# Succinyl-CoA : 3-ketoacid CoA transferase (SCOT) deficiency

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**Abstract**
*Succinyl-CoA : 3-ketoacid CoA transferase (SCOT) deficiency is a typical ketolytic defect, in which extrahepatic tissues cannot use the ketone bodies produced by the liver. It is a rare disease; up to now more than 20 SCOT-deficient patients were reported. This disorder is characterized clinically by intermittent ketoacidosis with, however, no clinical symptoms between these episodes. Ketoacidotic episodes are usually severe and the first episode develops in the neonatal period or early childhood (6-20mo). Some patients die of a sequela of the ketoacidotic attack. There is no characteristic organic acid profile and acylcarnitine profile. SCOT-deficient patients do not always have persistent ketosis. However, when it is present, persistent ketosis is an indicator of SCOT deficiency. It is important to consider this disorder in patients with ketotic/ketoacidotic episodes. Physicians should differentiate SCOT deficiency from physiological ketosis which is very common in childhood. Normal growth and development are expected under proper treatment which prevents the occurrence of severe ketoacidotic attacks.*

**Keywords**
Succinyl-CoA:3-ketoacid CoA transferase, SCOT, ketoacidosis, ketosis, persistent ketosis, permanent ketosis, ketolytic defect, ketone body, neonatal ketoacidosis, coma.

## Disease name and synonyms

Succinyl-CoA : 3-ketoacid CoA transferase (SCOT) deficiency (EC 2.8.3.5) is a mitochondrial matrix enzyme responsible for the formation of acetoacetyl-CoA by transfer of a CoA moiety from succinyl-CoA to acetoacetate. This step is the rate-limiting step in the utilization of ketone bodies. Extrahepatic tissues need

SCOT to use ketone bodies as an alternative energy source to glucose. Hence a complete deficiency in SCOT means that extrahepatic

tissues can not use the ketone bodies produced by the liver at all.
SCOT is also referred to as succinyl-CoA: acetate transferase.

**Diagnostic criteria/Definition**
Clinically SCOT deficiency is characterized by intermittent ketoacidotic events with, however, no symptoms between episodes (1). SCOT-deficient patients develop ketosis/ketoacidosis easily in ketogenic situations such as fasting, febrile illness, and other stresses. Neonatal onset is common. Although there are no clinical symptoms between episodes, ketone body levels are high even in postprandial times, and it is sometimes described as permanent/persistent ketosis. Recently it was revealed that some SCOT deficient patients whose mutations retained some residual activity did not have permanent ketosis. Hence permanent ketosis is a pathognomonic feature of SCOT deficiency if present, but the absence of permanent ketosis does not rule out SCOT deficiency (20). No typical organic acids or acylcarnitines allow physicians to diagnose SCOT deficiency. The diagnosis should be considered when the patients have the clinical manifestations described above (see also Clinical description). Enzyme assay is essential to confirm the diagnosis.

**Prevalence**
More than 20 SCOT-deficient patients were reported in the USA, Canada, France, the UK, Spain, the Netherlands, South Africa and Japan (2-14, and personal communication). SCOT deficiency may be undiagnosed in some patients with fatal neonatal ketoacidosis or with milder episodes of ketosis.

**Clinical description**
Clinical findings in 13 SCOT-deficient patients (1-14) were studied. No event usually occurs during pregnancy and delivery. All patients presented with ketoacidosis.

***Ketoacidotic episodes***
The first ketoacidotic attack occurred during the early neonatal period (2-4 days of age) in 5 patients. It differs from the rather late onset (4-24 months of age) of mitochondrial acetoacetyl-CoA thiolase deficiency (see the text on beta-ketothiolase deficiency). The symptoms of neonatal crisis are not specific, however, tachypnea due to metabolic acidosis is the most prominent clinical sign. Failure to do well, poor feeding, vomiting and lethargy may occur. Blood gas analysis reveals severe metabolic acidosis. In reported cases, blood pH and $HCO_3^-$ were respectively 6.88-7.12 and 3-8 mmol/l. Blood glucose level is usually normal. However, hypoglycemia was noted in two cases with neonatal onset (8, 14). Hence the presence of hypoglycemia can not exclude the diagnosis of SCOT deficiency. When measured, lactate, pyruvate, and ammonia levels are normal during ketoacidotic episodes. Urinary ketone bodies tests are positive. It should be noted that significant ketonuria during the neonatal period is nearly pathognomonic. Intravenous fluid therapy including glucose and sodium bicarbonate is an effective treatment for the episodes.
The remaining patients developed the first ketoacidotic episode between 6 and 22 months of age. The ketoacidotic attacks usually follow upper respiratory infection, gastroenteritis, and/or febrile condition. The symptoms of ketoacidotic episodes are usually the same as in neonatal episodes. However, unconsciousness is more common than in neonatal episodes. Lethargy is sometimes followed by coma.

***Between episodes***
There is no clinical symptom. However, it is worth noting that elevated ketone body levels have also been documented even when the patient is not fasting. Even after eating, SCOT-deficient patients have elevated serum levels of ketone bodies. SCOT deficiency can be suspected by this permanent/persistent ketonemia/uria. However, we diagnosed two other patients with a mild type of SCOT deficiency recently. They did not show permanent ketosis between episodes, but their acute episodes were as severe as those presented by other typical SCOT-deficient patients (20). Hence permanent ketosis is pathognomostic in SCOT deficiency but it is not always present in all SCOT-deficient patients.

***Complications***
Cardiomegaly was noticed in two patients, and one of them developed congestive heart failure (2, 4).

**Differential diagnosis**
Differential diagnosis includes all the disorders triggering ketoacidosis (ketosis). Ketosis should be assessed together with blood glucose levels. Although the presence of hypo/hyperglycemia can not exclude SCOT deficiency, normoglycemia is common in this disorder. Extreme hyperglycemia with ketosis suggests the presence of diabetes. In the case of hypoglycemia with ketosis, we should consider several conditions and disorders:

- hormonal defects such as glucocorticoid deficiency and growth hormone deficiency;
- defects in glucose and glycogen metabolism including glycogen synthase deficiency;
- ketotic hypoglycemia.

During an acute ketotic/ketoacidotic episode, at least blood gas, blood glucose, lactate, pyruvate, ammonia, and urinary organic acids should be examined. These data can exclude congenital lactic acidosis, other types of organic aciduria such as methylmalonic, propionic, isovaleric acidemias, and mitochondrial acetoacetyl-CoA thiolase deficiency. Salicylate poisoning can trigger ketoacidosis and ketone bodies can produce a false positive result in some screening tests for salicylate.

***Mitochondrial acetoacetyl-CoA thiolase (beta-ketothiolase deficiency, T2 deficiency), Ketotic hypoglycemia, Recurrent ketosis of childhood***

Ketotic hypoglycemia and recurrent ketosis of childhood are common causes of ketosis in childhood. So, if ketosis is more severe than typical hypoketotic hypoglycemia or recurrent ketosis of childhood, T2 deficiency and SCOT deficiency should be considered. T2 deficiency can be suspected with the urinary organic acid profile and SCOT deficiency has no characteristic organic acid profile. However, as suggested above, enzymatic confirmation for both T2 deficiency and SCOT deficiency appears to be preferable. T2 deficiency is also characterized by intermittent ketoacidotic episodes and no clinical symptoms between episodes. Neonatal onset of T2 deficiency is rare. Permanent ketosis is the most prominent feature of SCOT deficiency but not of T2 deficiency.

**Management including treatment**

***General management***

It is important to prevent the development of severe ketoacidosis, since SCOT-deficient patients develop ketoacidosis easily in ketogenic conditions.

*Diet:*

Mild restriction of protein intake (1.5-2.0 g/kg/day) is a reasonable treatment since excess protein intake may induce ketogenesis. A fat-rich diet also induces ketogenesis, and hence should be avoided. Three out of the 13 SCOT-deficient patients for whom information is available are on protein-restricted diets.

Some patients may receive frequent carbohydrate-rich meals.

*Oral sodium bicarbonate supplementation*

Two out of the 13 SCOT-deficient patients were supplemented with bicarbonate. This supplementation is possible if the patient presents with persistent ketosis and if the blood $HCO_3^-$ level is low.

*Monitoring*

Home monitoring of urinary ketones helps the parents to know the patient's condition. It is important for them to know the ketonuria levels of the patient before breakfast, in the postprandial period to make sure that the patient is in good health.

*Prophylactic glucose intake/infusion*

Prolonged fasting should be avoided. If the patient is febrile or vomits, intravenous glucose infusion should be considered. If urinary ketones are higher than usual in milder illness, some carbohydrate-rich snack or drink should be provided.

***Management of acute episodes***

It is important to suppress ketogenesis and to correct acidosis during acute episodes. Although the diagnosis is not usually confirmed during the first ketoacidotic crisis, the treatment of SCOT-deficient ketoacidosis is basically the same as that of ketoacidosis. Physicians recognize the patient as being in an emergency state with symptoms of vomiting, polypnea or dyspnea, hypotonus, unconsciousness. Routine laboratory tests (electrolytes, blood gas, glucose, ammonia, urinalysis, etc) may indicate severe metabolic acidosis, dehydration and ketonuria, with massive ketonuria. For further evaluation, in general, sample collections for lactic and pyruvic acids, amino acid analysis, urinary organic acid analysis are important at the initial stage.

Even when the patient shows normoglycemia, sufficient glucose infusion to maintain blood glucose levels in the upper normal is important to suppress ketogenesis. Intravenous fluid with glucose and appropriate electrolytes should be administered to maintain sufficient urine output. The treatment of metabolic acidosis is controversial. Initially a slow bolus of bicarbonate (1 mmol/kg over 10 min) may be given followed by a continuous infusion. Blood gas and electrolytes should be frequently checked to avoid rapid correction and hypernatremia. Aggressive alkalization may be deleterious and cause hypernatremia, hyperosmolarity, and paradoxical central nervous system acidosis.

## Etiology

***SCOT role in ketone body metabolism.***
Ketone bodies are important vectors of energy from the liver to extrahepatic tissues, especially when there is shortage of glucose. In hepatic mitochondria, ketone bodies are produced by using excess of acetyl-CoA mainly derived from accelerated fatty acid beta-oxidation. Part of the acetoacetate is converted into 3-hydroxybutyrate in the mitochondrial inner membrane by R-3-hydroxybutyrate dehydrogenase. In extrahepatic tissues, 3-hydroxybutyrate is converted into acetoacetate in the reverse reaction by R-3-hydroxybutyrate dehydrogenase. Acetoacetate is activated as acetoacetyl-CoA by SCOT, then mitochondrial acetoacetyl-CoA thiolase mediates thiolysis from acetoacetyl-CoA to acetyl-CoA. Acetyl-CoA is then used as an energy source via the tricarboxylic acid TCA cycle. Hence SCOT is essential for extrahepatic tissues to use ketone bodies as an energy source and SCOT abundance is a determinant of the ketolytic capacity of tissues (see SCOT protein and gene).

***SCOT protein and gene***
Human SCOT is a homodimer of the 56.2-kDa subunit (11, 15). SCOT protein is widely expressed in extrahepatic tissues and abundant in the heart and kidney (16). SCOT is scarcely detected in the liver (15). Human SCOT cDNA is about 3.2 kb long and encodes for a precursor of 520 amino acids, including a 39-amino acid leader polypeptide (11). The human *SCOT* gene spans more than 100 kb, contains 17 exons, and is located chromosome 5p12-p13 (12, gene locus OXCT). The 5' flanking region lacks a conventional TATA box but is GC-rich (12). Its basic promotor is Sp1 driven (unpublished data). Mutations were identified in 5 SCOT-deficient patients (11, 12, 17, 20, 21).

## Diagnostic methods

SCOT deficiency should be considered in children with severe or recurrent ketoacidosis or nonfasting ketosis. Clinical examination is essential in comparing the severity and frequency of ketosis with normal physiological response to stress. There is no pathognomostic metabolite in the urinary organic acid profile and acylcarnitine profile but they are useful for excluding other disorders. When permanent ketosis is present, SCOT deficiency can be suspected.
Repeated testing for blood ketone bodies, free fatty acid and ketonuria

24-hours metabolic profile
SCOT-deficient patients usually have high levels of blood ketone bodies, even in the postprandial period. Measurement of blood ketone bodies, free fatty acid and urinary ketones before breakfast, 1-2 hour after breakfast, just before lunch, 1-2 hour after lunch, etc. shows extraordinary high levels of ketone bodies compared to normal children.
Postprandial blood ketone levels in mild SCOT-deficient patients was much lower than typical SCOT-deficient patients but still higher than 0.1 mM (20).

***Fasting test***
A fasting test is not necessary for diagnosis of typical SCOT deficiency. This can be dangerous since it may give rise to a ketoacidotic attack. In SCOT-deficient patients, ketone bodies rapidly increase, FFA/KB ratio (FFA or free fatty acids; KB or ketone bodies) reaches a very low value, approximately 0.3, very early in the fast (1, 18). Even mild SCOT-deficient patients, blood levels of ketone bodies increased more rapidly than controls (20), hence, this test is useful to identify a mild SCOT-deficient patient lacking permanent ketosis.

***Enzyme assay***
An enzyme assay is essential for the diagnosis of SCOT deficiency. It is possible to assay SCOT activity in various tissues. Fibroblasts, peripheral lymphocytes and EB-transformed lymphoblasts are used in practical enzymatic diagnosis (7). Postmortem kidney, brain, and muscle were used for enzyme assay in the first reported patient (2). There is a high background residual activity when measured in fibroblasts: even fibroblasts with a null mutation had apparent residual activity (20-30% of control) (11). Hence current enzyme assay has sufficient specificity for enzymatic diagnosis of SCOT deficiency, but is not sensitive to evaluate residual activities.

***Molecular diagnosis***
SCOT protein detection by immunoblot analysis is useful to confirm diagnosis of SCOT deficiency. All the 8 SCOT-deficient fibroblasts tested had no detectable or extremely decreased SCOT protein (14; Fukao unpublished data). This is an additional method to enzyme assay. Human *SCOT* cDNA and gene has been cloned and mutations in several patients were identified (11, 12, 17). Hence, diagnosis at DNA level is possible. There are no sufficient data to discuss the presence of common mutations.

**Genetic counseling and prenatal diagnosis**
SCOT deficiency is an autosomal recessive disorder. As far as we know, no heterozygous carrier has clinical symptoms. It is important to identify asymptomatic SCOT-deficient siblings in familial analysis to avoid them developing ketoacidotic crises in the future.
Prenatal diagnosis can be made. Cultured amniocytes have measureable SCOT activity (13, 19). Chorionic villi have been reported to have lower SCOT activity than cultured amniocytes. Cultured amniocytes are preferable samples for enzyme assay. If mutations in the family have been identified, mutation detection of fetal DNA is a reliable test for prenatal diagnosis. Since about one half of SCOT-deficient patients develop the first ketoacidotic episode during the neonatal period, a high-risk baby should be managed carefully, providing him with sufficient glucose infusion.

**Unresolved questions**

***Clinical presentation of the mild type of SCOT deficiency***
SCOT-deficient patients with residual activity showed similar clinical manifestation in terms of frequency and severity of ketoacidotic crises but did not have a permanent ketosis. Their residual SCOT activity was estimated to be 25 % normal in fibroblasts.
Patients with a “milder” form of SCOT deficiency might be diagnosed as patients with severe recurrent ketosis of childhood although heterozygous carriers of a null mutation (hence, with 50% normal SCOT activity) have not showed clinical manifestation of ketoacidosis.

***Is SCOT deficiency really a rare inborn error of metabolism ?***
No characteristic metabolites can be found in blood and urinary samples. That is why patients may be undiagnosed or treated as "possible SCOT-deficient patients" without enzymatic confirmation.

***Are there any other inherited metabolic disorders presenting with intermittent ketoacidotic episodes?***
There are patients presenting with intermittent ketoacidotic episodes with normal SCOT and mitochondrial acetoacetyl-CoA thiolase activity.

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