REVIEW

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A Brief Overview of Fatty Acid Oxidation Disorders

Mehmet Cihan Balcı

İstanbul University Faculty of Medicine, Department of Nutrition and Metabolism, İstanbul, Türkiye

Abstract

A number of genetic disorders affecting every stage of fatty acid oxidation (FAO) have been identified. The most common manifestations are fasting-induced hypoglycemia and, less commonly, life-threatening coma. The research findings indicate chronic cardiomyopathy and muscle weakness. Less frequently, evidence of rhabdomyolysis is observed. The initial symptoms may manifest at various stages, ranging from the neonatal period to adulthood. The diagnosis of this condition is facilitated by detecting elevated levels of abnormal acylcarnitines, which can be measured by tandem mass spectrometry. During periods of acute illness, initiating intravenous fluid therapy containing dextrose is recommended to suppress lipolysis. In long-term treatment, the most significant aspect is the prevention of prolonged fasting. This review aims to provide information on the clinical findings, diagnosis, and treatment methods of FAO disorders.

Keywords: Fatty acid oxidation, Reye-like syndrome, Hypoketotic hypoglycemia, Cardiomyopathy, Rhabdomyolysis

INTRODUCTION

All cells, with the exception of adult erythrocytes, use mitochondrial fatty acid oxidation (FAO) as the primary mechanism for the breakdown of long-chain fatty acids.[1] The mechanism of FAO was identified by German chemist Georg Franz Knoop in the 1900s.[2] His seminal research on odd- and even-chain ω-phenyl fatty acids demonstrated that fatty acid metabolism proceeded via removal of two-carbon units sequentially. In addition to promoting oxidative phosphorylation and the tricarboxylic acid (TCA) cycle, FAO increases the production of ketone bodies in the liver. This pathway is made up of 25 enzymes and specific transport proteins.[3] Furthermore, the FAO has been found to play a significant role in the pathophysiology of common disorders such as insulin resistance, diabetes, obesity, kidney fibrosis and heart failure.[2]

CLINICAL MANIFESTATIONS

Numerous clinical diseases are caused by disorders of FAO. Patients may exhibit completely diverse symptoms even if they have the same mutation.[4] Hypoketotic hypoglycemia during catabolic states such as illness, fever, fasting, and exercise may be a clinical sign in patients with FAO disorders (FAODs). Hypoketotic hypoglycemia can progress to Reye-like syndrome, which may lead to coma or death. Carnitine transporter deficiency (CTD), very long-chain acyl-CoA dehydrogenase (VLCAD), trifunctional protein (TFP), long-chain hydroxyacyl-CoA dehydrogenase (LCHAD), carnitine acyl-carnitine translocase (CACT), and carnitine palmitoyltransferase-II (CPT-II) deficiencies may manifest as hypertrophic or dilated cardiomyopathy.[5,6] Although there have been documented exceptions to this trend, patients with CPT-IA and medium-chain acyl-CoA dehydrogenase (MCAD) deficiencies typically do not have cardiomyopathy.[5-7] Patients with FAOD disorders may also present with arrhythmias and conduction deficits, but they often do not have cardiomyopathy.[5,6] The presence of these symptoms in CTD, CPT-IA, and MCAD deficiencies (MCADDs) is also controversial.[6]

Furthermore, skeletal myopathy, which is characterized by rhabdomyolysis, myalgia, and muscle weakness, may manifest or develop in patients with an FAOD.[5,6] These symptoms are the most common in patients who present at a later age. Moderate lipid accumulation may be seen in muscle biopsies, primarily in type 1 fibers.[8] VLCAD-deficient patients had proximal myopathy

Address for Correspondence: Mehmet Cihan Balcı, İstanbul University Faculty of Medicine, Department of Nutrition and Metabolism, İstanbul, Türkiye
E-mail: mcbalci@istanbul.edu.tr **ORCID ID:** orcid.org/0000-0002-3384-8679

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whereas similar findings appeared in distal muscle groups in patients with LCHAD deficiency.[2]

Hepatomegaly likely reflects fatty liver.[6] Hepatic steatosis is primarily associated with MCADD, VLCAD deficiency (VLCADD), LCHAD/mitochondrial TFP deficiency, and multiple acyl-CoA dehydrogenase deficiency (MADD). Lipid accumulation in the liver results from inhibition of mitochondrial β-oxidation, thereby preventing hepatocytes from adequately using fatty acids as fuel during fasting, illness, or catabolic stress. Fatty acids that should be oxidized are instead re-esterified into triglycerides and retained in hepatocytes. Patients with LCHAD and MTP deficiencies may experience retinopathy and polyneuropathy (peripheral neuropathy).[9,10]

Hepatic, cardiac, and skeletal muscle signs and symptoms of early-onset multisystem failure are particularly common in long chain FAOD.[11] The heart has a continuously high energy demand to sustain contractile function. To secure continuous ATP production, the heart is a metabolic "omnivore" that can use many different substrates, depending on their availability.[12] FAO, however, is the preferred pathway for energy production in the heart, with more than half of ATP production derived from fatty acids. In contrast, the prenatal heart relies on glucose and lactate, but in the immediate postnatal period, when dietary fat is abundant, the heart switches to FAO as a source of energy.[13]

FAO is also crucial for ATP production in muscle; in particular, during exercise, FAO increases from rest to low-intensity exercise but does not increase further as exercise intensity increases. This pattern is in contrast to that seen for glucose and glycogen utilization, which always increase with exercise intensity. The sources of fatty acids also differ depending on the exercise intensity, with the contribution of plasma free fatty acids increasing with exercise intensity.[14]

In some patients, renal tubular disease may also be evident. Failure to supply the brain with glucose or ketones leads to neurological symptoms. Neonatal presentations usually feature undetectable protein expression or enzyme activity and are strongly associated with the severity of the mutation.[15]

The major manifestations of the late-onset forms of these disorders usually involve skeletal muscle or the heart. In these cases, residual enzyme activity and ketogenesis appear sufficient to preserve the liver and protect the brain from major involvement. Many patients with later-onset disease do not exhibit severe fasting intolerance but have exercise-induced rhabdomyolysis. In all long-chain FAOD that exhibit rhabdomyolysis, release of myoglobin may result in glomerular injury and acute renal failure.[11]

Many individuals are compound heterozygotes for a severe and a mild mutation, and intermediate forms of these long-chain FAODs exist. During fasting, these individuals are at risk of metabolic decompensation, hepatic failure, and potentially life-threatening hypertrophic cardiomyopathy. Additionally, some patients experience skeletal myopathy and are susceptible to acute muscle complaints, such as rhabdomyolysis, while under stress.[9,15,16]

Although the precise mechanisms causing heterogeneous presentations are still not completely known, as with many other enzyme deficiencies, the amount of residual activity of the enzyme is thought to define the clinical phenotype.[17] In addition to residual enzyme activity, other genetic and environmental factors have been found to be significant in the manifestation of disease. Heterogeneous clinical presentations within the same family provide particular evidence for this.[18] The marked intrafamilial phenotypic variability observed in FAODs suggests that the clinical course cannot be explained solely by the underlying pathogenic genotype. Even among relatives carrying the same disease-causing variant, presentations may range from severe neonatal or infantile disease to relatively mild, late-onset, or even apparently asymptomatic forms. This variability supports the concept that additional factors, including modifier genes, epigenetic mechanisms, residual enzyme activity, and environmental triggers such as fasting, intercurrent illness, dietary habits, and metabolic stress, contribute substantially to disease expression.

Carnitine Transporter Deficiency

Early childhood onset cardiomyopathy, with or without weakness and hypotonia, recurrent hypoglycemic hypoketotic seizures and/or coma, failure to thrive, and exceptionally low plasma and tissue carnitine concentrations are the hallmarks of CTD, a potentially fatal autosomal recessive disorder.[19] This condition exhibits phenotypic diversity; many patients develop symptomatic cardiomyopathy or recurrent hypoketotic hypoglycemia (Reye-like episodes) in early years of life.[4] Muscle hypotonia, modest developmental delay, failure to thrive, delayed walking, and poor growth are symptoms that newborns may initially exhibit. Some patients may have isolated cardiomyopathy, which can present with sudden death later in childhood. Within the same pedigree, both a symptomatic and symptomatic individuals have been reported.[18] Evidence suggests that compared to those who appear clinically, asymptomatic patients typically have slightly higher residual activity.[20] It is suggested carriers of a single *OCTN2* mutation may be susceptible to clinical illness if they experience enough stress.[19]

Carnitine Palmitoyltransferase-IA Deficiency

Related carnitine acyltransferases are encoded by 3 genes in the human genome. The liver isoform of CPT-I is encoded by *CPT-IA*, muscle-type CPT-I is encoded by CPT-IB, and CPT-IC encodes brain isoform.[21] The liver, kidney, lung, spleen, gut, pancreas, ovary, and fibroblasts all express CPT-IA isoform.[4]

The hepatic (and renal) CPT-IA deficiency is currently the sole known human CPT-I defect.[11] Patients with CPT-IA deficiency typically exhibit recurrent episodes of fasting-induced hepatic failure (Reye-like hepatic encephalopathy) with hypoketotic hypoglycemia, metabolic acidosis with elevated transaminases, hepatomegaly, hepatosteatosis, and mild to moderate hyperammonemia in infancy, reflecting the tissue localization of this isoform of CPT-IA.[11] Hypoglycemia stems from increased glucose utilization due to the inability to produce ketone bodies, and from decreased gluconeogenic capacity because of the absence of acetyl-CoA produced by FAO, a crucial activator of gluconeogenesis. The expression of CPT-IA in the renal tubular epithelium, which depends on FAO to sustain the high energy transport mechanisms, explains why renal tubular acidosis during catabolic periods has also been documented in a number of patients.[4]

Neonates have been documented to exhibit a variety of cardiac abnormalities, such as tachycardia, bradycardia, arrhythmias, right bundle branch block, and abrupt cardiac arrest.[4] One possible explanation is the expression of CPT-IA in the fetal heart, which persists until the neonatal stage.[22] Although hyperlipidemia is uncommon in other FAOD, hyperlipidemia with elevated triglycerides and/or cholesterol might be an additional feature of CPT-IA deficiency.[23] Hepatic VLDL production may be particularly favored by blockade of the outer mitochondrial membrane, leading to hyperlipidemia.

Carnitine Palmitoyltransferase-II Deficiency

There is one widely expressed isoform of the CPT-II enzyme.[4] There are three phenotypes of CPT-II deficiency: a lethal neonatal-onset form with congenital anomalies, a severe neonatal hepatocardiomuscular form, and a mild myopathic adult form.[4] Non-ketotic hypoglycemia, liver disease, hypotonia, cardiomyopathy, and congenital anomalies are the hallmarks of the fatal newborn phenotype.[24] The infantile form, whether there is cardiac disease or not, manifests as periods of decompensation with liver and skeletal muscle involvement, mainly as non-ketotic hypoglycemia caused by fasting and/or concurrent infection.[25] After childhood, cardiac symptoms are uncommon.[2]

About 50% of myopathic diseases are caused by the prevalent S113L mutation.[4] Because the frequent and high residual activity S113L mutation, causes the production of a thermolabile enzyme, the enzyme activity is further decreased by protein degradation during intense exercise when muscle temperature rises, aggravating the injury to the muscles.[4] The S113L variant, particularly in the homozygous state, is typically associated with the late-onset muscular form rather than with the severe neonatal or infantile forms. For infantile type CPT-II deficiency, there is no reliable genotype–phenotype correlation exists.[17]

Carnitine Acyl-Carnitine Translocase Deficiency

CACT deficiency causes heterogenous clinical phenotype.[26] Attenuated cases may manifest in the first few months of life, but severe neonatal-onset disease is most common, with symptoms emerging within two days of delivery.[26] Early-onset illness is characterized by hyperammonemia, cardiac arrhythmias, and an increased incidence of cardiac arrest. Clinical manifestations also include poor feeding, lethargy, hypoketotic hypoglycemia, hypotonia, transaminitis, liver dysfunction with hepatomegaly, and rhabdomyolysis. Cases of univentricular or biventricular hypertrophic cardiomyopathy, ranging from mild to severe, may improve with proper nutritional and medical interventions. Arrhythmia, especially ventricular tachycardia, is the most prominent cardiac manifestation during the neonatal period. This is followed by various tachyarrhythmias and bradyarrhythmias. Individuals with the early-onset form of the disease typically present with brain damage due to hyperammonemia. Patients with later-onset disease have milder symptoms and are less likely to experience recurrent hyperammonemia, leading to better developmental outcomes. Typically, carnitine levels are quite low (<5 μM).[2] In the plasma acylcarnitine profile, long-chain acylcarnitines are significantly elevated, whereas free carnitine levels are significantly reduced. Excess unsaturated species in urine organic acids can indicate severe dicarboxylic aciduria.[27] Differential diagnosis with genetic testing is necessary as this abnormal profile cannot be distinguished from that of neonatal CPT-2 deficiency.[27]

Very Long-chain Acyl-CoA Dehydrogenase Deficiency

The first rate-limiting stage of mitochondrial long-chain FAO is catalyzed by VLCAD.[11] Like other FAO enzymes, human VLCAD is highly active in the heart, liver, and skeletal muscle.[28] VLCADD is the most prevalent long-chain FAOD in the majority of populations.[29] The three main phenotypes of VLCADD are a late onset myopathic form, a milder childhood form that typically presents with hypoketotic hypoglycemia, but frequently has exercise intolerance and rhabdomyolysis as a significant feature, especially in older children and young adults.[4] A severe infantile phenotype manifests early in life with hypoglycemia, hepatic dysfunction, acidosis, and cardiomyopathy. Within the first few months, 75% of patients who survive early onset symptoms succumb to death.[30] Lower incidences of cardiomyopathy and hypoketotic hypoglycemia are features of childhood-onset

VLCADD, which is milder than early-onset. There has also been evidence of an association to rhabdomyolytic episodes in later childhood.[31]

Muscle pain and stiffness driven by exercise, fasting, temperature extremes, and occasionally infection are the hallmarks of the late-onset myopathic variants of both CPT-II and VLCADD.[4] Although about 20% of individuals will exhibit some lipid accumulation, muscle biopsies are often normal. When combined, these two conditions are the most prevalent inherited metabolic causes of rhabdomyolysis and myalgia in both adults and children.

Numerous *ACADVL* mutations have been identified, the most prevalent of which is c.848T>C.[32] The V243A mutation in the *VLCAD* gene has been identified in a large percentage of asymptomatic patients since newborn screening was implemented.[17] Which individuals, if any, may remain asymptomatic is unknown. There has also been evidence of a relationship between residual activity and clinical phenotype for VLCADD, with residual activities >10% indicating a milder phenotype.[33]

Long-Chain Hydroxyacyl-CoA Dehydrogenase Deficiency and Trifunctional Protein Deficiency

Isolated LCHADD is more common than TFP deficiency in relation to TFP functions.[4] Patients with TFP deficiency display a broad range of clinical symptoms, from mild to severe infantile presentation with hepatic indications to severe newborn manifestations such as cardiomyopathy and mortality.[18] Irreversible peripheral neuropathy and retinopathy presenting in TFP and LCHADD, have not been documented in any of the other long-chain FAOD.[17] Peripheral neuropathy develops in up to 80% of TFP deficient cases during long-term follow-up, according to various studies,[9,34] whereas in LCHADD, it is reported to occur only in 5–10% of cases.[35] In comparison, only 5–13% of patients with TFP deficiency and 30% to >50% of LCHADD patients are known to experience retinopathy.[9,34] These diseases typically manifest as episodic rhabdomyolysis during physical activity, illness, or fasting, however this may not show up for years following the initial neurological manifestation.[34,36] It has been suggested that the particular toxicity of the 3-hydroxacyl metabolites is the cause of the neuropathy and rhabdomyolysis observed in mild TFP deficiency.[37] One uncommon morbidity of both LCHADD and TFP deficiency is hypoparathyroidism.[38]

Mild TFP deficiency is uncommon and has a peculiar phenotype that shares characteristics with spinal muscular atrophy and inherited sensory-motor neuropathies.[34,36] In addition to symmetric weakness in the wrist and finger extensors, there is a gradual peripheral polyneuropathy that primarily affects the lower limbs starting in infancy or early childhood.[4] Exercise intolerance, planovalgus deformities, bilateral Achilles tendon contractures, and loss of vibratory sensation are potential manifestations.

Acute fatty liver of pregnancy and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome can occur in heterozygous pregnant female carriers of TFP mutations carrying a homozygously affected offspring.[11] The pathophysiology of all these extra issues with TFP defects is unknown, but it could be caused by the hazardous accumulation of 3-hydroxy fatty acid intermediates or by unidentified FAO pathway requirements in the retinal, placental, and neurological tissues.[11] Remarkably, none of the other FAO abnormalities have been linked to maternal HELLP syndrome.[17]

While some mutations in the *HADHA* or *HADHB* cause deficiencies in all three enzymes, the prevalent c.1528G>C *HADHA* mutation causes solely LCHADD.[34,37] Patients with mutations in both the *HADHA* and *HADHB* genes exhibit comparably diverse clinical symptoms, making clinical distinction between them impossible. Patients with LCHADD exhibit a variety of phenotypes despite having the same genotype, indicating the significance of other genetic and environmental variables.[35]

Medium-chain Acyl-CoA Dehydrogenase Deficiency

The most prevalent FAO condition is MCADD.[17] MCADD presents as primary hepatic failure accompanied by encephalopathy (Reye-like syndrome) characterized by moderately hypoketotic hypoglycemia.[39] The initial attack is fatal in 20% of cases.[40] According to reports, the death rate within the first 72 hours is 4%.[41] Patients with homozygous c.985A>G mutation have a severe genotype.[3] It should be noted that patients with MCADD may have ketones in their urine when tested with dipsticks during catabolic episodes.[11] This is hypothesised to result from the partial oxidation of long-chain acyl-CoAs to medium-chain acyl-CoAs, producing acetyl-CoA. Although there have been a few anecdotal reports of both cardiac and muscle complications, cardiac, renal, and skeletal muscle signs and symptoms have not yet been demonstrated to contribute to the MCADD phenotype.[40] It is possible that partial oxidation of long-chain fatty acids supplies enough acetyl-CoA to fulfill the requirements of skeletal and cardiac tissues in the great majority of MCADD patients.

Multiple Acyl-CoA Dehydrogenase Deficiency

Deficiencies of either electron transfer flavoprotein (ETF) or ETF-ubiquinone oxidoreductase (ETF-QO), result in MADD, a disorder of fatty acid, amino acid, and choline oxidation.[4] In addition to leg weakness and exercise intolerance with sporadic rhabdomyolysis, patients may exhibit cyclical vomiting, loss of appetite, and proximal muscle weakness affecting the neck, shoulders, hips, and/or respiratory muscles. Acute encephalopathy may be observed in certain patients.[4]

Three clinical phenotypes have been attributed to MADD; a mild or late-onset form, a neonatal form with congenital anomalies, and a neonatal form without congenital malformations.[17] Within the first 24 to 48 hours following a preterm birth, the first group of patients typically exhibits symptoms such as severe non-ketotic hypoglycemia, hypotonia, hepatomegaly, and deep metabolic acidosis. Numerous congenital anomalies, such as multicystic dysplastic kidney, sandal-foot deformity, external genital anomalies, and facial anomalies including low-set ears, large foreheads, hypertelorism, and hypoplastic facial features, are associated with this phenotype. It is believed that the accumulation of metabolites during pregnancy causes dysmorphic characteristics. Within the first twenty-four hours, the second group presents with hypotonia, tachypnea, hepatomegaly, metabolic acidosis, and hypoketotic hypoglycemia. Within the first week, the majority of these individuals die. Patients with severe cardiomyopathy survive only a few months despite prompt diagnosis and meticulous therapy. The third group of patients exhibits various clinical manifestations. In the initial months, these patients may exhibit hypoketotic hypoglycemia, metabolic acidosis, and sporadic vomiting episodes; in adulthood, they may develop Reye-like syndrome and proximal myopathy.[42] High-dose riboflavin treatment has been shown to be beneficial for patients with a moderate clinical presentation.

Riboflavin, also known as vitamin B2, is a precursor of flavin adenine dinucleotide (FAD), a cofactor of numerous dehydrogenases involved in cellular metabolism, including acyl-CoA dehydrogenases in FAO. Notably, riboflavin cannot be synthesized in the human body. Therefore, riboflavin is absorbed by the intestines from the diet, transported through the bloodstream, and taken up by tissue-specific riboflavin transporters. Inside the cell, riboflavin kinase converts riboflavin into flavin mononucleotide (FMN). FMN is adenylated to FAD-by-FAD synthase, encoded by FLAD1. Recently, mutations in FLAD1 were reported to cause a novel form of MADD.

Riboflavin transporter deficiency, comprising *RFVT1* and *RFVT2* (caused by biallelic pathogenic variants in *SLC52A2* and *SLC52A3*, respectively), is a rare neurologic condition characterized by progressive peripheral and cranial neuronopathy causing muscle weakness, with consequent respiratory compromise, vision loss, deafness, and sensory ataxia. The acylcarnitine profile in the blood is abnormal, with accumulation of short- and medium-chain (and sometimes long-chain) acylcarnitines. This can lead to patients being misdiagnosed with MADD. The diagnosis of *RFVT1* and *RFVT2* is established in an individual who has suggestive findings and biallelic pathogenic variants in either *SLC52A2* or *SLC52A3*.

The majority of these riboflavin-responsive MADD patients have been shown to have *ETF-DH* gene mutations, with the majority of these mutations occurring close to the ubiquinone binding pocket.[43] The precursor of FAD is riboflavin, and the capacity of FAD to function as a chemical chaperone that encourages the folding of specific misfolded ETF-QO proteins leads to riboflavin responsiveness.[36] Supplementing with riboflavin aids patients with specific mutations in the *ETF-DH* gene restore residual activity to a greater degree.[43] When riboflavin is administered, the clinical effect is typically rapid and apparent. The majority of patients are young adults or teens.[36]

Short Chain Acyl-CoA Dehydrogenase Deficiency

Short chain acyl-CoA dehydrogenase (SCAD) deficiency is now considered as a biochemical phenotype of uncertain clinical importance, despite the fact that it causes disruptions in certain metabolites consistent with an FAOD.[44] The pathogenesis of SCAD deficiency is poorly understood, and the condition's signs and symptoms have been incredibly variable.[45] Neurological, myopathic, and hepatic signs and symptoms were included in the very first description. Short-chain fatty acid intermediates were thought to cause neurological symptoms because they are volatile and more likely to cross the blood–brain barrier, but this hasn't been proven despite the availability of an animal model.[46] The majority of detected neonates with SCAD deficiency do not develop a clinical phenotype, according to current experience with diagnosis based on newborn screening.[47] Concerns have been raised about patients with SCAD deficiency being mistakenly classified as having a metabolic disorder and that using this as a diagnostic endpoint could lead to inadequate research into the underlying reasons of any symptoms[11].

DIAGNOSIS

Clinicians examining a patient with a preliminary diagnosis of FAOD should be aware of potential pitfalls that can lead to misdiagnosis. Since the FAO pathway is not active when the patient is clinically stable and normoglycaemic, the accumulation of pathological intermediate metabolites will not be significant. To obtain the most useful information about the patient's metabolic status, samples should be collected during metabolic decompensation, for example, at the time of presentation to the emergency department. Samples should be collected as soon as possible after the patient's presentation, before biochemical stabilisation is achieved. With correction of hypoglycemia, abnormal levels of intermediate metabolites will also rapidly return to normal.

The investigation should begin with tests that identify which tissues are affected during the attack and indicate which approach should be taken. These tests include blood gas

analysis, plasma or serum electrolyte measurements, glucose, lactate, and ammonia levels, liver function tests, creatine kinase levels, and urine ketone measurements.

Due to defective FAO, ketone synthesis is impaired. Consequently, even in cases of hypoglycemia resulting from catabolic processes in these patients, urinary ketone levels remain abnormally low (hypoketotic hypoglycemia). In the urine organic acid analysis, an increase in medium-chain dicarboxylic acid levels is observed alongside low ketone levels. Ketone positivity may be present in the urine of patients with MCADD owing to the metabolism of acetyl-CoA, which is produced by the partial oxidation of long-chain fatty acids.

When samples are collected for routine laboratory tests, it is appropriate to also collect samples for metabolic disease diagnostic tests to be performed in the second stage. These include measurements of carnitine (total and free), acylcarnitines, free fatty acids, beta-hydroxybutyrate, and acetoacetate in plasma and serum. Findings that may be observed in plasma acylcarnitine and urine organic acid analyses of FAODs are summarised in Table 1.

It is generally assumed that an abnormal acylcarnitine profile reflects the intramitochondrial accumulation of acyl-CoAs and, as such, indicates the substrate of the deficient enzyme in vivo. The accumulating acyl-CoAs are exported from the mitochondria as acylcarnitines via CPT-II, carnitine acetyltransferase, and CACT. The molecular mechanism of acylcarnitine export across the cell membrane is unresolved.

Rapid confirmation of a particular suspected enzyme deficiency can be performed in lymphocytes, as these cells express all enzymes involved in FAO.

Mutations causing certain diseases have been identified in FAODs. A variety of methodologies have been developed to facilitate mutation analysis using diverse biological samples. Mutation screening can be performed on samples obtained from whole blood or newborn screening cards. The identification of disease-causing mutations through genetic analysis serves to confirm the biochemical diagnosis. Furthermore, in the context of disease forms characterised by a genotype-phenotype relationship, it can provide prognostic insights and inform treatment decisions. This information is of particular significance for genetic counselling and preimplantation genetics.

TREATMENT

The extent to which FAO occurs is primarily determined by the rate of lipolysis in adipose tissue. Preventing prolonged starvation and administering emergency treatment regimens during intercurrent infections reduce FAO. Even in the fed state, cardiac and skeletal muscles use long-chain fatty acids as an energy

Table 1. Laboratory findings in fatty acid oxidation disorders.

	Plasma				Urine	
	Carnitine		Acyl-carnitine	C_{8}-C_{18} FFA	Organic acids	Acyl-glycine
	Co	AC/Co				
Membrane bound enzymes						
Carnitine transporter defect	↓	N	↓	N	N	N
CPT-I deficiency	N/↑	N	N	N	N	N
CACT deficiency	N/↓	↑	+	N	N	N
CPT-II deficiency (neonatal)	N/↓	↑	+	N	N	N
CPT-II deficiency (late onset)	N/↓	↑	+	N	N	N
VLCAD deficiency	N/↓	↑	+	+	+ (acute)	N
ETF-DH (MADD)	N/↓	↑	+	+	+	+
TFP deficiency	N/↓	↑	+ (acute)	+	+ (acute)	N
Mitochondrial matrix enzymes						
MCAD deficiency	N/↓	↑	+	+	+ (acute)	+
SCAD deficiency	N/↓	↑	+	N	+ (acute)	+
ETF-A (MADD)	N/↓	↑	+	+	+	+
ETF-B (MADD)	N/↓	↑	+	+	+	+

AC, acyl-carnitines; CACT, carnitine acylcarnitine translocase; CPT-I, carnitine palmitoyltransferase-I; CPT-II, carnitine palmitoyltransferase-II; ETF-A, electron transfer flavoprotein α subunit; ETF-B, electron transfer flavoprotein β subunit; ETF-DH, electron transfer flavoprotein dehydrogenase; FFA, free fatty acid; MADD, multiple acyl-CoA dehydrogenase; MCAD, medium-chain acyl-CoA dehydrogenase; SCAD, short-chain acyl-CoA dehydrogenase; TFP, trifunctional protein; VLCAD, very long-chain acyl-CoA dehydrogenase.

source. To minimise this, diets containing low amounts of long-chain fatty acids are implemented. When FAOD is suspected, the primary goal is to provide sufficient glucose to prevent lipolysis in target tissues. The main principles of nutritional therapy are as follows: calorie intake in the form of carbohydrates should be provided at regular intervals to prevent both hypoglycemia and the mobilisation of long-chain fatty acids from stores. When the proportion of long-chain fatty acids in the diet is reduced, essential fatty acid supplementation should be provided to prevent deficiency.

For patients with long-chain FAO defects, high-carbohydrate diets are insufficient to ensure adequate caloric intake. To solve this issue, medium-chain triglycerides (MCTs) offer a significant amount of the energy in the diet.[2] Many patients with a defect in one of the long-chain-specific enzymes receive dietary long-chain triglyceride restriction and MCT supplementation, which, in theory, would limit the supply of long-chain fatty acids whose degradation is impaired and provide, as an alternative, a medium-chain fatty acid substrate that can bypass the enzymatic defect. The assumption that 8-, 10-, and 12-carbon fatty acids can enter the mitochondria independently of the carnitine cycle underlies the recommendation to use MCT in the diet. MCTs' well-established ketogenic properties should be beneficial in long-chain FAODs. However, it is unclear whether MCTs should be provided continuously, or only immediately before or during periods of elevated energy demand. In fact, research on *VLCAD* KO mice indicates that while long-term MCT administration caused tissue fat buildup, MCTs are advantageous before exercise.[48] Furthermore, MCT supplementation before exercise enhanced heart function and substrate oxidation in patients with long-chain FAODs.[49]

One theory is that catalytic intermediate leakage from the TCA cycle is the cause of the heart and muscular disease in FAODs.[50] This theory led to the production of triheptanoin, a novel MCT that produces both acetyl-CoA and anaplerotic propionyl-CoA when the heptanoate is oxidized. Ketone bodies like beta-hydroxybutyrate and betahydroxypentoate can be produced from heptanoate.[51] The liver produces ketone bodies, which are then released into the bloodstream and absorbed by various tissues where they can be utilized as TCA cycle substrates and intermediates.[52] Remarkably, a fasting-induced impairment in anaplerosis was validated by recent research in the *LCAD* KO mice, and patients with an FAOD showed clinical improvement after receiving triheptanoin.[50,53]

Although the main treatment for carnitine transporter insufficiency is oral l-carnitine supplementation, it also helps remove harmful metabolites and prevents carnitine shortage in other FAODs. Heart and skeletal muscle tissues contain about 98% of the body's carnitine.[54] Carnitine transporters mediate the uptake of orally administered carnitine into cardiac and skeletal muscle. A single oral dose of l-carnitine has a half-life of 60.3±15 minutes, and regular oral ingestion is necessary to maintain carnitine levels.[54] Although patients with CTD take carnitine supplements, their plasma carnitine levels increase but do not fully normalize. For people with CTD, high-dose carnitine supplementation (up to 200–250 mg/kg/day) is typically necessary. Tissue carnitine levels are not reflected in plasma levels during use of oral l-carnitine supplements. It has been demonstrated that people with CTD have reduced beta oxidation capacity during exercise, which is somewhat recovered by carnitine supplementation.[55] Regrettably, excessive doses of carnitine supplements cause sweat, urine, and breath to smell fishy.

Patients with the *ETF-DH* mutation who have late-onset type MADD typically response favorably to coenzyme Q_{10} and riboflavin.[56]

Carnitine supplementation is frequently used to treat secondary carnitine deficiency in patients with other FAODs. The use of carnitine has been controversial due to the link between acylcarnitines and ventricular fibrillation in a cat model of acute ischemia.[57] Studies on animals reveal both negative and positive effects of carnitine.[58] Studies on humans that are currently available have not demonstrated positive effects.[57]

Footnotes

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