Biochemistry

Lecture(8): Diabetic ketoacidosis

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The Objectives

Diabetic emergencies:

1-Diabetic Ketoacidosis (DKA)

2-Hypperosmolar non-ketotic acidosis (HONK)

3-Hypoglycemia

DIABETIC EMERGENCIES

Diabetic emergencies are divided to those associated with hyperglycemia (DKA and HONK) and hypoglycemia. One must take proper history when dealing with an unconsious/disoriented diabetic to know which one it is.

(I)Diabetic ketoacidosis:

Definition: Triad of

(a) Hyperglycemia

(b) Ketonemia with ketonuria

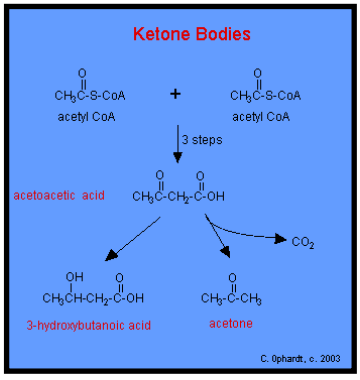
(c) High anion gap metabolic acidosis

Anion gap estimates unmeasured anions such as ketones. High anion gap >17

May be the first presentation of T1DM.

It is Characteristically associated with T1DM.

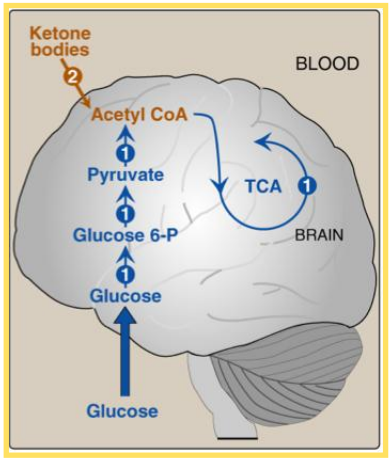
It has become increasingly common in T2DM.



Ketone bodies: ↑ proton H+ plasma conc. → acidosis

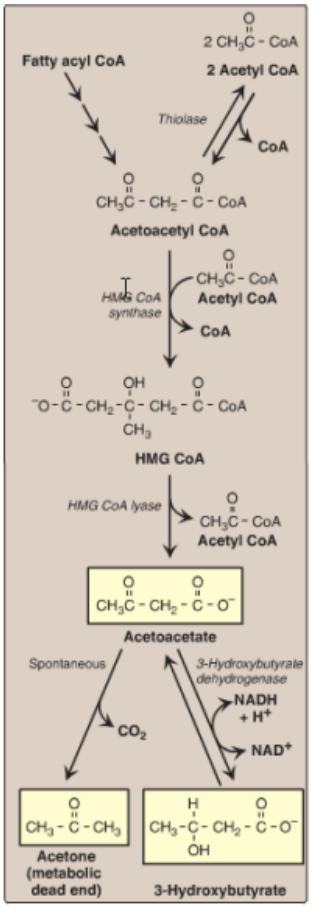
1. Acetoacetate (true acid.)
2. Acetone (metabolically inactive, may secreted from the lung, Decarboxylated, neutral, useful because of its distinctive odor .Volatile)
3. β-hydroxybutyrate (hydroxy acid.)

They are produced by the liver (ketogenesis) and utilized for energy production by peripheral tissues (Ketolysis). Water soluble. Cannot utilized in the liver.



- 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 since ketolysis produces energy.

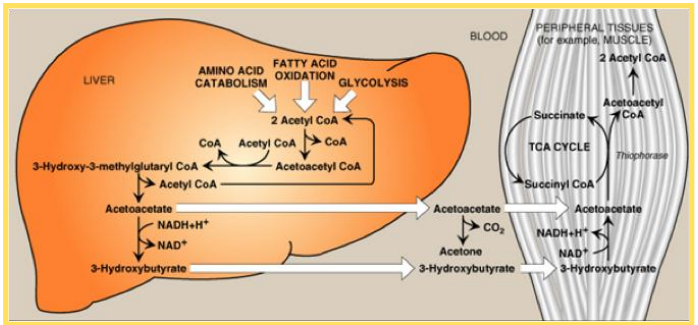
Ketone bodies synthesis = ketogenesis



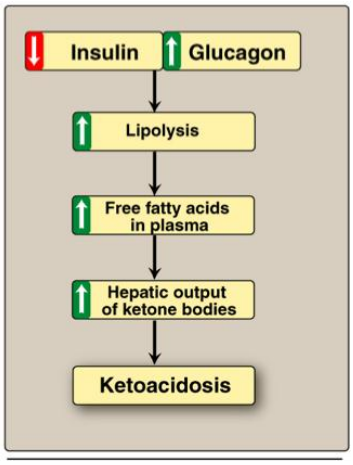
- Occurs in the mitochondria
- In uncontrolled DM there is ↑lipolysis in adipose tissue →↑ [FFA] mobilization to the liver
- ↑Hepatic FA oxidation ↑ acetyl CoA which will be channeled into KB synthesis
- HMG (hydroxymethyl glutaryl) CoA synthase is the rate limiting enzyme
- The first KB to be synthesized is acetoacetate which can be:
  - ➡ reduced to **β**-Hydroxybutyrate, or
  - ➡ spontaneously decarboxylated to acetone.
- 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

Oxaloacetate is used up in gluconeogenesis leading to hyperglycemia and acetyl CoA is used in ketogenesis leading to ketosis, both components of DKA.

Ketone body 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) and Acetoacetyl CoA is converted to acetyl CoAs.



Mechanisms and 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).

Manifestations:

- Fruity odor on the breath: acetone
- Acidosis: low blood pH because KBs are acids
- Dehydration: due to glucosuria (loss of skin turgor)

Precipitating factors:

- Infection (30-40%). Most commonly pneumonia and UTIs. Normal body's response to infection is increased production of glucose
- Inadequate insulin treatment or non-compliance (20%)
- Severe illness e.g., Myocardial infarction Stress (e.g, surgery) increases production of stress hormones (anti-insulin).
- Trauma
- Drugs: e.g., steroids, thiazides.

(II)Hyperosmolar non-ketotic state:

- 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%). Age increases mortality.

(III)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 occurs due to impaired protective responses to hypoglycemia

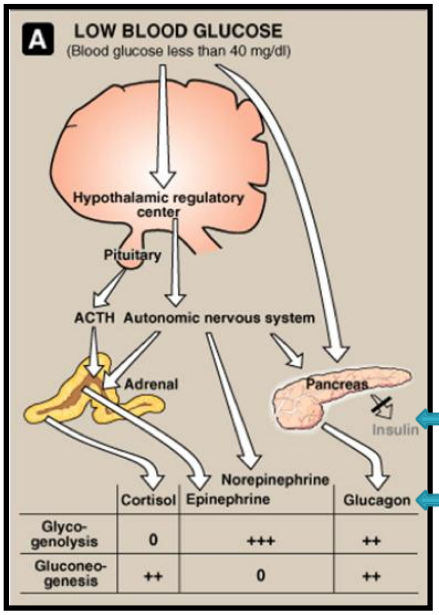
* Insulin is supplied exogenously and its release cannot be turned off (cannot be regulated)
* Glucagon & adrenaline response to hypoglycemia becomes impaired later in the course of DM

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) A gradual fall allows the body time to adjust and compensate resulting in a more insidious onset.

Early adrenergic symptoms	Neuroglycopenic signs
Pallor	Confusion
Diaphoresis	Slurred speech
Shakiness	Irrational or uncontrolled behavior
Hunger	Disorientation
Anxiety	Loss of consciousness
Irritability	Seizures
Headache	Pupillary sluggishness
Dizziness	Decreased response to noxious stimuli

"Normal" Hormonal mechanisms to prevent/correct hypoglycemia



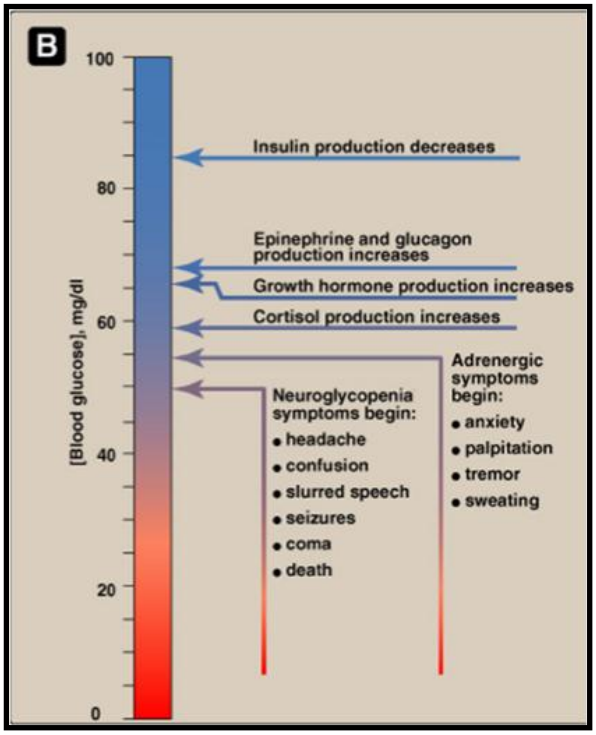
- As blood glucose falls, insulin is directly inhibited -1st response- and glucagon will be released.
- Special sensors in the hypothalamus are alerted the pituitary and the autonomic nervous system to release cortisol and CAs, respectively.

↓ Production of insulin

↑production of:
- Epinephrine & glucagon
- Growth hormone
- Cortisol

Compare this normal response to that of a diabetic. With time symptoms manifested by the adrenergic system and glucagon (as early as 2 years post diagnosis) are lost to autonomic neuropathy and impaired α cell function.

- This is to demonstrate the gradual stepwise activation of different systems to combat hypoglycemia and the observed symptoms.
- Release of epinephrine precedes its manifestations
- One must note that the onset of symptoms is relative to the level of blood glucose the individual is normally exposed to. For instance, a diabetic with an average of 160 might get tremors as early as 75mg/dL.



Case study

A CASE OF DKA

Scenario:

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.

Clinical 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

The admitting diagnosis was confirmed by the laboratory findings shown below:

Plasma analytes	Patient's results	Normal levels
Glucose (mmol/L)	50	4.2–5.6
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

Plasma analytes	Patient's results	Normal levels
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)	325	275–295
Hematocrit	0.500	0.354–0.444

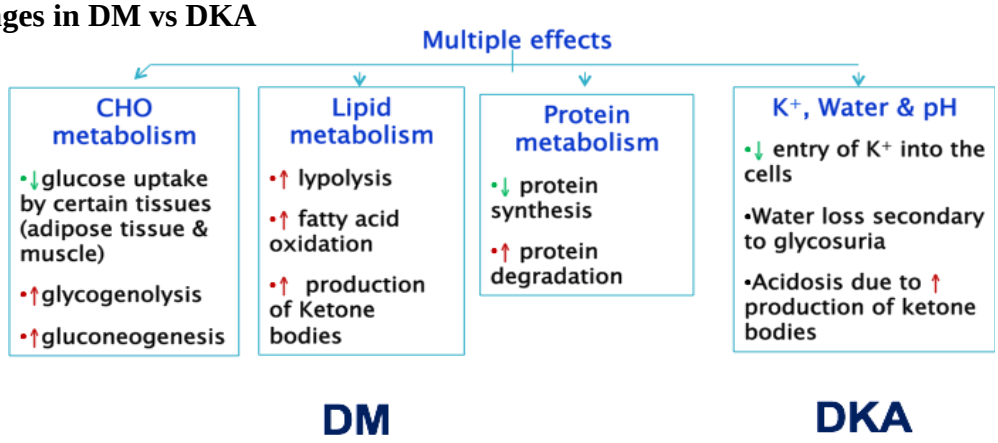
Urine analyte	Patient's results	Normal level
Glucose	++++	–
Ketoacids	++++	–

Interpretation of 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. Degradation of protein (for urea) 3. Dehydration
↑K^+	↓ Uptake of potassium by cells in the absence of insulin
↑ Plasma osmolality	Due to hyperglycemia and fluid loss

Since insulin results in influx of extracellular potassium, hypokalemia is common with institution of insulin

* **Metabolic changes in DM vs DKA**



Questions

1-Which one of the following is the rate limiting step in ketogenesis:

a)Thiophorase

b)HMG coA synthase

c)3-hydroxybutyrate dehydrogenase

e)HMG coA reductase

2-Which one of the following statements is incorrect regarding HONK:

a)Frank hyperglycemia is not always seen

b)Usually seen in an older age group

c)Associated with a high mortality rate

d)High anion gap is a common finding

3- Ketolysis does not occur in the liver because it lacks:

A.Thiophorase
B.Thiolase
C. 3-hydroxybutyrate dehydrogenase
D. HMG CoA Lyase

4-A hormonal response to hypoglycemia that is impaired in DM due to autonomic neuropathy:

a)Abnormal glucagon response

b)Diminished glycogen stores

c)Impaired activation of the adrenergic system

d)Insulin action is not inhibited

5. 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. D
3. A
4. C
5. A

Biochemistry Team

If you find any mistake, please contact us:)
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Thank you