

Citric Acid Cycle

? CITRIC ACID CYCLE (TCA CYCLE)

The final common oxidative pathway of carbohydrates, fats, and proteins.

Occurs in the **mitochondrial matrix**.

? OVERVIEW OF THE CYCLE

Acetyl-CoA (2C) + Oxaloacetate (4C) ? Citrate (6C) ? series of oxidative decarboxylations ? regeneration of oxaloacetate.

Produces **NADH, FADH?**, **GTP, CO?** ? used for ATP generation in ETC.

? REACTIONS OF THE TCA CYCLE (STEPWISE)

1. Acetyl-CoA + Oxaloacetate ? Citrate

- **Enzyme:** Citrate synthase
 - Key regulated step
 - Highly exergonic
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2. Citrate ? Isocitrate

- **Enzyme:** Aconitase
 - Requires **iron (Fe²⁺)**
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- Reversible isomerization
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3. Isocitrate → α-Ketoglutarate

- **Enzyme:** Isocitrate dehydrogenase
 - **NADH formed**
 - **CO₂ released**
 - First rate-limiting oxidative step
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4. α-Ketoglutarate → Succinyl-CoA

- **Enzyme:** α-Ketoglutarate dehydrogenase complex
 - Requires **TPP, lipoic acid, FAD, NAD⁺, CoA**
 - **NADH formed**
 - **CO₂ released**
-

5. Succinyl-CoA → Succinate

- **Enzyme:** Succinyl-CoA synthetase
 - **GTP formed**
 - Substrate-level phosphorylation
-

6. Succinate → Fumarate

- **Enzyme:** Succinate dehydrogenase
 - **FADH₂ formed**
 - Only TCA enzyme located in **inner mitochondrial membrane**
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7. Fumarate → Malate

- **Enzyme:** Fumarase
 - Hydration reaction
-

8. Malate → Oxaloacetate

- **Enzyme:** Malate dehydrogenase
 - **NADH formed**
 - Regenerates oxaloacetate → cycle continues
-

→ **ENERGETICS OF TCA CYCLE**

From **1 molecule of acetyl-CoA:**

- **3 NADH → 3 × 3 ATP = 9 ATP**
 - **1 FADH₂ → 2 ATP**
 - **1 GTP → 1 ATP**
 - **Total = 12 ATP per acetyl-CoA**
-

(Modern value using P/O ratios ? approx. **10 ATP**)

? SIGNIFICANCE OF TCA CYCLE

- Final common pathway for oxidation of **carbohydrates, fats, and proteins**
- Produces reducing equivalents **NADH, FADH?** for ATP production
- Generates intermediates for **biosynthesis**
- Provides **GTP** (substrate-level phosphorylation)
- Essential for neuronal and cardiac energy metabolism

? AMPHIBOLIC ROLE (Dual Anabolic + Catabolic)

TCA cycle serves **both**:

Catabolic functions

- Oxidation of acetyl-CoA ? CO?
- Formation of NADH/FADH? for oxidative phosphorylation

Anabolic functions

Intermediates act as precursors for synthesis of:

- Citrate ? fatty acids / cholesterol
- ?-KG ? glutamate ? amino acids

- Succinyl-CoA ? heme
- Malate ? gluconeogenesis
- Oxaloacetate ? aspartate ? amino acids

? ANAPLEROTIC REACTIONS (Refilling TCA intermediates)

- Pyruvate ? Oxaloacetate
 - Enzyme: Pyruvate carboxylase
 - Requires **biotin**
- Pyruvate ? Malate
- Amino acids ? ?-KG, Succinyl-CoA, Fumarate, Oxaloacetate

These reactions maintain cycle flow during high demand.

? REGULATION OF TCA CYCLE

Regulated at **three irreversible steps**:

1. Citrate Synthase

- Inhibited by: **ATP, NADH, citrate, succinyl-CoA**

2. Isocitrate Dehydrogenase

- Activated by: **ADP, Ca²⁺**

- Inhibited by: **ATP, NADH**

3. α -Ketoglutarate Dehydrogenase

- Activated by: **Ca^{2+}**
- Inhibited by: **Succinyl-CoA, NADH**

Overall inhibitors:

- **High ATP**
- **High NADH**
- **High succinyl-CoA**

Overall activators:

- **ADP**
- **Ca^{2+} (muscle contraction)**
- **High NAD $^+$**

α INTEGRATION OF METABOLISM WITH TCA CYCLE

Carbohydrates

- Glucose $\rightarrow$ pyruvate $\rightarrow$ acetyl-CoA $\rightarrow$ enters TCA.

Lipids

- β -oxidation ? acetyl-CoA ? enters TCA.
- Odd-chain fatty acids ? succinyl-CoA.

Proteins

- Glucogenic amino acids ? TCA intermediates (oxaloacetate, α -KG, fumarate).
- Ketogenic amino acids ? acetyl-CoA/acetoacetate.

Gluconeogenesis & TCA

- Malate shuttles oxaloacetate out of mitochondria.
- Oxaloacetate is key link between TCA and glucose formation.

Urea Cycle Link

- Fumarate ? aspartate shuttle connects TCA and urea cycle.

Fatty Acid Synthesis Link

- Citrate transported out ? acetyl-CoA for lipogenesis.

? HIGH-YIELD CLINICAL CORRELATIONS

- **Thiamine deficiency** ? inhibits α -KG dehydrogenase ? neurological symptoms (Wernicke's).
- **Arsenite** inhibits lipoic acid ? blocks α -KG dehydrogenase.
- **Fluoroacetate poisoning** inhibits aconitase ? TCA block.

- **Inherited fumarase deficiency** ? severe encephalopathy.

? IMPORTANT POINTS TO REMEMBER — CITRIC ACID CYCLE

? Basics & Location

- TCA cycle occurs in the **mitochondrial matrix**.
- Common oxidative pathway for **carbohydrates, fats, and proteins**.
- Each turn of the cycle oxidizes **acetyl-CoA** ? **CO?** + **NADH** + **FADH?** + **GTP**.

? Key Steps & Enzymes

- First step: **Citrate synthase** condenses oxaloacetate + acetyl-CoA.
- Only membrane-bound enzyme: **Succinate dehydrogenase** (Complex II of ETC).
- Two oxidative decarboxylations release **CO?**:
 - **Isocitrate dehydrogenase**
 - **?-Ketoglutarate dehydrogenase**

? Cofactor Requirements

- **?-Ketoglutarate dehydrogenase** uses:
TPP, FAD, NAD?, CoA, and lipoic acid (same as PDH complex).

- **Aconitase** requires **Fe²⁺**.
- **Succinate dehydrogenase** uses **FAD**.

? Energy Yield

From **1 acetyl-CoA**, TCA produces:

- **3 NADH** ? 9 ATP
- **1 FADH₂** ? 2 ATP
- **1 GTP** ? 1 ATP
- **Total** ? **12 ATP** (classic) or **10 ATP** (modern P/O ratio).

? Rate-Limiting & Regulatory Points

Major regulatory enzymes:

- **Isocitrate dehydrogenase** ? activated by **ADP, Ca²⁺**; inhibited by **ATP, NADH**.
- **Citrate synthase** ? inhibited by **ATP, NADH, citrate, succinyl-CoA**.
- **α-Ketoglutarate dehydrogenase** ? activated by **Ca²⁺**; inhibited by **NADH, succinyl-CoA**.

Overall inhibitors:

High **ATP**, high **NADH**.

Overall activators:

High **ADP**, high **NAD⁺**, high **Ca²⁺** (muscle contraction).

? Amphibolic Nature (Dual Role)

TCA cycle is both **catabolic** and **anabolic**.

Catabolic roles

- Oxidizes acetyl-CoA to **CO₂**.
- Produces NADH/FADH₂ for ATP formation.

Anabolic roles

Cycle intermediates form precursors for:

- Citrate ? fatty acids / cholesterol
- ?-Ketoglutarate ? glutamate ? amino acids
- Succinyl-CoA ? heme
- Oxaloacetate ? aspartate ? pyrimidines
- Malate ? gluconeogenesis

? Anaplerotic Reactions (Refilling TCA Pool)

- Pyruvate ? oxaloacetate (pyruvate carboxylase ? biotin dependent).
- Pyruvate ? malate.
- Amino acids ? TCA intermediates (e.g., valine/isoleucine ? succinyl-CoA).

These reactions keep the cycle running when intermediates are diverted for biosynthesis.

? Integration with Other Pathways

- **Glucose** enters TCA via pyruvate ? acetyl-CoA.
- **Fatty acids** enter as acetyl-CoA.
- **Amino acids** convert to ?-KG, succinyl-CoA, fumarate, or OAA.
- **Gluconeogenesis** uses malate ? oxaloacetate.
- **Urea cycle** connects via fumarate/aspartate shuttle.
- **Fatty acid synthesis** uses citrate transported out of mitochondria.

? TCA Cycle Inhibitors

- **Fluoroacetate** ? inhibits aconitase.
- **Arsenite** ? inhibits lipoic acid in ?-KG dehydrogenase.
- **Malonate** ? competitive inhibitor of succinate dehydrogenase.

? Clinical Significance

- **Thiamine deficiency** impairs PDH and ?-KG dehydrogenase ? neurological injury.
- **Fumarase deficiency** ? severe developmental delay.

- **Pyruvate accumulation** occurs when entry to TCA is blocked ? lactate formation (lactic acidosis).

? Ultra-Short Exam Capsule

- Occurs in mitochondrial matrix.
- Rate-limiting: **isocitrate dehydrogenase**.
- Produces NADH, FADH?, GTP.
- Amphibolic & anaplerotic roles are exam favorites.
- Ca^{2+} activates, ATP/NADH inhibit.
- Succinate dehydrogenase is only membrane-bound enzyme.

? CLINICAL CASE-BASED QUESTIONS — TCA CYCLE

1. Severe Thiamine Deficiency with Neurological Symptoms

A chronic alcoholic presents with confusion, ataxia, and ophthalmoplegia.

Labs show elevated **pyruvate and ?-ketoglutarate** in blood.

Diagnosis:

Wernicke's encephalopathy due to **thiamine deficiency**

Biochemical Basis:

Thiamine is required for **α-ketoglutarate dehydrogenase** and **pyruvate dehydrogenase** ?
TCA cycle slows ? accumulation of α-KG and pyruvate.

2. Infant with Lactic Acidosis After Minor Infection

A 6-month-old develops severe lactic acidosis after mild viral illness.
Serum pyruvate is high; TCA intermediates are low.

Diagnosis:

Pyruvate dehydrogenase deficiency

Biochemical Link:

Pyruvate cannot convert to acetyl-CoA ? enters lactate ? TCA cycle starved of acetyl-CoA.

3. Poisoning After Exposure to Rat Killer

A farmer develops vomiting, arrhythmias, and metabolic crisis.
Lab: Profound inhibition of TCA cycle; aconitase activity nearly zero.

Diagnosis:

Fluoroacetate poisoning

Mechanism:

Fluoroacetate ? fluorocitrate ? **inhibits aconitase** ? blocks citrate ? isocitrate step.

4. Muscle Contraction Increases ATP Turnover

During strenuous exercise, a patient's muscle biopsy shows activated **isocitrate dehydrogenase** and **α-KG dehydrogenase**.

Diagnosis:

This is **normal physiological activation**.

Key Mechanism:

Ca²⁺ released during contraction stimulates both enzymes, increasing TCA cycle flux.

5. Elderly Patient with Unexplained Hypoglycemia + High Citrate Levels

A 70-year-old woman develops fasting hypoglycemia.

Biochemistry: Elevated **citrate** in mitochondria.

Diagnosis:

TCA cycle slowing due to high ATP/NADH

Reason:

High-energy state inhibits citrate synthase, IDH, and α -KGDH $\rightarrow$ citrate builds up $\rightarrow$ exported to cytosol $\rightarrow$ inhibits glycolysis (via PFK-1).

6. Infant Born with Severe Neurodevelopmental Delay + High Fumarate

A newborn shows severe encephalopathy, seizures, and failure to thrive.

Urine shows increased **fumarate**.

Diagnosis:

Fumarase deficiency (rare, severe)

Mechanism:

Block at fumarate $\rightarrow$ malate step $\rightarrow$ TCA cycle collapse $\rightarrow$ low ATP $\rightarrow$ neurological deterioration.

7. Patient with Arsenic Exposure After Well Water Consumption

A farmer presents with garlic odor breath, neuropathy, and vomiting.
Blood tests reveal impaired **α-KG dehydrogenase** complex.

Diagnosis:

Arsenite poisoning

Biochemical Mechanism:

Arsenite binds **lipoic acid**, inhibiting PDH and α-KGDH → halts TCA cycle.

8. Patient with Chronic Hypoxia After COPD Exacerbation

A COPD patient has chronic low O₂ levels.
Mitochondrial NADH is very **high**.

Diagnosis:

Impaired oxidative phosphorylation

Explanation:

Low oxygen → ETC slows → NADH accumulates → inhibits TCA cycle (IDH, α-KGDH inhibited).

9. Bodybuilder Using High-Protein Diet

In a high-protein diet, blood **alanine and glutamate** are high.
TCA cycle intermediates are elevated.

Diagnosis:

Increased anaplerosis due to amino acids converting to α-KG, OAA, and fumarate.

10. Young Woman with Failed Weight Loss Despite Fasting

During prolonged fasting, her TCA cycle intermediate **oxaloacetate** is very low.

Diagnosis:

OAA diverted to **gluconeogenesis**, reducing TCA activity.

Effect:

Acetyl-CoA accumulates ? **ketogenesis increases**.

11. Patient with Exercise-Induced Muscle Fatigue

A 25-year-old athlete develops early fatigue.

Analysis shows reduced **succinate dehydrogenase** activity.

Diagnosis:

Mitochondrial Complex II defect

Effect:

TCA cycle and ETC both impaired ? decreased ATP production.

12. Young Man with High Blood Ammonia + Elevated ?-Ketoglutarate

A liver failure patient shows high **ammonia** and elevated **?-KG** depletion in the brain.

Diagnosis:

Ammonia toxicity affecting TCA cycle

Mechanism:

Ammonia + ?-KG ? glutamate

? deprives TCA of ?-KG ? ATP depletion ? cerebral edema.

13. Diabetic Patient with Ketonuria + Low TCA Activity

A type-1 diabetic shows high ketones.

TCA cycle intermediates (OAA, fumarate) are decreased.

Diagnosis:

TCA cycle suppression due to OAA depletion

Reason:

OAA used for gluconeogenesis ? acetyl-CoA enters **ketogenesis** instead of TCA.

14. Patient with Lipoic Acid Deficiency After Long-Term Antibiotics

A malnourished patient treated long-term with broad-spectrum antibiotics shows reduced PDH and α -KGDH activity.

Diagnosis:

Microbiome-related lipoic acid deficiency

Mechanism:

Lipoic acid needed for both PDH and α -KGDH ? TCA cycle slows.

15. Neonate with Pyruvate Accumulation + Elevated Lactate

Newborn has high blood lactate and normal oxygen levels.

TCA intermediates are markedly low.

Diagnosis:

Pyruvate carboxylase deficiency

Key Insight:

Cannot form **oxaloacetate** ? TCA cycle cannot proceed ? pyruvate ? lactate.

16. Patient with GTP Deficiency in Liver Injury

In liver disease, **GTP** generation is impaired.

Diagnosis:

Succinyl-CoA synthetase defect

Reason:

This reaction generates GTP ? required for many biosynthetic pathways.

17. Teenager with Weak Collagen Formation

High levels of **?-KG** in blood; normal TCA but poor collagen cross-linking.

Diagnosis:

Vitamin C deficiency affecting **?-KG**-dependent prolyl hydroxylase in collagen synthesis.

18. Patient with High Citrate in Cytosol + Fatty Liver

Middle-aged man with fatty liver shows high **cytosolic citrate**.

Diagnosis:

Citrate overflow into cytosol ? fatty acid synthesis activation

Mechanism:

Excess citrate ? ATP citrate lyase ? acetyl-CoA ? fatty acid synthesis ? hepatic steatosis.

19. Child with Recurrent Vomiting After Eating High-Carb Meals

Blood tests show spikes in lactate and pyruvate after glucose intake.

Diagnosis:

PDH complex deficiency ? pyruvate cannot enter TCA ? lactate ?

20. Man with Mitochondrial Disorder + Low ATP

Muscle biopsy shows defective **malate dehydrogenase**.

Diagnosis:

Reduced regeneration of **oxaloacetate** ? TCA cannot proceed ? ATP depression.

? MCQs — Citric Acid Cycle (TCA Cycle)

1. The TCA cycle occurs in which cellular compartment?

- A. Cytosol
- B. Nucleus
- C. Golgi
- D. **Mitochondrial matrix**

Answer: D

2. Which enzyme of TCA cycle is located in the inner mitochondrial membrane?

- A. Aconitase
- B. Malate dehydrogenase
- C. **Succinate dehydrogenase**
- D. Citrate synthase

Answer: C

3. The rate-limiting enzyme of TCA cycle is:

- A. Citrate synthase
- B. α -Ketoglutarate dehydrogenase
- C. **Isocitrate dehydrogenase**
- D. Malate dehydrogenase

Answer: C

4. Which reaction of the TCA cycle produces GTP?

- A. α -Ketoglutarate $\rightarrow$ Succinyl-CoA
- B. Malate $\rightarrow$ Oxaloacetate
- C. Succinyl-CoA $\rightarrow$ Succinate
- D. Fumarate $\rightarrow$ Malate

Answer: C

5. Which cofactor is required for α -ketoglutarate dehydrogenase?

- A. Biotin
- B. Vitamin C
- C. **TPP + Lipoic acid + FAD + NAD⁺ + CoA**

D. THF

Answer: C

6. Which enzyme requires iron (Fe^{2+})?

- A. Citrate synthase
- B. **Aconitase**
- C. Malate dehydrogenase
- D. Succinyl-CoA synthetase

Answer: B

7. Which step produces FADH_2 ?

- A. Malate $\rightarrow$ Oxaloacetate
- B. **Succinate $\rightarrow$ Fumarate**
- C. Citrate $\rightarrow$ Isocitrate
- D. α -KG $\rightarrow$ Succinyl-CoA

Answer: B

8. Total ATP yield from 1 molecule of acetyl-CoA (classic values):

- A. 6
- B. 8
- C. 10
- D. **12**

Answer: D

9. Succinyl-CoA is a precursor for synthesis of:

- A. Purines
- B. Pyrimidines
- C. **Heme**
- D. Fatty acids

Answer: C

10. Which compound inhibits succinate dehydrogenase?

- A. Rotenone
- B. **Malonate**
- C. Cyanide
- D. Fluoride

Answer: B

11. Fluoroacetate inhibits which enzyme?

- A. Succinate dehydrogenase
- B. Citrate synthase
- C. **Aconitase**
- D. Malate dehydrogenase

Answer: C

12. Arsenite inhibits which component of the TCA cycle?

- A. Citrate synthase
- B. Aconitase
- C. **α-Ketoglutarate dehydrogenase**

D. Fumarase

Answer: C

13. Which of the following increases TCA cycle activity?

- A. High ATP
- B. High NADH
- C. **High Ca^{2+}**
- D. High fatty acids

Answer: C

(Ca^{2+} stimulates IDH and α -KGDH during muscle contraction)

14. Which of the following decreases TCA cycle activity?

- A. High ADP
- B. **High NADH**
- C. High Ca^{2+}
- D. High pyruvate

Answer: B

15. Anaplerotic reaction that replenishes oxaloacetate:

- A. Pyruvate $\rightarrow$ Acetyl-CoA
- B. Malate $\rightarrow$ Fumarate
- C. **Pyruvate $\rightarrow$ Oxaloacetate (pyruvate carboxylase)**
- D. Fumarate $\rightarrow$ Malate

Answer: C

16. A patient with thiamine deficiency will have impaired:

- A. Malate dehydrogenase
- B. **α-Ketoglutarate dehydrogenase**
- C. Isocitrate dehydrogenase
- D. Succinate dehydrogenase

Answer: B

17. Which is the only substrate-level phosphorylation in the TCA cycle?

- A. Succinate → Fumarate
- B. **Succinyl-CoA → Succinate**
- C. Isocitrate → α-KG
- D. Malate → OAA

Answer: B

18. Citrate inhibits which glycolytic enzyme?

- A. Hexokinase
- B. Pyruvate kinase
- C. **PFK-1**
- D. Aldolase

Answer: C

19. High ATP and high NADH will:

- A. Activate IDH
- B. Activate citrate synthase
- C. **Inhibit TCA cycle globally**

D. Increase succinyl-CoA production

Answer: C

20. Which intermediate can directly participate in gluconeogenesis?

- A. Succinyl-CoA
- B. Fumarate
- C. **Malate**
- D. Acetyl-CoA

Answer: C

21. Which TCA intermediate links to the urea cycle via aspartate?

- A. Citrate
- B. **Oxaloacetate**
- C. Succinate
- D. Malate

Answer: B

22. α-Ketoglutarate is a precursor for which amino acid?

- A. Serine
- B. Alanine
- C. **Glutamate**
- D. Aspartate

Answer: C

23. Which vitamin deficiency impairs both PDH and α -KGDH?

- A. Vitamin B12
- B. Vitamin C
- C. Vitamin K
- D. **Vitamin B1 (Thiamine)**

Answer: D

24. In fasting, low oxaloacetate causes:

- A. Enhanced glycolysis
- B. **Increased ketone body formation**
- C. Inhibited α -oxidation
- D. Increased pyruvate carboxylase inhibition

Answer: B

25. A patient given a drug that inhibits lipoic acid will show elevated:

- A. Citrate
- B. Succinate
- C. **α -Ketoglutarate**
- D. Malate

Answer: C

? VIVA VOCE — CITRIC ACID CYCLE

1. Where does the TCA cycle occur?

In the **mitochondrial matrix**.

2. What is the common substrate entering the TCA cycle?

Acetyl-CoA.

3. Name the enzyme for the first step of the cycle.

Citrate synthase.

4. Which enzyme requires Fe²⁺??

Aconitase.

5. Which step produces GTP?

Succinyl-CoA → Succinate (succinyl-CoA synthetase).

6. What is the only membrane-bound TCA enzyme?

Succinate dehydrogenase (Complex II).

7. Which TCA enzyme produces FADH₂??

Succinate dehydrogenase.

8. Which enzyme produces NADH?

Isocitrate dehydrogenase, α-ketoglutarate dehydrogenase, and malate dehydrogenase.

9. Which two steps release CO₂??

- **Isocitrate → α-Ketoglutarate**
 - **α-Ketoglutarate → Succinyl-CoA**
-

10. What are the cofactors for α -ketoglutarate dehydrogenase?

TPP, lipoic acid, FAD, NAD⁺, CoA.

11. How many ATP equivalents are produced per acetyl-CoA?

Classically 12 ATP (modern value ~10).

12. Why is the cycle called amphibolic?

Because it is both catabolic and anabolic.

13. Which TCA intermediate is precursor for heme synthesis?

Succinyl-CoA.

14. Which intermediate links TCA and gluconeogenesis?

Malate (via malate shuttle).

15. Which intermediate forms the amino acid glutamate?

α -Ketoglutarate.

16. Which vitamin deficiency inhibits TCA cycle most severely?

Vitamin B1 (Thiamine) due to PDH and α -KGDH impairment.

17. What activates isocitrate dehydrogenase?

ADP and Ca²⁺.

18. What inhibits isocitrate dehydrogenase?

ATP and NADH.

19. What activates α -ketoglutarate dehydrogenase?

Ca²⁺.

20. What inhibits α -ketoglutarate dehydrogenase?

Succinyl-CoA and NADH.

21. What is an anaplerotic reaction?

A reaction that **replenishes TCA intermediates**.

22. Give one anaplerotic reaction.

Pyruvate $\rightarrow$ Oxaloacetate (pyruvate carboxylase).

23. What is the TCA cycle inhibitor found in rat poison?

Fluoroacetate (inhibits aconitase).

24. What inhibits succinate dehydrogenase competitively?

Malonate.

25. Why does high NADH inhibit TCA cycle?

High NADH indicates a **high-energy state** $\rightarrow$ reduces oxidative steps.

26. What happens to the TCA cycle during hypoxia?

It **slows down** because NADH cannot be oxidized in ETC.

27. What metabolic pathway depends directly on TCA cycle NADH/FADH??

Electron transport chain (ETC).

28. How does TCA link to urea cycle?

Via **fumarate ? aspartate shuttle**.

29. Why does fasting decrease TCA cycle activity?

Because **oxaloacetate is diverted to gluconeogenesis**, reducing cycle flow.

30. What happens to acetyl-CoA when OAA is low?

Enters **ketogenesis**.

31. Which disorder presents with ?-KG buildup and neurological issues?

Thiamine deficiency.

32. Which TCA enzyme is part of ETC as well?

Succinate dehydrogenase (Complex II).

33. What is the committed step of TCA?

Citrate synthesis.

34. Which ion activates two major TCA enzymes during muscle contraction?

Calcium (Ca^{2+}).

35. What inhibits ?-ketoglutarate dehydrogenase in arsenic poisoning?

Arsenite binds **lipoic acid**.

36. Which intermediate accumulates when citrate synthase is inhibited?

Oxaloacetate.

37. Name one medical condition where TCA cycle is severely impaired.

Mitochondrial myopathies / fumarase deficiency / PDH deficiency.

38. What is the effect of ATP on TCA cycle?

Inhibits major regulatory enzymes.

39. What ratio controls TCA cycle most strongly?

NAD⁺/NADH ratio.

40. What is the overall purpose of the TCA cycle?

To oxidize acetyl-CoA to **CO₂** while producing **high-energy reducing equivalents**.