (spontaneous decarboxylation)

Important

- Liver **produces** ketone bodies but **cannot use them** (lacks thiophorase enzyme)

? Ketolysis

Ketolysis is the **utilization of ketone bodies** for energy by extra-hepatic tissues.

Tissues that use ketone bodies:

- Brain (during starvation)
- Skeletal muscle
- Cardiac muscle
- Renal cortex

Steps:

1. **?-hydroxybutyrate ? acetoacetate**

2. Acetoacetate + succinyl-CoA ? acetoacetyl-CoA
    - Enzyme: **Succinyl-CoA:acetoacetate transferase (thiophorase)**
3. Acetoacetyl-CoA ? 2 acetyl-CoA
4. Acetyl-CoA enters TCA cycle ? ATP

Key point

Liver lacks thiophorase ? cannot utilize ketone bodies.

? Ketosis

Ketosis is the **accumulation of ketone bodies** in blood due to increased ketogenesis and/or decreased utilization.

Physiological ketosis

- Fasting
- Starvation
- Prolonged exercise
- Low-carb ketogenic diets
  Blood ketone levels mildly elevated; pH remains normal.

? Pathological Ketosis

1. Diabetic Ketoacidosis (DKA)

Occurs in uncontrolled **Type 1 diabetes**.

Mechanism:

- Low insulin ? high glucagon ? massive lipolysis
- Huge FFA influx to liver ? excessive ketogenesis
- Acetone ? fruity breath
- Severe acidosis ? Kussmaul breathing

2. Alcoholic Ketoacidosis

- Increased NADH ? impaired gluconeogenesis
- High fatty acid oxidation ? acetyl-CoA accumulates
- Leads to ketone overproduction

3. Starvation Ketosis

- Brain shifts to ketone use after 2–3 days
- Maximum ketone use at 20–30 days of starvation

? Regulation of Ketone Body Production

Stimulated by:

- Low insulin
- High glucagon
- High NADH/NAD? (alcohol)

- High fatty acid oxidation
- Low carbohydrate availability
- Decreased oxaloacetate (diverted for gluconeogenesis)

Inhibited by:

- Insulin
- High carbohydrate intake
- Low fatty acid supply
- Adequate oxaloacetate

? Clinical Correlations You Should Remember

1. DKA

- High blood ketones
- Metabolic acidosis
- Hyperventilation (Kussmaul)
- Fruity breath (acetone)

2. Starvation

- Ketones become **major brain fuel** (after 3 days)

3. Inborn errors

- HMG-CoA synthase deficiency ? impaired ketogenesis
- Thiophorase deficiency ? tissues cannot use ketones ? metabolic crisis

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? Ultra-Short Summary

- **Lipotropic factors** prevent fatty liver.
- **Ketone bodies**: acetoacetate, ?-hydroxybutyrate, acetone.
- **Ketogenesis** occurs in liver mitochondria.
- **Ketolysis** occurs in extra-hepatic tissues (not liver).
- **Ketosis** = elevated ketones; DKA = dangerous acidotic state.

? FAQs — COMPLETE CHAPTER: Fatty Acid Metabolism

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1. Where does digestion of dietary fat mainly occur?

In the **small intestine**, aided by bile salts and pancreatic lipase.

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2. What is the function of bile salts in fat digestion?

They **emulsify** fats, increasing surface area for enzymatic breakdown.

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3. Which enzyme is essential for pancreatic lipase activity?

Colipase.

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4. What are micelles?

Aggregates of fatty acids, 2-monoacylglycerol, cholesterol + bile salts that transport lipids to enterocytes.

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5. Where are chylomicrons formed?

In **intestinal mucosal cells (enterocytes)**.

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6. Which apoprotein is essential for chylomicron formation?

Apo-B48.

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7. What activates lipoprotein lipase (LPL) in adipose tissue?

Insulin.

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8. What is ?-oxidation?

Mitochondrial breakdown of fatty acids to produce **acetyl-CoA, NADH, FADH?**.

---

9. Which enzyme activates fatty acids before ?-oxidation?

Acyl-CoA synthetase, requiring ATP ? AMP + PPi.

---

10. What is the role of the carnitine shuttle?

Transports **long-chain fatty acyl-CoA** into mitochondria.

---

11. Which enzyme of the shuttle is inhibited by malonyl-CoA?

CPT-I (Carnitine Palmitoyl Transferase I).

---

12. What are the four reactions of ?-oxidation?

Oxidation ? hydration ? oxidation ? thiolysis.

---

13. Why does the liver generate ketone bodies during fasting?

Low insulin ? ? lipolysis ? ? acetyl-CoA ? limited OAA ? acetyl-CoA diverted to **ketogenesis**.

---

14. What are the three ketone bodies?

Acetoacetate, ?-hydroxybutyrate, acetone.

---

15. Why can’t the liver use ketone bodies?

It lacks **thiophorase (SCOT enzyme)**.

16. What is the rate-limiting enzyme of ketogenesis?

HMG-CoA synthase.

---

17. What causes the fruity breath odor in ketosis?

Acetone.

---

18. What is the ATP yield from complete oxidation of palmitic acid?

106 ATP (net).

---

19. What is produced at the end of odd-chain fatty acid oxidation?

Propionyl-CoA (3C).

---

20. Which vitamin is required for converting propionyl-CoA to succinyl-CoA?

Vitamin B??.

---

21. What is methylmalonic acidemia?

Organic aciduria due to **B?? deficiency** or **methylmalonyl-CoA mutase defect**.

---

22. What is ?-oxidation and where does it occur?

Oxidation in **peroxisomes** used for **branched-chain fatty acids** like phytanic acid.

---

23. Which disease results from defective ?-oxidation?

Refsum disease.

---

24. What is ?-oxidation?

ER-based oxidation at the **terminal carbon**, producing **dicarboxylic acids**.

---

25. In which condition do dicarboxylic acids appear in urine?

When ?-oxidation is defective (e.g., **MCAD deficiency**).

---

26. What is the starting molecule for fatty acid synthesis?

Acetyl-CoA, transported out of mitochondria as citrate.

---

27. What is the rate-limiting enzyme of fatty acid synthesis?

Acetyl-CoA carboxylase (ACC).

---

28. Which cofactor does ACC require?

Biotin.

29. What regulates ACC?

- Activated by **insulin**, citrate
- Inhibited by **glucagon, epinephrine, AMP-kinase**

---

30. What is the main product of fatty acid synthase (FAS)?

Palmitate (16-carbon saturated FA).

---

31. What is required for fatty acid synthesis?

NADPH, mainly from the **HMP shunt** and malic enzyme.

---

32. Where does fatty acid elongation occur?

ER and **mitochondria**.

---

33. What are TAGs synthesized from?

Glycerol-3-phosphate + fatty acyl-CoA.

---

34. Why can't adipose tissue use free glycerol?

It lacks **glycerol kinase**.

---

35. Which enzyme is responsible for fat mobilization during fasting?

Hormone-sensitive lipase (HSL).

---

36. What activates hormone-sensitive lipase?

Glucagon, epinephrine, via ? cAMP and PKA.

---

37. What inhibits hormone-sensitive lipase?

Insulin.

---

38. What is the liver–adipose tissue axis?

A metabolic partnership where adipose provides **FFAs & glycerol** to liver during fasting, and liver provides **VLDL & glucose** in fed state.

---

39. What are adipokines?

Signaling molecules from adipose tissue (e.g., leptin, adiponectin, TNF-?).

---

40. What changes occur to leptin in obesity?

Leptin levels ? but **leptin resistance** develops ? overeating.

---

41. Why do obese individuals develop insulin resistance?

Due to inflammatory adipokines: **TNF-?, IL-6, resistin**.

---

42. What is fatty liver?

Excess triglyceride accumulation in the liver due to:

- ? FFA supply
- ? lipogenesis
- ? ?-oxidation
- ? VLDL secretion

---

43. Which nutrient deficiency causes fatty liver?

Choline (lipotropic factor).

---

44. What is the difference between NAFLD and alcoholic fatty liver?

- NAFLD ? insulin resistance–driven
- Alcoholic ? high NADH inhibits ?-oxidation

---

45. What is the danger in diabetic ketoacidosis?

Severe **metabolic acidosis** from unchecked ketogenesis.

---

46. Why does ?-hydroxybutyrate predominate in DKA?

High **NADH/NAD? ratio** favors its formation over acetoacetate.

---

47. Why is ketosis mild in starvation?

Because insulin is low but **not completely absent** like in DKA.

---

48. Which tissues prefer ketone bodies as fuel?

Brain (after 2–3 days fasting), heart, skeletal muscle.

---

49. What is the function of lipotropic factors?

Help export fat from liver ? **prevent fatty liver**.

---

50. What is the final fate of ketone bodies in tissues?

Converted back to **acetyl-CoA** ? enters TCA ? ATP production.

? Clinical Problems — Fatty Acid Metabolism (Full Chapter)

---

1. Infant with hypoketotic hypoglycemia after overnight fasting

A 6-month-old infant presents with vomiting, seizures, and lethargy after a night of sleep.
Blood tests show **no ketone bodies**, severe hypoglycemia, and **dicarboxylic acids** in urine.

Diagnosis:

MCAD deficiency (Medium-chain acyl-CoA dehydrogenase deficiency)

Reason:

?-oxidation fails ? low acetyl-CoA ? low ketones ? ? ?-oxidation ? dicarboxylic acids.

---

2. Muscle pain & myoglobinuria after exercise

A 20-year-old male experiences extreme muscle cramps and cola-colored urine after strenuous exercise.
CK levels are high. Plasma free fatty acids rise after exercise.

Diagnosis:

CPT-II deficiency

Reason:

Fatty acids cannot enter mitochondria ? energy crisis in muscles ? rhabdomyolysis.

---

3. Child with developmental delay + high methylmalonic acid

A 1-year-old child has hypotonia, seizures, metabolic acidosis, and very high **methylmalonic acid** in urine.

Diagnosis:

Methylmalonic acidemia

Cause:

- Vitamin **B12 deficiency**, or
- **Methylmalonyl-CoA mutase defect**

Biochemical basis:

Propionyl-CoA cannot ? Succinyl-CoA.

---

4. Fasting adult with fruity breath & deep breathing

A 38-year-old diabetic man stops insulin for 2 days.
He arrives with abdominal pain, dehydration, and **Kussmaul breathing**. Breath smells fruity.

Diagnosis:

Diabetic ketoacidosis (DKA)

Key biochemical features:

- Excess lipolysis ? ? FFAs
- High acetyl-CoA ? massive **ketogenesis**
- High NADH ? ? ?-hydroxybutyrate
- Metabolic acidosis

---

5. Alcoholic with metabolic acidosis but normal glucose

A chronic alcoholic presents with abdominal pain, tachycardia, and severe acidosis.
Blood glucose is low or normal. Ketone levels are elevated.

Diagnosis:

Alcoholic ketoacidosis

Mechanism:

Ethanol metabolism ? ? NADH ? ? gluconeogenesis ? ? lipolysis ? ketone production.

---

6. Child with hepatomegaly & fatty liver but normal glucose

A 4-year-old child presents with enlarged liver.
No hypoglycemia.
Diet history reveals high intake of polished rice + low-protein diet.

Diagnosis:

Fatty liver due to choline deficiency

Reason:

? VLDL synthesis ? fat trapped in hepatocytes
(lack of lipotropic factors: choline, methionine).

---

7. Elderly woman with night blindness + neuropathy

A woman consuming huge amounts of dairy products develops neuropathy, retinitis pigmentosa, and scaly skin.

Diagnosis:

Refsum disease (?-oxidation defect)

Cause:

Defective **phytanoyl-CoA ?-hydroxylase** ? phytanic acid accumulation.

---

8. Obese man with insulin resistance & high triglycerides

A 45-year-old obese man has central obesity, low HDL, high LDL, high fasting glucose.

Diagnosis:

Metabolic syndrome

Mechanism:

Inflammatory adipokines (TNF-?, IL-6, resistin) ? insulin resistance
Visceral fat ? continuous FFA delivery to liver ? TAG & VLDL elevation.

---

9. Patient with fatty liver but no alcohol consumption

A 50-year-old non-drinker shows hepatomegaly, elevated ALT > AST, and ultrasound shows steatosis.

Diagnosis:

Non-alcoholic fatty liver disease (NAFLD)

Biochemical basis:

- Insulin resistance ? ? lipolysis ? ? FFA
- ? de novo lipogenesis
- ? ?-oxidation
- ? VLDL export

---

10. Severe fasting intolerance in infant

A 3-month-old infant becomes unresponsive after 6 hours without feeding.
Blood glucose is very low and ketone bodies are also low.

Diagnosis:

CPT-I deficiency

Mechanism:

Impaired transport of fatty acyl-CoA into mitochondria ? no ?-oxidation ? no ketones ? severe hypoglycemia.

---

11. Starving man with normal glucose & high ketones

A man fasting for 5 days has mild metabolic acidosis, ketonuria, but is alert and stable.

Diagnosis:

Physiological starvation ketosis

Reason:

Low insulin ? moderate ketogenesis
Brain begins using ketones ? glucose sparing.

---

12. Man with fatty liver + lactic acidosis after alcohol binge

A 30-year-old drinks heavily for 12 hours.
He has vomiting, high NADH levels, and fatty liver.

Diagnosis:

Alcohol-induced fatty liver

Biochemical reason:

High NADH inhibits:

- ?-oxidation
- TCA cycle
  Causing acetyl-CoA ? TAG accumulation.

---

13. Thin child with delayed puberty, low adipose & fatty liver

A 12-year-old child shows extreme leanness, liver steatosis, and high insulin levels.

Diagnosis:

Lipodystrophy

Reason:

Loss of adipose tissue ?
Glucose stored in liver ? fat deposited in liver ? insulin resistance.

---

14. Muscle weakness after high-fat meal

A man develops severe fatigue 30 minutes after a fatty meal.
Plasma long-chain acyl-carnitine levels are high.

Diagnosis:

Carnitine deficiency

Why?

Fat cannot enter mitochondria ? energy deficit.

---

15. Newborn with oily, large stool (steatorrhea)

A baby has bulky, foul-smelling stools.
History shows pancreatic insufficiency.

Diagnosis:

Impaired **fat digestion** due to ? pancreatic lipase.

---

16. Person on keto diet with ketonuria but normal pH

Ketonuria (+3)
Serum bicarbonate normal
No dehydration

Diagnosis:

Diet-induced physiological ketosis
Not dangerous — simply low carb intake ? ? ketogenesis.

---

17. Teenager collapses during football match

Glucose normal
Ketone bodies normal
Lactate high
Free fatty acids ?
Ammonia normal

Diagnosis:

?-oxidation defect (likely VLCAD or LCHAD deficiency)

---

18. Breastfed infant with vomiting after each feed

Vomiting + hepatomegaly
Positive reducing sugar
No glucose in urine
Early cataracts

Diagnosis:

Galactokinase deficiency
(Overlaps FA metabolism because cataract comes from galactitol via polyol pathway)

? MCQs — Fatty Acid Metabolism (Complete Chapter)

---

1. The enzyme required for activation of fatty acids before ?-oxidation is:

A. CPT-I
B. Acyl-CoA synthetase
C. Hormone-sensitive lipase
D. Fatty acid synthase

Answer: B
Explanation: Activates fatty acids to fatty acyl-CoA in cytosol.

---

2. Carnitine shuttle is required for transport of:

A. Short-chain fatty acids
B. Medium-chain fatty acids
C. Long-chain fatty acids
D. Ketone bodies

Answer: C

Explanation: Long-chain fatty acids cannot cross mitochondrial membrane without carnitine.

---

3. CPT-I is inhibited by:

A. Insulin

B. Glucagon

C. Malonyl-CoA

D. Citrate

Answer: C

Explanation: Malonyl-CoA prevents ?-oxidation during fatty acid synthesis.

---

4. End product of odd-chain fatty acid oxidation is:

A. Acetyl-CoA

B. Propionyl-CoA

C. Succinyl-CoA

D. Malonyl-CoA

Answer: B

Explanation: Final 3-carbon fragment is propionyl-CoA.

---

5. Conversion of propionyl-CoA to succinyl-CoA requires:

A. Vitamin B6

B. Vitamin B12

C. Biotin

D. Thiamine

Answer: B

Explanation: Methylmalonyl-CoA mutase needs vitamin B12.

6. Disease caused by defective ?-oxidation is:

A. MCAD deficiency
B. Refsum disease
C. Tay-Sachs disease
D. Gaucher disease

Answer: B
Explanation: Accumulation of phytanic acid due to ?-oxidation defect.

---

7. ?-oxidation occurs in:

A. Cytosol
B. Mitochondria
C. Endoplasmic reticulum
D. Peroxisomes

Answer: C
Explanation: Produces dicarboxylic acids when ?-oxidation is impaired.

---

8. Which enzyme is rate-limiting in fatty acid synthesis?

A. Fatty acid synthase
B. Acetyl-CoA carboxylase
C. HMG-CoA synthase
D. Glycogen phosphorylase

Answer: B
Explanation: ACC forms malonyl-CoA.

---

9. Fatty acid synthase (FAS) mainly produces:

A. Stearic acid
B. Oleic acid
C. Palmitic acid
D. Arachidonic acid

Answer: C
Explanation: De novo synthesis yields palmitate (16:0).

---

10. Essential lipotropic factor for preventing fatty liver:

A. Biotin
B. Thiamine
C. Choline
D. Niacin

Answer: C
Explanation: Needed for phosphatidylcholine ? VLDL formation.

---

11. Major fuel for the brain during prolonged fasting:

A. Glucose
B. Ketone bodies
C. Fatty acids
D. Lactate

Answer: B
Explanation: Brain uses ketones after 2–3 days of fasting.

---

12. Rate-limiting enzyme of ketogenesis:

A. HMG-CoA synthase
B. CPT-I
C. Thiophorase
D. Acetyl-CoA carboxylase

Answer: A

---

13. Liver cannot utilize ketone bodies because it lacks:

A. HMG-CoA synthase
B. Thiophorase
C. CPT-II
D. Acyl-CoA dehydrogenase

Answer: B

---

14. Fruity odor of breath in ketosis is due to:

A. Acetoacetate
B. ?-hydroxybutyrate
C. Acetone
D. Ethanol

Answer: C

---

15. ?-hydroxybutyrate predominates in diabetic ketoacidosis because:

A. Low NADH
B. High NADH
C. Low acetyl-CoA

D. Low fatty acid oxidation

Answer: B

---

16. Enzyme responsible for lipolysis during fasting is:

A. LPL
B. HSL
C. CPT-II
D. Acetyl-CoA carboxylase

Answer: B

---

17. Hormone that inhibits hormone-sensitive lipase:

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

Answer: C

---

18. Elevated dicarboxylic acids in urine suggest:

A. Increased ?-oxidation
B. Increased ?-oxidation
C. Decreased lipogenesis
D. Increased esterification

Answer: B

---

19. MCAD deficiency classically shows:

A. High ketones
B. Normal fatty acid oxidation
C. Hypoketotic hypoglycemia
D. Hyperketosis

Answer: C

---

20. Main source of NADPH for fatty acid synthesis:

A. Glycolysis
B. HMP shunt
C. TCA cycle
D. Mitochondrial ETC

Answer: B

---

21. Adipose tissue requires insulin for fat storage because insulin:

A. Activates HSL
B. Activates LPL
C. Inhibits glycolysis
D. Inhibits TAG formation

Answer: B

---

22. Brown adipose tissue produces heat through:

A. CPT-I
B. Uncoupling protein-1
C. Carnitine

D. FAS complex

Answer: B

---

23. Fatty liver in alcoholics is mainly due to:

A. Lack of lipoproteins
B. High NADH inhibiting ?-oxidation
C. Excess dietary fat
D. Elevated insulin

Answer: B

---

24. Hormone stimulating ketogenesis:

A. Insulin
B. Glucagon
C. TSH
D. Aldosterone

Answer: B

---

25. TAG synthesis in adipose tissue requires glycerol-3-phosphate derived from:

A. Glycerol kinase
B. Glycolysis
C. Pentose phosphate pathway
D. Amino acid breakdown

Answer: B
Explanation: Adipose lacks glycerol kinase; depends on glucose supply.

? Viva Voce — Fatty Acid Metabolism (Complete Chapter)

1. What is the primary site of fat digestion?

Small intestine, aided by bile salts and pancreatic lipase.

2. What is the role of bile salts in fat digestion?

They **emulsify fats**, increasing surface area for lipase action.

3. Which enzyme breaks down dietary triacylglycerols?

Pancreatic lipase, with the help of **colipase**.

4. What are mixed micelles?

Aggregates of fatty acids, 2-monoacylglycerol, cholesterol + bile salts used for absorption.

5. Where are chylomicrons formed?

In **intestinal mucosal cells (enterocytes)**.

6. What is the function of lipoprotein lipase (LPL)?

Hydrolyzes TAGs in **chylomicrons & VLDL** into FFAs for uptake into tissues.

7. Which hormone stimulates LPL in adipose tissue?

Insulin.

---

8. What is ?-oxidation?

Mitochondrial breakdown of fatty acids into **acetyl-CoA, NADH, FADH?**.

---

9. Where does activation of fatty acids occur?

In the **cytosol**, via **acyl-CoA synthetase**.

---

10. Why is the carnitine shuttle needed?

It transports **long-chain fatty acyl-CoA** into mitochondria.

---

11. Which enzyme in the carnitine shuttle is inhibited by malonyl-CoA?

CPT-I.

---

12. How many carbons are removed in each cycle of ?-oxidation?

Two carbons as acetyl-CoA.

---

13. What is the net ATP yield from palmitic acid?

106 ATP.

14. What is the final product of odd-chain fatty acid oxidation?

Propionyl-CoA.

---

15. Which vitamin is essential for converting propionyl-CoA to succinyl-CoA?

Vitamin B??.

---

16. What is ?-oxidation?

Oxidation of **branched-chain fatty acids** (e.g., phytanic acid) in **peroxisomes**.

---

17. Name a disease caused by defective ?-oxidation.

Refsum disease.

---

18. What is ?-oxidation and where does it occur?

Oxidation at the **terminal carbon** of a fatty acid; occurs in the **endoplasmic reticulum**, forming dicarboxylic acids.

---

19. When does ?-oxidation increase?

When ?-oxidation is defective (e.g., **MCAD deficiency**).

---

20. What is the rate-limiting enzyme of fatty acid synthesis?

Acetyl-CoA carboxylase (ACC).

---

21. Which cofactor does ACC require?

Biotin.

---

22. What is the starting substrate for de novo fatty acid synthesis?

Acetyl-CoA, transported out of mitochondria as citrate.

---

23. What is the main product of fatty acid synthase?

Palmitate (16-carbon saturated fatty acid).

---

24. What is the major source of NADPH for fatty acid synthesis?

HMP shunt and **malic enzyme**.

---

25. Why can't adipose tissue use free glycerol for TAG synthesis?

It lacks **glycerol kinase**.

---

26. Which enzyme breaks down stored TAGs during fasting?

Hormone-sensitive lipase (HSL).

27. Which hormone inhibits HSL?

Insulin.

---

28. Which hormones activate HSL?

Glucagon, epinephrine, norepinephrine, via ? cAMP.

---

29. What is the liver–adipose tissue axis?

A metabolic partnership where:

- Liver sends **VLDL & glucose** to adipose tissue
- Adipose sends **FFAs & glycerol** to liver

---

30. Why does obesity lead to insulin resistance?

Because adipose tissue releases **inflammatory adipokines** (TNF-?, IL-6, resistin).

---

31. What hormone is elevated in obesity but ineffective?

Leptin ? due to **leptin resistance**.

---

32. What causes fatty liver in obesity or diabetes?

- ? FFA delivery to liver
- ? de novo lipogenesis
- ? ?-oxidation
- ? VLDL secretion

---

33. Which nutrient deficiency leads to fatty liver?

Choline (lipotropic factor).

---

34. What are ketone bodies?

Acetoacetate, ?-hydroxybutyrate, acetone.

---

35. Where does ketogenesis occur?

In **mitochondria of liver**.

---

36. Why does the liver produce ketone bodies but not use them?

It lacks **thiophorase (SCOT)**.

---

37. What is the rate-limiting enzyme of ketogenesis?

HMG-CoA synthase.

---

38. Which ketone body causes fruity breath?

Acetone.

---

39. Why is ketosis mild during starvation?

Because insulin is low but not absent, so ketone production is controlled.

---

40. What is the biochemical feature of diabetic ketoacidosis (DKA)?

High ketones + metabolic acidosis + high NADH/NAD? ? ? ?-hydroxybutyrate.