What do you know about ketone bodies??

Elsayed Abdelkreem

Assistant Lecturer
Department of Pediatrics,
Faculty of Medicine,
Sohag University.

Case presentation

- 9 months-old boy
- History of mild gastroenteritis of 24 hours duration .
- Presented to ER with acidotic breathing, vomiting, dehydration, and altered mental status.
- Arterial blood gases showed severe metabolic acidosis:

pH 6.9 **HCO_3** 5 mmol/L **Base deficit** -29 **pCO_2** 18 mmHg

- Urinary ketones ++++

What do you think??

DKA??

Case presentation

- **Blood sugar 70 mg/dl**
- Creatinine 0.9 mg/dl
- Electrolytes, liver functions, other routine labs: unremarkable

The child developed recurrent similar episodes of nondiabetic ketoacidosis following minor infections

Outlines

- What are the ketone bodies?
- Why they are important?
- Production and utilization.
- Disorders
  - Excess ketones (ketosis and ketoacidosis)
  - Lack of ketones (hypoketosis)
- Beta-ketothiolase deficiency
- Diagnostic clues and case scenarios

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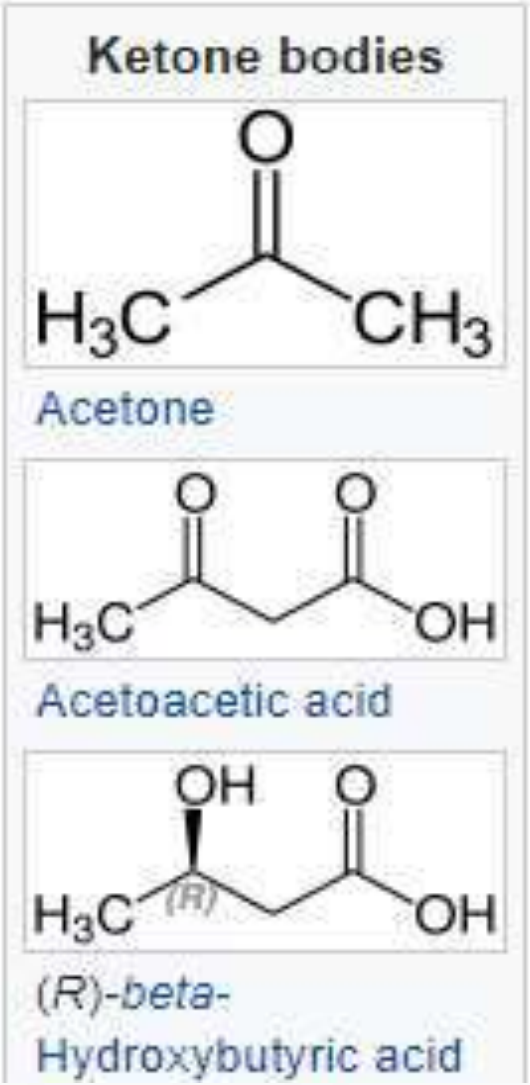
What are the ketone bodies?

- ***Acetoacetate (AcAc), 3-hydroxybutyrate (3HB) and acetone*** are called as ketones.
- Acetone is produced by decarboxylation from acetoacetate.
- Acetoacetate and 3-hydroxybutyrate are short chain carboxylic acids, so accumulation of them causes ketoacidosis.



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Why they are important?

- Ketone bodies are important ***energy sources***.
- They can be utilized by most tissues except the liver.
- Under normal physiological conditions,

ketone bodies are the only energy sources for the brain when glucose supply is low.

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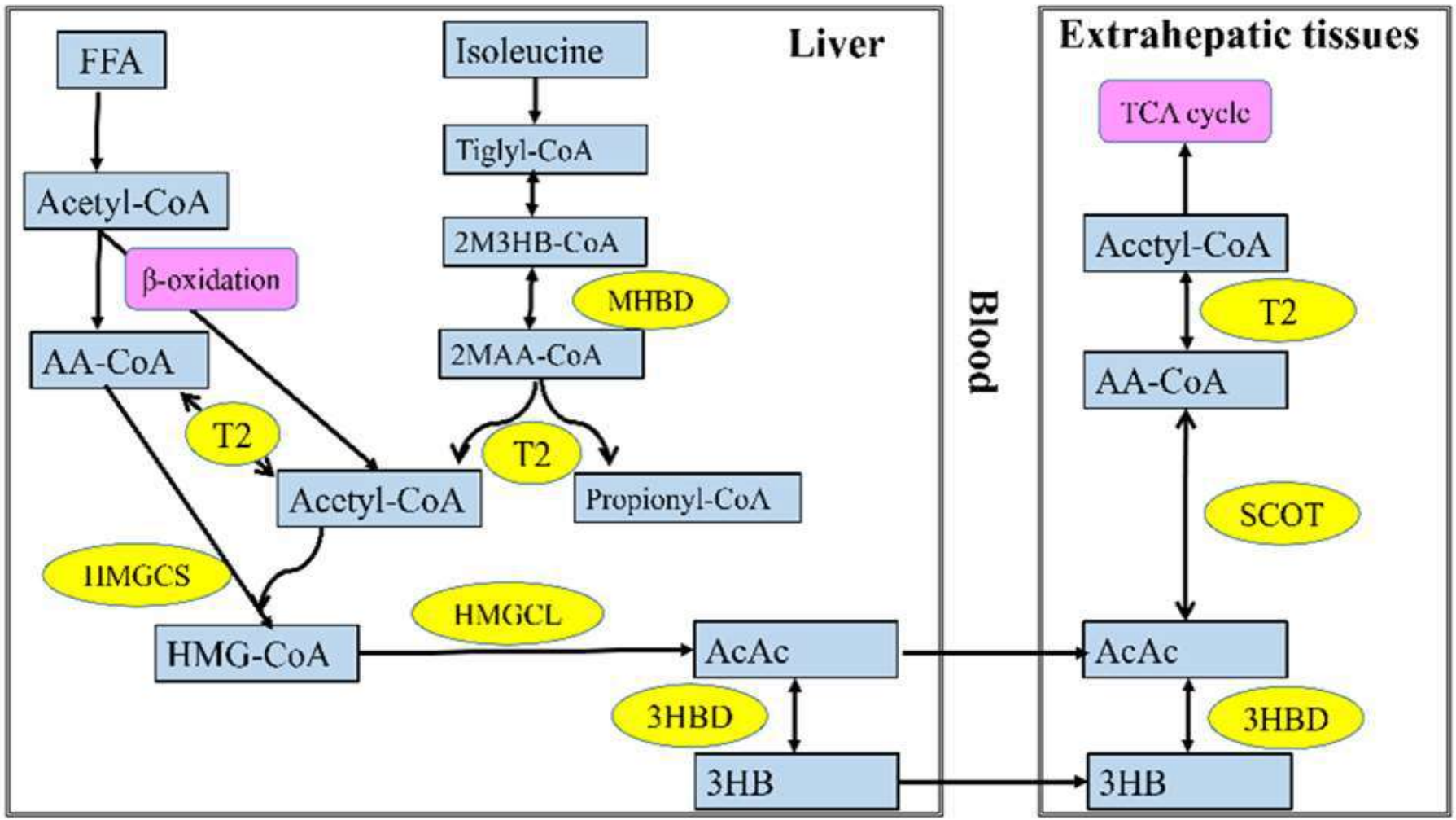
Production and utilization

- ketone body synthesis starts in the ***liver*** by the β-oxidation of free fatty acids (FFA), supplied from adipose tissues, to produce acetyl-CoA and acetoacetyl-CoA.
- This is followed by several enzymatic steps to produce ketone bodies (Acetoacetate and 3-hydroxybutyrate) that are excreted into blood.
- Ketone bodies can then be utilized by extrahepatic tissues for energy production through several enzymatic steps.

Production and utilization



Control of ketone body synthesis

- ***Ketogenic triggers*** includes fasting, febrile illnesses, vomiting and diarrhea.
- ***Glucagon and catecholamines*** induce free fatty acids mobilization from adipose tissue and fatty acid oxidation and ketogenesis.
- ***Insulin*** suppresses these steps and inhibits ketogenesis.

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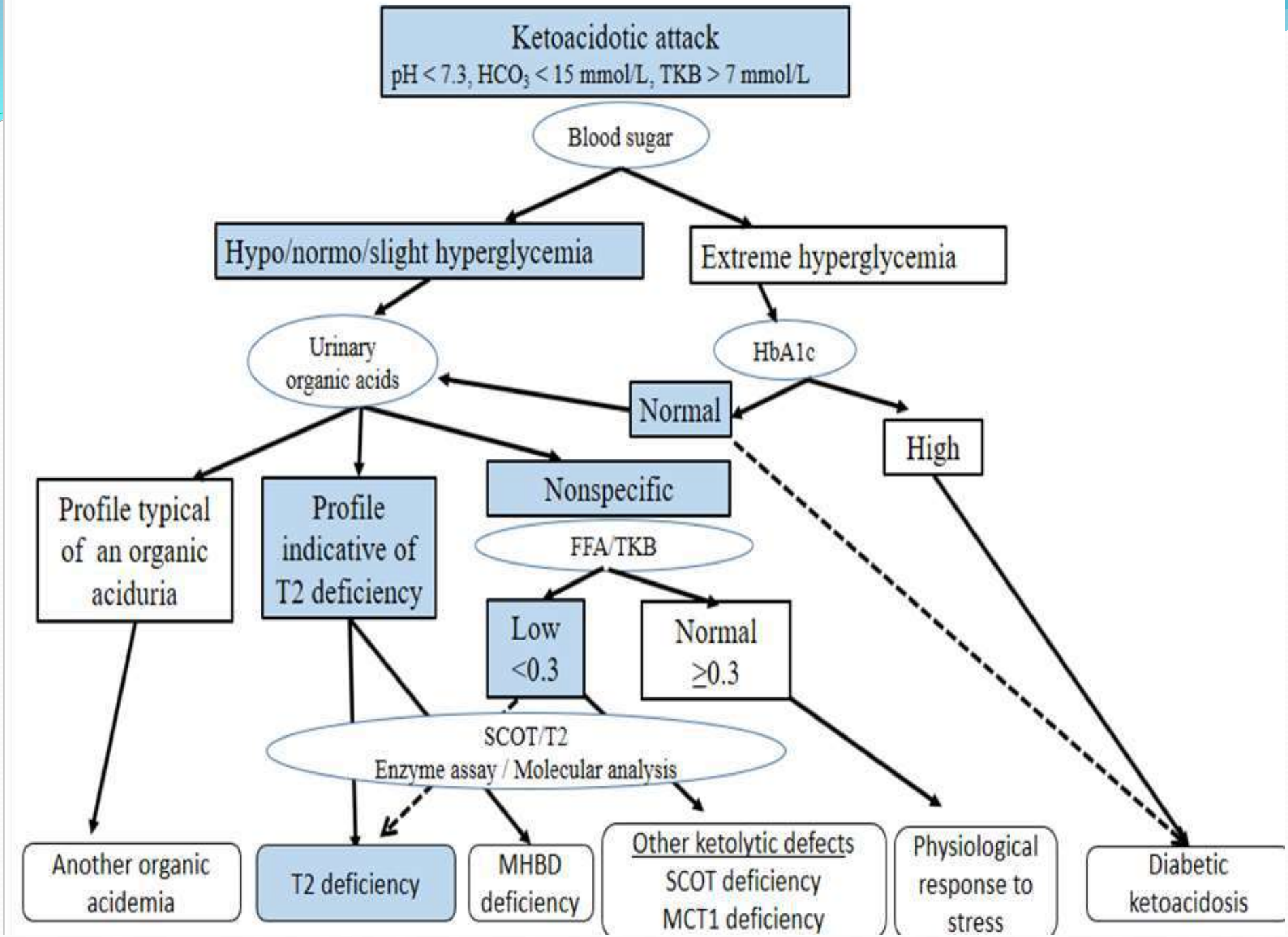
Ketosis and ketoacidosis

- ***Normal Blood Ketone level*** in children depends on time of last feeding; it can range from 0.05 mmol/L (postprndial) up to 6 mmol/L (after 24-hour fasting).
- ***Ketosis*** means a blood ketone level is more than ***0.2 mmol/L***.
- ***Ketoacidosis*** means a blood ketone level ***≥7 mmol/L*** in association with metabolic acidosis (pH <7.3, HCO_3^- < 15 mmol/L).

Ketosis and ketoacidosis

Causes

- ***Endocrinal:*** Diabetic ketoacidosis, Addison disease.
- ***Physiological response to stress, ketotic hypoglycemia.***
- ***Intoxications:*** Salicylates
- ***Inborn errors of metabolism***
  - Organic acidemias
  - Glucose and glycogen (glycogen synthase deficiency)
  - Disorders in ketone body utilizations
    - ***Beta-ketothiolase (T2) deficiency***
    - Succinyl-CoA:3-oxoacid CoA transferase (SCOT) deficiency


Ketoacidotic attack
pH < 7.3, HCO3 < 15 mmol/L, TKB > 7 mmol/L
Blood sugar
Hypo/normo/slight hyperglycemia
Extreme hyperglycemia
Urinary organic acids
HbA1c
Normal
High
Profile typical of an organic aciduria
Profile indicative of T2 deficiency
Nonspecific
FFA/TKB
Low <0.3
Normal ≥0.3
SCOT/T2
Enzyme assay / Molecular analysis
Another organic acidemia
T2 deficiency
MHBD deficiency
Other ketolytic defects
SCOT deficiency
MCT1 deficiency
Physiological response to stress
Diabetic ketoacidosis

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Hypoketosis

Causes

- ***Hyperinsulinism.***
- ***Fatty acid oxidation defects.***
- ***Disorders in ketone body synthesis.***

Nonketotic hypoglycemia is a serious condition because body organs (particularly the brain) lack both energy sources (blood glucose and ketones).

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Beta-ketothiolase deficiency

- An inherited metabolic disease of isoleucine catabolism and ketone body utilization.
- Clinically characterized by intermittent episodes of ketoacidosis usually between 6 – 24 months of age, following fasting or febrile disease.
- About 100 patients have been reported worldwide.

Beta-ketothiolase deficiency

- Research collaboration has started in 2015 between the Departments of Pediatrics at Sohag University (Egypt) and Gifu University (Japan).
- Between Feb 2015 and Jul 2017, we identified ***23 new patients*** with beta-ketothiolase deficiency, including ***the first two Egyptian patients confirmed on the molecular level***.

Beta-ketothiolase deficiency

Results of our research work.

- International conferences.
- International peer reviewed Journals.

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- **Diagnostic clues and case scenarios**

Useful diagnostic clues for ketone body disorders

- Blood glucose
- Total ketone bodies (TKB)
- Free fatty acids (FFA)
- Insulin.

➢ ***Consider clinical situation (like fasting).***

Useful diagnostic clues for ketone body disorders

Useful equations

FFA/TKB (in mmol/dl; during early fasting)

<0.3 defect in ketone body utilization

>2.5 defect in ketogenesis/fatty acid oxidation

TKB×blood glucose (in mmol/dl; if hypoglycemia)

>14 defect in ketone body utilization

Case scenario (1)

3-yr-old child with ketosis (TKB 7.0 mmol/L)

- After a 10-hr fast
- Glucose 5 mmol/L
- FFA 1.5 mmol/L

(FFA/TKB 0.21)

Probable diagnosis??

FFA/TKB (in mmol/dl; during early fasting)

<0.3 defect in ketone body utilization

>2.5 defect in ketogenesis/fatty acid oxidation

Defect in Ketone body utilization

Case scenario (2)

3-yr-old child with ketosis (TKB 7.0 mmol/L)

- After a 24-hr fast
- Glucose 2.6 mmol/L
- FFA 2.8 mmol/L

(FFA/TKB 0.4)

Probable diagnosis??

FFA/TKB (in mmol/dl; during early fasting)

<0.3 defect in ketone body utilization

>2.5 defect in ketogenesis/fatty acid oxidation

Physiological Response to a long fast

Case scenario (3)

A hypoglycemic 2-yr-old child (Glucose 1.4 mmol/L)

- TKB 11 mmol/L
- FFA 3.0 mmol/L

FFA/TKB=0.27

TKB×blood glucose=15.4

- Probable diagnosis??

FFA/TKB

<0.3 defect in ketone body utilization

>2.5 defect in ketogenesis/fatty acid oxidation

TKB×blood glucose

>14 defect in ketone body utilization

Defect in Ketone body utilization

Case scenario (4)

A hypoglycemic 2-yr-old child (Glucose 1.4 mmol/L)

- TKB 7.0 mmol/L
- FFA 3.0 mmol/L

FFA/TKB=0.43

TKB×blood glucose=10

- Probable diagnosis??

FFA/TKB

<0.3 defect in ketone body utilization

>2.5 defect in ketogenesis/fatty acid oxidation

TKB×blood glucose

>14 defect in ketone body utilization

Ketotic hypoglycemia

Case scenario (5)

A hypoglycemic 2-yr-old child (Glucose 1.4 mmol/L)

- TKB 0.3 mmol/L
- FFA 3.0 mmol/L

  FFA/TKB=10
- Probable diagnosis??

FFA/TKB

<0.3 defect in ketone body utilization

>2.5 defect in ketogenesis/fatty acid oxidation

Defect in Ketogenesis/fatty acid oxidation

Case scenario (6)

A hypoglycemic 2-yr-old child (Glucose 1.4 mmol/L)

- TKB 0.3 mmol/L
- FFA 0.4 mmol/L

  FFA/TKB=1.33
- Probable diagnosis??

FFA/TKB

<0.3 defect in ketone body utilization

>2.5 defect in ketogenesis/fatty acid oxidation

Hyperinsulinism

Thank You