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REVIEW ARTICLE

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Metabolic basis and treatment of citrin deficiency

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Abstract

Citrin deficiency is a hereditary disorder caused by *SLC25A13* mutations and manifests as neonatal intrahepatic cholestasis (NICCD), failure to thrive and dyslipidemia (FTTDCD), and adult-onset type II citrullinemia (CTLN2). Citrin is a component of the malate-aspartate nicotinamide adenine dinucleotide hydrogen (NADH) shuttle, an essential shuttle for hepatic glycolysis. Hepatic glycolysis and the coupled lipogenesis are impaired in citrin deficiency. Hepatic lipogenesis plays a significant role in fat supply during growth spurt periods: the fetal period, infancy, and puberty. Growth impairment in these periods is characteristic of citrin deficiency. Hepatocytes with citrin deficiency cannot use glucose and fatty acids as energy sources due to defects in the NADH shuttle and downregulation of peroxisome proliferator-activated receptor α (PPARα), respectively. An energy deficit in hepatocytes is considered a fundamental pathogenesis of citrin deficiency. Medium-chain triglyceride (MCT) supplementation with a lactose-restricted formula and MCT supplementation under a low-carbohydrate diet are recommended for NICCD and CTLN2, respectively. MCT supplementation therapy can provide energy to hepatocytes, promote lipogenesis, correct the cytosolic NAD^+/NADH ratio via the malate-citrate shuttle and improve ammonia detoxification, and it is a reasonable therapy for citrin deficiency. It is very important to administer MCT at a dose equivalent to the liver's energy requirements in divided doses with meals. MCT supplementation therapy is certainly promising for promoting growth spurts during infancy and adolescence and for preventing CTLN2 onset. Intravenous administration of solutions containing fructose is contraindicated, and persistent hyperglycemia should be avoided due to glucose intoxication for patients receiving hyperalimentation or with complicating diabetes.

KEYWORDS

adult-onset type II citrullinemia (CTLN2), citrin deficiency, failure to thrive and dyslipidemia by citrin deficiency (FTTDCD), medium-chain triglyceride (MCT), neonatal intrahepatic cholestasis by citrin deficiency (NICCD)

1 | INTRODUCTION

Citrin deficiency is an autosomal recessive disorder caused by mutations in *SLC25A13* and is prevalent in East Asia. Citrin deficiency manifests as age-dependent phenotypes. Children with citrin deficiency are born with a small body size, and nearly half of the patients develop neonatal intrahepatic cholestasis caused by citrin

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deficiency (NICCD: OMIM 605814). Symptoms of NICCD generally resolve after 6 months of age. After recovery of NICCD, most patients show a protein- and fat-rich food preference but with no apparent symptoms. However, some patients complain of severe fatigue, recurrent episodes of hypoglycemia, and failure to thrive and dyslipidemia caused by citrin deficiency (FTTDCD). In adulthood, less than 10% of patients develop hyperammonemic encephalopathy as citrullinemia type 2 (CTLN2: OMIM 603417) and require liver transplantation as a definitive therapy.[1,2]

Citrin is an aspartate/glutamate transporter that is mainly expressed in hepatic mitochondria and is a component of the malate-aspartate reduced nicotinamide adenine dinucleotide (NADH) shuttle. Citrin forms an essential shuttle for hepatic glycolysis and citrin deficiency is basically characterized by impairment of hepatic glycolysis. On the other hand, clinical manifestations of citrin deficiency are growth failure, neonatal cholestasis, steatosis, dyslipidemia, citrullinemia, and hyperammonemia.

A lactose-restricted and medium-chain triglyceride (MCT)-enriched formula and a supplement with fat-soluble vitamins have been used for the treatment of NICCD. A decrease in the NAD^+/NADH ratio was hypothesized to be involved in the pathogenesis of citrin deficiency, and sodium pyruvate was administered to the patients with FTTDCD or CTLN2, with the aim of increasing the cytosol NAD^+/NADH ratio. Mutoh et al[3] reported that administration of sodium pyruvate and arginine with a low-carbohydrate diet to a patient at an early stage of CTLN2 improved her clinical condition and laboratory findings. However, the effect was not marked. Yazaki et al[4] treated 15 CTLN2 patients with sodium pyruvate under a low-carbohydrate diet and found a decrease in the frequency of hyperammonemic encephalopathy in 11 patients. However, the treatment did not prevent relapse of encephalopathy or improve the Fischer ratio or citrullinemia.

In 2012, we reported that a lactose-restricted and MCT-supplemented formula is very effective for treatment of NICCD.[5] We noticed that the MCT supplementation quickly improved cholestasis and that its marked therapeutic effect seemed not to be simply derived from improving intestinal absorption. Considering the metabolic impairment of citrin deficiency, we extended the clinical trials of MCT supplementation therapy with a low-carbohydrate formula to CTLN2 patients and found that this therapy improved unconsciousness in a day, prevented the recurrence of hyperammonemic encephalopathy, and steadily improved both the general condition and liver condition.[6,7] Recently, Kose et al[8] also confirmed the effect of MCT supplementation therapy in patients with NICCD or CTLN2. The aim of this review is to provide an overview of the pathogenesis of citrin deficiency and to introduce the metabolic effects of MCT supplementation therapy.

2 | ETIOLOGY

Citrin is a Ca^{2+}-binding aspartate/glutamate carrier that transfers cytosolic reducing equivalents to the mitochondria as part of the malate-aspartate NADH shuttle. Citrin, encoded by *SLC25A13* (chromosome 7q.21.3), is expressed mainly in the liver and is essential for hepatic glycolysis. Citrin deficiency is a recessive inherited disease caused by *SLC25A13* mutations.[1] All *SLC25A13* mutations detected in the patients are loss-of-function mutations and do not show any genotype-phenotype relationship. Eleven mutations are prevalent in Japanese individuals, and the frequency of homozygotes or compound heterozygotes has been calculated to be 1/7100.[9]

2.1 | Pathogenesis

2.1.1 | Impairment of glycolysis, lipogenesis, and energy metabolism in hepatocytes

The liver consumes 20% of the daily caloric requirements, and hepatocytes use glucose and fatty acids as energy sources during postprandial and fasting states, respectively.[10] Hepatocytes take up glucose during hyperglycemia in the postprandial state, using a majority of the glucose for the synthesis of glycogen and a small portion as an energy source or for de novo lipogenesis. Hepatic de novo lipogenesis is coupled with glycolysis and upregulates peroxisome proliferator-activated receptor α (PPARα).[11] Hepatic glycolysis and de novo lipogenesis are impaired in citrin deficiency, leading to the downregulation of PPARα (Figure 1A). Downregulation of PPARα is associated with fatty liver and hyperlipidemia.[12] Hepatocytes with citrin deficiency cannot use glucose and fatty acids as energy sources due to impairment of glycolysis and beta-oxidation, respectively, leading to energy deficit.

After birth, the energy source of the liver switches from glutamine to glucose and fatty acids. The main carbohydrate in milk is lactose and galactose metabolism is also inhibited at the step involving UDP-glucose 4-epimerase-mediated catalysis because of increased cytosolic NADH.[5] The accumulation of toxic galactose metabolites is an exacerbating factor of NICCD.

Hepatic de novo lipogenesis in adults has roles to monitor nutritional status and control energy metabolism via the regulation of PPARα.[11] In contrast, it likely has a significant role in fat supply during growth spurt periods: the fetal period (during the third trimester), infancy

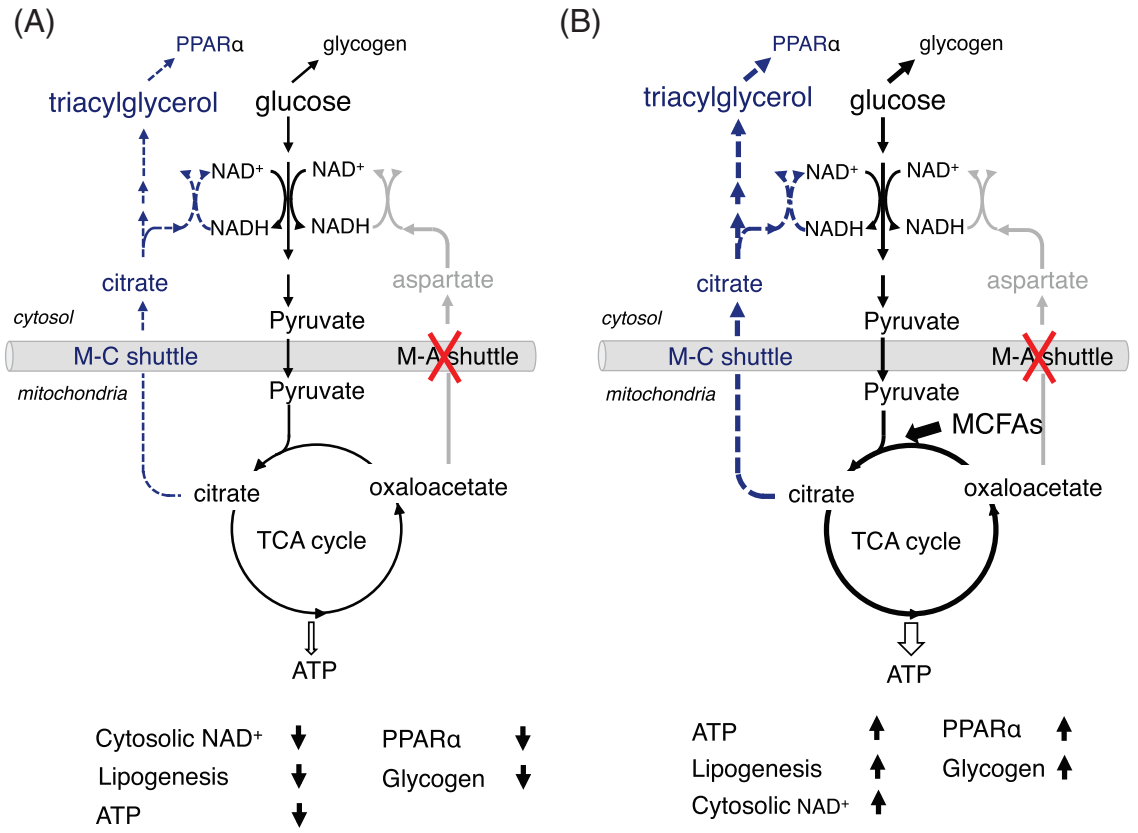

FIGURE 1 A, Glucose metabolism in the liver of patients with citrin deficiency. B, Metabolic changes caused by MCT supplementation. ATP, adenosine triphosphate, MA shuttle, malate–aspartate shuttle, MC shuttle, malate-citrate shuttle, MCFAs, medium-chain free fatty acids, PPARα, peroxisome proliferator-activated receptor α, TCA cycle, tricarboxylic acid cycle. Black lines represent glycolysis, glycogenesis, and the TCA cycle, and blue dotted lines show de novo lipogenesis

(during the first 6 months of age), and puberty. Growth impairment during these periods is a hallmark of citrin deficiency.[13]

The dietary preference for and effectiveness of a low-carbohydrate diet in citrin deficiency are probably associated with the metabolic impairment.[14] Amino acids and fatty acids can generate ATP independent of the NADH shuttle. The metabolic sensing function of the liver is present, with consequent effects on the brain from the liver.[15] Hypoglycemia is frequently found in children with citrin deficiency because of inadequate carbohydrate intake due to preference,[2] impairment of gluconeogenesis,[16] and decreased hepatic glycogen storage due to the energy deficit in hepatocytes.

2.1.2 | Impairment of ammonia detoxification systems

There are two major ammonia detoxification systems, namely, ureagenesis and glutamine synthetase (GS), in the liver. Impairment of either system causes hyperammonemia. Citrullinemia (521 ± 290 μmol/L) is observed in patients with NICCD and CTLN2 and reflects an impairment of the argininosuccinate synthase 1 (ASS1) step of the urea cycle.[2] ASS1 catalyzes the adenosine triphosphate (ATP)-dependent synthesis of argininosuccinate in the cytosol from citrulline and aspartate. Citrin transports aspartate from mitochondria to the cytosol, and citrin deficiency is predicted to result in a deficiency of aspartate as a substrate for ASS1. A decrease in hepatic ASS1 enzyme activity was observed in most CTLN2 patients.[17] However, its reduction is not enough to cause hyperammonemia as in patients with benign citrullinemia type 1 (<1000 μmol/L).[7,14] Aminograms indicated that hepatic GS impairment rather than ASS1 impairment was the main contributor to hyperammonemia in CTLN2.[7,14] Impairment of the hepatic GS system is likely caused by a deficiency of ATP and/or substrates in hepatocytes.[7] Immunohistochemical analysis revealed a decrease in ASS1-positive hepatocytes and an increase and wide distribution of GS-positive hepatocytes in CTLN2, suggesting an impairment of liver zonation.[7]

2.1.3 | Carbohydrate toxicity

Infusion of glycerol- and fructose-containing osmotic agents has been reported to produce a lethal effect in CTLN2 patients.[18] A carbohydrate-rich diet and a lactose (galactose)-containing formula were reported to exacerbate CTLN2 and NICCD, respectively. Saheki et al[19] considered that carbohydrate is toxic for the patients with citrin deficiency. For the unfavorable effects of carbohydrates, one possible mechanism is that carbohydrates are harmful (toxic) for the patients' hepatocytes and the other is that a carbohydrate-rich diet cannot provide enough energy to the patients' hepatocytes due to metabolic impairment. Infusion of glycerol- and fructose-containing osmotic agents in CTLN2 patients and a lactose (galactose)-rich formula in NICCD patients are predicted to have harmful effects on hepatocytes. Fructose is rapidly taken up and metabolized in hepatocytes quite differently from glucose and parenteral fructose administration, even in healthy controls, resulting in the accumulation of metabolites (fructose 1-phosphate), the trapping of inorganic phosphate (Pi), and a decrease in ATP in hepatocytes.[20] Patients with citrin deficiency have defects in fructose and glycerol metabolism at the step involving catalysis by glyceraldehyde 3-phosphate dehydrogenase and glycerol 3-phosphate dehydrogenase, respectively, due to a defect in the NADH shuttle and definitely exhibit ATP depletion in hepatocytes, leading to death caused by these infusions.[18] This is similar to the lethality that can arise due to parenteral fructose loading in patients with hereditary fructose intolerance (aldolase B deficiency).[21] Galactose metabolism is also inhibited, leading to accumulation of toxic metabolites as described.

As for glucose metabolism, hepatic glucose uptake and metabolism are limited under normoglycemia, owing to the low-glucose affinity of glucose transporter 2 (GLUT2).[10] However, persistent hyperglycemia is predicted to increase glucose uptake and lead to metabolite accumulation, ATP depletion, and hepatocyte damage. Hyperalimentation was reported to exacerbate CTLN2.[22] A female patient with CTLN2 received hyperalimentation due to anorexia and weight loss 5 years after radical mastectomy and subtotal gastrectomy and developed hyperammonemic encephalopathy accompanied by hyperglycemia. Her condition was improved by a low-glucose infusion. After recovery, she received hyperalimentation again and had a similar episode. We also reported two CTLN2 patients: one case presented with hyperammonemic encephalopathy accompanied by type 2 diabetes mellitus (DM), and the other presented with hyperammonemic encephalopathy relapse upon the onset of DM after several years of remission following MCT supplementation therapy.[23] Both exhibited favorable results upon using antidiabetic and MCT supplementation therapies. These results indicated that glucose becomes toxic during persistent hyperglycemia and that control of blood glucose is very important, especially for patients who receive hyperalimentation or glucose infusion[21] and patients whose condition is complicated by DM.[23]

3 | MEDIUM-CHAIN TRIGLYCERIDE SUPPLEMENT THERAPY

An energy deficit in hepatocytes is a fundamental defect of citrin deficiency, as described. MCT is rapidly hydrolyzed and is absorbed mainly as medium-chain free fatty acids (MCFAs), which reach the liver via the portal vein and are metabolized to acetyl-CoA and ATP by beta-oxidation and enhance TCA cycle activity in hepatocytes.[24-27] Energy provided to hepatocytes by MCT supplementation can promote lipogenesis and glycogenesis and contribute to lipid and glucose homeostasis. De novo lipogenesis can increase the cytosolic NAD^+/NADH ratio through the malate-citrate shuttle, leading to increased carbohydrate intake and PPARα upregulation, resulting in the improvement of fatty liver (Figure 1B). MCT supplementation also improves ammonia detoxification as described in the treatment for CTLN2 and is known to reduce oxidative stress and inflammation and decrease feeding, likely due to an increase in ATP content.[14,26,27]

The liver consumes 20% of the daily caloric requirement, which can be supplemented by MCT in symptomatic patients. The intake of MCT with meals is very important for providing energy to hepatocytes. Figures 2A & 2B show the changes in the levels of blood glucose and free fatty acids, respectively, in nine healthy adults who were provided with a meal of white rice containing 75 g of available carbohydrate.[28] The meal increased blood glucose levels, induced insulin secretion, suppressed the mobilization of fatty acids from adipocytes, and decreased the levels of fatty acids. Free fatty acids are the only energy source available for hepatocytes with citrin deficiency. Regarding the metabolism of MCT, Metges and Wolfram[29] studied the rates of elimination ^{13}C as CO_2 in five healthy adults after oral [^{13}C] trioctanoate administration. After oral administration, the ^{13}C peak was observed after approximately 40 minutes, and the mean rate of oxidation was approximately 35% within 7.5 hours after administration. MCT can be absorbed and metabolized quickly, and intake of MCT with meals can supply energy to hepatocytes during periods of energy shortage (Figure 2C). It has also been described that peak MCT metabolism was observed at 3 hours after administration.[30]

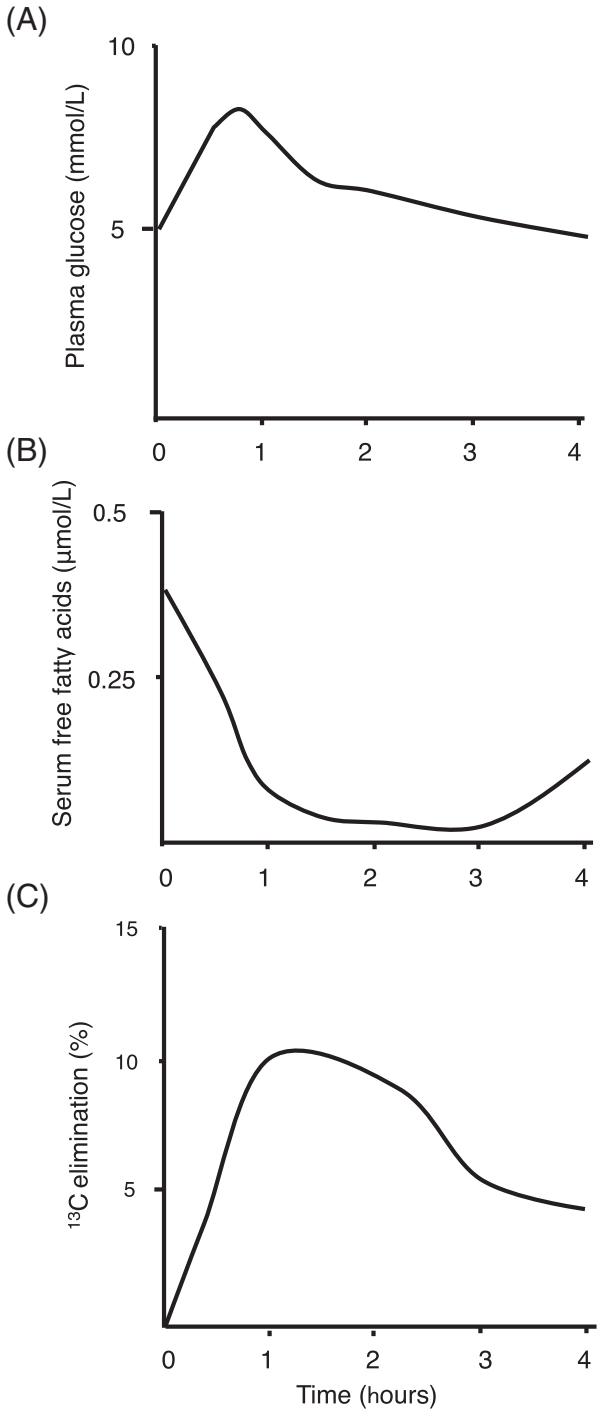

FIGURE 2 Postprandial plasma glucose, A, and serum-free fatty acid, B, levels after ingestion of white rice. Sakuma et al[28] loaded white rice containing 75 g of carbohydrates to nine healthy adults (six men and three women) and measured plasma glucose and serum-free fatty acid levels. A,B shows the means of the data. C, ^{13}C elimination rates (% of applied dose) after oral administration of ^{13}C-labeled trioctanoate. Metges and Wolfram[29] loaded ^{13}C-labeled trioctanoate to five healthy adults (two men and three women), measured the ^{13}C enrichment in breath CO_2 by isotope-ratio mass spectrometry, and calculated metabolic rates by determining $\Delta\delta^{13}C_{PDB}$ (‰). C shows the mean ^{13}C elimination rates, which were calculated from the data

It is very important to take MCT at a dose equivalent to the liver's energy requirements, via three divided doses with meals.

4 | TREATMENT FOR EACH PHENOTYPE

4.1 | NICCD

After birth, the switching of the liver's energy source, the intake of lactose (galactose), and the increase in energy demand for a growth spurt are likely associated with the onset of NICCD. Patients showing galactosemia can be treated with lactose-free milk (including soy milk) and MCT supplementation.[5] The formula is prepared by mixing 100 mL of lactose-free milk with 2 mL of MCT oil, in which MCT constitutes 20% of the total calories. Patients without galactosemia can be treated with ordinary milk or breast milk supplemented with MCT oil. MCT oil is similarly supplemented as in the lactose-free formula. MCT supplementation therapy can improve cholestasis, citrullinemia, and the patient's general condition within a week, which could be a diagnostic clue. If patients have a deficiency of fat-soluble vitamins, these vitamins should be provided as supplements. Symptoms generally improve after the age of 6 months and resolve by the age of 12 months even in untreated patients. However, MCT supplementation may be desirable until the age of 3 years because of the myelination of the central nervous system.[13]

4.2 | FTTDCD

After NICCD recovery, most individuals do not exhibit any symptoms, but some complain of recurrent hypoglycemia, growth failure, fatigability, hyperlipidemia, and pancreatitis. To avoid hypoglycemia, the daily requirement of carbohydrates should be administered: 100 g/day to 1-year-old children and 130 g/day to children who are 5 years old or older. For other foods, the individuals can eat as many protein- and fat-rich foods as they like. For more strongly symptomatic individuals or overweight individuals, MCT should also be administered at a dose equivalent to the liver's energy requirements in three divided doses with meals. MCT administration can improve their condition, decrease feeding, and prevent obesity.[24-27]

4.3 | CTLN2

MCT supplementation therapy with a low-carbohydrate formula is recommended for the management of

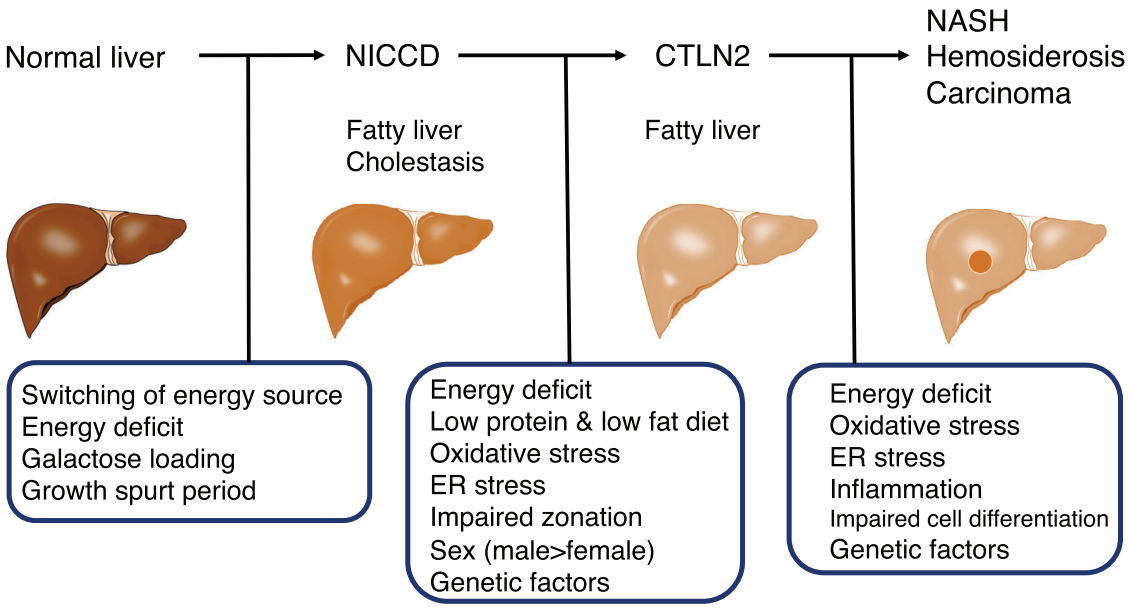

FIGURE 3 Progression of hepatic damage in citrin deficiency. ER stress, endoplasmic reticulum stress

CTLN2.[6,7,14] The daily doses of MCT for a man (large adult) and a woman (small adult) are 45 and 30 mL, respectively, in three divided doses with meals. The low-carbohydrate formula contains the daily energy requirement (1700-2800 kcal/day), and the protein:fat:carbohydrate ratio is 10-20:35-50:40-45. The treatment promptly improved hyperammonemia, which was accompanied by an increase in plasma glutamine levels and a moderate decrease in plasma citrulline levels. The therapy was likely to enhance the ASS1 and GS (ATP-requiring enzymes) reaction by providing the energy. After long-term therapy, plasma citrulline levels, and the distribution of ASS1- and GS-positive hepatocytes were normalized in patients with early treatment.[7] Hyperammonemia was also improved in patients with delayed treatment, however, plasma citrulline levels were not normalized even after long-term therapy. These indicated that GS impairment is the main contributor to hyperammonemia and early and long-term MCT supplement therapy is necessary to normalize liver zonation.

Infusion of glycerol- and fructose-containing osmotic agents has been reported to produce a lethal effect and is therefore contraindicated. Infusion of fructose-containing solutions also should be avoided.[18] Persistent hyperglycemia should be avoided during hyperalimentation and in patients whose condition is complicated by DM.[22,23]

5 | PROGNOSIS

A hepatic energy deficit is a fundamental defect of citrin deficiency. A chronic energy deficit is predicted to cause fatty liver, nonalcoholic steatohepatitis (NASH) and hepatocellular carcinoma via oxidative stress, endoplasmic reticulum stress, inflammation, and abnormal cell differentiation (Figure 3).[7,12,31] MCT supplementation is a reasonable therapy for citrin deficiency, and early treatment can improve the prognosis with normal growth.

6 | LIMITATIONS OF MCT SUPPLEMENTATION THERAPY AND PROSPECTIVE ASPECTS OF CITRIN DEFICIENCY

Studies of MCT supplementation therapy have been based on small case reports. Studies with many patients are needed to clarify the pathogenesis and confirm the efficacy of MCT supplementation therapy.

Recently, Rabinovich et al[32] reported that citrin plays a significant role in regulating cellular energy during carcinogenesis and suggested that targeting citrin may be beneficial for cancer therapy. They mentioned in the report that citrin-depleted cancer cells increased NAD^+ biosynthesis by supplementation with the NAD^+ precursor nicotinamide mononucleotide. There is no information on the NAD^+ content in the liver with citrin deficiency. However, nicotinamide administration is effective for treatment of nonalcoholic fatty liver disease (NAFLD) without systemic side effects,[33] and nicotinamide supplementation may be worth trying as a supplemental therapy. Cao et al[34] reported an mRNA therapy that improved metabolic and behavioral abnormalities in a murine model of citrin deficiency. Further investigation is required to develop more effective and safe treatments for citrin deficiency.

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CONFLICT OF INTEREST

The author declares no conflicts of interest.

ETHICS STATEMENT

The ethics committee of the Yamagata University School of Medicine approved the original research projects. All procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients included in the study.

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