Diabetic Ketoacidosis (DKA)

Biochemistry Teamwork

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Diabetic emergencies

- Diabetic Ketoacidosis (DKA)
- Hyperosmolar hyperglycaemic state (HHS)= Hypperosmolar non-ketotic acidosis (HONK)
- Hypoglycemia

Diabetic Ketoacidosis (DKA)

Metabolic acidosis:
1-high anion gap =>17
2- low anion gap = <17

- **Triad of hyperglycemia, high anion gap metabolic acidosis, and ketonemia**
- **Characteristically associated with T1DM**
- **It has become increasingly common in T2DM**
- **DKA may be the first presentation of T1DM**

Patient with T1DM have more chance to develop DKA than patient with T2DM

Ketone Bodies *(Water soluble compounds)*

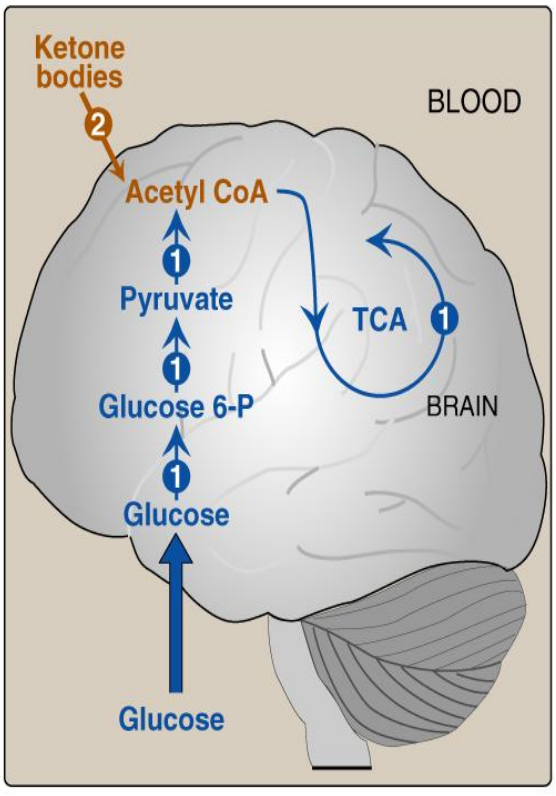
↑ proton H+ plasma conc. ➔ acidosis

1. **Acetoacetate**
2. **Acetone**
3. **β-Hydroxybutyrate**
4. **They are produced by the liver (ketogenesis) and utilized for energy production by peripheral tissues (Ketolysis)**

Acetone is metabolically inactive, is excreted in the breath; helps in diagnosis

Normally, glucose is the primary fuel for the brain.
It can penetrate the blood brain barrier.
The brain's GLUT is insulin-independent.

If glucose is not available for the brain, the brain can utilize plasma ketone bodies, that can penetrate the blood brain barrier, and serve as fuel molecules.
(Ketolysis produces energy)



Ketone bodies synthesis = Ketogenesis

- Occurs in the hepatocyte mitochondria
- In uncontrolled DM there is ↑lipolysis in adipose tissue →↑ [FFA] mobilization to liver

→↑hepatic FA oxidation →↑ acetyl CoA which will be channeled into KB synthesis

- HMG (Hydroxymethylglutaryl) CoA synthase is the rate limiting enzyme
- The first KB to be synthesized is acetoacetate.

Acetoacetate can be:

- reduced to β-Hydroxybutyrate (3-hydroxybutyrate), or
- spontaneously decarboxylated to acetone.

- ↑hepatic FA oxidation →↑ acetyl CoA which will be channeled into KB synthesis
- Acetyl CoA + oxaloacetate (OAA) → Krebs cycle
- ↑ Acetyl CoA production activates pyruvate carboxylase
- Pyruvate carboxylase converts pyruvic acid into OAA
- OAA is used for gluconeogenesis (rather than Krebs cycle)
- Acetyl CoA is channeled into KB synthesis

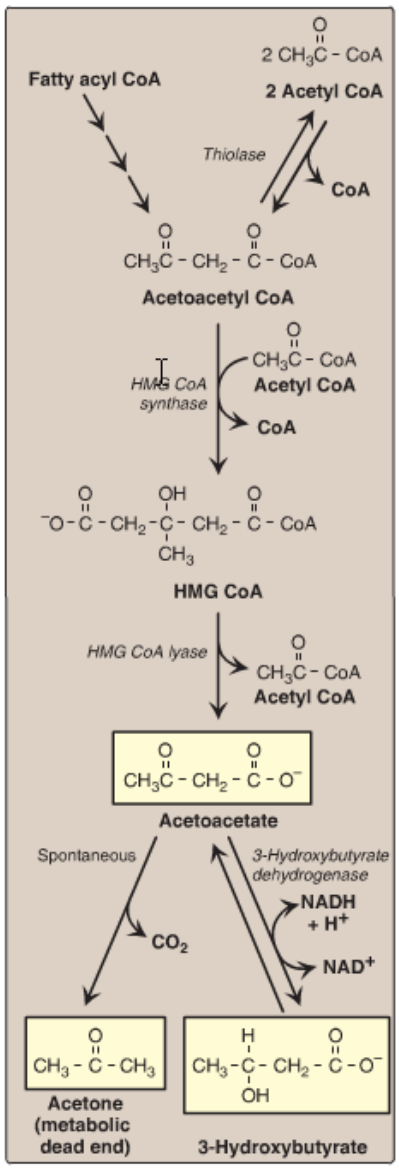


Figure 16.22
Synthesis of ketone bodies. HMG =

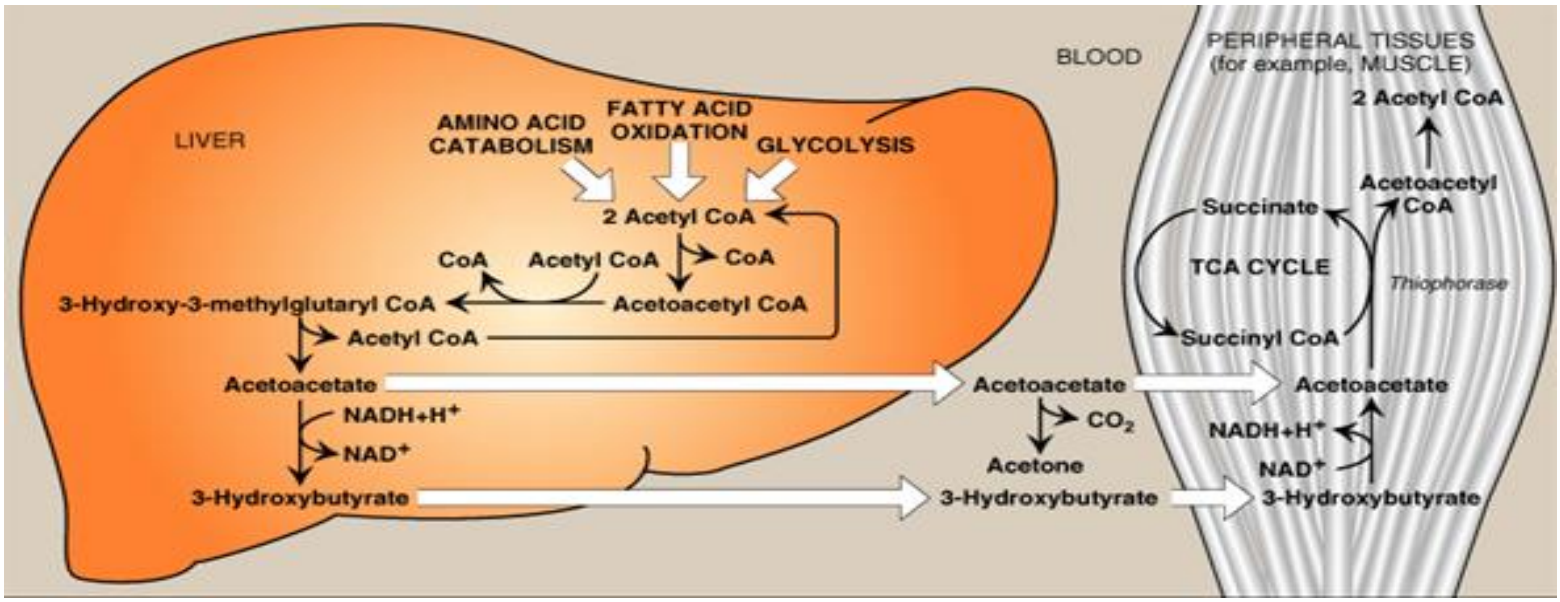
In a nutshell
OAA ➔ gluneogenesis ➔ hyperglycemia
Acetyl CoA ➔ ketogenesis ➔ ketonemia
} DKA

EXTRA NOTE: HMG CoA is important in cholesterol synthesis.

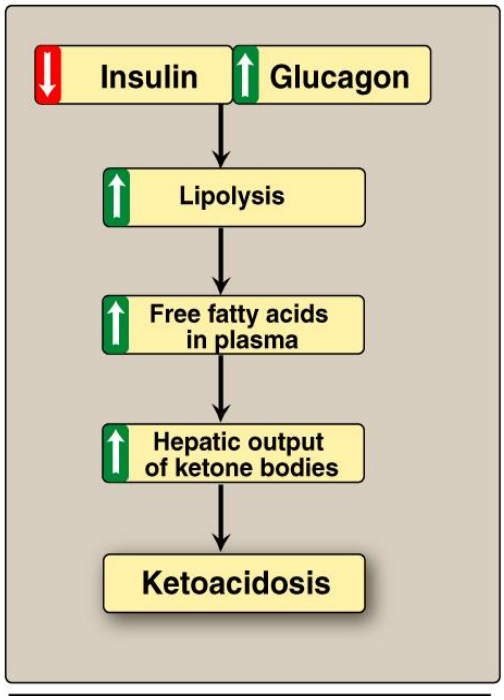
Acetyl coA is the precursor of ketone bodies.
In diabetes, Glucagon overwhelm insulin effect, thus Oxaloacetate used in gluconeogenesis process rather than Krebs cycle, because gluconeogenesis is stimulated by glucagon while insulin stimulate krebs cycle.

Ketone Bodies Utilization = Ketolysis

- Takes place in extrahepatic tissues
- Occurs in the mitochondria (so cannot occur in RBCs)
- Does not occur in the liver (as the liver lacks the thiophorase enzyme required for ketolysis)
- β-Hydroxybutyrate is oxidized to acetoacetate (by a dehydrogenase)
- Acetoacetate is converted to acetoacetyl CoA (catalyzed by thiophorase)
- Acetoacetyl CoA is converted to acetyl CoAs.



Mechanisms & Manifestations of DKA



In uncontrolled DM there is ↑lipolysis in adipose tissue → ↑ [FFA] → ↑ mobilization of FFA to liver → ↑hepatic FA oxidation → ↑ hepatic acetyl CoA which will be utilized in KB synthesis (ketogenesis) → ketoacidosis

- **In uncontrolled DM the rate of ketogenesis is > the rate of ketolysis → ketonemia (↑[KB] in blood)→ ketonuria (↑[KB] in urine).**

- **<u>Manifestations of DKA:</u>**
  Fruity odor on the breath (acetone)
  Acidosis (low pH of blood because KBs are acids)
  Dehydration (due to glucosuria 'glucose drags H2O')

Precipitating factors for DKA

↑ketogenesis, ↓ketolysis → ketonemia.

- **Infection (30-40%)(due to oxidative stress)**

  Infections result in dehydration which also precipitates the development of DKA.

  DKA in uncontrolled diabetes is triggered by infections in 30-40% of cases (e.g. UTI, tonsillitis)
- **Inadequate insulin treatment or non-compliance (20%)**
- **Severe illness e.g., Myocardial infarction**
- **Trauma**
- **Drugs: e.g., steroids(tceffe cinegotebaid sti ot eud)**

EXTRA: Physical or mental stress produces hormones like cortisol, epinephrine which act in opposition to insulin's action.

Hyperosmolar hyperglycaemic state (HHS)

Or Hyperosmolar non-ketotic acidosis (HONK)

- **Little or no accumulation of ketone bodies**
- **Serum [glucose] is often >50 mmol/L (HYPERGLYCEMIA)**
- **Plasma osmolality may reach 380 mosmol/Kg (normal 275-295)**
- **Neurological abnormalities are frequently present**
- **Insulin levels are insufficient to allow appropriate glucose utilization but are adequate to prevent lipolysis and subsequent ketogenesis**
- **Usually occurs in elderly patients with T2DM**
- **Has a substantially higher mortality than DKA (up to 15%)**

Numbers not to be memorized – Dr. Reem

Hypoglycemia

- **Common complication of treatment with insulin or oral hypoglycaemics**
- **More common in patients with T1DM**
- **Characterized by:**
  - **CNS Symptoms (confusion, aberrant behavior, or coma)**
  - **Low blood [Glucose]**
  - **Symptoms resolved within minutes following the administration of glucose**

Hypoglycemia is a medical emergency, Why ?

- **The brain has absolute requirement for a continuous supply of glucose**
- **Transient hypoglycemia → cerebral dysfunction**
- **Severe, prolonged hypoglycemia → brain death**

Hypoglycemia, continued..

- **Hypoglycemia occurs due to impaired protective responses to hypoglycemia:**
  - **Insulin is supplied exogenously and its release cannot be turned off** (lowers glucose levels continuously)
  - **Glucagon & adrenaline response to hypoglycemia becomes impaired later in the course of DM**

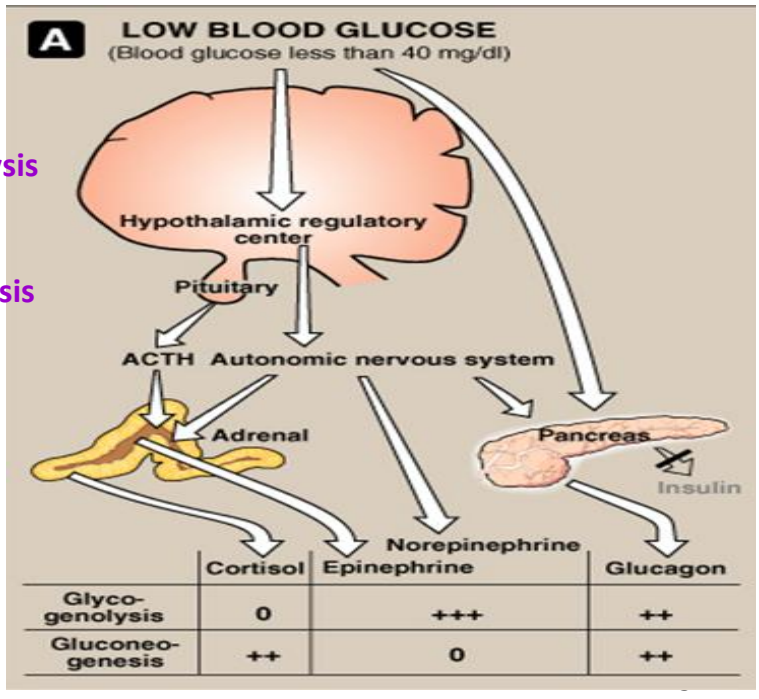
Clinical presentation:

- **Symptoms of sympathetic overactivity**(plasma [glucose] <3.6 mmol/L, abrupt fall)**: anxiety, tremors, sweating & palpitation.**

- **Symptoms of neuroglycopenia** (plasma [glucose] <2.6 mmol/L, gradual fall)**: headache, confusion, drowziness and ultimately loss of consciousness or seizures** (at plasma [glucose] <1.5 mmol/L)

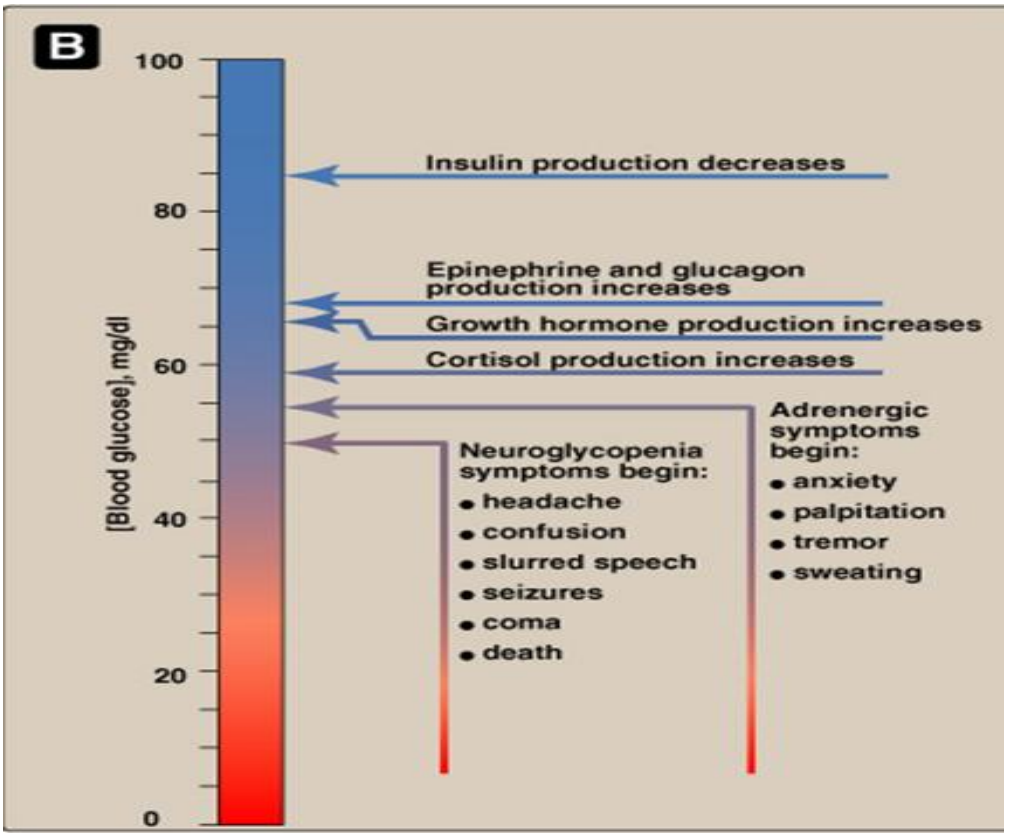
Hormonal mechanisms to prevent or correct hypoglycemia:

- ↓ **Production of insulin**
- ↑**production of:**
  - **Epinephrine & glucagon** → ↑ glycogenolysis
  - **Growth hormone**
  - **Cortisol** → ↑gluconeogenesis



Glycemic thresholds for the various responses to hypoglycemia:

Be familiar with the steps, not to be memorized. – Dr. Reem.



A CASE of DKA

A 14-year-old girl was admitted to a children's hospital in coma. Her mother stated that the girl had been in good health until approximately 2 weeks previously, when she developed a sore throat and moderate fever. She subsequently lost her appetite and generally did not feel well. Several days before admission she began to complain of undue thirst and also started to get up several times during the night to urinate. However, on the day of admission the girl had started to vomit, had become drowsy and difficult to arouse, and accordingly had been brought to the emergency department.

On examination:

- She was dehydrated
- Her skin was cold
- She was breathing in a deep sighing manner (Kussmaul respiration)
- Her breath had a fruity odor
- Her blood pressure was 90/60 mmHg (N: 120/80)
- Her pulse rate 115/min.
- She could not be aroused

A provisional diagnosis of T1DM with complicating ketoacidosis and coma (DKA) was made by the intern on duty

Laboratory findings

blood results

Plasma analytes	Patient's results	Normal levels
Glucose (mmol/L)	50	4.2-6.1
Ketoacids	++++	(trace)
Bicarbonate (mmol/L)	6	22-30
Arterial blood pH	7.07	7.35-7.45
Na^+ (mmol/L)	136	136-146
Cl^- (mmol/L)	100	102-109
PCO_2 (kPa)	2.7	4.3-6.0
*Anion gap (mmol/L)	35.5	7-16
K^+ (mmol/L)	5.5	3.5-5.0
Urea nitrogen (mmol/L)	15	2.5-7.1
Creatinine (μmol/L)	200	44-80
Albumin (g/L)	50	41-53
Osmolality (mOsm/kg serum water)	325	275-295
Hematocrit	0.500	0.354-0.444

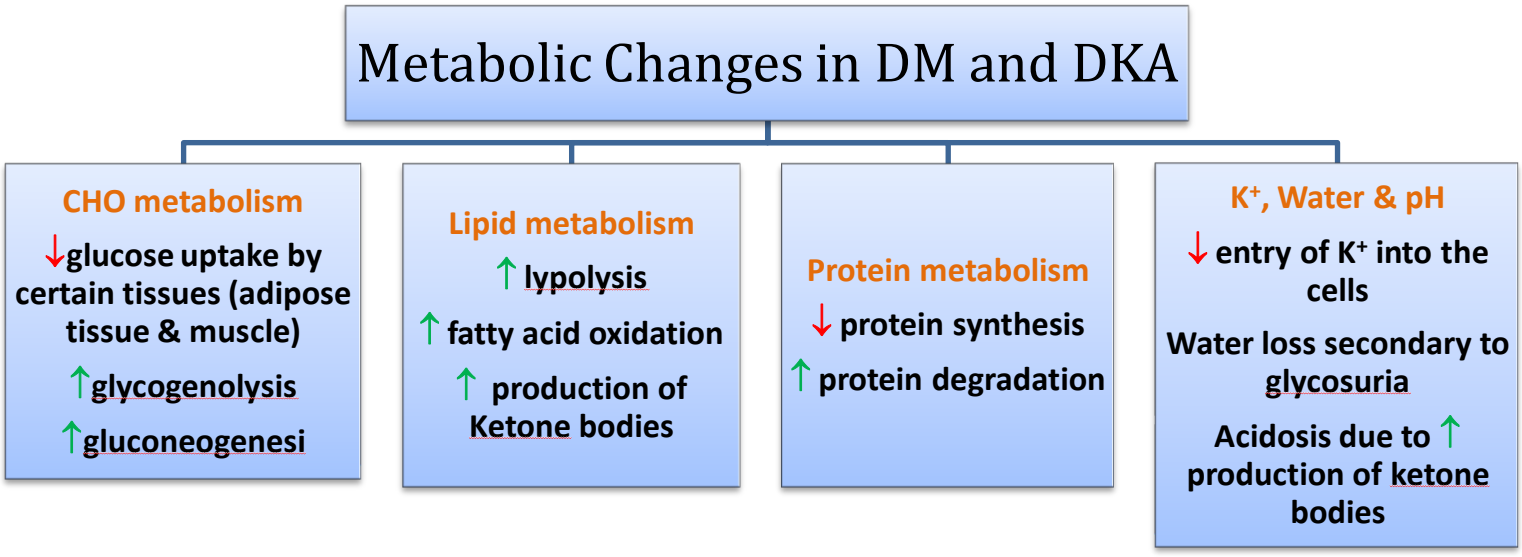
*Anion gap (A^-)= (Na^+ + K^+)– (HCO_3^- + Cl^-)

Urine results

Urine analyte	Patient's results	Normal levels
Glucose	++++	-
Ketoacids	++++	-

Interpretation of Laboratory findings

Results	Interpretation
Hyperglycemia	Confirm the diagnosis of DKA
Glucosuria	
Ketonemia	
Ketonuria	
↓pH	Severe metabolic acidosis due to ↑ production of ketone bodies
↓bicarbonate and PCO_2	Metabolic acidosis with partial respiratory compensation (the hyperventilation)
↑anion gap	Due to ↑ ketone bodies in the blood
↑urea&creatinine	1. Renal impairment (dehydration →↓ blood volume →↓ renal perfusion) 2. Dehydration 3. Degradation of protein (for urea) hcihw nilusni fo level wol fo esuaceb tceffe cilobana na tog sah
↑K^+	↓ Uptake of potassium by cells in the absence of insulin
↑ Plasma osmolality	Due to hyperglycemia and fluid loss



Questions:

1. Which one of the following is the rate limiting enzyme of ketogenesis?

A. Thiolase

B. HMG CoA synthase

C. HMG CoA lyase

D. 3-hydroxybutyrate dehydrogenase

2. Ketolysis does not occur in the liver because it lacks:

A. Thiophorase

B. Thiolase

C. 3-hydroxybutyrate dehydrogenase

D. HMG CoA Lyase

3. Which one of the following is the first response to hypoglycemia?

A. Insulin production decreases

B. Epinephrine and Glucagon production increases

C. Growth hormone production increases

D. Cortisol production increases

1=B / 2=A / 3=A