THE PHYSIOLOGY OF FASTING
AND FATTY ACID OXIDATION DEFECTS

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Time after eating

Source of glucose / energy

food

glycogen

gluconeogenesis, muscle

gluconeogenesis, other

fatty acid oxidation
FED STATE

• The body uses glucose and nutrients from the last meal.
• The body/brain relies on glucose as the prime source of energy.
• The body synthesizes fat.
FED STATE to FASTING STATE:

Step One

- When eaten food is no longer a source of glucose or energy, stored glycogen in the liver gets broken down to form glucose.
- As the body’s stores of glycogen are used up, the body starts to make “new” sugar from various sources including lactate and amino acids (from muscle).
- The body/brain continues to rely on sugar as the prime source of energy.
- The body synthesizes fat.
FED STATE to FASTING STATE:

*Step Two*

- Some glucose is still formed by the body (gluconeogenesis), but not from amino acids (muscle).
- Fat is oxidized to form ketones.
- During prolonged fasting, the body relies on fat conversion to ketones as the prime source of energy.
Time after eating

Source of glucose / energy:
- food
- glycogen
  - gluconeogenesis, muscle
  - gluconeogenesis, other
  - fatty acid oxidation
Glycogen Storage Disease

- Stored sugar or glycogen cannot be accessed.
- Infants cannot go for longer than 3-4 hours without feeding.
- After 3-4 hours, hypoglycemia occurs.
- Glycogen cannot be broken down but just accumulates in the liver, causing liver enlargement.
Time after eating

Source of glucose / energy

food

glycogen

gluconeogenesis, muscle

gluconeogenesis, other

fatty acid oxidation
Disorders of Gluconeogenesis

- Glucose cannot be synthesized from certain substrates.
- Patients with severe disease are very affected neurologically – low muscle tone or spastic, seizures, developmentally delayed, failure to thrive.
- Lactic acid is usually elevated chronically.
- Symptoms, lactic acid become worse with fasting; hypoglycemia may occur at that time.
Time after eating

Source of glucose / energy

- food
- glycogen
- gluconeogenesis, muscle
- gluconeogenesis, other
- fatty acid oxidation
Fatty Acid Oxidation Disorders

• When eating well, and while otherwise healthy, patients may show no symptoms.
• When food intake is inadequate and/or the patient is sick and food intake cannot keep up with demand, symptoms may occur.
Fatty Acid Oxidation Disorders

- Nausea and vomiting
- Encephalopathy – lethargy, coma, seizures
- Liver enlargement, dysfunction
- Muscle and heart muscle dysfunction
- +/- Hypoglycemia
Encephalopathy: Causes

- Fatty acid oxidation disorders are disorders of energy metabolism in which the brain “runs out of energy”:
  - glucose stores are exhausted.
  - ketone production is diminished.
- The accumulating metabolites are toxic to the brain, causing brain swelling and coma.
FATTY ACIDS

CoA

FATTY ACYL CoA

β-OXIDATION

ACETYL CoA

KETONES
Encephalopathy: Causes

- The low concentrations of CoA and the accumulation of fatty acyl CoA molecules interfere with normal energy production in the Krebs cycle.
- Inadequate amounts of acetyl CoA impair gluconeogenesis or production of glucose in the body.
CLINICAL APPLICATIONS
CLINICAL APPLICATIONS

- Fasting avoidance is the cornerstone of therapy
Fasting Avoidance

• If you rely on glucose and avoid relying on fat, symptoms are minimized.

• Exception: in long chain fatty acid oxidation defects, heart muscle and skeletal muscle depend on both glucose and fat.
CLINICAL APPLICATIONS

• Fasting avoidance is the cornerstone of therapy

• *Is fat restriction necessary? Fat synthesis is not impaired (under healthy conditions).*
TR’s Story

• TR was born following a normal pregnancy, labor and delivery. Developed hypoglycemia (12 mg/dL) on day 2 with associated lethargy and mottling.
• At four months, she became sweaty with feedings and often choked.
• At five months, she became irritable and less responsive and had staring spells.
• Examination revealed a gallop and murmur.
• Testing revealed cardiomyopathy & heart failure.
TR’s Story (continued…)

• Metabolic testing revealed a diagnosis of VLCAD (very long chain acyl CoA dehydrogenase) deficiency. Enzyme testing confirmed the diagnosis.
• TR’s diet: 30-35% of calories from fat -
  – 90% of fat from medium chain triglycerides
  – 10% of fat from long chain fat
• Carnitine given to maintain normal levels.
• Night-time feeds ended at 30 months; given corn starch instead with MCT during the day.
TR’s Story (continued…)

- Heart size normalized over 24 months.
- Ventricular hypertrophy resolved by four years.
- Intercurrent illnesses associated with elevated liver enzymes and CPK; resolve with intravenous fluids.
Fat Restriction

- When sick, energy demands rise and food intake diminishes; the body will use dietary fat to make ketones.
- The diet during times of illness should be high in carbohydrate and low in fat.
- Fat restriction may not be so important when the patient is otherwise healthy.
CLINICAL APPLICATIONS

• Fasting avoidance is the cornerstone of therapy
• Is fat restriction necessary?
• *Medium chain fat supplementation (for long chain fatty acid oxidation disorders).*
DIETARY FAT AND BODY FAT STORES ARE LONG CHAIN IN LENGTH
LONG CHAIN FATTY
ACYL CoA

Mitochondrial Membrane
LONG CHAIN FATTY
ACYL CoA

CARNITINE

Mitochondrial Membrane
LONG CHAIN FATTY ACYL CoA

CARNITINE

Mitochondrial Membrane

CARNITINE

LONG CHAIN FATTY ACYL CoA
Mitochondrial Membrane

CARNITINE

LONG CHAIN FATTY ACYL CoA
Mitochondrial Membrane

LONG CHAIN FATTY ACYL CoA
LONG CHAIN FATTY ACYL CoA

LONG CHAIN β-OXIDATION ENZYMES
Mitochondrial Membrane

LONG CHAIN FATTY ACYL CoA

NEW KETONE BODY
Mitochondrial Membrane

LONG CHAIN FATTY ACYL CoA

LONG CHAIN β-OXIDATION ENZYMES
Mitochondrial Membrane

LONG CHAIN FATTY ACYL CoA

NEW KETONE BODY
Mitochondrial Membrane

LONG CHAIN FATTY ACYL CoA

LONG CHAIN β-OXIDATION ENZYMES
Mitochondrial
Membrane

MEDIUM CHAIN FATTY ACYL CoA

NEW KETONE BODY
Mitochondrial Membrane

MEDIUM CHAIN FATTY ACYL CoA

MEDIUM CHAIN β-OXIDATION ENZYMES
Mitochondrial Membrane

MEDIUM CHAIN FATTY ACYL CoA
Mitochondrial Membrane

MEDIUM CHAIN FATTY ACYL CoA

MEDIUM CHAIN β-OXIDATION ENZYMES
Mitochondrial Membrane

SHORT CHAIN FATTY ACYL CoA

SHORT CHAIN β-OXIDATION ENZYMES
Mitochondrial Membrane

SHORT CHAIN FATTY ACYL CoA

SHORT CHAIN β-OXIDATION ENZYMES
Mitochondrial Membrane

SHORT CHAIN FATTY ACYL CoA
MEDIUM CHAIN FATTY ACYL CoA

CARNITINE

Mitochondrial Membrane

MEDIUM CHAIN FATTY ACYL CoA
Medium Chain Triglycerides

• MCT does not require carnitine, often deficient in any sick person, to be transported into the liver.
• MCT does not require oxidation by those enzymes that break down long chain fat; it *bypasses* them, and is broken down to form ketones using other, working enzymes.
• Important for long chain fatty acid defects
TR’s Story (continued…)

• TR continued to avoid prolonged fasting and watched her fat intake but stopped taking daily MCT supplement.
• Complained of muscle cramping after exercising, increased muscle fatigue, jaw cramping in the morning.
• CPK levels ran 4000-5000 (normal < 300).
• Once MCT supplementation restarted, symptoms diminished significantly, and CPK levels normalized.
CLINICAL APPLICATIONS

- Fasting avoidance is the cornerstone of therapy
- Is fat restriction necessary?
- Medium chain fat supplementation (in long chain fatty acid oxidation disorders).
- *The role of carnitine.*
The Role of Carnitine

- Carnitine binds to the fatty acid oxidation intermediate molecules and facilitates their excretion for the body.
- Its benefit during periods of health are unclear; often levels are normal at these times. Deficiencies should be corrected.
- The benefit is more obvious when the patient is sick and producing large amounts of fatty acid intermediates.
Potentially Toxic
LONG CHAIN
FATTY ACYL CoA

CARNITINE

LONG CHAIN
FATTY
ACYLCARNITINE
CLINICAL APPLICATIONS

• Fasting avoidance is the cornerstone of therapy
• Is fat restriction necessary?
• Medium chain fat supplementation (in long chain fatty acid oxidation disorders).
• The role of carnitine.
• *Glucose monitoring.*
Free Fatty Acids,
Ketones,
mM

Hours of Fasting

Stanley et al, 1990

Free Fatty Acids

Glucose

Ketones

MCAD Deficiency
Glucose Monitoring

- Problem: Lethargy and coma can occur in the absence of a low blood sugar.
- Glucometer readings (if not hypoglycemic) may offer a false sense of security.
- The patient should be evaluated and treated if symptoms of concern are present whether or not hypoglycemia is present.
CLINICAL APPLICATIONS

• Fasting avoidance is the cornerstone of therapy
• Is fat restriction necessary?
• Medium chain fat supplementation (in long chain fatty acid oxidation disorders).
• The role of carnitine.
• Glucose monitoring.
• *When sick, give 10% dextrose at >1.25 maintenance rate.*
Why 10% Dextrose When Sick?

- “Catabolism”, including glycogen breakdown, and eventually gluconeogenesis and fatty acid oxidation, occurs when the amount of dietary or IV glucose falls below the basal glucose production rate in liver.

- Bier et al, 1977, determined this rate:
  \[ y = 0.0014 \times x^3 - 0.214 \times x^2 + 10.411 \times x - 9.084 \]
  \[ y = \text{glucose production rate (mg/min)} \]
  \[ x = \text{body weight (kg)} \]
Example: 10 kg child

- \[ y = 0.0014 \times 3 - 0.214 \times 2 + 10.411 \times x - 9.084 \]
  
  \[ y = \text{glucose production rate (mg/min)} \]
  \[ x = \text{body weight (kg)} \]

- Basal glucose production rate = 75.03 mg/min of glucose (or 7.5 mg/kg/min)

- 10% dextrose at maintenance provides 70 mg/min (or 7.0 mg/kg/min)

- 10% dextrose at 1.25 maintenance provides 87 mg/min (or 8.7 mg/kg/min)
PREVENTION is the *best* approach

*Newborn screening*…. 

- Allows pre-symptomatic monitoring.
- Allows early intervention when symptoms arise.
- Allows prevention of complications that occur during metabolic crises.
NEWBORN SCREENING

• PRO:
  – *Allows prevention of serious morbidity and mortality*

• CON:
  – *In some identified patients, it is difficult to prove whether or not they have clinically-significant disease.*
Approach to Confirming a Diagnosis

• Blood and urine testing (especially when sick)
• Skin fibroblast fatty acid oxidation testing
• Skin fibroblast enzyme testing
• ?Liver enzyme testing
• DNA testing
Approach to Confirming a Diagnosis

- Monitored fasting study, to evaluate the patient’s physiologic response to fasting
Approach to Confirming a Diagnosis

• Monitored fasting study –
  – Admit when healthy.
  – Fast for a prolonged period of time.
  – Monitor the physiologic response to fasting (e.g., fatty acids, ketones).
  – Monitor glucose.
  – When glucose drops or patient’s mental status changes – draw final tests, then administer glucose and allow to eat.
  – Allows a “bottom-line” conclusion.
DG’s Story

• Well until 7 months of age; developed viral illness.
• Became lethargic, seen by pediatrician who diagnosed hypoglycemia with inappropriately low ketones in the urine.
• Urine sent for organic acid analysis: showed inappropriately low ketones and pattern suggestive of medium chain ketoacyl CoA thiolase deficiency.
DG’s Story (continued…)

• Repeat blood and urine tests not informative.
• Skin biopsy did not show an abnormality in oxidation.
• The parents consented to a fasting study to evaluate DG’s physiologic response to fasting; she was 26 months old.
• At 17 hours of fasting, glucose dropped <50 mg/dL. “Critical specimens” obtained.
DG’s Story (continued…)

• DG showed a normal free fatty acid and ketone response.
• Other testing (acylcarnitines, acylglycines) all normal.
< sigh >
THERE’S SO MUCH MORE TO LEARN.
Thanks for listening.

Now go eat something.