Biochemistry Team 435

جامعة الملك سعود
King Saud University 1957

DIABETIC KETOACIDOSIS

* Please check out this link to know if there are any changes or additions.

Revised by
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Color index: Important | Doctors notes | Further explanation.

OBJECTIVES:

- ✓ Unknown 😬.

Diabetic emergencies

Diabetic Ketoacidosis (DKA). | **Hyperosmolar hyperglycaemic state (HHS)** | **Hypoglycemia**

1. Diabetic Ketoacidosis (DKA).

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

Because in the later stages of DM TYPE TWO , there is SEVERE insulin depletion So ketone production is increased
Also there is an increase in the life expectancy , so there are more people living in old age with other chronic diseases which increases production of ketone bodies , hence DKA is increasing in type 2

❖ Ketone bodies:

- They are produced by the **liver** (ketogenesis) and utilized for energy production **by peripheral tissues** (Ketolysis).

Dr sumbul stressed that the liver can only synthesize ketones but cannot use them
And peripheral tissues only use them but cannot synthesize them

Ketone bodies

- **Acetoacetate** (acid)
- **Acetone** (not an acid)
- **β-Hydroxybutyrate** (Acid)

Note that:
- **Retinopathy and nephropathy** are due to **CHRONIC** HYPERGLYCEMIA
- **DKA and HHS** are due to **ACUTE** HYPERGLYCEMIA

❖ **What will u see in the lab of a person with DKA?**
Decreased PH and bicarbonate with increased blood glucose and ketones

❖ **How does metabolic acidosis become compensated?** By hyperventilation (Kaussmal breathing)

Diabetic emergencies

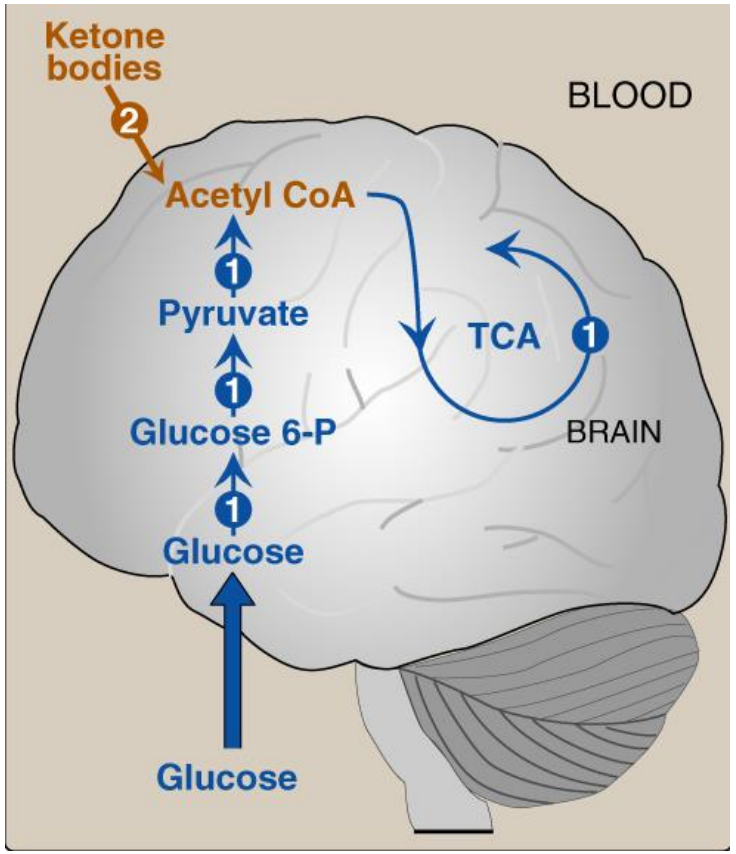
Diabetic Ketoacidosis (DKA). | **Hyperosmolar hyperglycaemic state (HHS)** | **Hypoglycemia**

1. Diabetic Ketoacidosis (DKA).

❖ Brain and Ketone bodies:

- ✓ Normally, glucose is the **primary** fuel for the brain. The brain always prefers glucose as a source of fuel , but if glucose is not available then it can use ketone bodies
- ✓ 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.



Explanation:

1-Glucose enters brain cells.
2-then turns to **glucose -6- phosphate** then to **pyruvate**.
3- pyruvate then turns to **acetyl co A** .
4-acetyl co A then enters **TCA CYCLE** to produce energy BUT if glucose is not available :

- ketone bodies enter the brain cell
- oxidation of ketones also yields acetyl co A which then enters TCA

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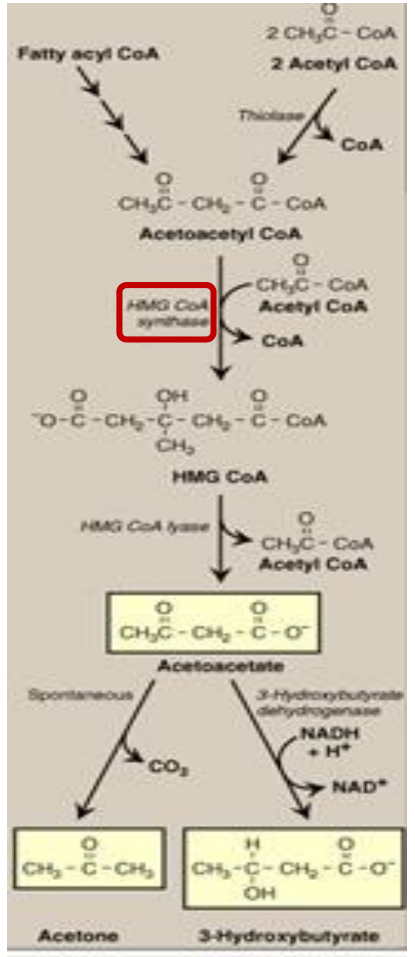
❖ Ketone Bodies Synthesis(Ketogenesis):

- **Occurs in:** Hepatocyte mitochondria.
- **How?**

In uncontrolled DM there is ↑**lipolysis** in adipose tissue → **↑ [FFA] mobilization to liver** → ↑hepatic FA **oxidation** → **↑ acetyl CoA which:**

Here we have three fates for acetyl CoA

1. **Acetyl CoA + oxaloacetate (OAA) →** Krebs cycle
   - We need both of them for Keps cycle to occur
2. ↑ Acetyl CoA production activates **pyruvate carboxylase**
   - Converts **pyruvic acid into OAA**
   - OAA is used for **gluconeogenesis** (rather than Krebs cycle)
3. channeled into **KB** synthesis.
   - **HMG CoA synthase** "rate limiting enzyme" acts on Acetyl coA forming HMG coA
   - HMG CoA lyase acts on HMG coA forming → **acetoacetate** "The first KB to be synthesized"
     - **Acetoacetate can be:**
       - reduced to β-Hydroxybutyrate or
       - spontaneously decarboxylated to acetone



الخطوات معنا..

DR.SUMBUL'S NOTES

الكلام حطيناه للأمانة العلمية فيه اشياء قالتها الدكتورة وميب بالسلايدز وصعبة مانكتبه.. اهم شي اللي بالاحمر.. الباقي راجع لكم

What you should know:

1. **acetoacetyl CoA is acted upon by HMG -Co A synthase to form HMG Co A**
2. **HMG Co A is acted upon by HMG Co A lyase to form acetoacetate**
3. **Acetoacetate has two products:- acetone (spontaneous) - 3 hydroxybutarate by 3-hydroxybutarate dehydrogenase**

- IT IS IMPORTANT TO KNOW THAT beta-hydroxybutyrate is the prevalent ketone in ketoacidosis (So levels are helpful in diagnosis of DKA)

CONSIDERATIONS in diagnosis of DKA:

-In a clinical setting, once you have measured the ketones , do not measure them again after treatment (DO NOT DO A SERIAL MEASUREMENT)

once you start treatment beta hydroxybutarate starts to breakdown to acetoacetate(problem of high ketone levels is being resolved)

But when you measure again the acetoacetate will be high So this may lead to the diagnosis of a false positive of DKA

***So diagnosis depends on the the INITIAL nitroprusside test and the blood PH**

Diagnosis of DKA:

Whenever we want to measure ketones, the test that is available in labs only measures **acetoacetate** (This test is called **nitroprusside test**)

In a normal physiological condition:

- The rate of ketogenesis = rate of degradation so there is no build up of ketone bodies in the blood (so no ketone build up in blood)
- the amount of acetoacetate is = beta hydroxybutarate

When the patient has DKA:

- A lot of ketone bodies are being formed, and the amount of acetoacetate is high But if you compare the levels of betahydroxybutarate to acetoacetate the ratio could be as high 6 to 1.

➢ So when you measure acetoacetate you will **not** get a clear picture of the amount of ketones in the blood (hence this test will NOT detect the SEVERITY of ketoacidosis) ,That is why measuring PH is also important in diagnosing DKA

*note that there are specific tests to measure only betahydroxybutarate BUT they are not available in most labs

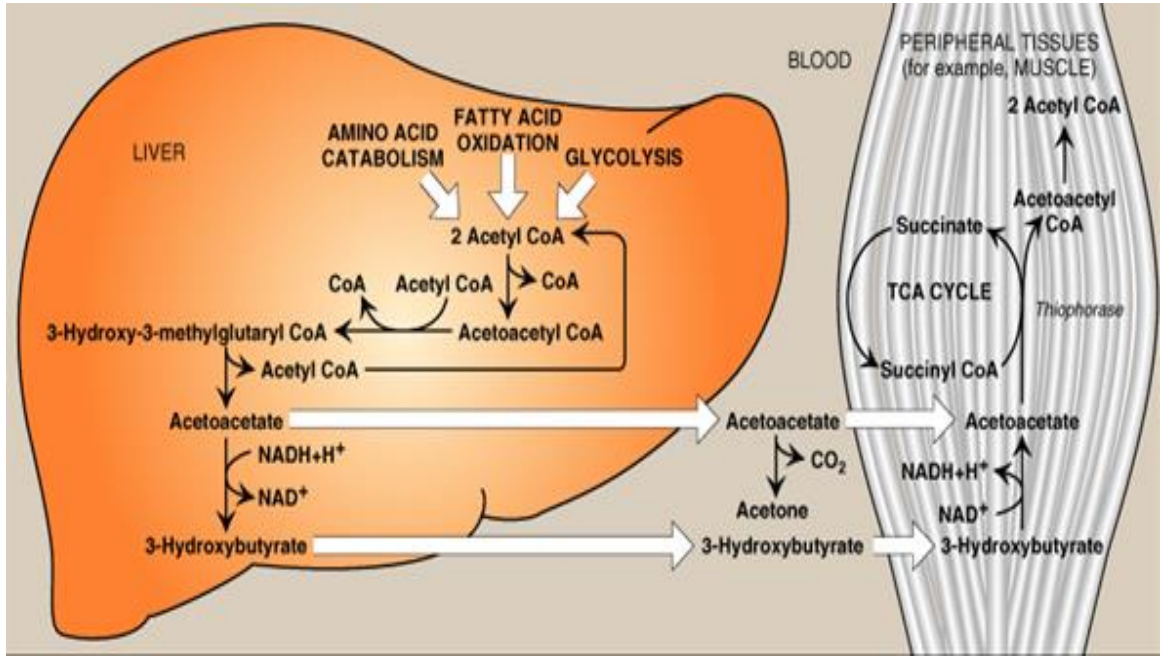
So the nitroprusside test is still used even though it is not that accurate in terms of severity of the disease

Diabetic emergencies

Diabetic Ketoacidosis (DKA). | **Hyperosmolar hyperglycaemic state (HHS)** | **Hypoglycemia**

❖ Ketone Bodies Utilization (Ketolysis) :

- **Takes place in**: extrahepatic tissues
- **Occurs in:** the mitochondria (so cannot occur in RBCs) because RBCs lack mitochondria
- Does not occur in the liver (as the liver lacks the thiophorase enzyme required for ketolysis).



How?

1- **β-Hydroxybutyrate** is oxidized to **acetoacetate** (by a **dehydrogenase**)

2- **Acetoacetate** is converted to **acetoacetyl CoA** (catalyzed by **thiophorase**)

3- **Acetoacetyl CoA** is converted to **acetyl CoAs.**

1-Amino acid catabolism and fatty acid oxidation and glycolysis give acetyl CoA → 2-Acetyl CoA gives **acetoacetate** which then turns to 3-hydroxybutarate → 3-this **3-hydroxybutarate goes** to the **bloodstream** which then enters the **peripheral tissues**. → 4-in the peripheral tissues : **3 hydroxybutarate** is converted into **acetoacetate** by **dehydrogenase** → 5-acetoacetate is turned to **acetoacetyl CoA** by **thiophorase** → 6-acetoacetyl COA is then converted to **acetyl COA** which can enter the **TCA cycle**

Diabetic emergencies

- **Diabetic Ketoacidosis (DKA).**
- **Hyperosmolar hyperglycaemic state (HHS)**
- **Hypoglycemia**

Diabetic Ketoacidosis (DKA).

Manifestations of DKA

- **Fruity odor** on breath (because of acetone)
- **Acidosis** (low pH of blood because KBs are acids)
- **Dehydration** (due to glucosuria and vomiting)

Precipitating factors for DKA

- ***Infection (30-40%)**
- Inadequate insulin treatment or non-compliance **(20%)**
- **Severe illness** (e.g. Myocardial infarction)
- Trauma
- Drugs (e.g. steroids)

***How does infection precipitate ketoacidosis?**

During infection the metabolic rate increases so we require more energy thus we require more glucose

This glucose in the case of diabetes is not available to the cell so the body forms ketones instead THUS DKA develops

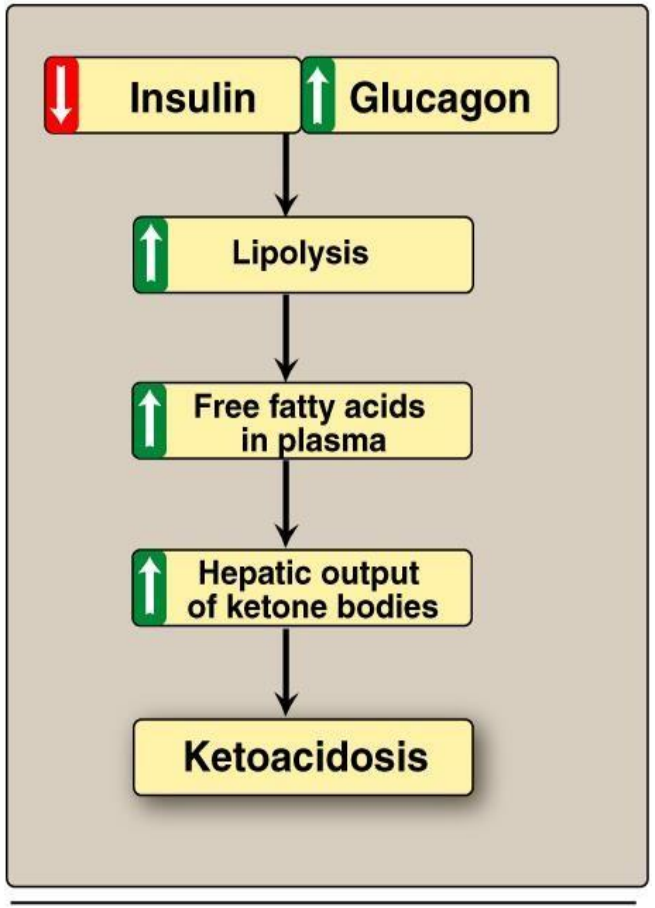
Diabetic emergencies

Diabetic Ketoacidosis (DKA). | **Hyperosmolar hyperglycaemic state (HHS)** | **Hypoglycemia**

❖ Mechanism 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).** Because the excess ketone bodies in the blood exceed the renal threshold



- FFAs: free fatty acids.
- Other than liver, Acetyl CoA in most tissues is used in Krebs cycle to form ATP.

Diabetic emergencies

Diabetic Ketoacidosis (DKA). | Hyperosmolar hyperglycaemic state (HHS) | Hypoglycemia

2. Hyperosmolar hyperglycaemic state (HHS)

❖ **Also called:** Hyperosmolar Non-ketotic acidosis (HONK).

❖ In HHS (i.e. HONK), insufficient to allow appropriate glucose utilization but are **adequate to prevent lipolysis and subsequent ketogenesis.** Insulin is deficient but **not enough** to induce lipolysis and ketogensis!! (this is a special characteristic of T2DM). That's why T1DM patients are thinner than T1DM, cuz proteolysis & lipolysis occur in their bodies.

❖ **Occurs in:** in **elderly with T2DM.**

❖ **Mortality:** substantially **higher mortality** than DKA (up to **15%**).

Clinical features:	
Serum glucose:	Serum glucose is often > **50 mmol/L**
Ketone bodies:	Little or **NO** accumulation of ketone bodies
Plasma osmolality:	High Plasma osmolality that could reach **380 mosmol/Kg** (Normal range 275-295). In this condition there is more blood glucose, so there is more dehydration which increases the blood's osmolality
Neurological abnormalities	

HHS & DKA

HHS

Diabetic emergencies

Diabetic Ketoacidosis (DKA). | **Hyperosmolar hyperglycaemic state (HHS)** | **Hypoglycemia**

3. Hypoglycemia

A common complication of treatment with insulin or oral hypoglycemic

Occurs due to?	Impaired protective responses to hypoglycemia: 1- Insulin is supplied **exogenously or oral hypoglycemics** and their release cannot be turned off. 2- Glucagon & adrenaline response to hypoglycemia becomes **impaired** later in the course of DM. ➢ **More common in:** patients with **T1**DM.
Why it's a medical emergency?	Because the brain has absolute requirement for a **continuous** supply of glucose. • **Transient** hypoglycemia → cerebral dysfunction • **Severe**, prolonged hypoglycemia → brain death Hypoglycemia → ketone bodies compensation in the brain → coma & then death
Treatment:	Administration of **glucose** (Symptoms will resolve within minutes)
Clinical manifestations:	1- **CNS Symptoms** (confusion, aberrant behavior, or coma) 2- **Low blood glucose conc.**

الانسولين\الهايبوجلايسمك درقز تنزل مستوى الجلوكوز والى حد ما تأثيرهم يحتاج انه ينعكس أو يتوقف علشان يكون فيه توازن وماندخل بحالة هايبوجلايسميا

- فاللي يصير هنا ان الشخص ياخذ الانسولين ووظيفة الجلوكاجون "المعاكسة للانسولين" بتكون مختلة فيدخل الشخص بهايبو..
- اختلال الجلوكاجون بيظهر بالمراحل المتأخرة من المرض ليش؟ لأن الالفا سلز بتبدأ تتدمر وتتعطل.

ليش نقول عن هالحالة انها حالة طارئة ولازمها تدخل؟

- لأن الدماغ يحتاج جلوكوز بشكل مستمر كمصدر للطاقة وأي تغييرات بتسبب له مشكلة ولو كان الجلوكوز مره قليل وطول وهو قليل ممكن انه يسبب موت دماغي!

Diabetic emergencies

- Diabetic Ketoacidosis (DKA).
- Hyperosmolar hyperglycaemic state (HHS)
- Hypoglycemia

3. Hypoglycemia

Clinical manifestations:		
Plasma [glucose] < **1.5** mmol/L	Plasma [glucose] < **2.6** mmol/L. (gradual fall)	plasma [glucose] < **3.6** mmol/L. (abrupt fall)
Seizures and **ultimately loss** of consciousness	Symptoms of **neuroglycopenia**	Symptoms of **sympathetic overactivity**
	• Headache. • Confusion. • Drowsiness	• Anxiety. • Palpitation. • Tremor. • Sweating.

< **1.5** mmol/L < **2.6** mmol/L. < **3.6** mmol/L

Diabetic emergencies

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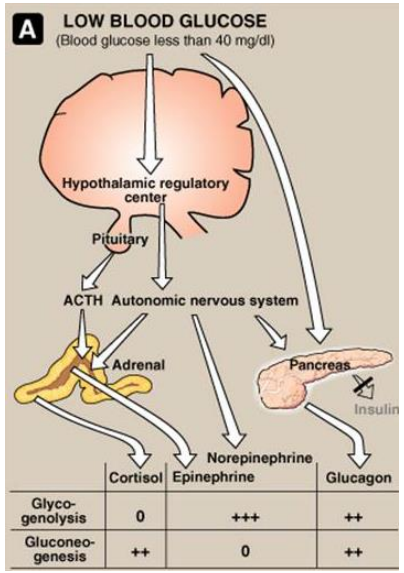
3. Hypoglycemia



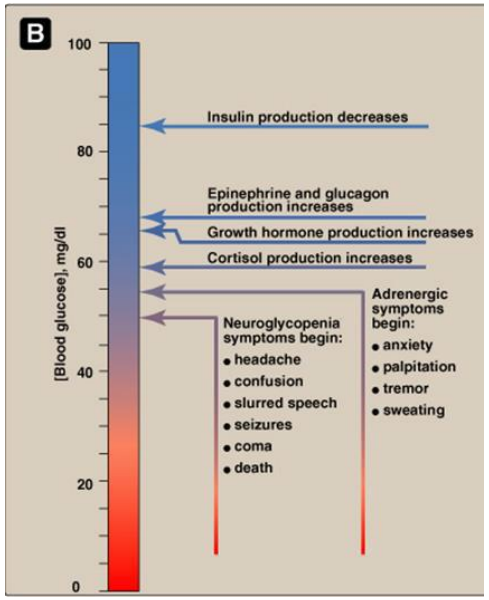
Hormonal mechanisms to prevent or correct hypoglycemia:

- ↓ Production of: insulin
- ↑production of: Epinephrine, glucagon, Growth hormone & Cortisol

▪ **Explanation:**

when we have low blood glucose (less than 40 mg/dl) our brain get a signal which will secret: (ACTH —> adrenal gland —> cortisol & epinephrine), (norepinephrine) & (glucagon from pancreas). no insulin production!

- cortisol will increase gluconeogenesis.
- epinephrine & nor epinephrine will increase glycogenolysis.
- glucagon will increase both gluconeogenesis & glycogenolysis.



Glycemic thresholds for the various responses to hypoglycemia:

- Normal range is **70-100** mg/dl.
- When it gets below **70 mg/dl** → ↓ production of insulin.
- **Further ↓:**
  - ↑ production of Epinephrine & Glucagon.
  - ↑ GH production.
  - ↑ Cortisol production.
- **At 55 mg/dl** → Adrenergic symptoms begin.
- **Below 50** → neuroglycopenia symptoms begin.

METABOLIC CHANGES IN DM AND DKA

DM			DKA
CHO metabolism	**Lipid metabolism**	**Protein metabolism**	**K+, Water & pH**
↓**glucose uptake** by certain tissues (adipose tissue & muscle)	↑ **lipolysis**	↓ **protein synthesis**	↓ **entry** of **K+** into the cells
↑**glycogenolysis** (lasts for about a day)	↑ **fatty acid oxidation**	↑ **protein degradation**	**Water loss** secondary to glycosuria
↑**gluconeogenesis**	↑ production of **Ketone bodies**	protein degradation will gives AA which will be use in glucose formation	**Acidosis** due to ↑ production of ketone bodies

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.

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

Plasma analytes	patient result	Normal levels
Glucose (mmol/L)	50	3.9-5.6
Ketoacids	++++	(trace)
Bicarbonate (mmol/L)	6	22-30
Arterial blood pH	7.07	7.35-7.45
Na+ (mmol/L)	136 here it is normal but usually it is decreased	136-146
Cl- (mmol/L)	100	102-109
PCO2 (kPa)	2.7 (low due to hyperventilation)	4.3-6.0
*Anion gap (mmol/L)	35.5 due to decreased HCO3	7-16
K+ (mmol/L)	5.5	3.5-5.0
Urea nitrogen (mmol/L)	15 high due to protein catabolism	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 high due to dehydration	0.354-0.444

Urine analytes	Patient result	Normal levels
Glucose	++++	-
Ketoacids	++++	-

*Anion gap (A-)= (Na+ + K+)– (HCO3- + Cl-

Dehydration

high Glucose in blood

Dehydration

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 (with hypothermia)→↓ renal perfusion) 2. **Dehydration** 3. **Degradation** of **protein** (for urea)
↑**K^+**	↓ Uptake of potassium by cells in the **absence of insulin**. And also because the high H+ ions in the blood go into the cells So the intracellular potassium goes out into the blood to maintain the neutrality
↑ **Plasma osmolality**	Due to **hyperglycemia** and **fluid loss**

Check your understanding!

Q1: hyperkalemia in diabetic ketoacidosis is due to?

A. Aldosterone deficiency
B. Insulin deficiency
C. Excess cortisol
D. Excess renin

Q2: Ketonuria is caused by?

A. Elevated 3-hydroxybutyrate in urine.
B. Elevated acetoacetate in blood.
C. Elevated Triacylglycerol in urine.
D. Elevated glucose in blood.

Q3: Regarding T1DM with complicating ketoacidosis and coma, which of following Laboratory findings is true:

A. Glucouria
B. Decrease Plasma osmolality
C. Increased pH
D. Hypokalemia

Q4:Which of following is precipitating factors for DKA:

A. Infection
B. Drugs e.g., steroids
C. Inadequate insulin treatment or non-compliance
D. All of the above

Q5: In order to diagnose patient with diabetic ketoacidosis (DKA), the patient must have the triad of:

A. Hypoglycemia, metabolic acidosis with high anion gap, and ketonemia
B. Hyperglycemia, metabolic alkalosis with high anion gap, and ketonemia
C. Hyperglycemia, metabolic acidosis with high anion gap, and ketonemia
D. Hyperglycemia, metabolic acidosis with low anion gap, and ketonemia

1.B 2.A 3.A 4.D 5.C

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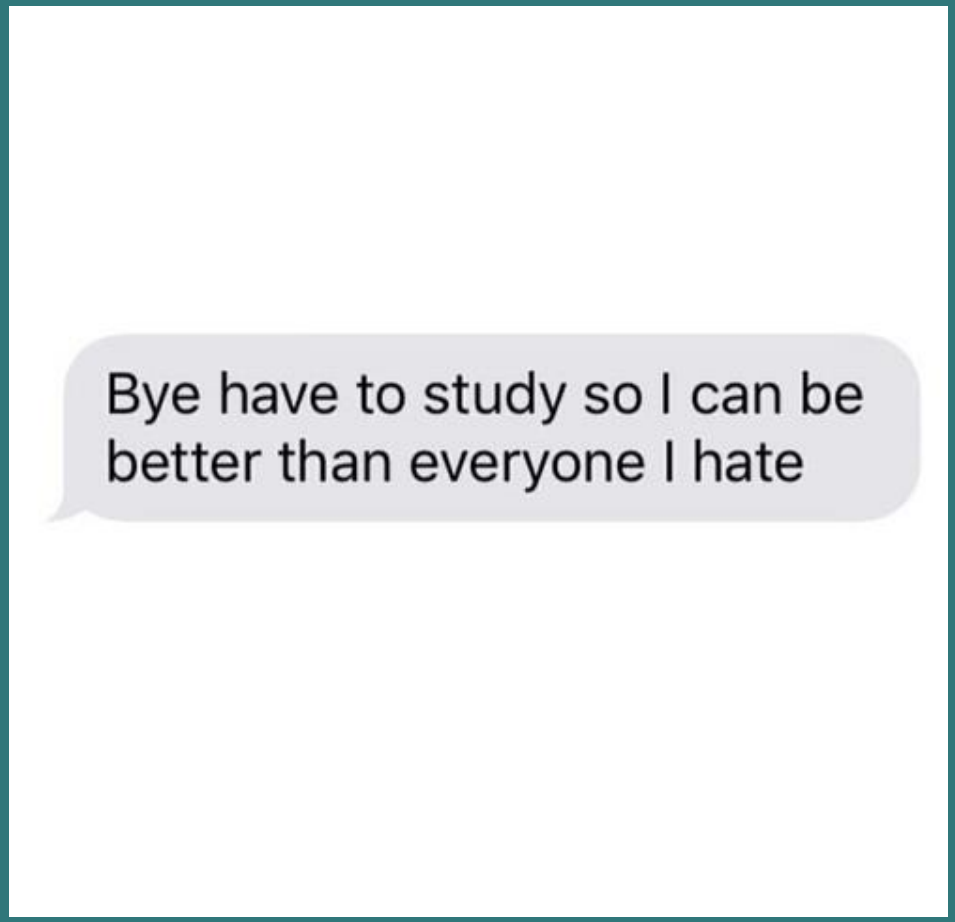

Resources:

- 435's slides and notes.
- Biochemistry: Lippincott's illustrated reviews – 6th edition.

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