Biochemistry Bandits 434

DIABETIC KETOACIDOSIS (DKA)

❖ Important ❖ Extra ❖ Biochemistry Edit

INTRODUCTION

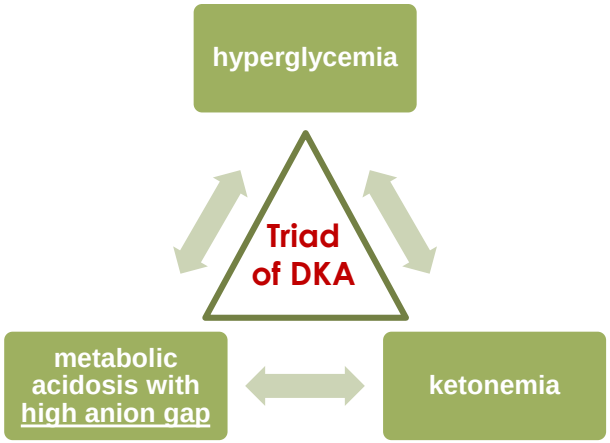
Diabetic emergencies

1:Diabetic Ketoacidosis (DKA)

- More common with T1DM
- DKA may be the first presentation of T1DM

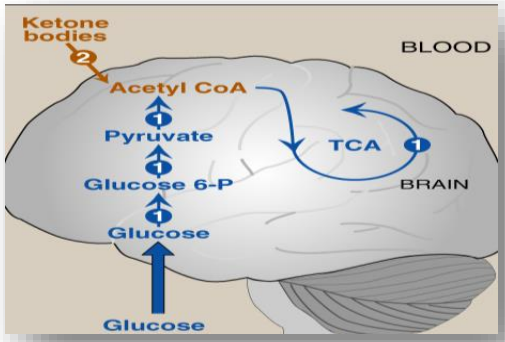
2:Hyperosmolar hyperglycaemic state (HHS)
or Hypperosmolar non-ketotic acidosis (HONK)

3:Hypoglycemia



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, (in case of starvation) the brain can utilize plasma **ketone bodies**, that can penetrate the blood brain barrier, and serve as fuel molecules.



Ketone Bodies

- **Acetoacetate**
- **Acetone** → not metabolically active ,ones in blood it is going to be breathed out, important for the diagnosis (fruity odor)
- **β-Hydroxybutyrate**

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

liver cannot utilize them because it lacks one of the enzymes

Ketogenesis

Occurs in the *hepatocyte mitochondria*

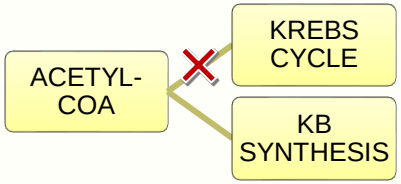
1:In uncontrolled DM there is ↑lipolysis in adipose tissue → ↑ [FFA] mobilization to liver

→ ↑hepatic FA oxidation → ↑ acetyl CoA which will be channeled into KB synthesis NOT TO KREBS CYCLE

Acetyl CoA + oxaloacetate (OAA) → Krebs cycle

↑ Acetyl CoA production activates pyruvate carboxylase

Pyruvate carboxylase converts pyruvic acid into OAA

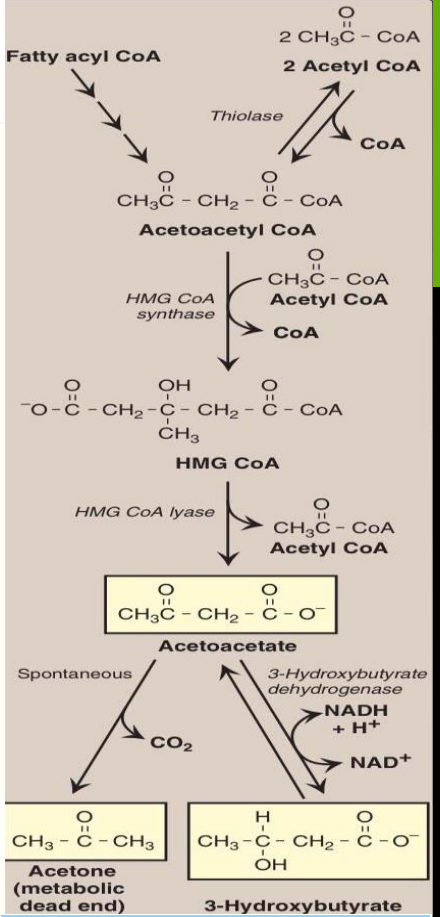


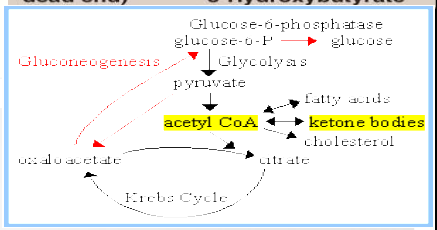
→ OAA is used for gluconeogenesis (rather than Krebs cycle)

HMG CoA synthase is the rate limiting enzyme (this enzyme is located in the mitochondria, unlike the cytosolic HMG CoA of the cholesterol pathway)

The first KB to be synthesized is **acetoacetate**.

- **Acetoacetate can be:**
  reduced to β-Hydroxybutyrate, OR spontaneously decarboxylated to aceton





EXTRA:FOR BETTER UNDERSTANDING

Pathogenesis: absolute or sever insulin deficiency causes :

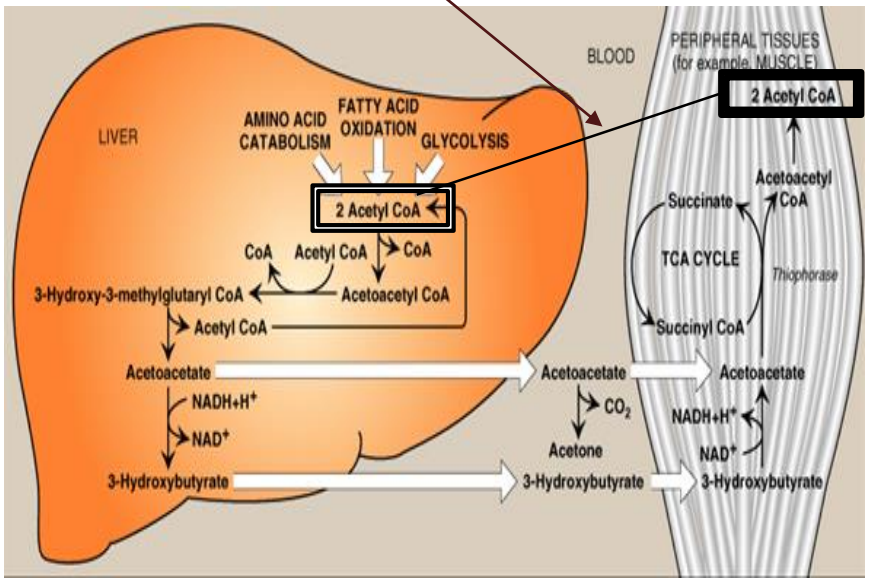
- Impaired glucose utilization in peripheral tissues →causes hyperglycemia
- Increase secretion of glucagon (removal of the inhibitory effect of insulin)→ increase glycogenolysis and gluconeogenesis
- Increased glycogenolysis
- Increased hepatic and renal gluconeogenesis → that is why the level of OAA is low in the liver = it is used in this process
- Increase lipolysis (related to increased activity of hormone sensitive lipase which releases free fatty acids and glycerol) → increase FFA in the blood → go to the liver → high production of Ketone Bodies → exceed the capacity of the peripheral tissue to utilize them → accumulate in the blood → decrease PH =ketoacidosis(normally the liver produce ketone bodies but in low amount so the body can use them without accumulation)
  the difference between DKA and HHS is = in DKA sever insulin deficiency → no insulin →cannot prevent lipolysis ,while in HHS there is modret insulin deficiency → can prevent lipolysis → so no lipolysis → no ketone bodies

KETOLYSIS

- Takes place in extrahepatic tissues (NOT in the liver as the liver lacks the thiophorase enzyme required for ketolysis
- Occurs in the mitochondria (so cannot occur in RBCs)
- 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→ with OAA** → Krebs cycle = energy

**Unlike the liver peripheral tissue has abundant amount of OAA → because there is no gluconeogenesis

Acetyl CoA IS the precursor and the end-product of the ketone bodies



Mechanisms & Manifestations of DKA

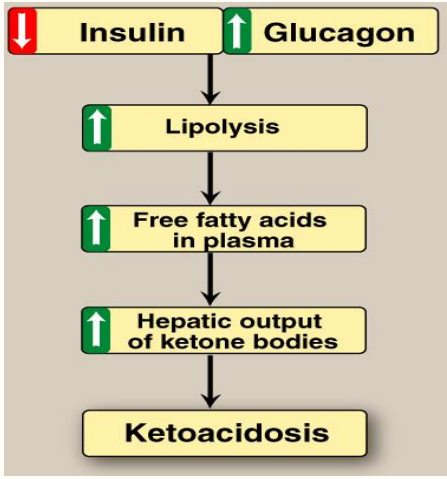
In uncontrolled DM the rate of ketogenesis is highr the rate of ketolysis → ketonemia (↑[KB] in blood)→ ketonuria (↑[KB] in urine).

Manifestations of DKA:

Fruity odor on the breath (acetone)

Acidosis (low pH of blood because KBs are acids)

Dehydration (due to glucosuria)

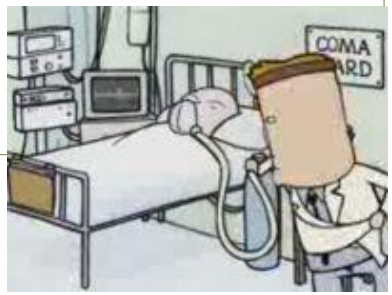


Precipitating factors for DKA :

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

HYPEROSMOLAR HYPERGLYCEMIC STATE (HHS) OR HYPEROSMOLAR NON-KETOTIC ACIDOSIS (HONK)

- Little or no accumulation of ketone bodies
- Serum [glucose] is often >50 mmol/L
- Plasma osmolality may reach 380 mosmol/Kg (normal 275-295)
- Neurological abnormalities are frequently present
- [1]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 →they still have insulin unlike T1DM
- Has a substantially higher mortality than DKA (up to 15%) →Age increases mortality



❖ Hypoglycemia

- **Common complication of treatment with insulin or oral hypoglycaemics**
- **More common in patients with T1DM**
- **Characterized by:**
  1. **CNS Symptoms (confusion, aberrant behavior, or coma)**
  2. **Low blood [Glucose]**
  3. **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**

[1]the concentration of insulin required to suppress lipolysis is only one-tenth that required to promote glucose utilization Thus, more moderate insulin deficiency, as occurs in HHS, might be associated with sufficient insulin activity to block lipolysis (and therefore ketoacid formation) but not enough to promote glucose utilization and prevent the development of hyperglycemia More severe insulin deficiency generates ketoacidosis.

HYPOGLYCEMIA

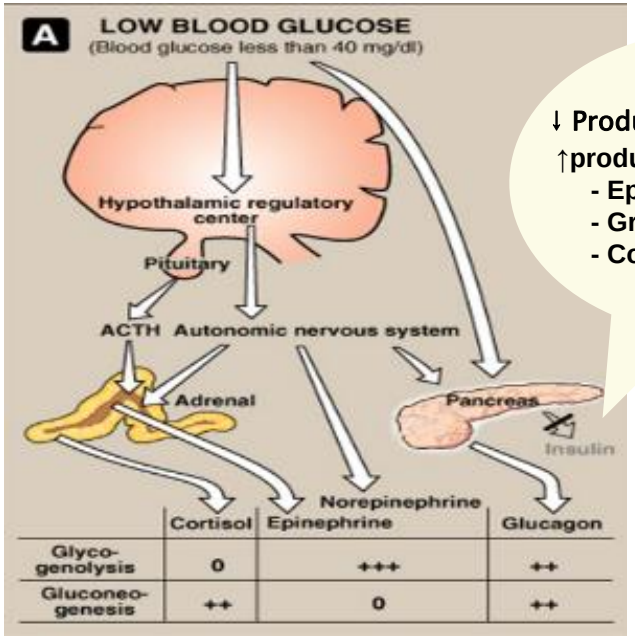
Hormonal mechanisms to prevent or correct hypoglycemia

Hypoglycemia occurs due to impaired protective responses to low blood glucose:

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

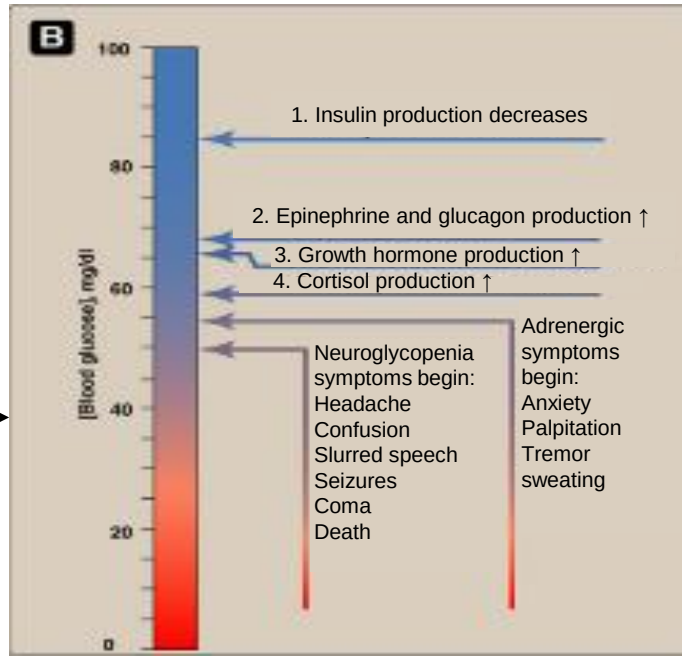
Clinical presentation:

- Abrupt or acute fall of plasma glucose ,<3.6 mmol/L = Symptoms of sympathetic overactivity (Anxiety, tremors,sweating & palpitation)
- Gradual fall of plasma glucose <2.6 mmol/L = Symptoms of neuroglycopenia (headache, confusion, drowziness and ultimately loss of consciousness or seizures (at plasma [glucose] <1.5 mmol/L)



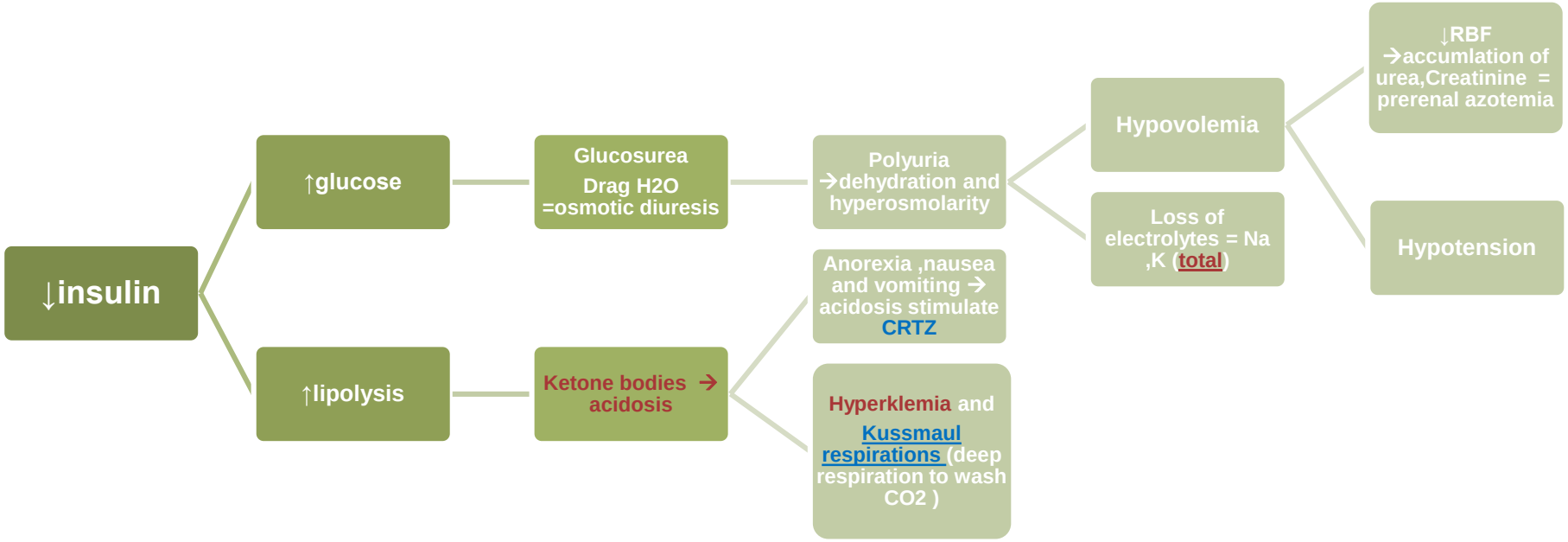
↓ Production of insulin
↑production of:
- Epinephrine & glucagon
- Growth hormone
- Cortisol

Glycemic thresholds for the various responses to hypoglycemia:



In normal person hypoglycemia is uncommon because of the physiological and behavioral mechanisms that normally prevent or rapidly correct hypoglycemia =
1: Glucose level became less than 40 → decrease in insulin secretion
2:increase glucagon secretion →increase glycogenolysis and gluconeogenesis & increase in epinephrine secretion →glycogenolysis
3:increase GH 4:increase cortisol → gluconeogenesis

EXTRA



[1]RBF=RENAL BLOOD FLOW

[2]Total body potassium loss is usually present despite normal or high serum potassium levels. Potassium levels may appear to be high due to the transcellular shift of potassium out of cells. This is not due to ketoacidosis directly but rather is due to insulin deficiency and hyperosmolality.

A large part of the shifted extracellular potassium is lost in urine because of osmotic diuresis.

Also, when ketoacids are excreted, they are usually excreted with Na or K in the urine, leading to further K loss.

Vomiting may also contribute to potassium loss in these patients

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

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

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^-)**

CONT.

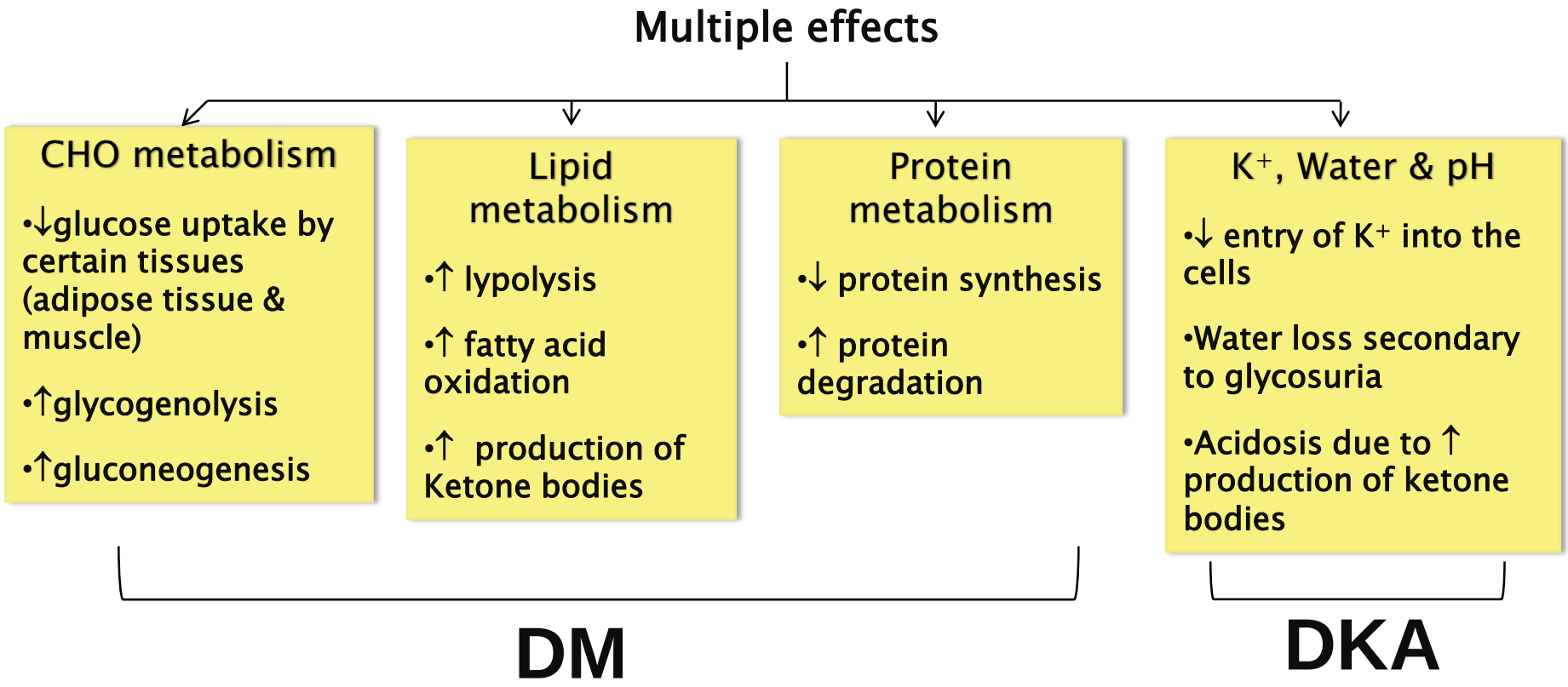
Laboratory findings: Urine results

Urine analyte	Patient's results	Normal level
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)**
↑K^+	**↓ Uptake of potassium by cells in the absence of insulin**
↑ Plasma osmolality	**Due to hyperglycemia and fluid loss**

Metabolic Changes in DM and DKA



MCQs

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

4.Which one of the following statements is incorrect regarding HHS :

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

5.What is the most participating factor for DKA?

A. Infection

B. Stress

C. Steroid thereby

D. trauma

6. DKA is very common in …. While HHS is common in ....?

A. OLD ...YOUNG

B. Young patient .... old patient

C. DM2 ....DM1

D. Diabetic patient with infection DM1

1.B 2.A 3.A 4.D 5.A 6.B

SAQs

Common causes of DKA?

1:low insulin
2:missed insulin dose
3:increased stress/infection that causes hyperglycemia
4:insulin resistance

What are the participating factor for DKA ?

1:Infection

2:Inadequate insulin treatment or non-compliance

3:Severe illness e.g., Myocardial infarction

4:Trauma

5:Drugs: e.g., steroids

The differential diagnosis in diabetic patient with coma ?

1:Diabetic Ketoacidosis (DKA)

2:Hyperosmolar hyperglycaemic state (HHS)

or Hypperosmolar non-ketotic acidosis (HONK)

3:Hypoglycemia

Biochemistry Bandits 434

اللهم إني استودعتك ما قرأت وما حفظت وما تعلمت فرده لي
عند حاجتي إليه إنك على كل شيء قدير

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