

Understanding patient, caregiver, and healthcare provider perspectives of the management of long-chain fatty acid oxidation disorders

Eileen Sullivan Baker, Jennifer Botham, Tasia Rechisky, Evelyn Romano, Daniel Garcia and Susan A. Berry

Abstract: Long-chain fatty acid oxidation disorders (LC-FAODs) are a group of rare, inherited, metabolic disorders that can lead to a wide range of symptoms that predominantly affect organ systems with high energy needs, such as the heart, liver, skeletal muscle, and nervous system. Clinical management primarily consists of close attention to and monitoring of diet and activity and avoidance of prolonged fasting. In addition, patients and caregivers must be alert for signs of life-threatening metabolic decompensation. As a result, LC-FAODs can have significant and wide-ranging impacts on the lives of patients and their caregivers. This article describes the effects of LC-FAODs at different life stages and in the context of the North American healthcare system from the perspective of a group of patients, caregivers, and healthcare providers ($n=6$). We explain how challenges and needs change throughout life. Following an early diagnosis, an adjustment phase occurs during which caregivers may feel overwhelmed by their new roles and deeply concerned for their children's futures. As children grow, they become more aware of the differences between themselves and their peers, and with increasing independence comes more responsibility for managing their own condition. Major life events, such as new employment and moving house, pose challenges for people of all ages. In addition, it may be difficult to find and connect with qualified and experienced healthcare providers; navigate the health insurance system; and educate and align primary, specialist, and emergency care providers. We propose several strategies to improve the care of patients with LC-FAODs, such as educating local healthcare teams, improving trust between patients/caregivers and healthcare providers, and raising awareness of the challenges faced by patients and caregivers across the different life stages.

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Plain language summary

Living with long-chain fatty acid oxidation disorders from the point of view of patient, caregiver, and healthcare providers.

What is a long-chain fatty acid oxidation disorder?

- Long-chain fatty acid oxidation disorders (or LC-FAODs for short) are rare health conditions in which the body cannot use certain types of fats for energy.
- People with LC-FAODs may have many symptoms. The symptoms mainly affect the muscles, heart, nerves, and liver.

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- LC-FAODs are managed by closely watching what is eaten and when, and how much activity is done.
 - This can be very stressful.
 - Looking out for signs of serious health problems and working out which healthcare team to see and when can also be worrying.
- For this reason, LC-FAODs can have an impact on the mental health of people living with LC-FAODs and their caregivers.

What is this article about?

- We describe how LC-FAODs affect people at different times in their lives.
- We write from our point of view as patients, caregivers, and healthcare providers in the United States.
- We explain how challenges and needs change over time.
 - Initially, parents may find it hard to adjust to caring for a child with an LC-FAOD. They may also be very worried about their child.
 - As people grow older, they must learn to manage their condition on their own.
 - They also need to adjust to major life changes such as moving house and starting a new job.
- We also talk about how it can be hard to find doctors who know about LC-FAODs because the conditions are so rare.
- We suggest ways to improve care for people with LC-FAODs and their families, for example:
 - Getting healthcare teams to help each other learn about LC-FAODs by sharing knowledge with each other
 - Helping people learn about the challenges faced by people with LC-FAODs
 - Improving the trust between patients and healthcare providers.

Keywords: caregiver, long-chain fatty acid oxidation disorder, metabolic condition, patient

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Long-chain fatty acid oxidation disorders

Disease etiology, manifestations, and management

Long-chain fatty acid oxidation disorders (LC-FAODs) are a group of rare, inherited, autosomal recessive metabolic disorders caused by pathogenic variants in genes encoding enzymes and transport proteins involved in fatty acid metabolism in the mitochondria.¹⁻³ There are several LC-FAOD types; each is defined by the specific enzyme or transport protein that is affected.^{2,4} Clinical manifestations vary widely; common symptoms across all LC-FAODs include hypoketotic hypoglycemia, hepatic dysfunction,

cardiomyopathy, skeletal myopathy, rhabdomyolysis, and sudden death.^{1,2} Phenotypes also vary and range from acute critical illness in infancy to exercise intolerance in adulthood, and there is no standard disease progression.¹

Clinical management of LC-FAODs focuses largely on dietary restriction of long-chain fats, avoidance of prolonged fasting, supplementation with medium-chain triglycerides, a moderate increase in carbohydrate intake, and, where accessible, treatment with the purified 7-carbon chain triglyceride, triheptanoin.¹ Early diagnosis via newborn screening programs followed by rapid dietary modification improves outcomes for many

individuals,⁵⁻⁷ but many still experience acute life-threatening events and/or long-term neuro-pathic symptoms.⁸

Impact on patients and caregivers

These acute events and ongoing symptoms, coupled with complex and time-consuming dietary modifications, have significant impacts on patients and their caregivers. For example, some caregivers report via surveys and interviews that they have had to leave their jobs to accommodate the many lifestyle changes required by their children,^{9,10} such as managing exposure to triggers of acute episodic crises and monitoring diet and weight, periods of fasting and associated energy levels, and signs and symptoms of decompensation.¹¹ The need to prevent fasting by feeding at regular and frequent intervals can present particular challenges, especially in the early days after diagnosis.³ These ongoing and significant challenges affect many aspects of patient and caregiver quality of life, including social and physical functioning, interpersonal relationships, work, schooling, emotional and psychological well-being, daily activities, and sleep.^{9,11,12}

In addition, individuals with LC-FAODs require multiple and frequent interactions with healthcare providers from various disciplines, with some parents of children with inherited metabolic disorders requiring detailed spreadsheets to manage their child's many appointments.¹⁰ Caregiver experience with these healthcare providers varies; although experience with metabolic disease specialists is generally positive, many report negative experiences with healthcare providers who are unfamiliar with the child and/or the condition.¹⁰

Objective and methods

Although the impact of LC-FAODs on quality of life, work, school, physical activity, and social participation for patients and caregivers has been reported previously,^{9,11} the impact of LC-FAODs at specific life stages and in the context of the healthcare system has not yet been explored. To gain insights into these issues, we present our perspectives and experiences. We are a diverse group of people (all from different locations and care centers around North America) affected by, or caring for individuals affected by, LC-FAODs

(one patient, three caregivers, one metabolic dietician, and one medical genetics physician).

Our perspectives were compiled via ongoing, open, unstructured, verbal, and written discussions. Initial topics were proposed based on insights gathered from patient advocacy teams in the community; these topics were discussed at formal virtual meetings (where minutes were taken) and follow-up emails. Authors, who are all experts on this journey aspect of the disease, selected the most important topics that they aligned on, and the themes presented here developed organically through the virtual and online conversations. The themes are reported with the goal of educating physicians and other members of the healthcare team about the everyday impact of LC-FAODs on patients and caregivers. In particular, we highlight our experiences navigating the healthcare systems in the United States (US) and Canada to identify key challenges and propose new ways of supporting people affected by LC-FAODs.

Perspectives on the management of LC-FAODs

Evolution of patient needs and caregiver roles over time

In our experience, and as reported by others in the literature,^{9,11} LC-FAODs impact many dimensions of patients' and caregivers' lives. The key domains identified during our discussions were mental and emotional wellness, finances, social interactions and relationships, caregiver burden, meal planning, physical stamina and endurance, school and careers, and travel. As patients and caregivers, we act as informed experts, advocates, and educators, and these roles evolve throughout life (Figure 1).

The period following early diagnosis. Receiving an LC-FAOD diagnosis soon after birth can be highly emotional for parents, and they may be overwhelmed by their new role. Parents must learn about the condition and underlying metabolic pathways and change their previously established routines, including those for feeding and exercise. Caregivers may worry about metabolic decompensation events and uncertainties about the progression of the disease.

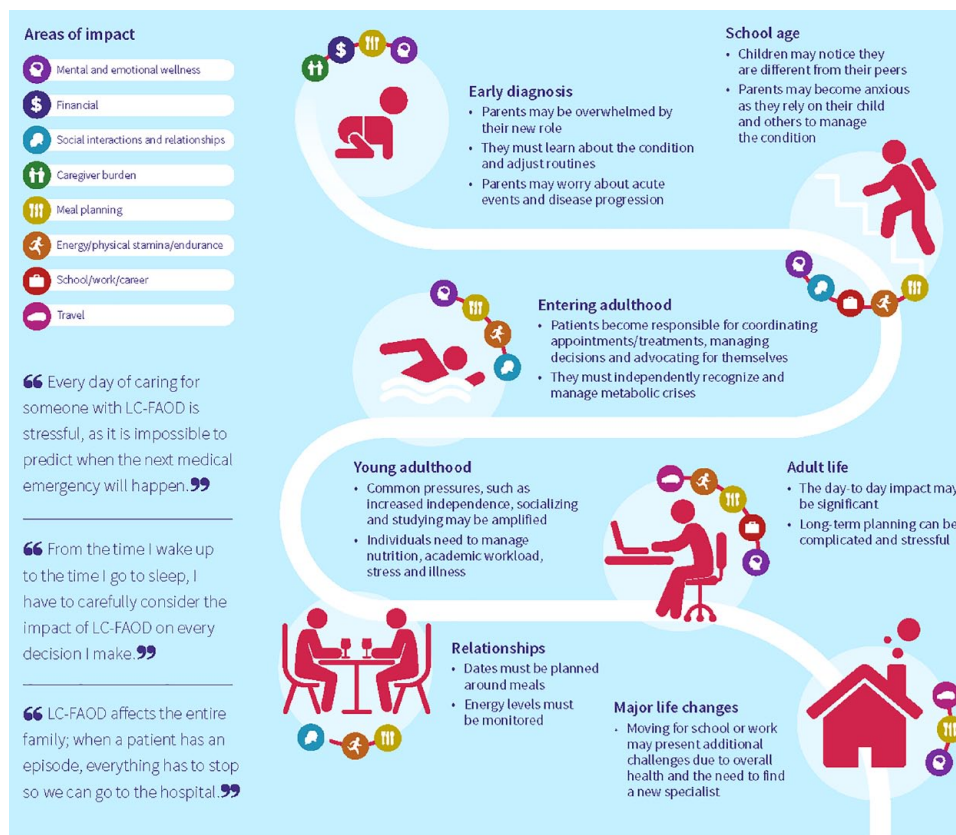


Figure 1. Impact of long-chain fatty acid oxidation disorders (LC-FAODs) on patients and caregivers at different life stages.

Given there is no standard approach to managing LC-FAODs, we have found identifying useful information and connecting with support networks helpful. This can enable caregivers and patients to take on the role of the LC-FAOD expert, with the knowledge to discern fact from opinion in online communities and stay abreast of the latest research. Staying up to date with research is a task that can be particularly important if the patient’s healthcare team does not have a special interest or extensive expertise in LC-FAODs. Alternatively, parents may choose to learn from the management protocols that other families have established and highlights the importance of sharing experiences.

School age. As young patients grow up, their social circles expand, and they may begin to notice that they differ from their peers in terms of meal planning, physical activities/abilities, and stamina. As parents and caregivers, we may experience increasing anxiety as our children reach school age because we must rely on the vigilance

of others and the maturity of our children to manage their conditions.

Entering adulthood. As patients grow into adulthood, they become more responsible for managing their own conditions. They must be their own advocates, coordinate their appointments and treatments, manage decisions among their healthcare teams, learn to recognize the signs of metabolic crises, and know what actions to take. Students with LC-FAODs face additional challenges as they move from managing just their daily needs (sleep, hydration, and food) to the more rigorous learning required in an academic setting and the changing energy needs when exams and larger projects are due. These needs can prevent some individuals from pursuing educational opportunities if robust insurance options that would cover their medical expenses and medications are not available.

To better support individuals during this time, the medical community should be aware of this

mental strain; patients may become vague or confused if they are receiving insufficient fuel from food or hydration, and they may fall behind or be perceived as being of lower intelligence or incapable of the work required. This can lead to a sense of guilt if they are unable to keep up at school, in social settings, or at work, and these feelings may persist throughout their lives.

Young adulthood. In our experience, the pressures common to all young people, such as increased independence, social opportunities, and student pressures and responsibilities, are amplified in those with LC-FAODs. Patients must manage their own nutrition, meals, stress, exertion, rest, academic workload, and illness, while also informing teachers and classmates about their conditions. Even dating can be challenging as dates must be carefully planned around mealtimes, and energy levels must be monitored to prevent metabolic decompensation events.

As caregivers, it can be difficult to know how to adequately equip our children for the journey into adulthood and beyond; care coordinators or similar healthcare providers can provide much-needed guidance but are not always available.

Moving through adult life stages. Long-term planning of family, careers, retirement, and similar milestones may be complicated by unknowns, such as research gaps and a lack of long-term support, which may lead to anxiety and depression. In our experience, the mental energy and time required to manage an illness so heavily influenced by diet, stress, and activity is substantial and may cause longer-term mental health challenges. The mental load carried by adult patients with LC-FAODs may be compounded by the challenges of moving for school or work, which may be restricted by overall health and complicated by the requirement to find a new specialist in an area where options may be limited. In addition, hospital stays can become more difficult to arrange as adults, shifting yet more care responsibilities to patients.

Navigating the healthcare system

As individuals with LC-FAODs and their caregivers, we must, by necessity, interact regularly and widely with the healthcare system. Every step of that journey may be challenging, from finding a suitable healthcare team, navigating the health

insurance landscape, educating multiple and diverse healthcare providers about LC-FAODs, and ensuring management goals align to sharing knowledge with those who have limited or no experience with the condition. We describe our experiences in navigating that journey and provide possible solutions to key barriers to accessible and comprehensive care.

Connecting with a suitable healthcare team. In our experience, finding healthcare providers with specific expertise may be challenging. Expert geneticists and metabolic dietitians often reside at academic institutions and may be difficult to find and access. Further, many specialists only practice in children's hospitals, making the transition from pediatric to adult care challenging and particularly problematic when an individual is no longer considered a child but requires hospitalization and care from a specialist practicing in the pediatric setting. As there may be even fewer LC-FAOD specialists in adult hospitals, finding an adult care team can be extremely difficult.

In some cases, a lack of suitable options can force families to relocate; patients who need to move may also be limited by the need to reside near experienced healthcare providers. We have found that physicians can help patients and their caregivers find more knowledgeable healthcare providers closer to home or work with remote care providers to lessen the burden.

Navigating health insurance. In many countries, patients and caregivers must also navigate the insurance coverage landscape. Of note, we have found that many insurance companies do not cover conditions with medication that might be considered food supplements or novel treatment. Several appeals may be needed, and obtaining proper care may be time-consuming. Further, healthcare providers can find it challenging to ensure authorization and coverage when ordering tests and following up with insurance providers.

Educating and aligning healthcare providers. Effective patient management requires an informed metabolic care team; however, there may be times, such as in crisis situations, when the specialist team may not be available. On some occasions, it has fallen to patients and caregivers to act as experts and inform unfamiliar healthcare providers (e.g. with an emergency protocol), source different healthcare providers, and/or manage healthcare

records. In particular, we have found that nonspecialists do not always understand nutritional needs, such as intravenous hydration and calorie sources, and their lack of knowledge about specific LC-FAODs may mean that they are unable to recognize severe symptoms.

Sometimes, as patients and caregivers, we may need to serve as intermediaries to align the multidisciplinary team. However, when a person with an LC-FAOD is admitted to the hospital with an acute illness (related to LC-FAODs or otherwise), we may not have the capacity to guide the healthcare providers and hospital staff ourselves. In this case, we believe that existing relationships between emergency room staff and healthcare providers/metabolic specialists familiar with LC-FAODs are invaluable, and where possible, we recommend establishing these connections via intrainstitutional links before an emergency situation occurs. There is a clear need within the medical community to break down communication barriers and encourage providers to be receptive to new information from more educated peers inside and outside of their institutions.

When pre-existing relationships between acute care teams and experienced care providers and metabolic specialists do not exist, primary physicians and specialists may need to act as advocates to guide treatment. On occasion, we have seen emergency treatment letters or plans provided by specialists ignored, with resistance from emergency room staff when we ask for these to be followed. This situation may be avoided or lessened if the primary healthcare provider takes the lead in establishing this knowledge base and educating, raising awareness, and building relationships prior to an acute event. Escalation to hospital management, emergency department heads, and individual providers may be necessary if existing protocols and advice are not accepted.

Knowledge sharing by patients and caregivers. Although as patients we may be more informed than our healthcare providers, we may experience resistance when suggesting tests or treatments. When healthcare providers are willing to listen and are receptive to new information from informed patients and caregivers, the burden is lessened for all people involved (patients, caregivers, and healthcare providers). Further, as patients and caregivers, our role as educators usually

extends beyond the physician and care team – we also need to educate school staff, extra-curricular activity staff, playmate parents, colleagues, peers, partners, and workplace managers and supervisors.

Improving the care of patients with LC-FAODs

Underpinned by our collective experiences as patients, caregivers, and healthcare providers providing care to individuals with LC-FAODs, and based on conversations with others in similar situations, we have developed a series of recommendations to improve the care of individuals with LC-FAODs (Figure 2). At the core is improving awareness and education about LC-FAODs among patients, caregivers, and healthcare providers, which we believe will improve patient care and enhance connections between and within the LC-FAOD community and the healthcare providers caring for them, including nonspecialists. In particular, education on acute management of the disease is important for emergency situations, not only for healthcare providers but also educating families on how to communicate quickly and effectively about the disease during this time.

Limitations

A limitation of our work is that it represents the experiences of a small group of patients, caregivers, and healthcare providers living and working in North America. Given that our study group was only six people, our breadth of experience is relatively narrow and may have influenced the outcomes. This is not an exhaustive survey, and nor does it capture experiences in different countries and healthcare systems. Nevertheless, the challenges and unmet needs we have identified align with previous studies in LC-FAODs and other genetic metabolic conditions.^{9–12}

Conclusion

Our experiences and those of others illustrate the significant impacts LC-FAODs can have on all facets of life for patients and caregivers, particularly on physical and mental health. As patients and caregivers, we experience considerable anxiety and stress, ranging from fear of what the future may hold to concern about the social challenges faced by our young children with their significant dietary and physical limitations. We must

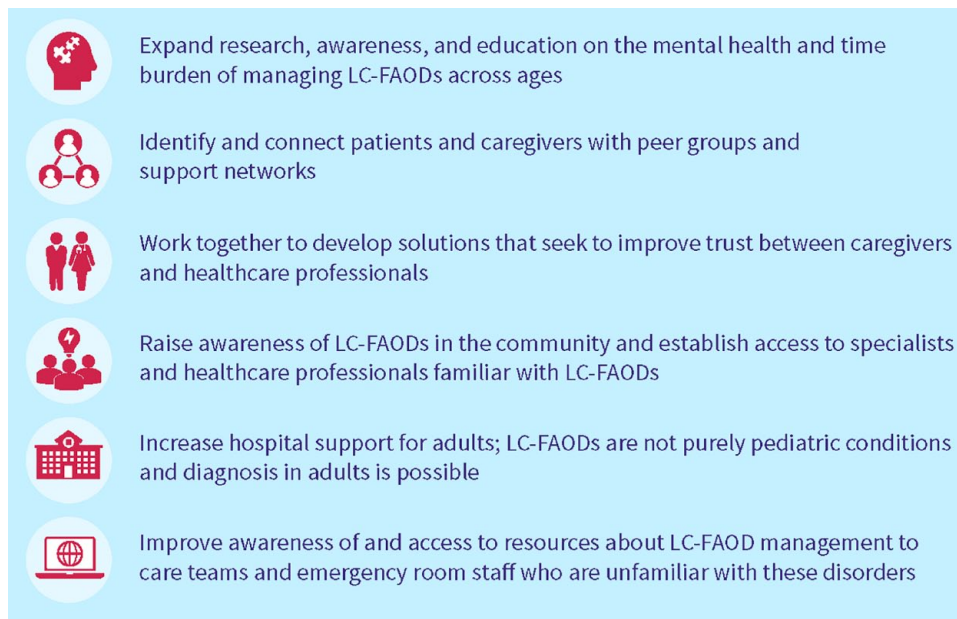


Figure 2. Recommendations for improving the care of individuals with long-chain fatty acid oxidation disorders (LC-FAODs).

be constantly vigilant for potentially life-threatening metabolic decompensations, and this adds to the already significant mental load we carry. Further, because the nature and severity of LC-FAOD symptoms vary widely, it can be challenging to find advice and support when managing rarer symptoms, even within the LC-FAOD community.

There are many opportunities within the healthcare system to improve the lives of those living with LC-FAODs, including provision of more specialized metabolic clinics and improved coordination of care, especially in hospitals. Increased awareness among healthcare providers is a significant unmet need, with research suggesting that healthcare providers may not even be aware of the full range of symptoms experienced by individuals with LC-FAODs.

Overall, our discussions and those with our peers highlight the significant challenges patients with LC-FAODs and their caregivers face throughout life as well as navigating the US and Canadian healthcare systems. LC-FAODs impact more than the energy metabolism of patients; they affect nearly every decision patients and caregivers make in life and require management of chronic symptoms and daily struggles, as well as

constant vigilance to minimize acute, potentially life-threatening metabolic decompensations. The burden of navigating the healthcare system adds to these challenges, a burden that has been under-recognized to date. We believe that increased willingness of healthcare providers and emergency staff to learn and communicate openly with patients, caregivers, and other healthcare providers can help improve LC-FAOD management and enhance quality of life for patients and their caregivers.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Eileen Sullivan Baker: Conceptualization, Writing – review & editing.

Jennifer Botham: Conceptualization, Writing – review & editing.

Tasia Rechinsky: Conceptualization, Writing – review & editing.

Evelyn Romano: Conceptualization, Writing – review & editing.

Daniel Garcia: Conceptualization, Writing – review & editing.

Susan A. Berry: Conceptualization, Writing – review & editing.

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Competing interests

E.S.B., J.B., T.S., and E.R. declare no conflicts of interest. D.G. is an employee and shareholder of Ultragenyx Pharmaceutical, Inc. S.A.B. declares no conflicts of interest.

Availability of data and materials

Not applicable.

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