Citrin Foundation

Research Support Cure

Your Guide to Citrin Deficiency

WHAT IS CITRIN?

There are about 20,000 unique genes in our body that lead to the creation of various proteins. These proteins are essential for the normal functioning of our body.

Of these genes, SLC25A13 is a gene responsible for creating a protein called 'citrin'. Citrin is present within some cells inside our body and its job is to help the body produce energy from food sources such as carbohydrates and to maintain normal metabolism. Broadly speaking, metabolism is the biological process by which the body breaks down food to produce energy, utilize nutrients for growth and repair, and remove harmful bodily waste.

Under normal conditions inside our cells, citrin transports an amino acid called glutamate from one location (cytosol) to another (mitochondria), and in a reverse exchange, it grabs another amino acid called aspartate from the mitochondria and sends it to the cytosol. This process is essential to maintaining normal metabolism and health.

WHAT IS CITRIN DEFICIENCY?

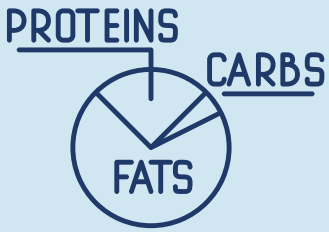
In citrin deficiency, the SLC25A13 gene is mutated and as a result, either no citrin protein is produced, or incomplete/dysfunctional citrin is made that does not function normally. Citrin deficiency primarily affects the liver's functions because the citrin protein is most abundantly expressed in the liver. Citrin deficiency impedes the movement of glutamate and aspartate between the cytosol and mitochondria and impairs energy generation from food sources such as carbohydrates and overall metabolic functions are affected.

Citrin deficiency is an inherited genetic condition that is autosomal recessive, meaning that the condition will only manifest if a child receives two copies of a mutated SLC25A13 gene (e.g., 1 mutant copy each from both parents). Individuals who inherit only 1 copy of the mutant gene do not manifest the condition but are known as 'carriers' and have a chance of passing the condition to their offspring if their partner also carries another defective copy of the gene. Citrin deficiency is a metabolic condition and a urea cycle disorder. Urea cycle disorders affect your body's ability to remove harmful ammonia from the blood in the form of urea which is gotten rid of in urine.

Although a cure does not currently exist, with proper diet management and frequent monitoring, patients can lead a relatively normal life.

CLINICAL PRESENTATIONS OF CITRIN DEFICIENCY

A hallmark symptom of citrin deficiency that many patients exhibit is a peculiar food preference that is rich in proteins and fats while being low in carbohydrates. Citrin deficiency patients often avoid consuming too much carbohydrates and tend to dislike sweet-tasting foods. Excessive consumption of carbohydrates or sugar-rich foods often makes citrin deficiency patients feel unwell.



While the clinical presentations of citrin deficiency are often diverse amongst patients, the condition can be categorized into distinct phenotypes based on the age of patients, as summarized in Table 1.

TABLE 1. CLINICAL PRESENTATIONS OF CITRIN DEFICIENCY

PATIENT AGE	DISEASE PHENOTYPE	PRIMARY SYMPTOMS	OTHER POSSIBLE SYMPTOMS
Newborn (0-1 years)	Neonatal Intrahepatic Cholestasis Caused by Citrin Deficiency (NICCD)	Persistent jaundice, failure to thrive, hepatomegaly, cholestasis, diffuse fatty liver, and parenchymal cell infiltration. Symptoms typically resolve after the first year of age	Abnormal bleeding, vitamin K deficiency, hypoproteinemia, galactosemia
Childhood (1-11 years)	Silent/Adaptation period	Strong preference for protein/fat-rich foods, aversion to carbohydrate-rich foods and sugars	Hypoglycemia, fatigue, fatty liver, occasional stomach discomfort
	Failure to Thrive and Dyslipidemia caused by Citrin Deficiency (FTTDCD)	Strong preference for protein/fat-rich foods and sugars, fatigue, hypoglycemia, gastrointestinal disorders, and growth impairment	Pancreatitis, hyperlipidemia, hepatoma, fatty liver
Adolescence/ Adulthood (11+ years)	Adolescent and adult citrin deficiency (AACD)	Strong preference for protein/fat-rich foods, aversion to carbohydrate-rich foods and sugars, fatigue, hyperammonemia, citrullinemia, acute hepatic encephalopathy, and conscious disturbances.	Pancreatitis, hyperlipidemia, hepatoma, fatty liver, low body mass index (BMI)

MANAGEMENT

Below are the general treatment options for patients with citrin deficiency.
Please always consult your attending doctor regarding treatment as the condition and its severity may be very different for each patient.

Diet Management

- Maintain a low carbohydrate, high-protein, high-fat diet. Based on the 2019 Citrin Deficiency Guidelines published by the Japan Society of Inherited Metabolic Disorders, the recommended PFC ratio for citrin deficiency patients is Protein: 15% – 25%, Fat: 40% – 50%, Carbohydrate: 30% – 40%.
- Try to consume a variety of sources of fat and avoid relying on animal fat by actively opting for more healthy options such as vegetable-derived fat like olive oil.
- For patients of any age, it is very important to eat frequently by having breakfast, lunch, dinner, and consuming snacks in between meals.

MCT Supplements

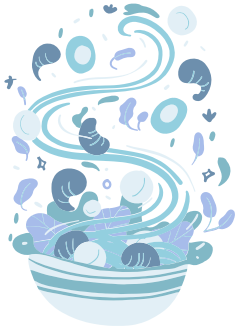
MCT (medium-chain triglycerides) is different from usual fat as it directly provides energy to the liver. This is important for citrin deficiency patients as they have an energy deficiency in the liver. As MCT is not commonly found in foods, citrin deficiency patients are recommended to take MCT oil as a supplement. MCT-enriched formula / MCT-supplemented breast milk (please consult your doctor for dosage) is recommended for NICCD patients.

Post-NICCD:

- It is best to take MCT oil with your meals, in divided portions throughout the day.
- One recommended dose for MCT after the age of one is 1g/kg/day, with a maximum daily dose of 40g. If patients are unable to tolerate this dose due to stomach discomfort, they may lower the dose accordingly.

Some suggested methods of consuming MCT oil are as follows:

- Blend it in your smoothies or drinks
- Mix it in your salad or add it to boiled vegetables
- Add it to your soup and stir it well
- Having it as a dip with bread



PREVENTION

Based on current research in citrin deficiency, maintaining a high protein and fat, low carbohydrate diet, with frequent meals and MCT supplementation may prevent the onset and/or worsening of symptoms associated with FTTDCD or AACD.

PRECAUTIONS

High carbohydrate diet

While a low protein/high carbohydrate diet may be recommended for other classical urea cycle enzyme deficiencies to prevent hyperammonemia, this can be harmful to individuals with citrin deficiency.

Infusion of sugars, such as glycerol, fructose, and glucose

The use of glycerol or high sugar-containing infusions should be avoided in citrin deficiency patients as they have been reported to worsen symptoms and may even be fatal. However, mannitol infusions appear to be well-tolerated and safe for citrin deficiency patients.

Alcohol

Alcohol consumption, even in small quantities, can trigger the onset of AACD and should be strictly avoided by patients.

Medications

Early reports have shown that acetaminophen (or paracetamol) and rabeprazole may trigger AACD. However, since these initial reports, there have not been further cases documented, which suggests that the effects of these drugs may be limited. Care should be taken, and symptoms monitored closely if these drugs need to be prescribed.

SUPPORT

Citrin Foundation is a patient-driven, not-for-profit organization set up to support patients and their families and to conduct research to better understand the condition and develop new therapies. The ultimate goal of the Foundation is finding a cure for citrin deficiency, and the founders have committed USD30m for the next decade towards achieving this.

The Foundation has created a dedicated patient website with useful tips, patient stories and age-specific resources

We support a global community through sharing information and resources on Instagram, X, Facebook and YouTube

We have a growing archive of recipes that are suitable for the CD diet

We host a range of information sessions, webinars and in-person meet-ups for patients and their families

We run peer support groups for family members and adult patients

The Foundation publishes a quarterly newsletter with updates on research, events and resources

patient.citrinfoundation.org

If there is any support that you feel you need which we do not provide please email our patient engagement team: patients@citrinfoundation.org

OPPORTUNITIES TO GET INVOLVED

By joining our global patient community, you will have the opportunity to take on a number of roles and get involved in different projects.

SIGN UP TO OUR PATIENT REGISTRY

By joining our registry, you contribute directly to ongoing research efforts, helping to uncover new insights and develop more effective interventions. It will also allow us to better serve and support you and the wider community. If you are interested in joining our registry please scan the QR code below or go to our patient website to sign up as a member of the Foundation.

JOIN THE COMMUNITY

- Sign up as a member of the Foundation via our website
- Follow us on social media
- Join one of our peer support groups
- Apply to join our International Patient Committee

PARTICIPATE IN RESEARCH

Consider taking part in our research studies. For more information, feel free to get in touch with us via email or social media. We will keep our members informed of new research opportunities as they arise.

STAY IN TOUCH

Citrin Foundation @citrinfdn @citrinfoundation

Email Enquiries

General
For general information enquiries: info@citrinfoundation.org

Patient & Family
For patients, caregivers, or healthcare professionals seeking information, support, or guidance related to citrin deficiency: patients@citrinfoundation.org

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