

# Metabolism of Fatty Acids

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

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### ? Digestion of Fats

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Dietary fats are mainly:

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

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

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### 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).

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## ? Absorption of Fats

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### 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

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### β-oxidation of Fatty Acids

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

- **Acetyl-CoA**
- **NADH**
- **FADH<sub>2</sub>**

These products enter TCA cycle and electron transport chain.

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### 1. Activation of Fatty Acids

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Before entering mitochondria:

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

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### 2. Transport into Mitochondria (Carnitine Shuttle)

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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)

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## 3. Steps of $\beta$ -Oxidation (One Cycle)

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

### Step 1: Oxidation

Fatty acyl-CoA → trans- $\beta^2$ -enoyl-CoA

Produces **FADH<sub>2</sub>**

### 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.

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### → Energy Yield from →-Oxidation

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

- 7 cycles of →-oxidation
- 8 Acetyl-CoA
- 7 NADH
- 7 FADH<sub>2</sub>

Total ATP → **106 ATP** per palmitate.

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

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### → Regulation of →-Oxidation

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#### 1. CPT-I inhibition by malonyl-CoA

Prevents simultaneous:

- FA synthesis
- FA oxidation

## 2. Availability of NAD<sup>+</sup> / FAD

Needed for oxidation steps.

## 3. Hormonal control

- **Insulin** ↑ β-oxidation
- **Glucagon** ↑ β-oxidation

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## ? Clinical Correlations

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### 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  $\alpha$ -oxidation
- Phytanic acid accumulation
- Retinitis pigmentosa, neuropathy

(Important when discussing special FA pathways)

### ? Energetics of $\alpha$ -Oxidation

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

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### Example: Palmitic Acid (16 carbons)

It undergoes **7 cycles** of  $\beta$ -oxidation.

#### Products from $\beta$ -oxidation

- 7  $\text{FADH}_2$
- 7  $\text{NADH}$
- 8 Acetyl-CoA

#### ATP yield

- Each  $\text{FADH}_2$   $\rightarrow$  **1.5 ATP**  $\rightarrow 7 \times 1.5 = \mathbf{10.5 \text{ ATP}}$
- Each  $\text{NADH}$   $\rightarrow$  **2.5 ATP**  $\rightarrow 7 \times 2.5 = \mathbf{17.5 \text{ ATP}}$
- Each Acetyl-CoA  $\rightarrow$  **10 ATP** in TCA  $\rightarrow 8 \times 10 = \mathbf{80 \text{ ATP}}$

**Total = 108 ATP**

Minus **2 ATP** used during activation  $\rightarrow$  **Net = 106 ATP**

(This is the value usually quoted in exams.)

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### $\beta$ 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  $\times$  4 ATP) + (Number of Acetyl-CoA  $\times$  10 ATP ) ]  $\times$  2  
(Using modern ATP values)

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## ? Oxidation of Odd-Chain Fatty Acids

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Odd-chain fatty acids are found mainly in:

- Dairy fats
- Ruminant animals
- Some plant fats

$\beta$ -oxidation proceeds normally until the last cycle.

**End products:**

- Multiple **Acetyl-CoA (2-carbon units)**
  - One **Propionyl-CoA (3-carbon unit)**
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## Conversion of Propionyl-CoA to Succinyl-CoA

### 1. Propionyl-CoA $\rightarrow$ Methylmalonyl-CoA

- Enzyme: Propionyl-CoA carboxylase
- Requires **Biotin**

## 2. Methylmalonyl-CoA → Succinyl-CoA

- Enzyme: Methylmalonyl-CoA mutase
- Requires **Vitamin B<sub>12</sub> (cobalamin)**

## 3. Succinyl-CoA enters TCA cycle

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### Clinical Correlation

- Vitamin **B<sub>12</sub> deficiency** → methylmalonic acidemia, methylmalonic aciduria
  - Causes neurological damage
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### α-oxidation of Fatty Acids

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

**Main substrate:**

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

**Why α-oxidation fails:**

A methyl group at α-carbon blocks dehydrogenation.

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### Steps of α-Oxidation

- Hydroxylation at the **α-carbon**
  - Removal of 1 carbon → forms **pristanic acid**
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- Pristanic acid enters  **$\beta$ -oxidation**

Occurs mainly in **peroxisomes**.

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### Clinical Correlation – Refsum Disease

- Defect in **phytanoyl-CoA  $\beta$ -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

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### **$\alpha$ $\beta$ -Oxidation of Fatty Acids**

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$\alpha$ -oxidation occurs when  $\beta$ -oxidation is impaired or overloaded.

#### Site:

**Endoplasmic reticulum** (mostly liver & kidney)

**Process:**

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

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### Clinical Importance

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

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### $\alpha$ Summary for Quick Revision

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**$\beta$ -Oxidation:** mitochondrial, produces Acetyl-CoA, NADH, FADH $\alpha$

**Odd-Chain FA:** produce Propionyl-CoA  $\alpha$  Succinyl-CoA (requires B $\alpha\alpha$ )

**$\alpha$ -Oxidation:** handles branched-chain fatty acids (phytanic acid)

**$\alpha$ -Oxidation:** ER pathway  $\alpha$  produces dicarboxylic acids, active when  $\beta$ -oxidation is blocked

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### $\alpha$ Organic Acidurias

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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  $\alpha$  **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.

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## **? De Novo Synthesis of Fatty Acids**

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Occurs mainly in:

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

Occurs in the **cytosol**.

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## 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<sub>2</sub> ? **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.

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## 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

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## ? Elongation of Fatty Acids

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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  $\beta$ -oxidation in reverse (but uses NADPH)

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## ? Desaturation (Bonus – Needed for completeness)

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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  $\gamma$ -linolenic acids** are **essential fatty acids**

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## ? Synthesis of Triglycerides (Triacylglycerols)

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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**
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## ? Clinical Correlations

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### 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

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

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### 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.

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### 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

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## ? 2. Lipid Mobilization (Fasting State)

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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)**.

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## ? Hormone-Sensitive Lipase (HSL)

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

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### ? 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)

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### ? 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**.

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### ? 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**

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

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### **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

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## ? 4. Clinical Correlations

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### 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

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## ? 5. Summary (Ultra-Short)

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- **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

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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.

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### ? 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.

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## ? 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.

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## ? 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.**

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### ? Obesity

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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)
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## ? 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- $\alpha$ , IL-6**

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

## **D. Resistin**

- Promotes insulin resistance

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## **? 2. Metabolic Consequences of Obesity**

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

- **Non-alcoholic fatty liver disease (NAFLD)**
  - **Atherosclerosis**
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### **? 3. Causes of Obesity**

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

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## ? Fatty Liver (Hepatic Steatosis)

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

**Types:**

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

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## ? 1. Causes of Fatty Liver

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### 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 β-oxidation
- Promotes fat deposition

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

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Step 1: ↑ FFA supply from adipose tissue

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

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

Step 4: ↓ VLDL secretion

↑ TAG accumulation in hepatocytes

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## 3. Clinical Features

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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

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#### ? 4. Complications

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

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#### ? 5. Reversible vs Irreversible

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

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#### ? Integrated Summary

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**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

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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

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

### Three ketone bodies:

1. **Acetoacetate**

2. **β-hydroxybutyrate**

3. **Acetone** (volatile, exhaled; fruity breath smell)

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## ? Ketogenesis

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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)

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#### ? Ketolysis

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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.**

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## ? Ketosis

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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

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### 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<sup>+</sup> (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

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#### 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

---

## ? Ultra-Short Summary

---

- **Lipotropic factors** prevent fatty liver.
- **Ketone bodies:** acetoacetate,  $\beta$ -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.

---

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

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

---

### 3. Which enzyme is essential for pancreatic lipase activity?

Colipase.

---

### 4. What are micelles?

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

---

### 5. Where are chylomicrons formed?

In intestinal mucosal cells (enterocytes).

---

### 6. Which apoprotein is essential for chylomicron formation?

Apo-B48.

---

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

Insulin.

---

### 8. What is $\beta$ -oxidation?

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

---

### 9. Which enzyme activates fatty acids before $\beta$ -oxidation?

Acyl-CoA synthetase, requiring ATP  $\rightarrow$  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 $\beta$ -oxidation?

Oxidation  $\rightarrow$  hydration  $\rightarrow$  oxidation  $\rightarrow$  thiolysis.

---

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

Low insulin  $\rightarrow$  lipolysis  $\rightarrow$  acetyl-CoA  $\rightarrow$  limited OAA  $\rightarrow$  acetyl-CoA diverted to **ketogenesis**.

---

### 14. What are the three ketone bodies?

Acetoacetate,  $\beta$ -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 $\alpha$ -oxidation and where does it occur?

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

---

## 23. Which disease results from defective $\alpha$ -oxidation?

**Refsum disease.**

---

## 24. What is $\omega$ -oxidation?

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

---

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

When  $\alpha$ -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- $\alpha$** , **IL-6**, **resistin**.

---

#### 42. What is fatty liver?

Excess triglyceride accumulation in the liver due to:

- ? FFA supply
  - ? lipogenesis
  - ?  $\beta$ -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  $\beta$ -oxidation
-

#### 45. What is the danger in diabetic ketoacidosis?

Severe **metabolic acidosis** from unchecked ketogenesis.

---

#### 46. Why does $\beta$ -hydroxybutyrate predominate in DKA?

High **NADH/NAD<sup>+</sup> 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** (α-oxidation defect)

**Cause:**

Defective **phytanoyl-CoA α-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- $\alpha$ , IL-6, resistin)  $\rightarrow$  insulin resistance

Visceral fat  $\rightarrow$  continuous FFA delivery to liver  $\rightarrow$  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  $\rightarrow$  lipolysis  $\rightarrow$  FFA
  - $\rightarrow$  de novo lipogenesis
  - $\rightarrow$   $\beta$ -oxidation
  - $\rightarrow$  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  $\beta$ -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:

- $\beta$ -oxidation
  - TCA cycle
- Causing acetyl-CoA  $\rightarrow$  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  $\rightarrow$

Glucose stored in liver  $\rightarrow$  fat deposited in liver  $\rightarrow$  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  $\rightarrow$  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 $\beta$ -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  $\beta$ -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  $\alpha$ -oxidation is:**

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

**Answer: B**

**Explanation:** Accumulation of phytanic acid due to  $\alpha$ -oxidation defect.

---

**7.  $\alpha$ -oxidation occurs in:**

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

**Answer: C**

**Explanation:** Produces dicarboxylic acids when  $\alpha$ -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.  $\beta$ -hydroxybutyrate
- C. Acetone
- D. Ethanol

**Answer: C**

---

### 15. $\beta$ -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  $\beta$ -oxidation
- B. Increased  $\omega$ -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  $\beta$ -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.

### 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 $\beta$ -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 $\beta$ -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<sub>12</sub>.

---

16. What is  $\alpha$ -oxidation?

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

---

17. Name a disease caused by defective  $\alpha$ -oxidation.

Refsum disease.

---

18. What is  $\omega$ -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  $\omega$ -oxidation increase?

When  $\omega$ -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
  - ?  $\beta$ -oxidation
  - ? VLDL secretion
- 

### 33. Which nutrient deficiency leads to fatty liver?

**Choline** (lipotropic factor).

---

### 34. What are ketone bodies?

Acetoacetate,  $\beta$ -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<sup>+</sup> → 3-hydroxybutyrate.