

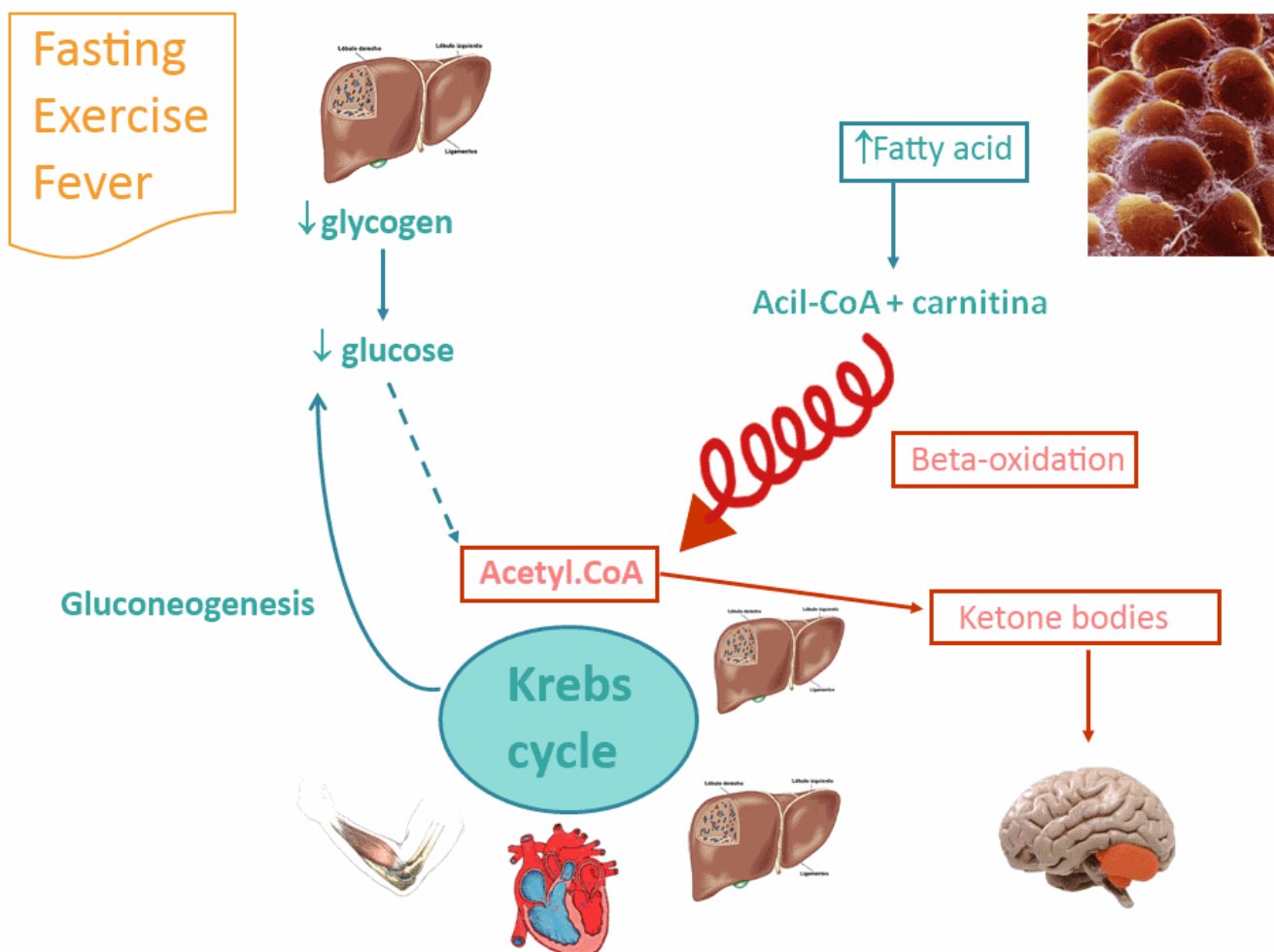
BETA-KETOTHIOLASE DEFICIENCY

WHAT IS BETA-KETOTHIOLASE DEFICIENCY?

Beta-ketothiolase deficiency is caused by mutations in the **ACAT1 gene** that encodes this mitochondrial enzyme involved in ketolysis (ketone body utilization). The defects of ketolysis give rise to an excess of ketone bodies, due to its deficient utilization. Patients develop **intermittent ketoacidosis**, which may be accompanied by impaired consciousness.

WHAT ARE KETONE BODIES?

Ketone bodies, 3-hydroxybutyrate (HB) and acetoacetate (AA) generate in β -oxidation of fatty acids and have an important role in **energy metabolism**.



During prolonged fasting and exercise, or in febrile processes where there are major energy needs, the energy supplied by glucose is insufficient and fatty acids are mobilized from adipose tissue (body fat). They are activated in the form of acyl-CoA and are transported bound to the carnitine inside the liver mitochondria and there they are oxidized by a series of chain reactions (beta oxidation), which act as a spiral. At each turn of the spiral acetyl-CoA is

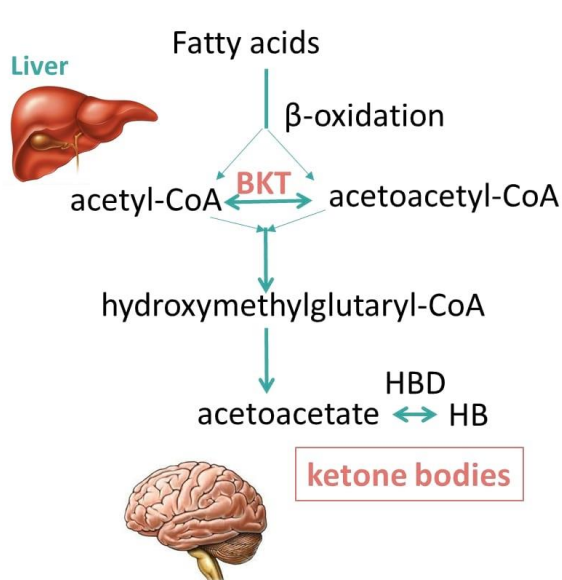
released and a fatty acid of two carbons less is formed, which continues with the beta oxidation until the complete degradation of the chain. (See <https://www.guiametabolica.org/ecm/defectos-v-oxidacion>).

Ketone bodies are formed in the liver from acetyl-CoA and acetoacetyl-CoA, in a process called ketogenesis. Ketone bodies are exported from the liver to other tissues, such as the **brain**, where it is especially important when there is a shortage of glucose as a source of energy.

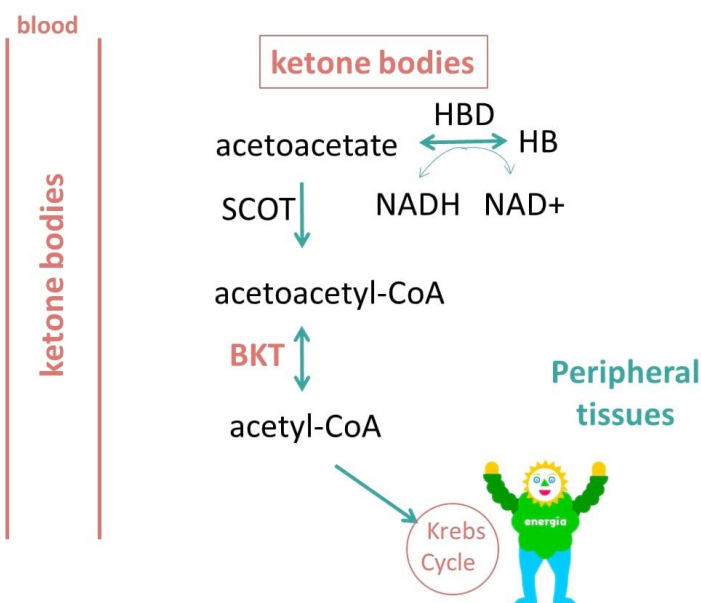
Acetoacetate is converted into 3-hydroxybutyrate (HB) by a reversible reaction catalyzed by the NAD⁺-dependent 3-hydroxybutyrate dehydrogenase (HBD), so that their respective concentrations depend on **the state of intra- or extramitochondrial oxidation-reduction**.

WHAT IS KETOLYSIS?

Ketogenesis



Ketolysis



Ketolysis consists of the **peripheral utilization of ketone bodies**. Ketone bodies generated in the liver pass to the blood and from there to the peripheral tissues according to their energetic requirements. To do this, HB is converted to acetoacetate by HBD and acetoacetate is activated to acetoacetyl-CoA by the enzyme **succinyl-CoA transferase (SCOT)** and finally cleaved to acetyl-CoA by **beta-ketothiolase (BKT)**. Acetyl-CoA **produces energy** through the Krebs cycle.

Although ketolysis is a **reversible pathway**, in **extrahepatic tissues** it tends to the production of acetyl-CoA, that is, towards **ketolysis**, whereas in the **liver** it tends to the formation of acetoacetyl-CoA to give rise to **ketogenesis**.

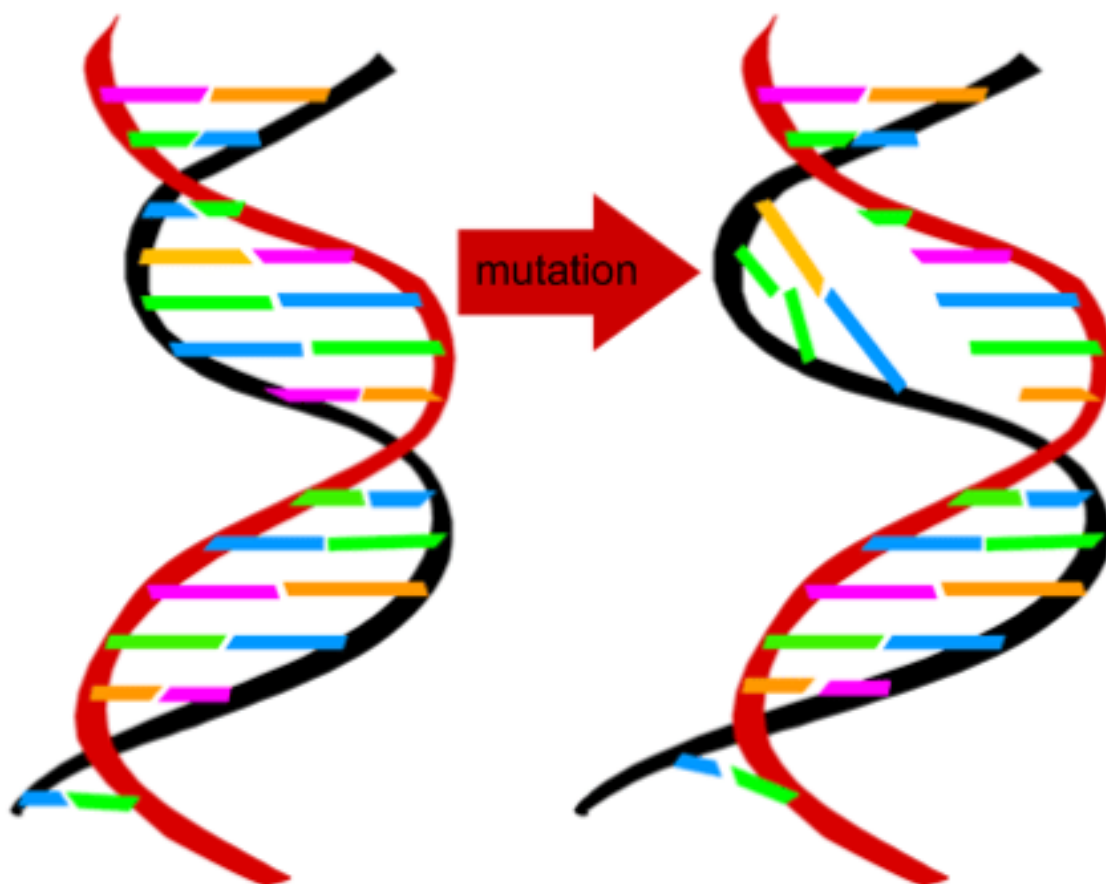
Ketone bodies play an important role as **vectors of energy transport from the liver to peripheral tissues** where they are used (heart, kidney, etc.), especially when there is a shortage of glucose. The **brain** can use ketone bodies as an alternative energy source of glucose.

WHAT DOES HAPPEN IN A KETOLYSIS DEFECT?

A ketolysis defect occurs when there is a deficiency of one of the two enzymes involved in this process (**SCOT or BKT**), being much more frequent the defect of BKT. A defect in ketolysis leads to **excessive accumulation of ketone bodies**, due to poor utilization of ketone bodies.

WHY DOES A BKT DEFICIENCY HAPPEN?

Each of the metabolic reactions that are going to generate the compounds that form our body is genetically determined (codified). We all inherit from our parents the correct or altered information that determines metabolic reactions. If we inherit a total or partially altered information, that metabolic step will not function correctly, and this may lead to an **inborn metabolic error**. **Beta-ketothiolase deficiency** is caused by **mutations** (stable and hereditary changes) in the **ACAT1 gene** that encodes this enzymatic protein.



BKT deficiency is a genetic disorder of **autosomal recessive inheritance**, which means that parents are usually carriers of a **ACAT1 gene mutation** without presenting symptoms. If both parents transmit the mutation to their baby, this will present a **BKT deficiency**, with consequent clinical manifestations.

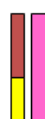
Autosomal recessive inheritance



Carrier
father



Carrier
mother



healthy

carrier

carrier

affected

CLINICAL PRESENTATION OF BKT DEFICIENCY

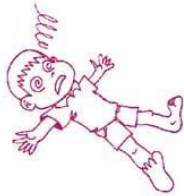
Most patients present with symptoms between one month and two years of age. The clinical picture is characterized by the presence of **intermittent ketoacidosis**, with **decompensations associated with catabolic stress** (fasting, fever, physical stress, infections), and may be associated with vomiting, hypotonia and an altered state of consciousness and lesions of basal ganglia. Episodes of severe decompensation in undiagnosed patients may lead to neurological sequelae, such as psychomotor retardation. Patients are usually asymptomatic between crises. Asymptomatic cases discovered by the family study of an affected case have been described.

The genotype is not an indicator of clinical severity, so that siblings with the same mutations may present different clinical severity.

DIAGNOSIS OF BKT DEFICIENCY

The disease is characterized by the appearance of **intermittent ketoacidosis** in episodes of decompensation. Therefore, the finding of a high concentration of ketone bodies in the absence of hypoglycemia that should have triggered it, as well as normal free fatty acids, suggests a defect in ketolysis, which requires its verification. However, normoglycemia is not a constant feature, and some cases present with hypoglycemia, and even hyperglycemia, which may mislead the diagnosis towards a diabetic ketoacidosis. The finding of a consistent ketosis despite good clinical and nutritional status may suggest the presence of a ketolysis defect.

Diagnosis of BKT deficiency



Clinical suspicion?

ketoacidosis with normogluccemia

Biochemical study

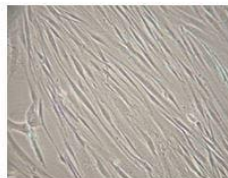
Genetic study



↑ ketone bodies
↑ normogluccemia
↑ acylcarnitines?



tiglylglycine?



↓ BKT activity



mutations in ACAT1 gene

On the other hand, as the final product of the catabolism of the ketogenic amino acid **isoleucine** is acetyl-CoA, a defect of mitochondrial BKT also interferes isoleucine degradation and some metabolites of the catabolism of this amino acid accumulate, especially **tiglylglycine**, whose finding in patients' urine may be helpful for diagnosis. Patients with severe mutations in the **ACAT1 gene** usually excrete these metabolites, as well as increased blood acylcarnitines, but their absence has been observed in patients with milder mutations, which makes their diagnosis difficult, because it should be based only on increased non justified ketosis.

The **enzymatic determination of BKT in fibroblasts** can demonstrate the enzymatic defect, which will be confirmed by the **mutational study of the ACAT1 gene**.

TREATMENT OF BKT DEFICIENCY

In **acute decompensations**, hypoglycemia should be treated and the formation of ketone bodies should be avoided. Bicarbonate must be provided to prevent the acidosis that develop easily in the decompensations. Dehydration should also be prevented by means of fluid therapy.

To prevent episodes of decompensation, **fasting should be avoided**, which would trigger the formation of ketone bodies that cannot be effectively used.

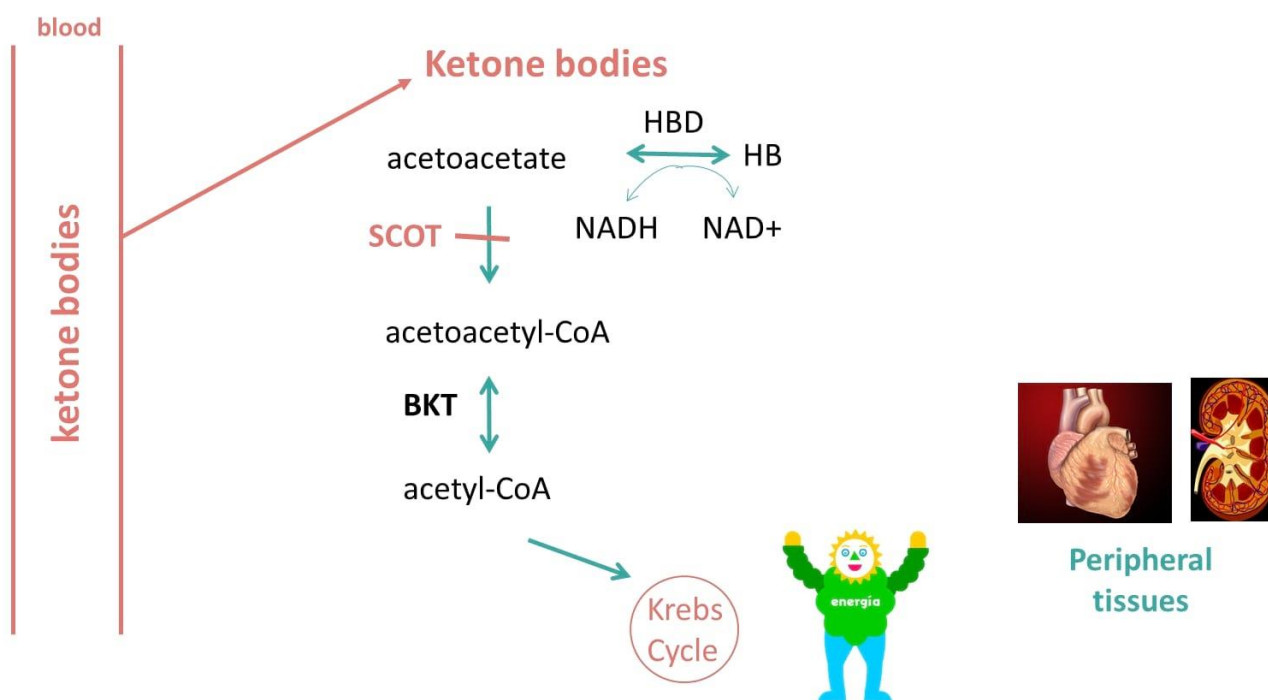
Patients may benefit from a moderately hypoproteic diet to avoid excessive formation of ketogenic amino acids (isoleucine, leucine), which are acetyl-CoA precursors. However, a clear benefit of this diet has not been demonstrated.

DEFICIENCY OF SUCCINYL-COA TRANSFERASA (SCOT)

Succinyl CoA transferase (SCOT) deficiency is caused by mutations in the **OXCT1 gene**, which encodes this enzyme involved in **ketolysis**. SCOT activates acetoacetate to convert to acetoacetyl-CoA, which is cleaved by BKT to produce acetyl-CoA, which enters the Krebs cycle to produce energy.

Patients develop **ketoacidosis during a ketogenic stress** (fever, extreme physical exercise) that occurs before hypoglycaemia. The generated ketone bodies cannot be used to produce energy due to the blockage in the ketolysis pathway. In this case there is no block in the degradation of isoleucine, therefore the metabolites of this amino acid in the urine of the patients will not be observed.

Ketolysis: SCOT deficiency



Clinical features usually appear in the first days of life in half of the patients described with SCOT deficiency, and before the 2 years in the other half, which differs from BKT deficiency features of later appearance. Ketosis is usually permanent in cases with severe mutations, unlike the intermittent ketosis described in BKT deficiency.

The **diagnosis** should be based only on clinical suspicion, since there are no metabolites of isoleucine in the analysis of organic acids, which could be suggestive of this defect.

The **treatment** of these patients is the same described for BKT deficiency (avoiding hypoglycemia and excessive production of ketone bodies and avoiding hyperproteic diets).

The **defects of ketolysis** are metabolic diseases that, without diagnosis or treatment, can have serious consequences in case of metabolic decompensation. However, early diagnosis and treatment greatly improve the prognosis of these diseases.



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