TEMPLE

Tools Enabling Metabolic Parents LEarning

Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency

Introductory information

Written by:
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Reviewed & Revised for North America
by: S. van Calcar

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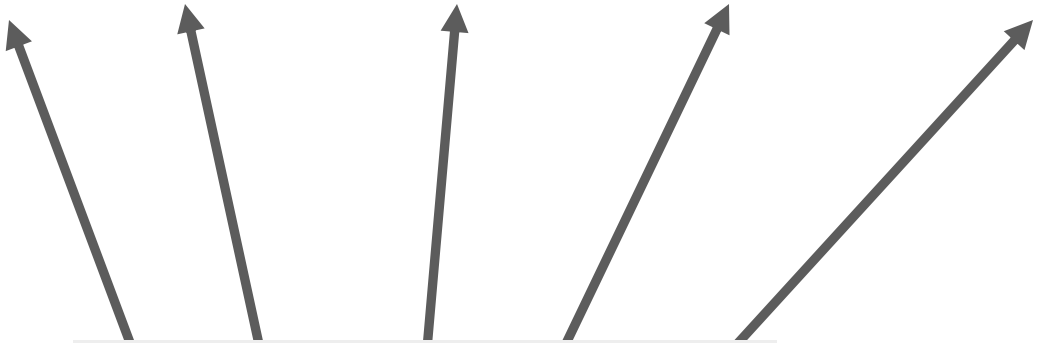
Long-chain L-3-hydroxyacyl-CoA dehydrogenase



LCHAD deficiency

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Mitochondrial trifunctional protein deficiency

Abbreviations: TFP or MTP Deficiency

Mitochondrial trifunctional protein deficiency is a special form of LCHAD deficiency.

TFP deficiency includes deficits in the activity of the LCHAD enzyme and of two other enzymes. The disease is far less common than deficiency of only the LCHAD enzyme. The symptoms and the treatment of TFP deficiency are similar to those of LCHAD deficiency. The inheritance mode of TFP deficiency is exactly the same as for the LCHAD deficiency.

Thus, the following information on LCHAD deficiency also applies to TFP deficiency.

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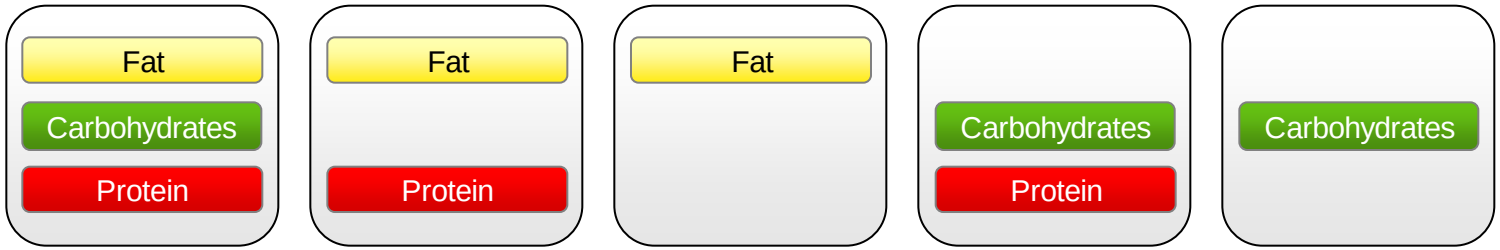
Food – Components of a typical diet

Natural Food



eg. milk, yogurt, nuts

eg. meat, poultry, fish, eggs, cheese

eg. oil, butter, margarine

eg. fruit, vegetables, cereals, rice, pasta

eg. sugar, lemonade

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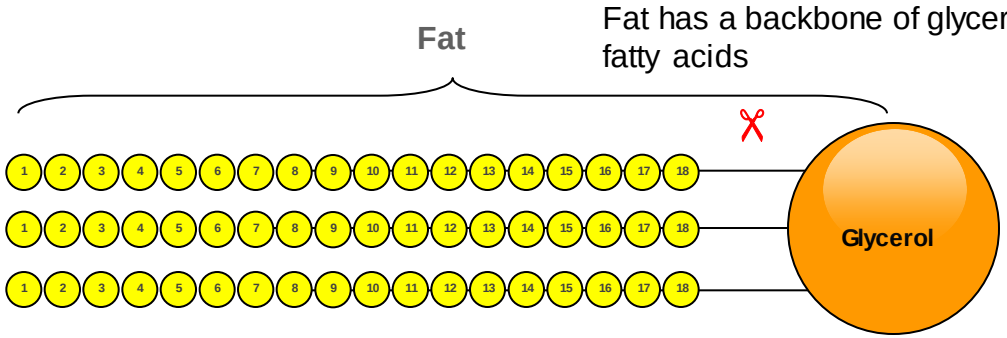
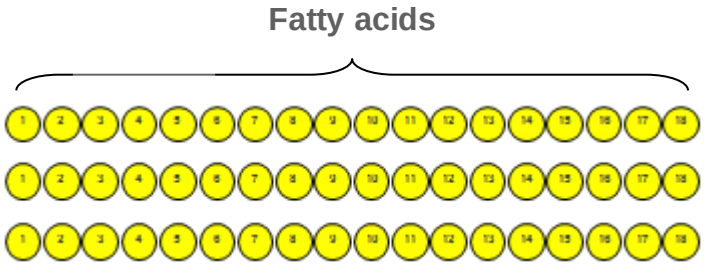
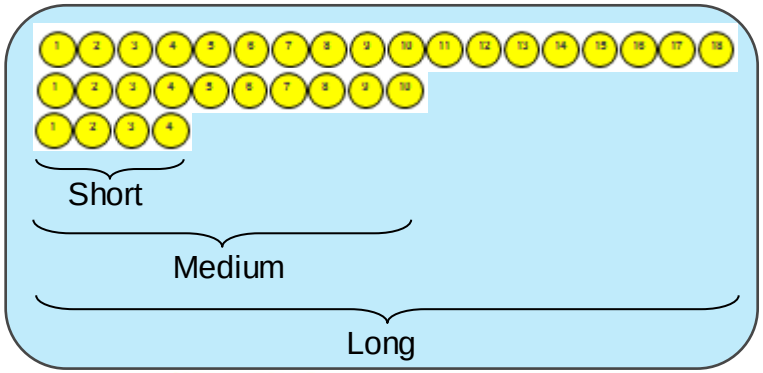
Fat vs Fatty Acids



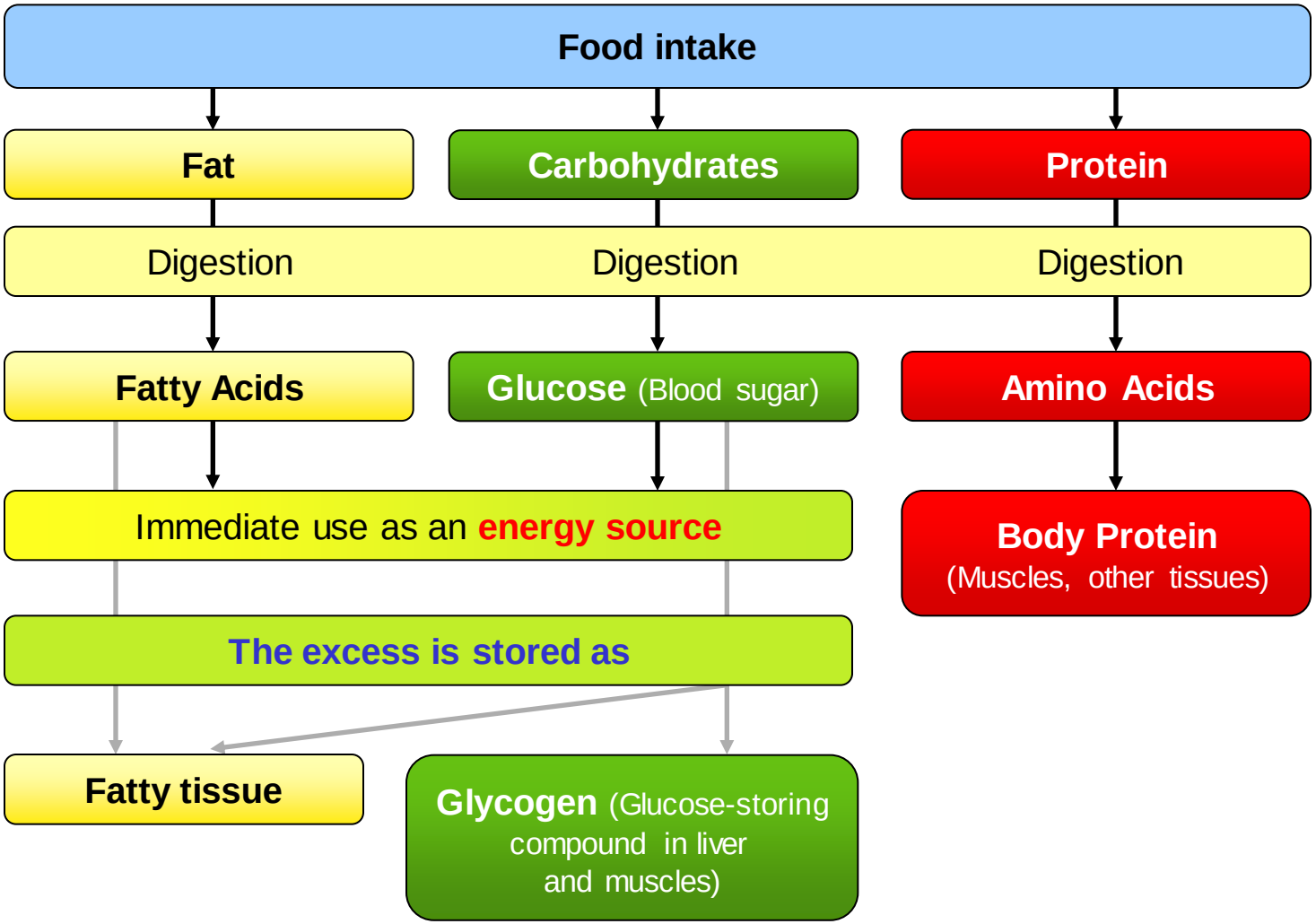
Fatty acids are made from chains of carbon atoms. There are different lengths of fatty acids; short-chain, medium-chain, and long-chain.





Long-chain fatty acids	> 12	carbon atoms
Medium-chain fatty acids	6-12	carbon atoms
Short-chain fatty acids	< 6	carbon atoms

How the body uses these nutrients



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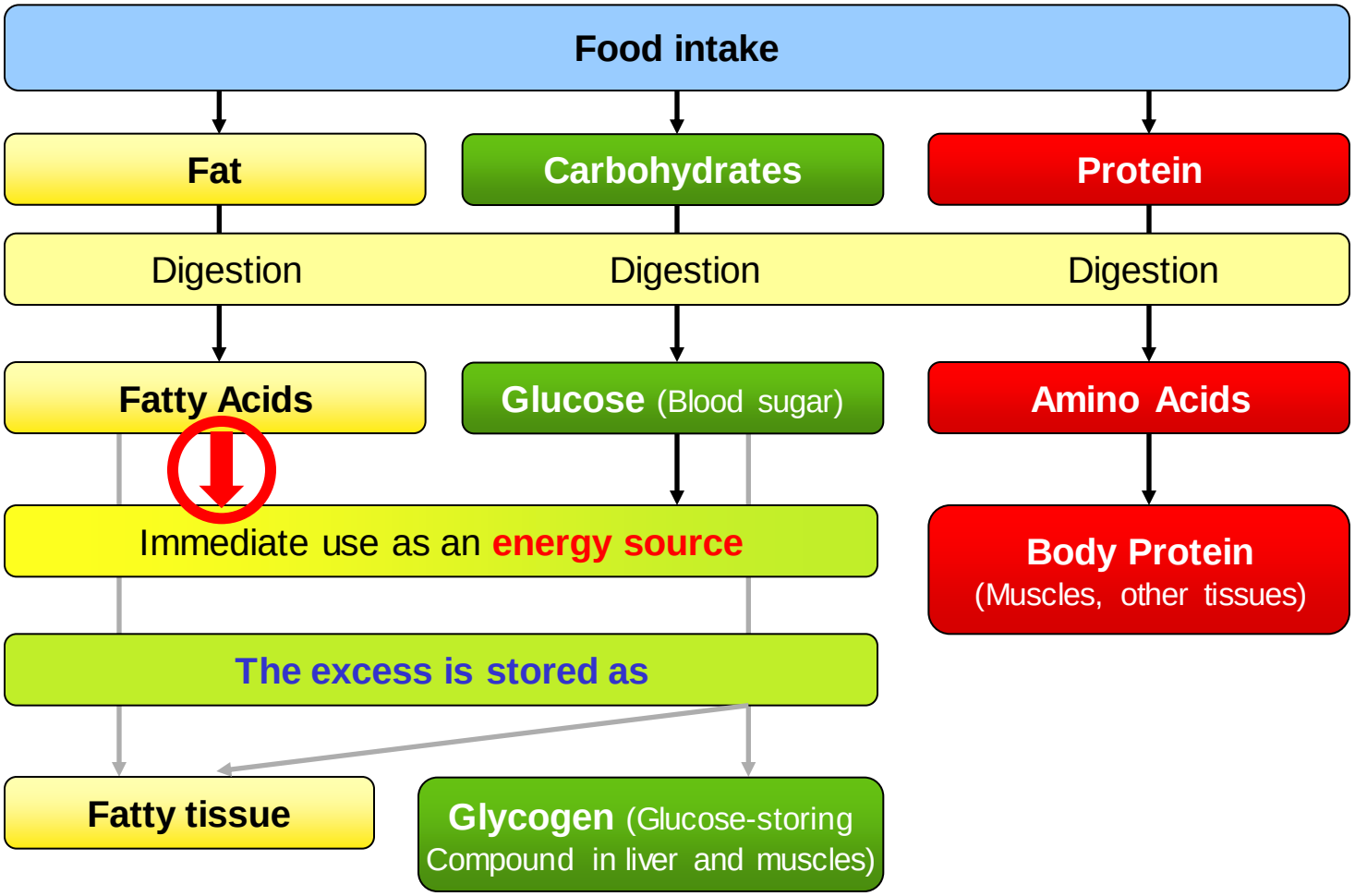
In LCHAD deficiency, there is a problem using some fatty acids



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Enzymes

Enzymes are proteins that facilitate various chemical reactions in the body. They are involved in the biosynthesis (anabolism) and the degradation (catabolism) of all the substances in the body. This is called **metabolism**.

Acyl-CoA dehydrogenases are enzymes that are required to break down fatty acids. The enzyme LCHAD (**l**ong-**c**hain 3-**h**ydroxy**a**cyl-CoA **d**ehydrogenase) breaks down "long-chain" fatty acids.

In LCHAD deficiency the activity of the LCHAD enzyme is greatly reduced.

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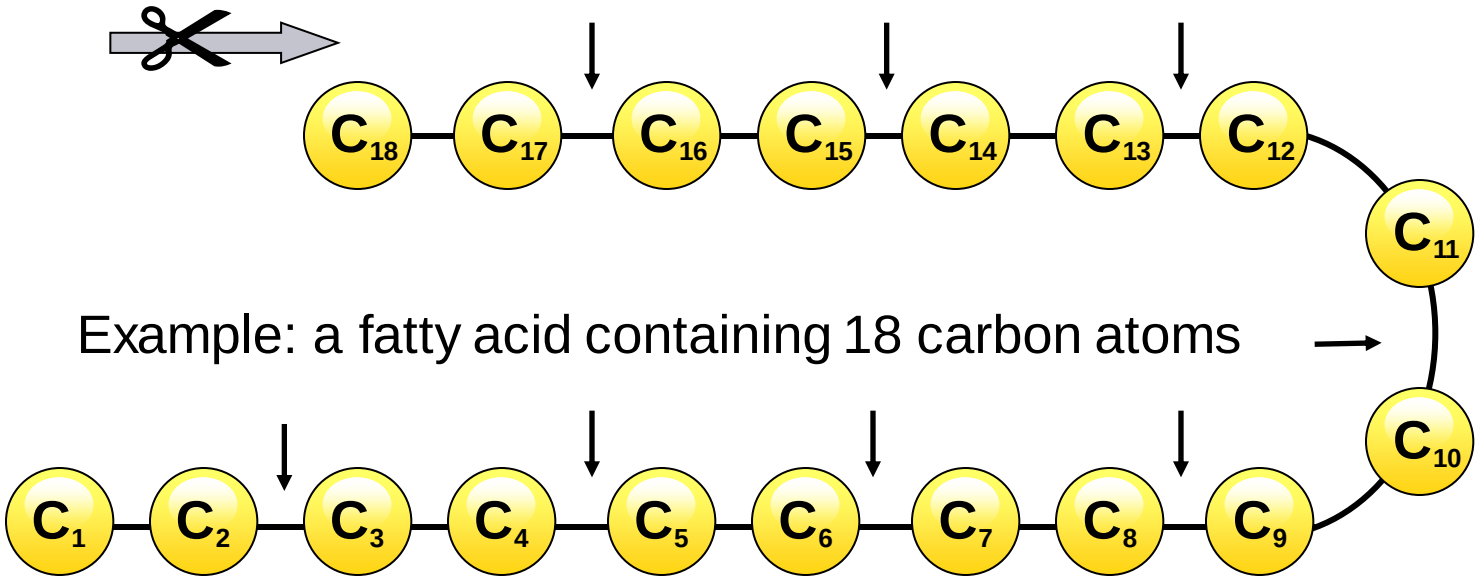
Fatty Acids

Consist of chains of carbon (=C) atoms



Example: a fatty acid containing 18 carbon atoms

Long-chain fatty acids:	> 12	carbon atoms
Medium-chain fatty acids:	6-12	carbon atoms
Short-chain fatty acids:	< 6	carbon atoms

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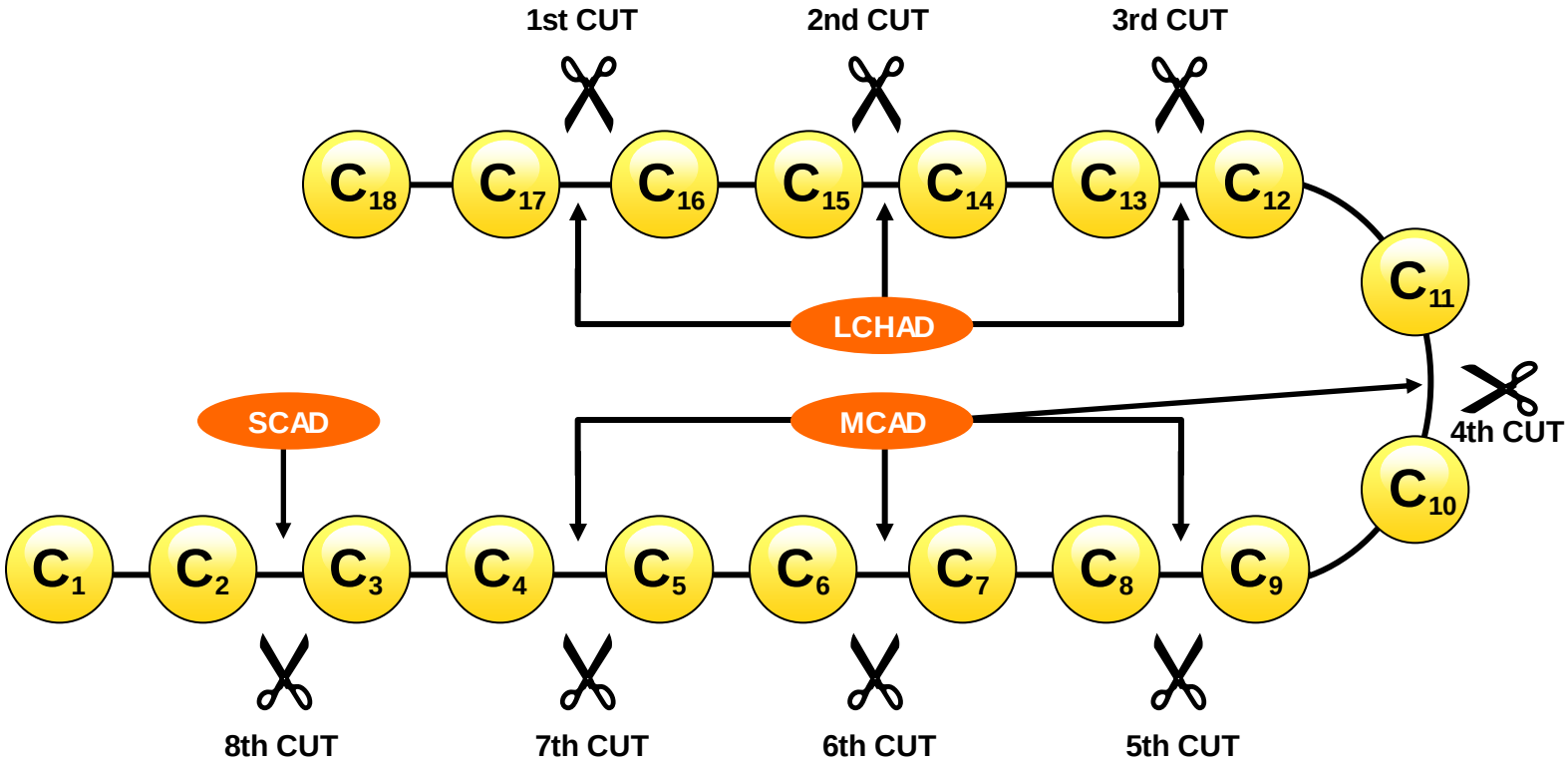
How enzymes break down a fatty acid

3 enzymes are needed for this process:

The enzyme LCHAD starts, the enzyme MCAD continues, the enzyme SCAD finishes



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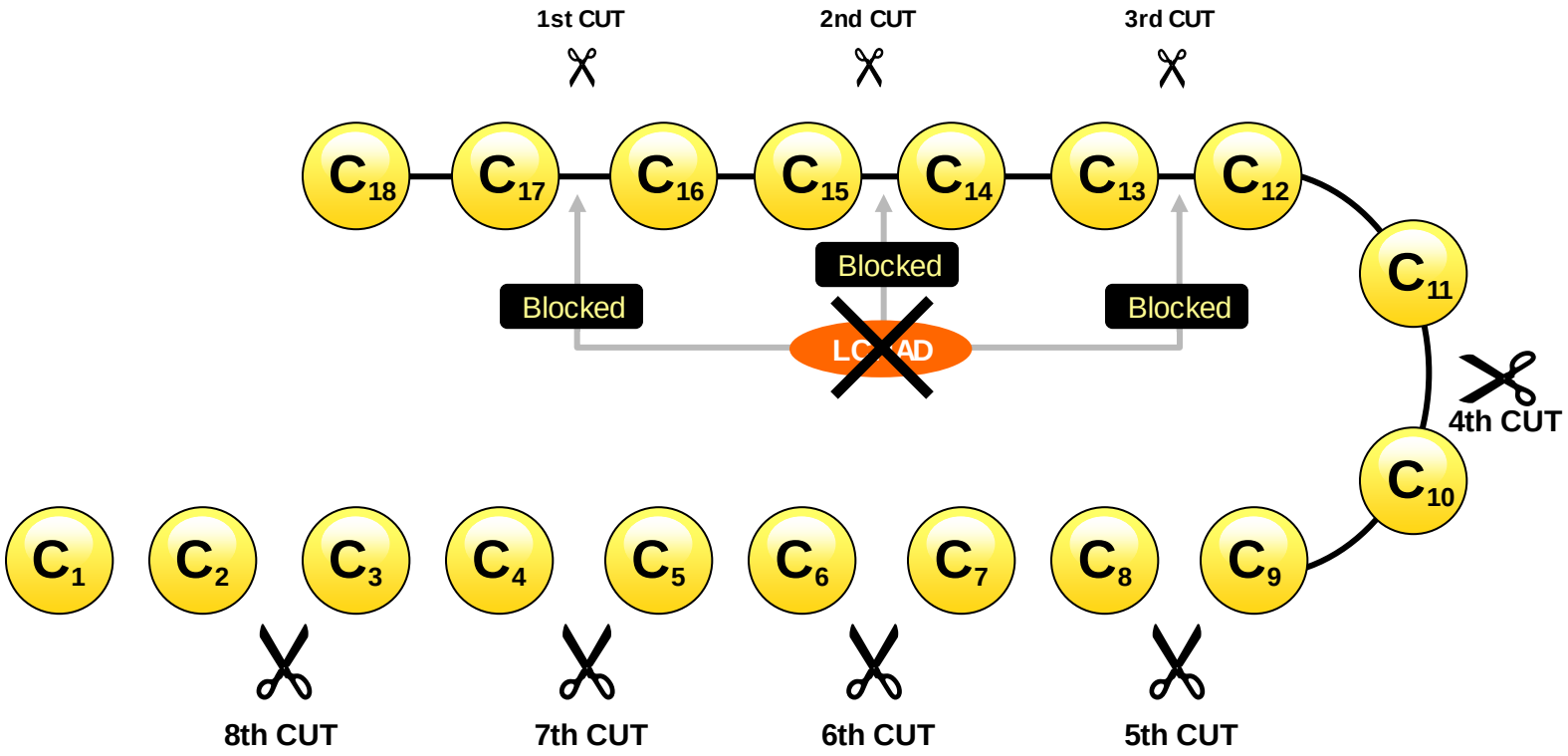
In LCHAD deficiency, long-chain fatty acids can not be broken down

The chain of carbon molecules in long-chain fatty acids cannot be broken down



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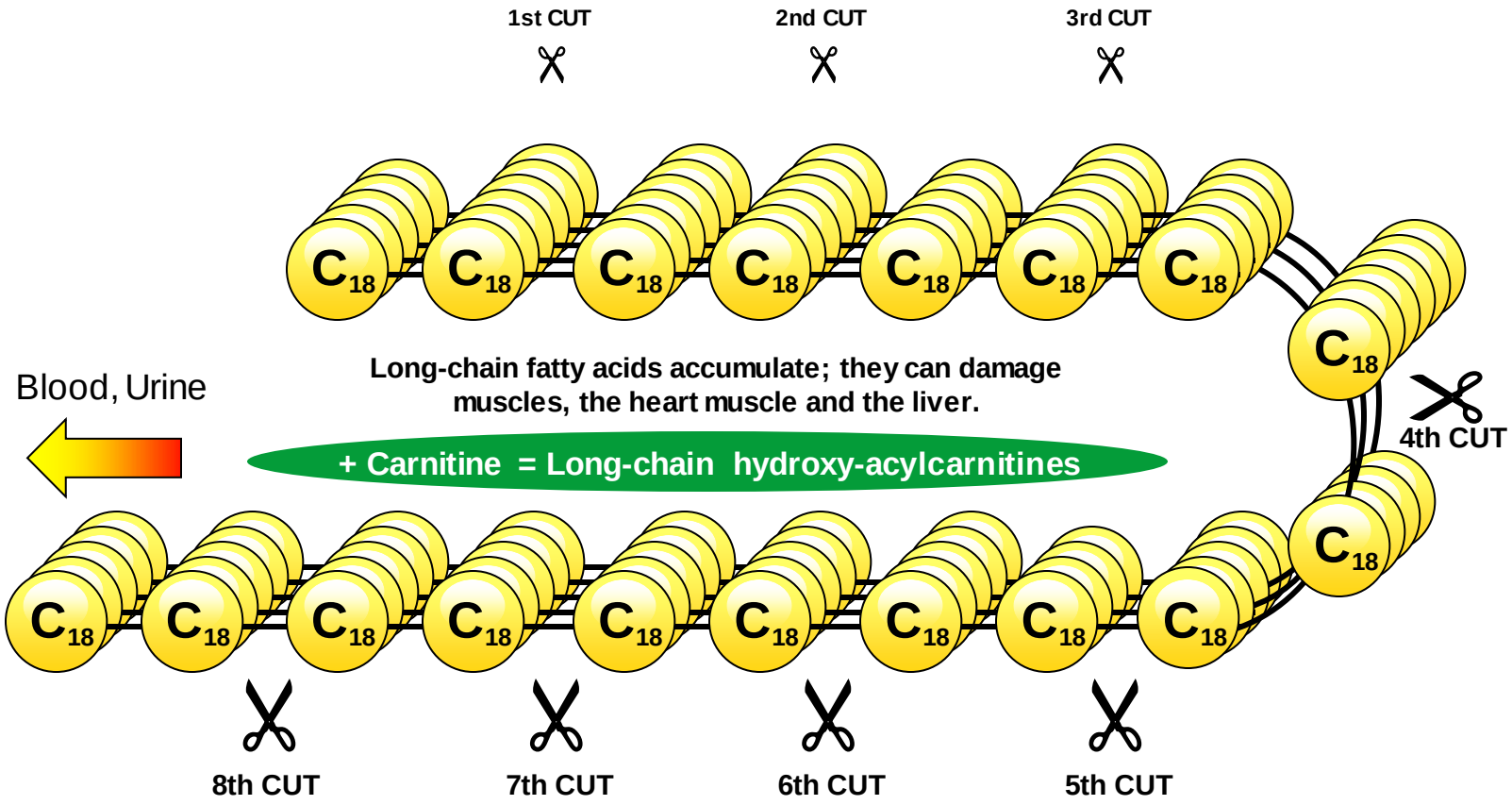
In LCHAD deficiency, long-chain fatty acids build-up and form long-chain hydroxy-acylcarnitines



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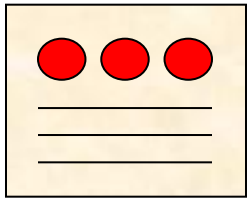
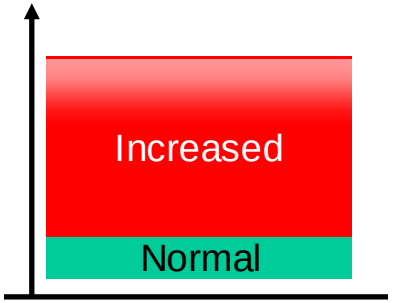
Diagnosis of LCHAD deficiency

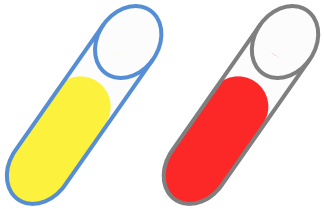


Dried blood spots

Newborn/Metabolic screening

Long-chain hydroxy-acylcarnitines in blood



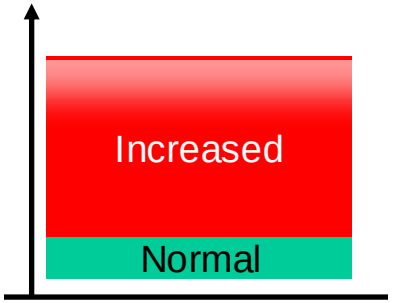


Urine sample

Blood sample

Confirmation of diagnosis

Abnormal compounds from long-chain hydroxy-fatty acids + long-chain hydroxy-acylcarnitines in urine and in blood plasma



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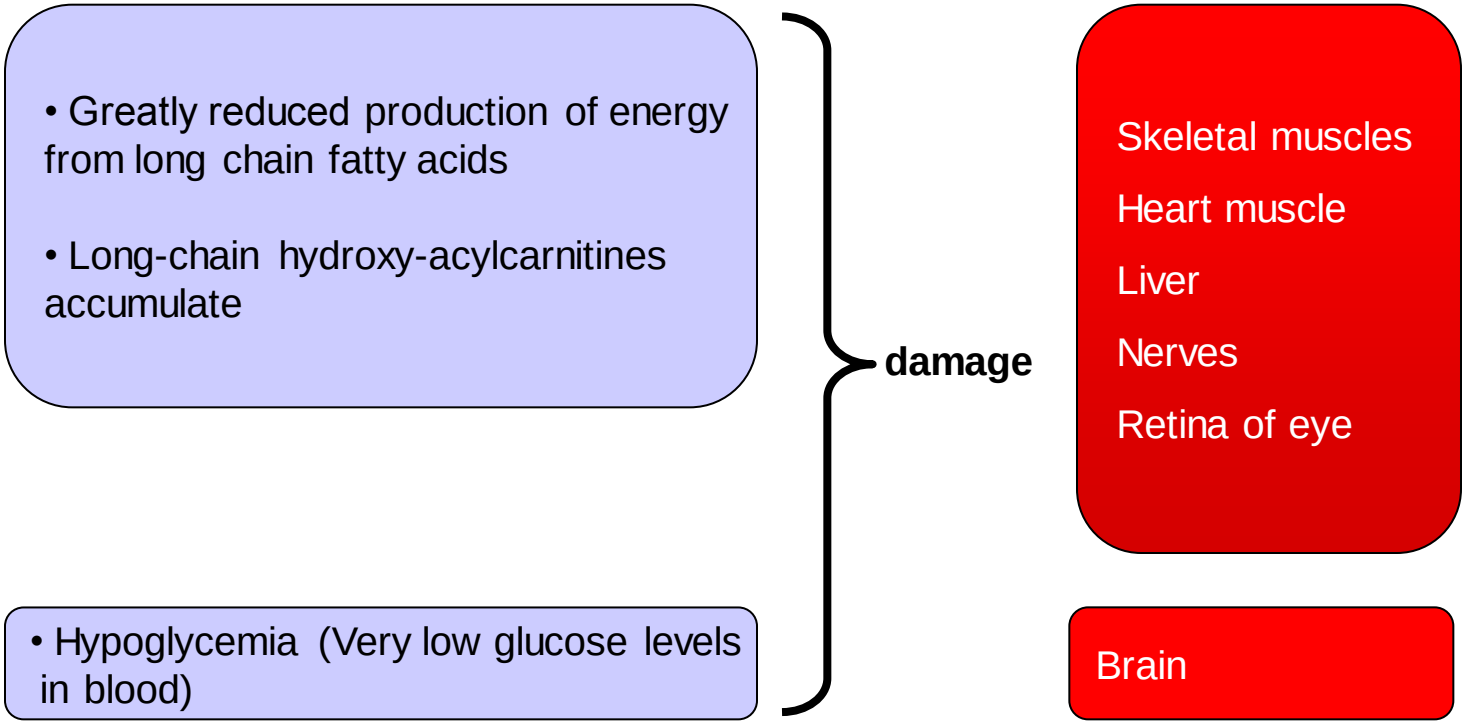
Pathogenesis of LCHAD deficiency



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The principles of dietary management for LCHAD deficiency

Avoid the need to use long-chain fatty acids as "fuel" for energy production.

by means of

1. **Avoid fasting too long**
   Fasting is the time when your child isn't drinking or eating anything
2. **Limit fat from the diet (Fat in the diet is all long chain fat)**
3. **Replace long-chain fatty acids in the food with medium-chain fatty acids (MCT-supplements)**
4. **Consume sources of glucose before, during and after exercise**

Energy production from long-chain fatty acids is defective.

Energy production from medium-chain fatty acids is intact.

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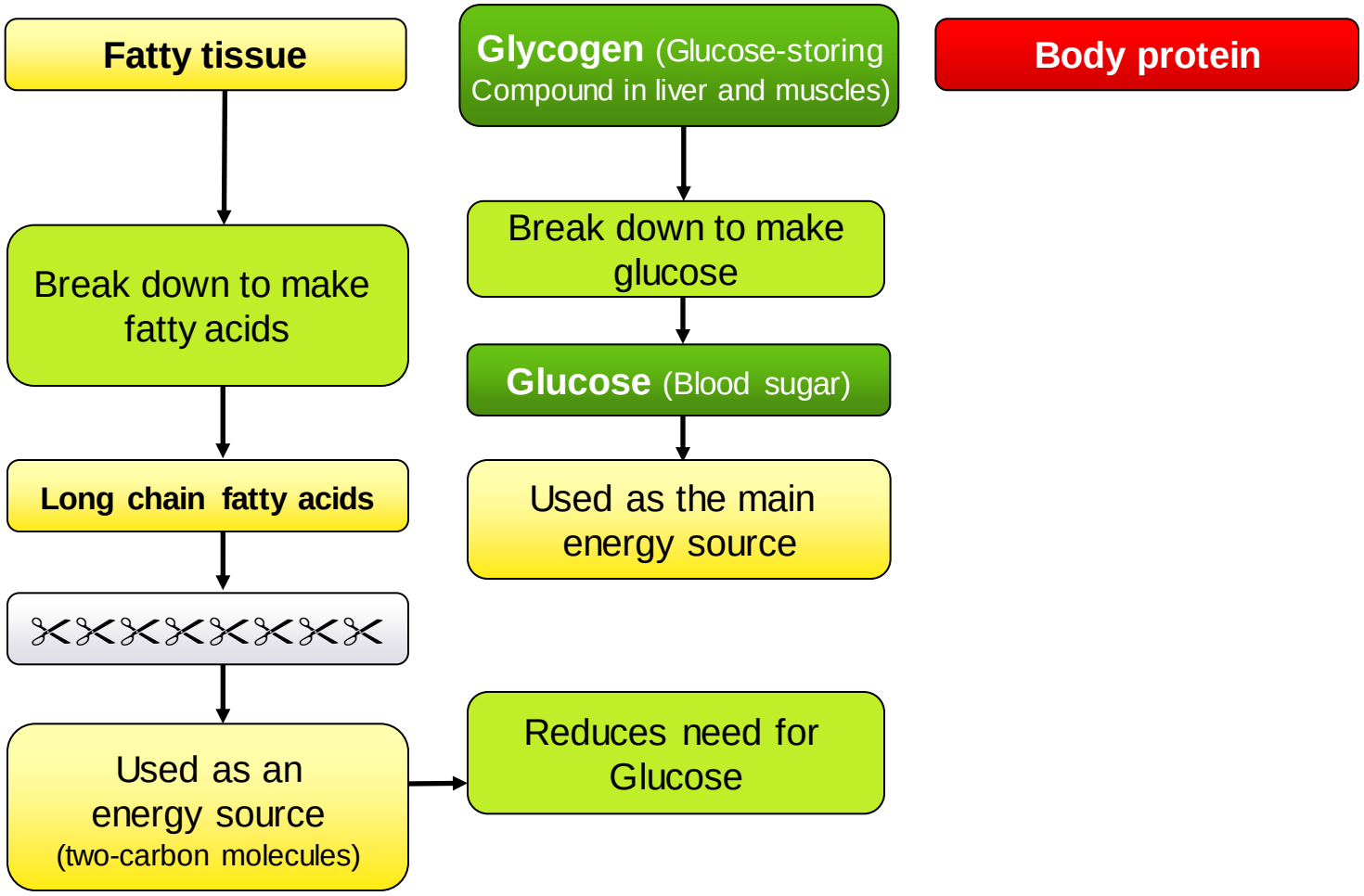
What happens during Fasting?



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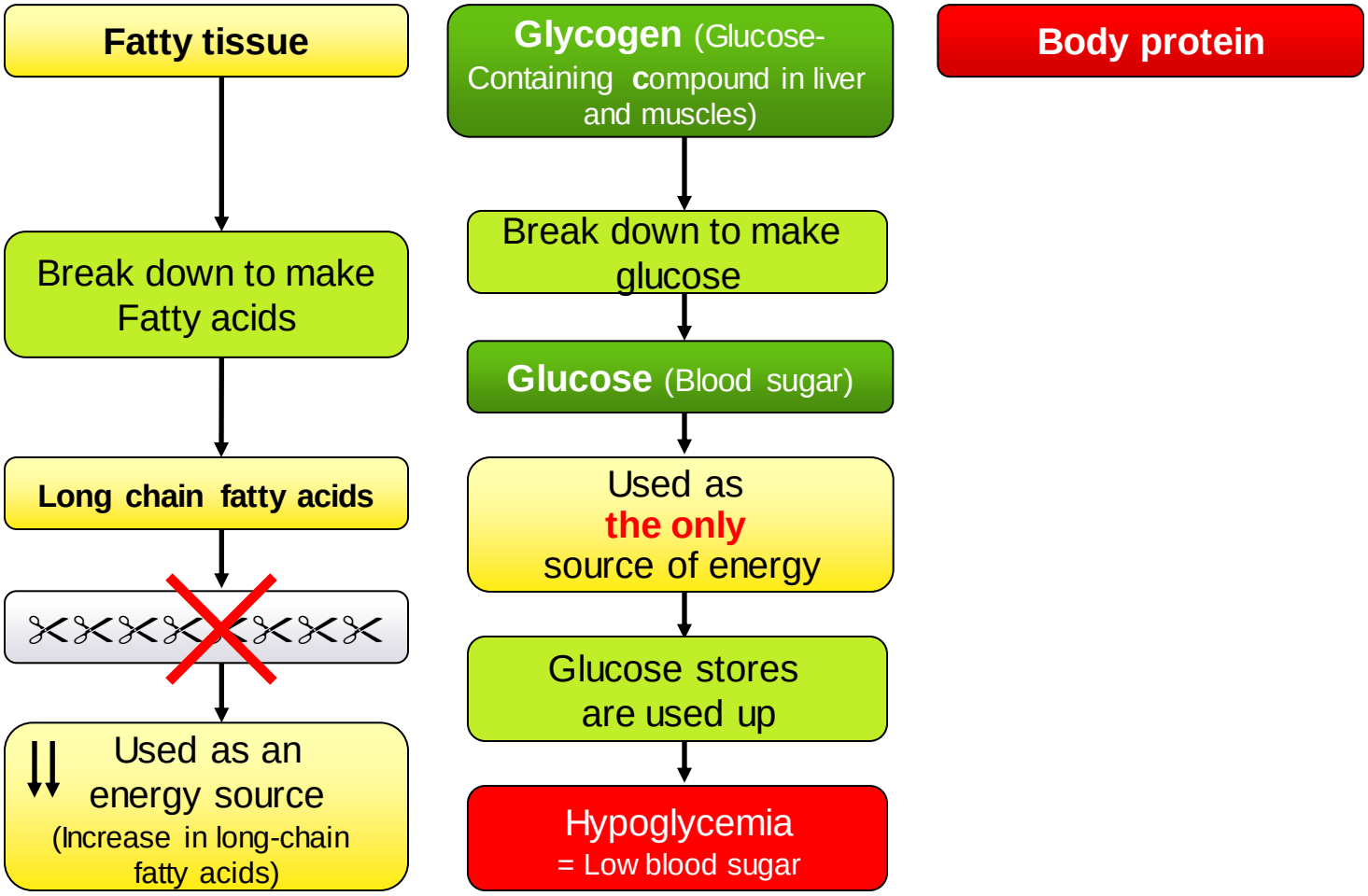
LCHAD deficiency:

Problems develop during fasting



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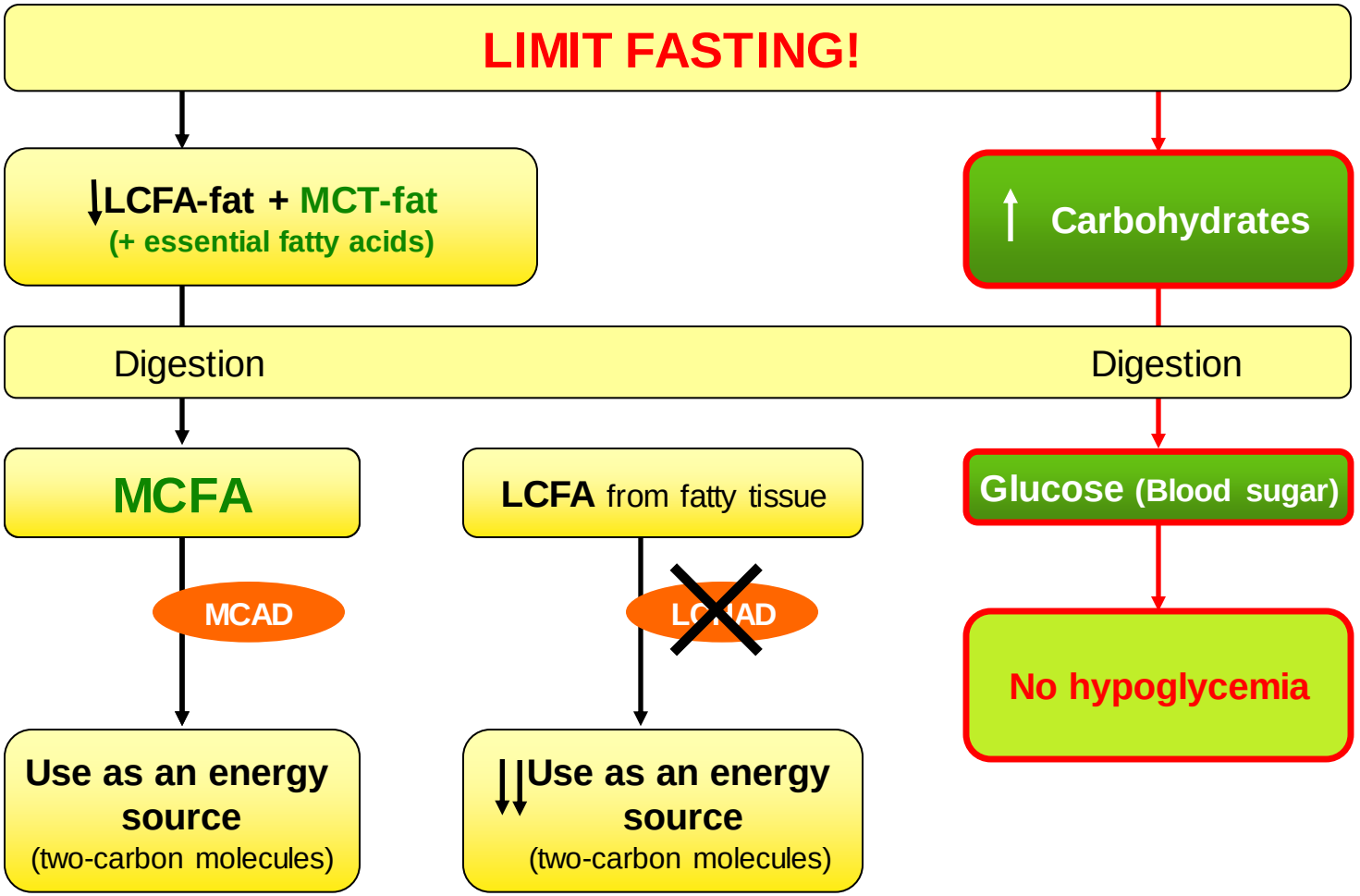
Dietary management: Avoid fasting too long



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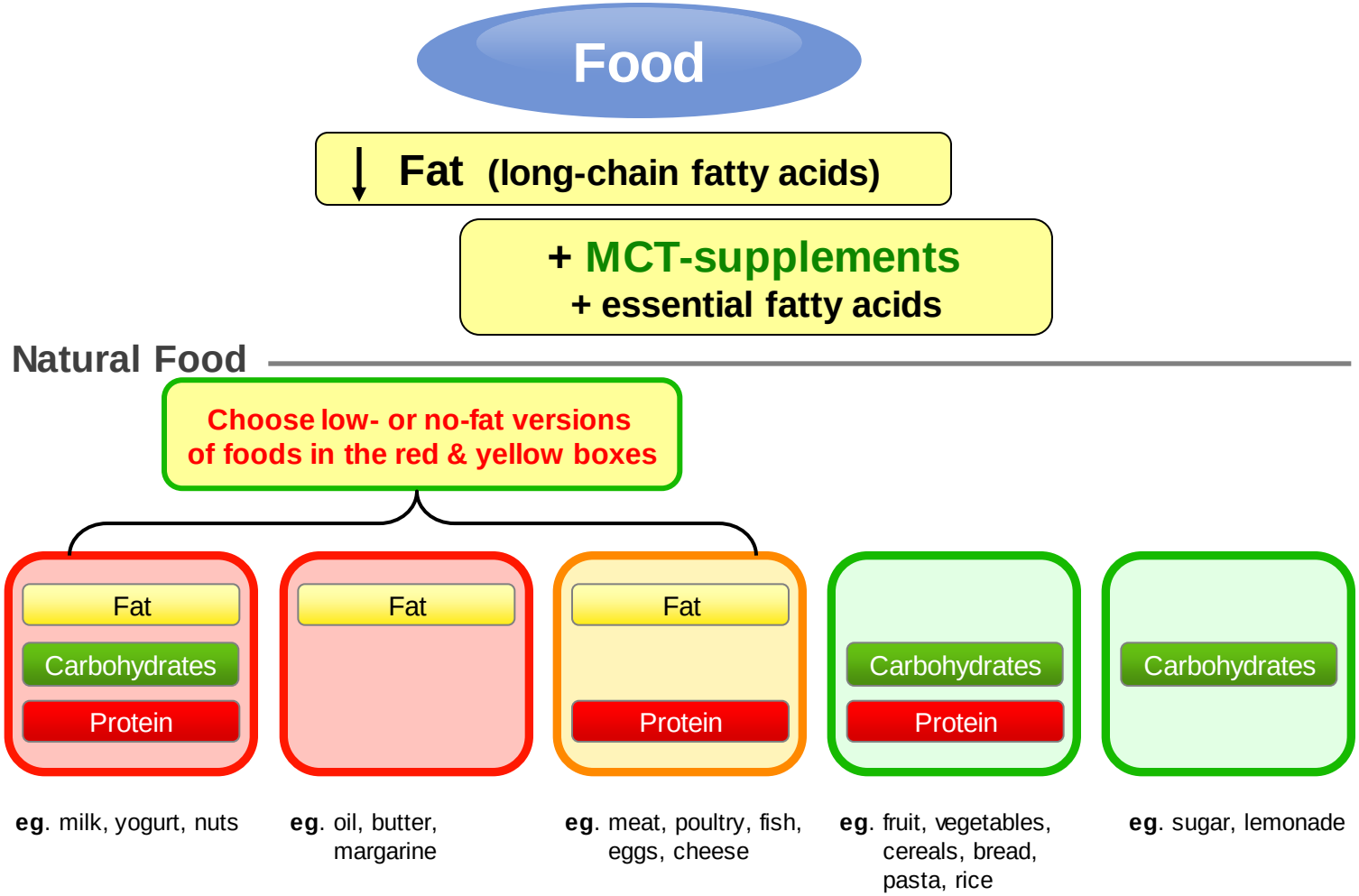
Dietary Management: very-low-fat diet + MCT-supplements



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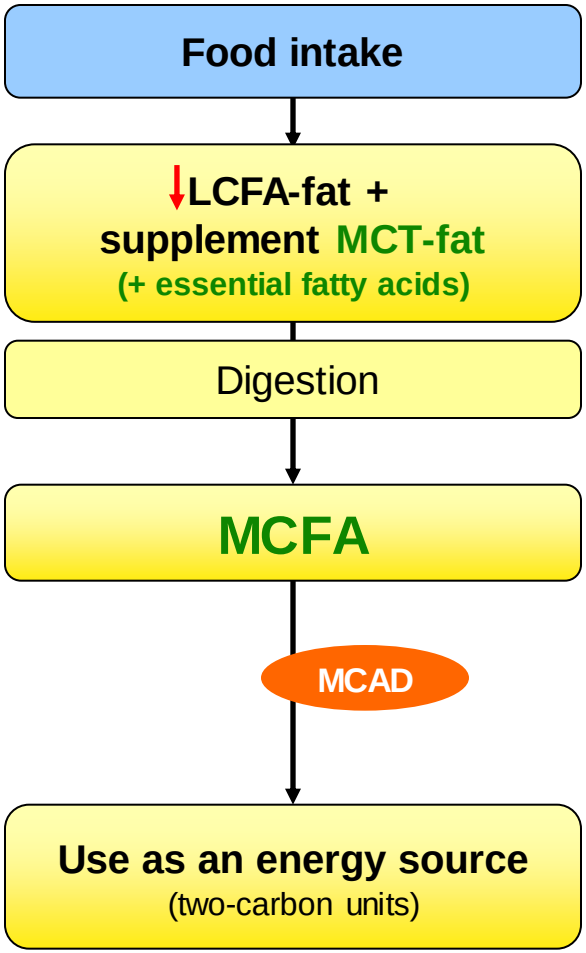
Dietary Management: very low-fat diet + MCT-supplements



Abbreviations:

LCFA-fat = Fat from long-chain fatty acids (LCFA)

MCT-fat = Fat from medium-chain fatty acids (MCFA)

MCAD = enzyme that breaks down medium chain fatty acids

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Illness and other stresses can cause problems for patients with LCHAD deficiency

- **What causes problems?**

Decreased energy production from long chain fatty acids
Toxicity of long chain hydroxy-acylcarnitines and other metabolites
Hypoglycemia (low blood sugar)

- **When can problems occur?**

Illness, especially with vomiting and poor food intake
Infections
Prolonged fasting
Excessive exercise (when older)
Surgery and anesthesia

- **What can happen?**

Heart problems – enlarged heart (cardiomyopathy), abnormal beats (arrhythmia)
Liver problems
Muscle breakdown – muscle pain, blood in urine
Problems with consciousness – coma is possible

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Illness and other stressors can cause problems for patients with LCHAD deficiency

- **Symptoms to watch out for**

Vomiting

Increased sleepiness (lethargy)

Child is more difficult to wake up

Complains that muscles ache

- **Necessary measures**

Reduce fasting time.

Offer a maltodextrin solution, juice or other food or beverage that will provide glucose.

An emergency room visit to start an intravenous glucose infusion may be necessary.

During fasting periods before anesthesia/surgery - always initiate an intravenous glucose infusion.

→ **Intravenous fat emulsions should NEVER be used!**

Ask your clinic for an Emergency Protocol!

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Chromosomes, Genes, Mutations

A **chromosome** is like a cookbook.

A **gene** is like a recipe in a cookbook.

A **mutation** is like an error in the recipe or even a complete lack of a recipe.

The **enzyme** LCHAD is produced constantly in the body following a specific recipe (**gene**). If the gene carries abnormal **mutations,** the **enzyme** cannot function correctly or be properly produced.

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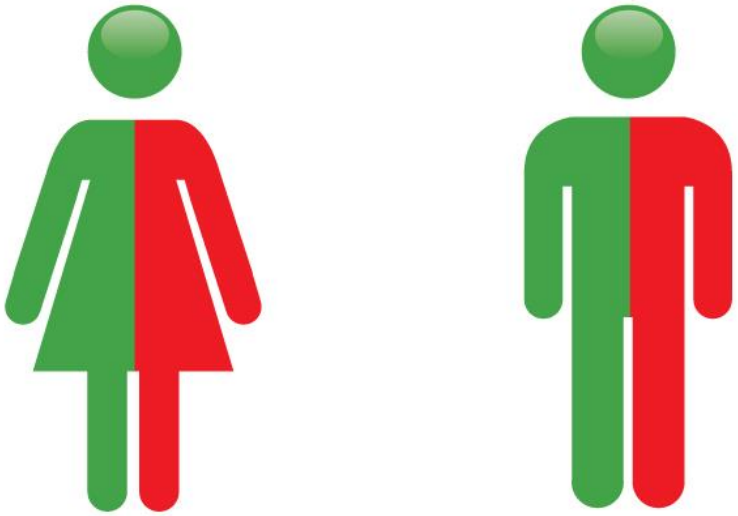
Inheritance of LCHAD deficiency

Both parents are carriers in autosomal-recessive inheritance

Mother is a carrier of **LCHAD deficiency**



Father is a carrier of **LCHAD deficiency**

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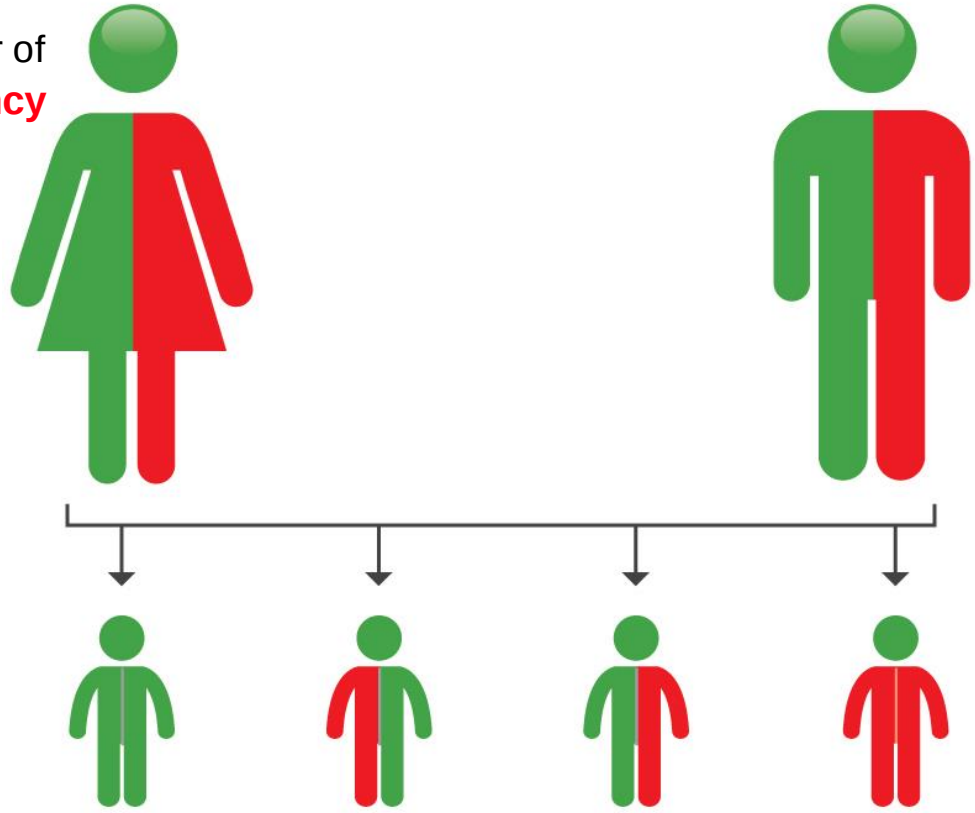
Inheritance of LCHAD deficiency

There are 4 possible combinations for any child born to parents who are carriers

Mother is a carrier of **LCHAD deficiency**

Father is a carrier of **LCHAD deficiency**



Child **will not** be a carrier of **LCHAD deficiency**

Child **will be** a carrier of **LCHAD deficiency**

Child **will have LCHAD deficiency**

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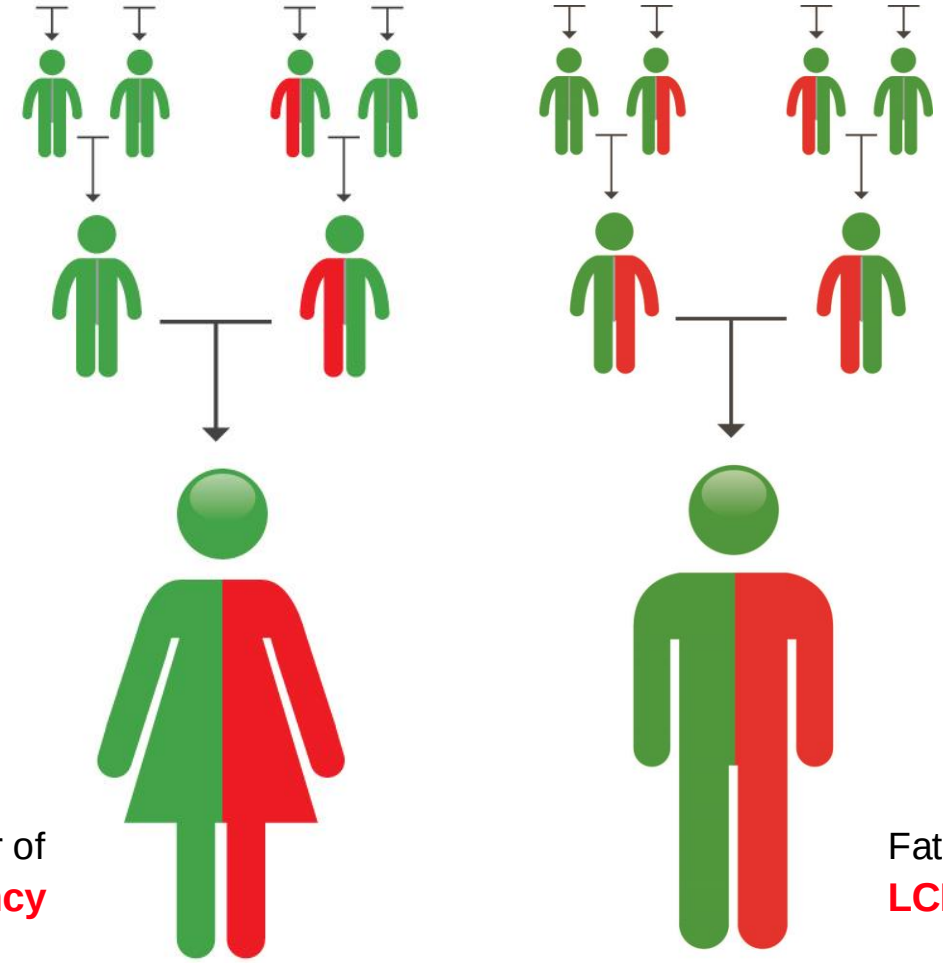
Inheritance of LCHAD deficiency

How LCHAD deficiency is inherited in families



Mother is a carrier of **LCHAD deficiency**

Father is a carrier of **LCHAD deficiency**

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Prognosis of LCHAD deficiency

Optimal Management

1. Reduction of long-chain fatty acids in diet and supplement MCT-fat
2. Plus essential fatty acids
3. Avoid fasting too long
4. Caution with illness, especially if child refuses to eat or is vomiting

Result

- Developmental delay of varying severity
- Muscle weakness and muscle pain associated with excessive exercise can still occur
- Some abnormalities in function of the nerves
- Retinopathy (Visual disturbances)

Follow-up

Laboratory tests
- **Special tests**
- Acylcarnitines
- Carnitine
- Essential fatty acids
- **Routine tests**
- Muscle enzymes
- Liver tests

Physical development
- Height and weight, head circumference

- **Cardiology consultations**
- **Monitoring motor and developmental skills**
- **Neurology consultations**
- **Ophthalmology consultations (examination of the eye)**

Insufficient Management

1. Insufficient reduction in dietary fat and MCT supplementation
2. Fasting too long
3. Insufficient preventive measures during illness or other stresses.

Result

- Life-threatening hypoglycemic episodes with unconsciousness, brain edema, coma, permanent brain damage

Sudden death

- Cardiomyopathy
- Skeletal muscle weakness

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