بسم الله الرحمن الرحيم

RESPIRATORY BLOCK

Fatty acid oxidation

إعداد الطالبات

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دعواتكم لنا بالتوفيق في الدارين

Fatty acids activated when it carried by CoA to enter the cell

- That is mean when it carried by coA it will be active and this Consume energy
- If we don't oxidative the fatty acids we will not tack energy
  Then we go to the storage and consume it (it's happen in fasting state)

✓ Stored in: adipose tissue

✓ In the form: TAG
- Hydrolyze TAG → Glycerol + 3 Fatty Acids
- Complete oxidation → $CO_2 + H_2O$ + energy (9 kcal/g of fat)

TAG
- Highly reduces → a lot of amount of energy (ATP)
- Mostly anhydrous (little H_2O)

Why? Because it will give H^+ in high amount

✓ TAG: provide concentrated storage of metabolic energy

Release of fatty acids from TAG in adipose tissue

By HSL: hormone-sensitive lipase (which broken the Fatty acids)

Active → phosphorelated HSL

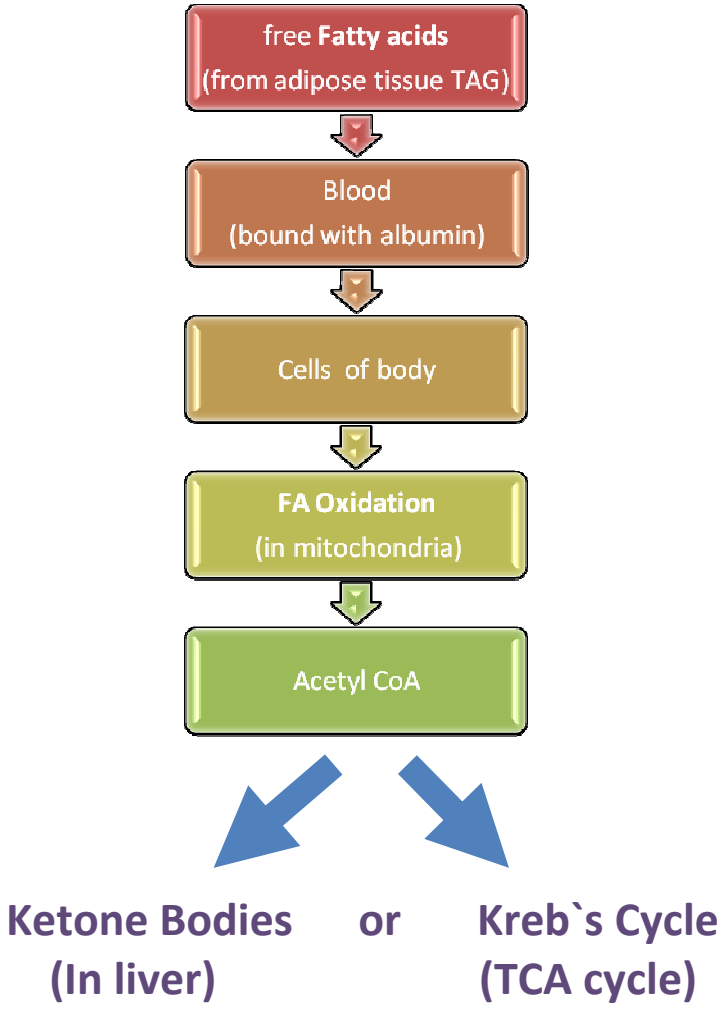
An active → dephophorelated HSL

HSL: hormone sensitive lipase

- When HSL be active?
- in fasting state, (↑ glucagon & epinephrine) and no glucose → ↑ cAMP
- When HSL be an active?
- fed state, glucose is available (↑ Insulin)

Fate (the end) of free fatty acids (released from TAG)

- **HSL hydrolyses of TAG by removing fatty acid from carbon number 1, 3 (1 or 3 OR 1 and 3)**
- **Then it will reduce it to glycerol + FA (fatty acid)**



FFA (free fatty acid) is not used by RBCs. Why? Because there is no mitochondria
FFA is not used by the brain (BBB) blood brain barrier

β-oxidation of fatty acids

It is the major pathway for catabolism of saturated fatty acid in mitochondria, in which 2-carbon fragments are successively removed from carboxyl end of the fatty acyl CoA
Producing: acetyl CoA, NADH and $FADH_2$.

Transport of Fatty acids to mitochondria

In mitochondria
- ***Long*-chain FA indirectly passes**
- **Medium or small-chain FA directly passes**

Long-chain FA > 12 carbon

So what will do the long FA?

Its need to *carination* to carry it and enter the mitochondria (*_^ مثل الواسطه فيعتبرcarinitine)

By using carnitine shuttle (must be β-carbon, no branches)

Shuttle: أي ينقل ماده ثم يعود مره أخرى

enzymes of the shuttle:

- **carnitine acyltransferase-I or carnitine palmotyltransferase-II (*CAT-I or CPT-I*)**
- **carnitine acyl transferase-II or carnitine palmotyltransferase-II (*CAT-II or CPT-II*)**

Carnitine Shuttle & Enzymes

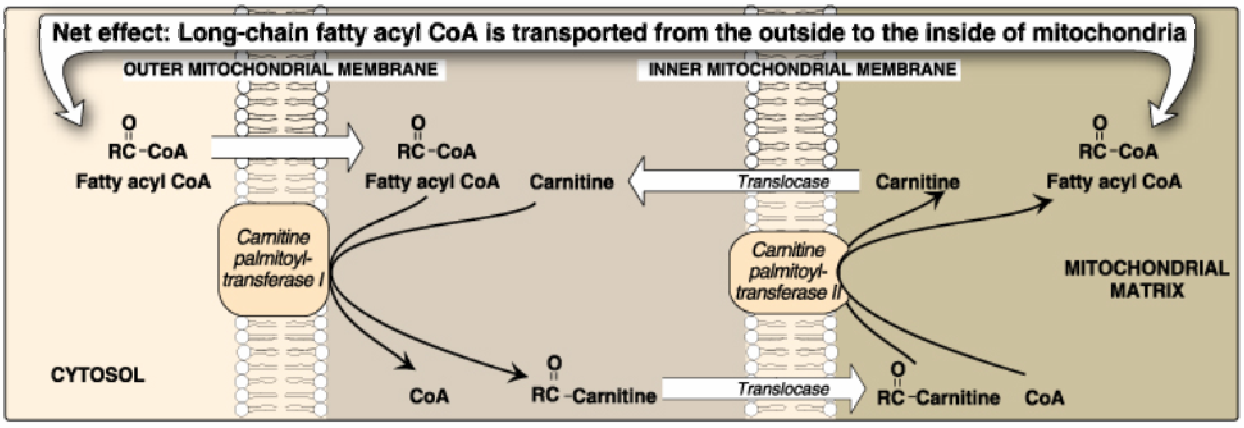


Figure 16.16
Carnitine shuttle.

Mitochondria consist of tow layer:

1. **inner membrane**
2. **outer membrane**

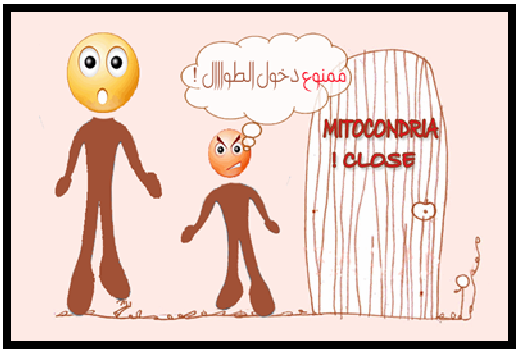
- **LCFA (long-chain fatty acid): transport in the cytosol → converted to acyl CoA →**
  - **The inner membrane:**
    Impermeable to CoA. So needs specialized carrier → carnitine
    - **Rate limiting transport process → carnitine shuttle**

By enzyme: thiokinase

(Long-chaun fatty acyl CoA synthesis)

✓ Present on the outer mitochondria membrane

Carnitine shuttle



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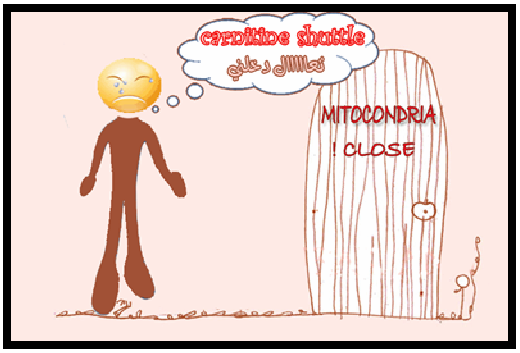

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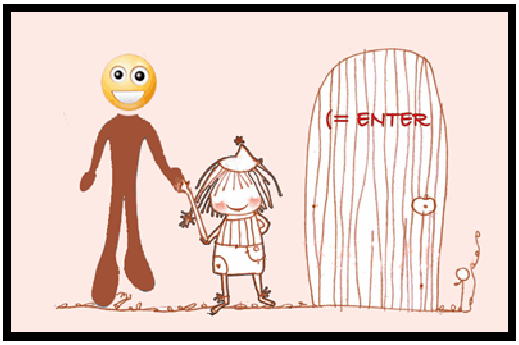

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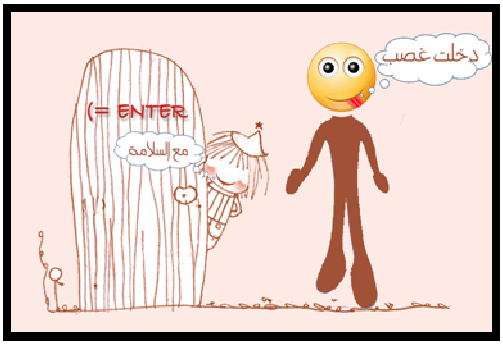


(4)

1-outer mitochondria membrane:

- **Reaction: fatty acyle CoA + carnitine ⟶ acyl carnitine + free CoA**
  - **Expaine what happen there:**
  - **Acyl group is transferred to carnitine (from the inner membrane)**
- **Help by enzyme:**

(CAT-I or CPT-I)

2-inner mitochondria membrane:

- **Reaction: acyl carnitine enter the matrix in exchange for a free carnitine**
- **Help by enzyme:**

Carnitine-acylcanitine translocase

3-matrix:

- **reaction: acyl carnitine + free CoA ⟶ Acyl CoA + free carnitine**
- **Help by enzyme:**

(CAT-II or CPT-II)

- **Inhibitor: malonyl CoA ⟶ inhibits CPT-I**
  - **Present in fatty acid synthesis in the cytosol**

- Prevents newly formed palmitate from entering mitochondria

Acetyl CoA/CoA ratio ⟶ it will increase ⟶ decrease in thiolase reaction and oxidation

- **Source of carnitine:**
  - Diet: particularly in meat products
  - Tissues: in the liver and kidney ⟶ from amino acids lysine and methionine
    By enzyme pathway (and are dependent on endogenous synthesis or diet)
  - In skeletal and cardiac muscle cannot synthesize it
    But…97% storage of carnitine on them!
    Why? Because the need it

❖ **Carnitine deficiency:**

- lead to decreased ability of tissues to use long-chain FA as source of fuel as they are not transported to the mitochondria
- **primary causes:**
- caused by *congenital deficiencies* of :
- - one of enzymes of the carnitine shuttle

1- Genetic CPT-I deficiency:
affects the liver ⟶ cannot use LCFA for fuel
So, liver cannot perform gluconeogenesis (synthesis of glucose during fasting)
- Can lead to Hypoglycaemia (نقص الجليكوز في الدم) ⟶coma ⟶death

2- CPT-II deficiency: occur in skeletal & cardiac muscles
Symptoms: cardiomyopathy, muscle weakness, myoglobinemia (myoglobin نقص)
After exercise

- - one of the components of renal tubular reabsorption o f carnitine
- - one of the components of carnitine uptake of carnitine by cells

- **Secondary causes:**
- liver diseases: decreased synthesis of carnitine
- malnutrition or strictly vegetarians: diminshed carnitine in food
- increased demand for carnitine e.g. In fever, pregnancy, etc
- Haemodialysis: due to removal of carnitine from blood

***Treatment** of carnitine deficiencies:*

- Avoiding prolonged fasting.

- Diet should be rich in carbohydrates , low in long-chain fatty acids & supplemented with medium chain fatty acids.

Reactions of β-oxidation

The Result ⟶ shorting fatty acid chain by 2-carbons

1. The β-carbon is oxidized to Enoyl CoA
   By Acyl CoA dehydrogenases ⟶ produce 1 $FADH_2$
2. Hydration
3. Second oxidation ⟶ produce 1 NADH
4. Thiolitic cleavage by β-ketoacyl-CoA thiolase ⟶ produce acetyl CoA
   - **Note:** acetyl CoA is a positive allosterc effective of pyruvate carboxylase.

- The cycle is repeated **(n/2- 1)** times for saturated even Numbered carbon chains.
  - The last cycle produces **2 acetyl CoA**
  - **For example:**
    fatty acid consist of 16 carbons (palmitoyl CoA) :
    16/2 = 8 -1 = **7 cycle**

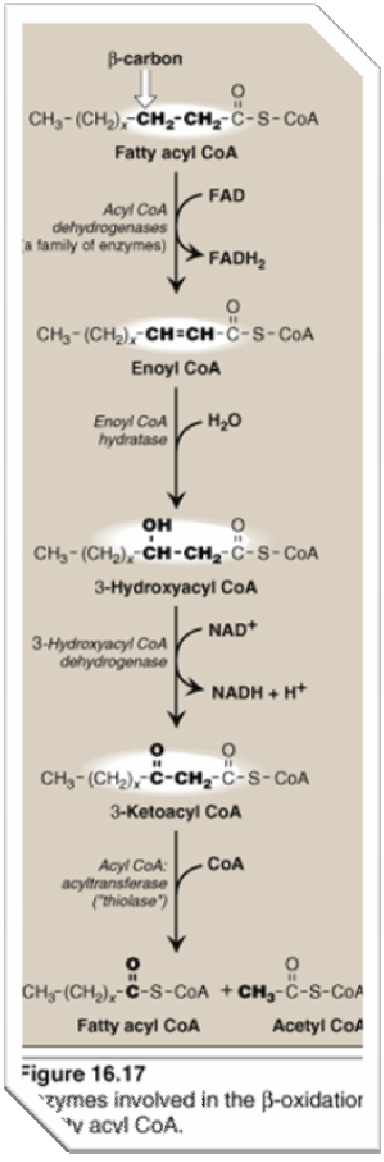


Figure 16.17
...zymes involved in the β-oxidation ...y acyl CoA.

And the last cycle (no. 7) produce **2 acetyl CoA**

And from each cycle produce 1 NADH and 1 $FADH_2$

- **So *Energy yield* from fatty acid oxidation for this example:**
  - 8 acetyl CoA ⟶ Kreb Cycle TCA cycle ⟶ 8 X 12 = 96 ATP
  - 7 NADH ⟶ ETC ⟶ 7 X 3 = 21 ATP
  - 7 FADH2 ⟶ ETC ⟶ 7 X 2 = 14 ATP

All yield: **131 ATPs**

Activation of fatty acid requires **2 ATP**

Net energy gained: **129 ATPs** from one molecule of palmitate

Short- & medium- chain fatty acids:

- FA < 12 carbons.
- can cross the inner mitochondrial membrane without aid of Carnitine or the CPT system
- Activated to their CoA derivatives by matrix enzymes → oxidized

Medium chian:

- Plentiful in human milk
- Is not subject to inhibition by malanyl CoA **why?**
  Because it does not depend on CPT-I

Medium chain fatty acyl acyl CoA dehydrogenase deficiency (MCAD):

- Autosomal recessive disorder (إظطراب وراثي)
- One of the most common inborn errors of metabolism
- Cause decrease of fatty acid oxidation
- Severe hypoglycaemia occurs (as tissues do not get use fatty acids as a source of energy & must rely on glucose)
- Infants are particularly affected by MCAD deficiency as they rely on milk(provide nourishment for them) → which contains primarily MCAD → could cause sudden infant death syndrome (SIDS) or Reye syndrome
- Treatment: carbohydrate rich diet

Alpha-oxidation of fatty acids (Oxidation of branched-chain fatty acids):

- Fatty acid: branched, methyl group on β-carbon → example (phytanic acid)
- Enzyme: alpha -hydroxylase → hydroxylates at alpha-carbon → Product β decarboxyleted → activated to CoA derivative

Deficiency: (Refsum disease) → rare Autosomal recessive disorder
Results in accumulation of phytanic acid in blood & tissues → Neurologic symptoms

Treatment: diet restriction to reduce disease progression

Ketone bodies :

❖ synthesized in liver mitochondria by converting acetyl CoA(derived from the oxidation of fatty acids) to

1- Acetoacetate

2- 3-hydroxybutyrate (or b-hydroxybutyrate)

- (functional ketone bodies , organic acid)
- transported via blood to peripheral tissues. .

3- Acetone (nonmetabolized side product) , released from the body by respiration

❖ Ketone bodies are important sources of energy for peripheral tissues:

- Transported in the blood without albumin or lipoprotein carriers (as do other lipids) → because they are soluble in aqueous solution.
- Liver produce ketone bodies when the amount of acetyl CoA present exceeds oxidative capacity of liver
- Ketone bodies are used by extra hepatic tissues in proportion to their concentration (use all the ketone bodies in the blood)
- In peripheral tissues, they are converted to acetyl CoA → Acetyl CoA is oxidized by Kreb`s cycle (TCA cycle) to yield energy (ATPs)
- They are important sources of energy during prolonged periods of fasting especially for the brain as: - can pass BBB: (while FAs cannot).
  - Glucose in blood available in fasting is not sufficient .

Ketogenesis(Synthesis of ketone bodies in the liver):

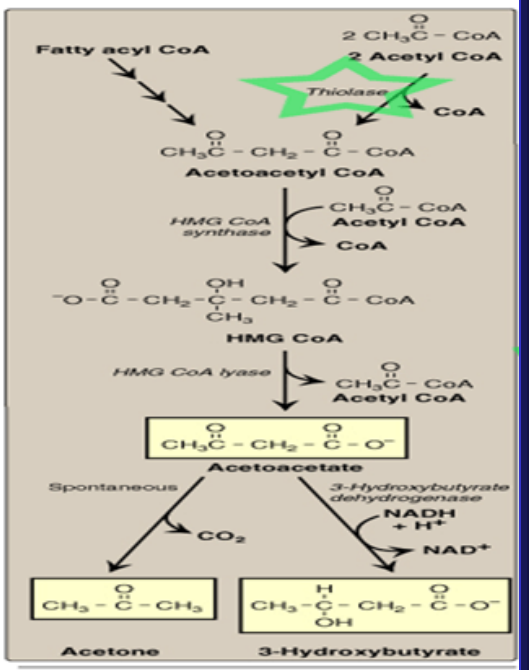


Figure 16.22
Synthesis of ketone bodies. HMG = hydroxymethylglutaryl CoA.

- ✓ **During fasting : adipose tissue releases fatty acid → liver is flooded**
- ✓ **Liver breaks down fatty acid to acetyl CoA (in large amounts)**
- ✓ **Acetyl CoA does not find enough oxalacetate to be incorporated in TCA cycle (oxalacetate which is used for gluconeogenesis isn't enough) so, excess acetyl CoA is shifted to form ketone bodies.**

a. **2 acetyl CoA + broken down fatty acyl CoA → acetoacetyl CoA + CoA**

Reverse thiolase reaction of fatty acid oxidation

b. **Acetoacetyl CoA + acetyl CoA → 3-hydroxy-3-methylglutaryl CoA + CoA**

Enzyme: mitochondrial HMG- CoA synthase

❖ **What is the rate limiting step in synthesis of ketone bodies?**

HMG- CoA synthase.

Present in significant quantities in the liver

c. **HMG- CoA → acetoacetate + acetyl CoA.**

Enzyme: HMG- CoA lyase

d. **Acetoacetate: a) - NADH + H^+ → 3-hydroxybutyrate (in liver)**

b) - acetone + CO_2 by spontaneous decarboxylation (blood)

- ✓ **regulation: equilibrium between the two reactions is determined by NAD^+/NADH ratio**

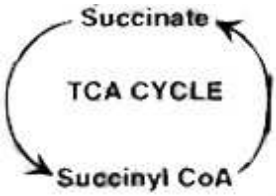
↓ NAD^+/NADH ratio during fatty acid oxidation → 3-Hydroxybutarate synthesis

Ketolysis (Use of Ketone bodies by peripheral tissues):

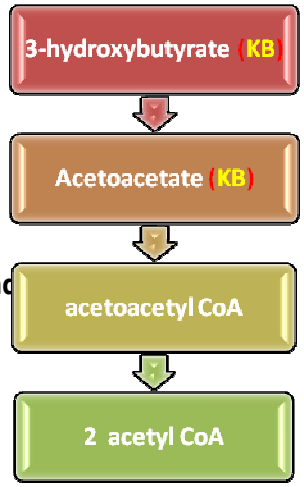
✓ **Use of ketone bodies occurs in the peripheral tissues**

a. **3-Hydroxybutarate → acetoacetate + NADH**

Enzyme: 3-Hydroxybutarate dehydrogenase

b. **Acetoacetate +** 

→ acetoacetyl CoA (reversible reaction)



Enzyme: succinyl CoA : acetoacetate transferase (thiophrase)

c. **Acetoacetyl CoA → 2 acetyl CoA**

Tissues:

➢ **A)- extrahepatic: efficiently oxidize acetoacetate and 3-Hydroxybutarate by ketolysis, including the brain.**

- **Tissues Without mitochondria →can not**

➢ **B)- liver: produce Ketone bodies only**

- **Unable to use it as fuel because it doesn't have thiophrase**

❖ **Can the liver oxidize ketone bodies and why?**

NO, because it doesn't have thiophrase

KETOGENESIS *and* KETOLYSIS

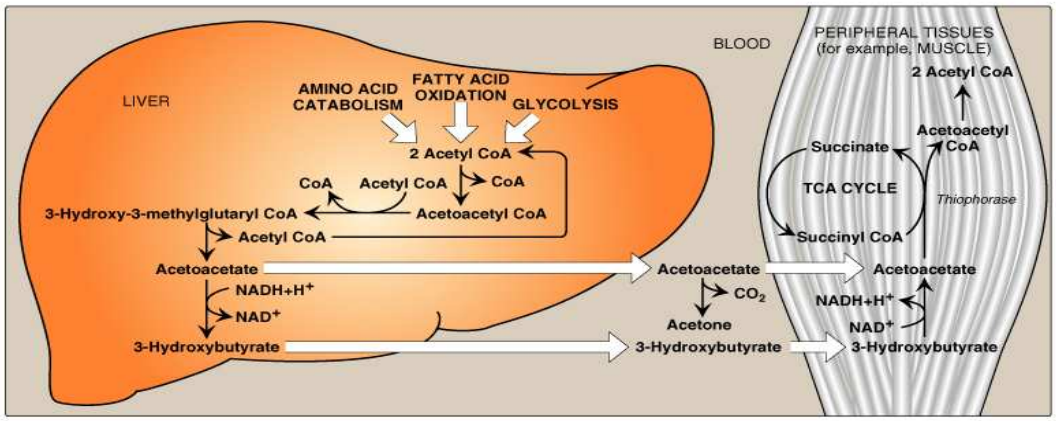


Figure 16.23
Ketone body synthesis in the liver and use in peripheral tissues.

Type 1 Diabetes Mellitus when uncontrolled:

- ✓ Excessive amount of acetyl CoA produced from high fatty degeneration
- ✓ ↓ NAD^+ pool ↑ NADH pool → slows TCA cycle.
- ✓ Acetyl CoA is forced into ketone body pathway
- ✓ Leads to:
- ketonemia: (increased KB in blood) occurs when rate of production of ketone bodies (KETOGENESIS) is greater than rate of their use (KETOLYSIS) (can reach 90 mg/dl)
- Ketonuria: increased KB in the urine (5000 mg/24hours)

❖ Ketoacidosis:

- ✓ blood academia, mechanism:
- Ketone body has pKa=4 → loses H^+ in the blood →lowers blood pH
- Ketone body and glucose excreted in the urine (by osmosis) → increase volume of urine → increased number of H^+ in decreased plasma volume and dehydration.
- Symptom: fruity odor (رائحة) in breath (from increased acetone production).

❖ Manifestations of diabetic ketoacidosis

- ketonemia: KB in blood more than 3 mg/dl, may reach 90 mg/dl
- Ketonuria: KB in urine may reach 5000 mg/24 hours
- Fruity odour on the breath :due to increased acetone production
- Acidosis زياده الحموضه & acidemia حموضه الدم
- Dehydration: due to increased urine volume due to excess
- excretion of KB & glucose

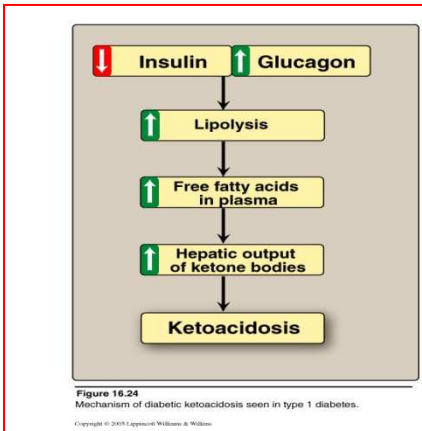
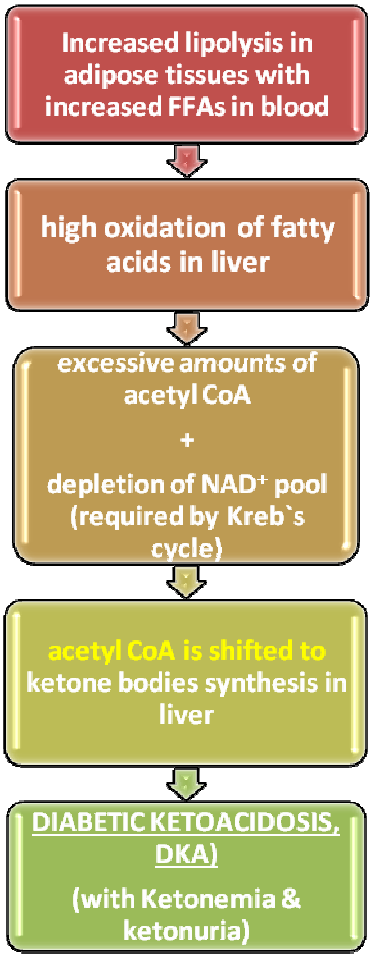


Figure 16.24
Mechanism of diabetic ketoacidosis seen in type 1 diabetes.

what happen in diabetes mellitus that are related to keton body?

↑glucagon and ↓ insulin → work on HSL → ↑ lipolysis→ ↑FA in blood → ↑acetyl CoA→↑ formation of keton bodies in the liver→ketoacidosis.



تم ولله الحمد

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