

# Nutrition and Mitochondrial Fatty Acid Oxidation Defects

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## INTRODUCTION

Three forms of energy (fuel) are used by the body: glucose, fatty acids and ketone bodies. Glucose, after eating and until its storage form (glycogen) (gly-co-gen) is used up, is the major source of fuel for all of the body except heart muscle. Breads, cereals, fruits, milk, pastas, sugar and root vegetables furnish most of the carbohydrate used to make glucose. Carbohydrate supplies from 45% to 60% of fuel (measured in units called Calories) in the American diet. Some 6% of liver and 1% of muscle are glycogen, the storage form of glucose. Liver glycogen helps keep blood glucose concentration in the normal range while muscle glycogen supplies fuel to muscle. The liver of an adult has 12 to 18 hours of glycogen while an infant or child's liver may become glycogen depleted in much less time.

Some amino acids (building blocks of protein) obtained from food protein and body protein may be used by the body to make glucose after glycogen stores are depleted. This may occur after fasting; during illness with fever, vomiting, diarrhea or poor appetite or following injury. Protein sources are cheese, eggs, meat, milk, poultry, seafood and dried beans and peas. Normally 8% to 15% of Calories are provided by protein.

Fatty acids, obtained from food fat, supply about 38% of Calories in the American diet. The breast-fed baby gets about 55% of its energy as fat. Milk, butter, cheese, cream, margarines, meat, oils, poultry, and seafoods supply fat. Fatty acids can be short, medium, long and very long chain. Only two of the long chain fatty acids are essential -linoleic and linolenic acids. The remaining fatty acids help supply energy to infants and children whose stomachs are not large enough to hold all the protein and carbohydrate required to fill all their energy needs. Fatty acids supply over two times the amount of fuel as the same weight of carbohydrate and protein. **Fatty acids are the main source of energy for the heart at all times. During fasting and any time liver and muscle glycogen is depleted, fatty acids become the main fuel for the entire body.**

Fatty acids are also used to make ketone bodies, an energy source for the brain when glycogen stores are depleted. Other body tissues and organs also use ketone bodies for fuel, as needed. About 25 enzymes and carrier proteins help in this process. Any of these enzymes or carriers may be deficient and cause a mitochondrial fatty acid oxidation defect (FAOD). Mitochondria are compartments within cells that contain the enzymes that change fatty acids to the form of fuel required by the body. Thus, they are called the powerhouses of the cells.

## MITOCHONDRIAL FATTY ACID OXIDATION DEFECTS

In order for fatty acids to be used for fuel, they must first enter cells from the blood. This is accomplished by carriers. Although now in the cell, the fatty acid must enter the mitochondria. This step requires that the long chain fatty acids be attached to a hitch called coenzyme A (CoA) by enzymes named synthetases (sin-the-tases). The fatty acid is now renamed acyl-CoA (a-sil-CoA). Pantothenic acid is part of CoA.

Several uses may be made of the acyl-CoAs but we will only discuss what happens to them when all the body's glycogen has been used. The acyl groups must pass through the walls of the mitochondria and to do so must be fastened to carnitine. Before attachment to carnitine can occur, the CoA is removed. The removal of CoA and connection of carnitine are carried out by the enzyme CPT I (carnitine-palmitoyl transferase) to form acyl-carnitine. The CoA is now free to be used for other tasks as well as to be fastened to other fatty acids. The acyl- carnitine is carried across the mitochondrial wall by carriers (translocases).

Now in the powerhouses of the cells, the carnitine is removed from the acyl group and a new CoA is fastened. The carnitine is moved out of the mitochondria to be reused. The enzymes that carry out these steps are called CPT II. Four different enzymes (dehydrogenases) now act on acyl-CoA groups of different chain lengths (short, medium, long, and very long) to form compounds (electrons). Enzymes carry these electrons to a system of other enzymes that changes them to the special form of fuel used by the body. One

group of enzymes requires riboflavin (vitamin B2) and others require niacin to help them work. Defects have been found in all the carriers and enzymes needed to help the body use fatty acids for fuel. One disorder resulting from defects in this system is called glutaricaciduria type II.

### **CLINICAL SYMPTOM**

Inability to use fatty acids for fuel requires changes in the diet to prevent symptoms that may lead to death. Low or very low blood glucose concentrations brought about by fasting, injury, infection or other stress may occur in patients with an FAOD. Some of the other most common clinical features of the mitochondrial FAODs are given below:

| <b>FEATURE</b>  | <b>DEFECT/DISORDER</b>  |
|---|---|
| Acidosis, metabolic   | Glutaricaciduria type II  |
| Acute liver failure during pregnancy  | CPT I; translocases; very long, long, medium, short chain FAODs; glutaricaciduria type II |
| Disorders of heart and muscle function  | CPT II; translocases; very long chain FAODs; glutaricaciduria type II                     |
| Elevated blood ammonia concentrations   | Very long, medium and short chain FAODs; CPT I  |
| Muscle loss with excretion of a compound similar to hemoglobin, brought on by exercise (rhabdomyolysis)(rab-doe-my-o-lysis) | CPT II; very long, long and short chain FAODs   |
| Failure to thrive   | Medium and short chain FAODs  |
| Fat stores in muscle including heart  | Glutaricaciduria type II  |
| Malformations of brain and kidney   | CPT II, glutaricaciduria type II  |
| Severe liver disease  | CPT I; CPT II; translocases; very long and medium chain FAODs                             |

### **TREATMENT**

Several causes for the symptoms seen in patients with FAODs have been suggested. Some physicians suggest that the acyl-Co A groups are toxic when made in large amounts as during fasting and other stresses. Others theorize that free CoA and carnitine may not be present in adequate amounts during stress to carry out their other functions. Increased blood ammonia concentrations, low blood glucose concentrations, and decreased ketone body formation have also been suggested as causes for the symptoms.

Because of the differences of opinions as to the causes of symptoms, treatment varies. Also, therapy differs somewhat during an acute illness from that given during long term care. A metabolic physician should examine the ill patient and prescribe the appropriate therapy. If the patient does not live near a metabolic clinical center, the metabolic physician and dietitian will prepare "sick-day" directions for the family/patient to carry with them at all times.

The approaches or strategies used in long-term treatment are given in the table below:

| <b>STRATEGY OR NUTRIENT</b>   | <b>ENZYME DEFECT</b>   |
|---|--|
| Avoid fasting   | All FAODs. All physicians agree on this strategy.  |
| L-carnitine. Administer in amounts to maintain normal plasma free carnitine.  | All FAODs. Not all physicians agree on this strategy.  |
| Restrict fat to about 40% of Calories if one-half the fat is supplied by MCTs (medium chain triglycerides)  | Very long and long chain FAODs. Not all physicians restrict fat.   |
| Restrict fat to 30% or less of Calories   | Medium and short chain FAODs. MCTs MUST NOT be used with these enzyme defects. Not all physicians restrict fat.  |
| Supply required linoleic acid-3% of total Calorie intake.   | All FAODs. Deficiency has been reported with severe fat restriction in FAODs.  |
| Supply 1% of total Calories as linolenic acid   | All FAODs.   |
| Protein to supply 10% to 15% of Calories  | All FAODs except glutaricaciduria type II in which protein may require restriction.  |
| Carbohydrate to supply energy (Calories) not provided by fat and protein. Uncooked cornstarch, after 8-9 months of age, may be used to give some of the carbohydrate Calories | All FAODs.   |
| Riboflavin (vitamin B2), 120-200 mg daily, by mouth, with food. Administer in 30 mg doses for best absorption.  | Try with glutaricacidura type II. May or may not help. Try with multiple acyl-CoA dehydrogenase deficiency. Improvement in some patients with short chain FAODs. |
| Triheptanoic acid   | Undergoing clinical trials in very long, long and short chain FAODs, CPT I, CPT II and translocases. Not yet approved by Food and Drug Administration for use.   |
| Ceatine monohydrate   | Very long and long chain FAODs. Improved muscle function in a few patients.  |

Sources of linoleic and linolenic acids include canola, walnut, soybean and wheat germ oils. Once a container of these oils is opened, it should be recapped and refrigerated between use to prevent spoilage.

### **OUTCOMES OF TREATED PATIENTS**

Outcomes of patients with FAODs is variable since newborn screening and early therapy have only recently begun. No large-scale clinical trials have been conducted to determine the best approaches to

therapy. However, a few case studies and anecdotal reports suggest that outcomes may be excellent with newborn screening and therapy begun in the newborn period.

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[Please note (from DLG): With new research, there are some alternative nutritional approaches available so be sure to discuss the various options with your FOD specialist and metabolic nutritionist.]