Case scenarios: inborn errors of metabolism presenting with hypoglycemia

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Case scenario 1

- 4 month old male infant presented to ER with lethargy and abnormal movement noticed this morning.
- Around 8 am when the mother tried to wake him up to feed him, he was lethargic with very weak cry. The mother rushed to the hospital and in her way she noticed twitching of right upper arm that lasted for about 1 minute.

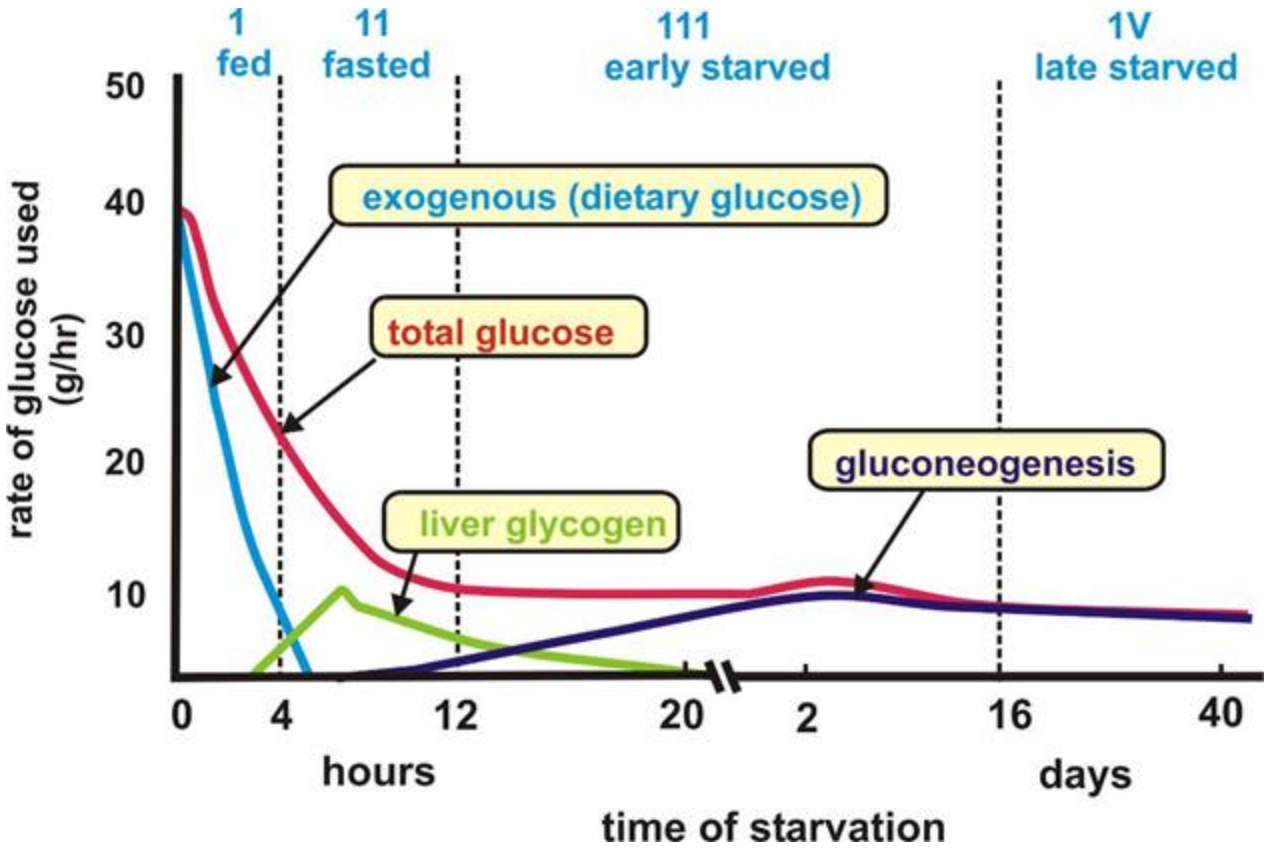
- No fever, vomiting, or respiratory distress
- No history of sick contact
- FT, uncomplicated perinatal course.
- Exclusive breast feeding Q3-4 hours.
- Last feed was 2 am.
- Vaccination up to date
- Family history: the second child for his parents who are cousins.

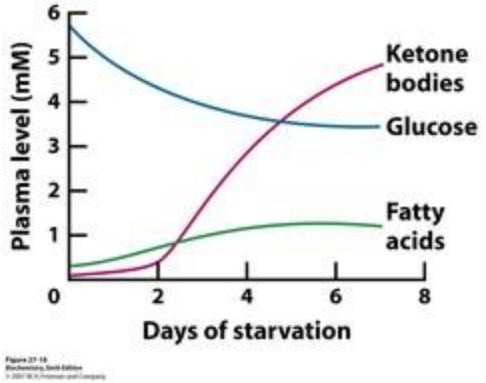
- In ER he was pale and lethargic with very weak cry.
- VS: tachypnea, no fever
- Chest and heart: normal
- Abdomen: distended with liver felt 8 cm BCM
- Neuro: lethargic, reduced limb movement, hypotonia

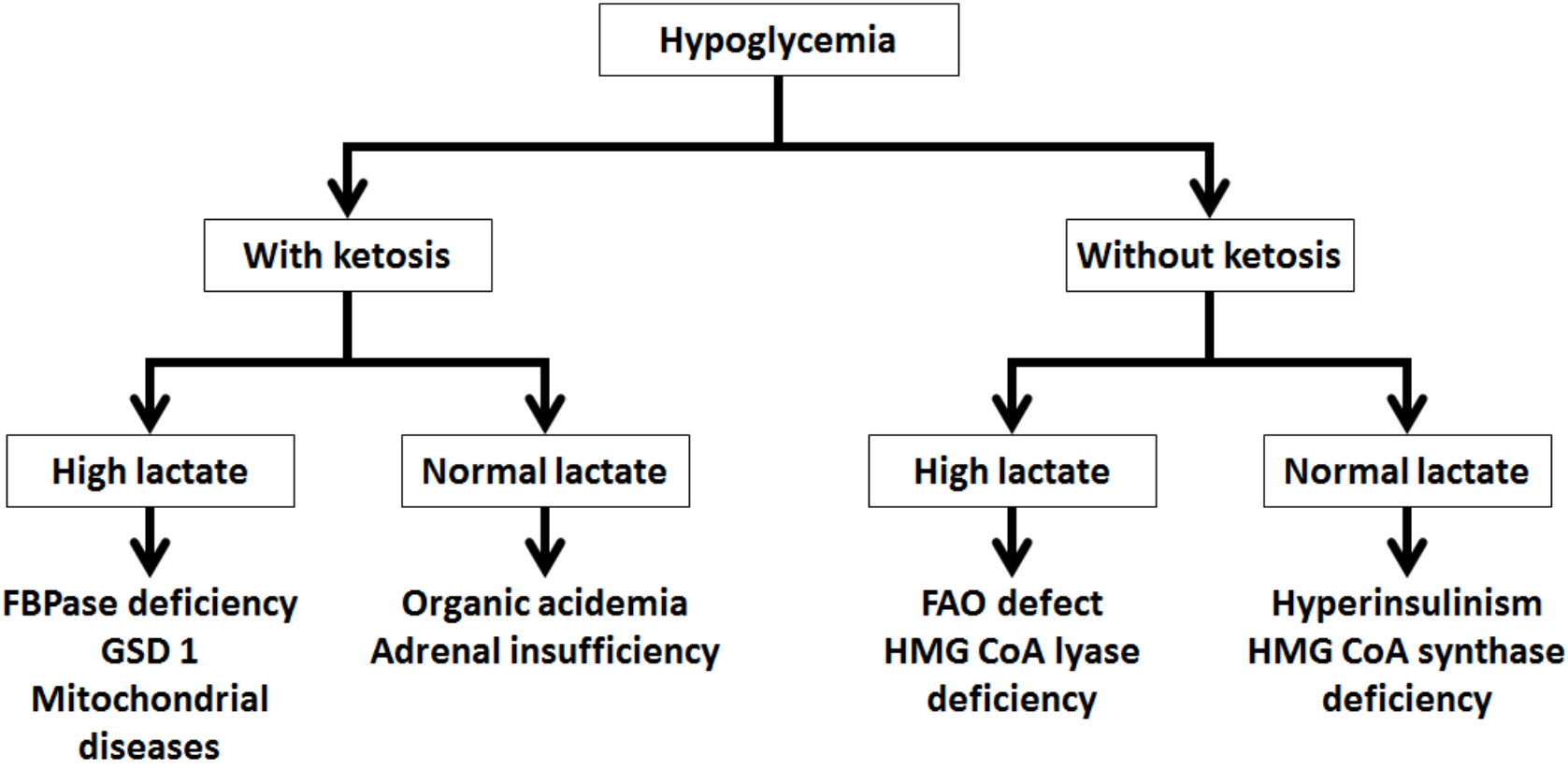
- What to do next?

- Glucose <5 mg/dl (<0.3 mmol/L)

- The most likely Dx?


1
fed
11
fasted
111
early starved
1V
late starved
rate of glucose used (g/hr)
50
40
30
20
10
exogenous (dietary glucose)
total glucose
liver glycogen
gluconeogenesis
0
4
12
20
2
16
40
hours
days
time of starvation


Plasma level (mM)
6
5
4
3
2
1
0
2
4
6
8
Days of starvation
Ketone bodies
Glucose
Fatty acids


Hypoglycemia
With ketosis
Without ketosis
High lactate
Normal lactate
High lactate
Normal lactate
FBPase deficiency
GSD 1
Mitochondrial diseases
Organic acidemia
Adrenal insufficiency
FAO defect
HMG CoA lyase deficiency
Hyperinsulinism
HMG CoA synthase deficiency

Fructose 1,6 bisphosphatase deficiency

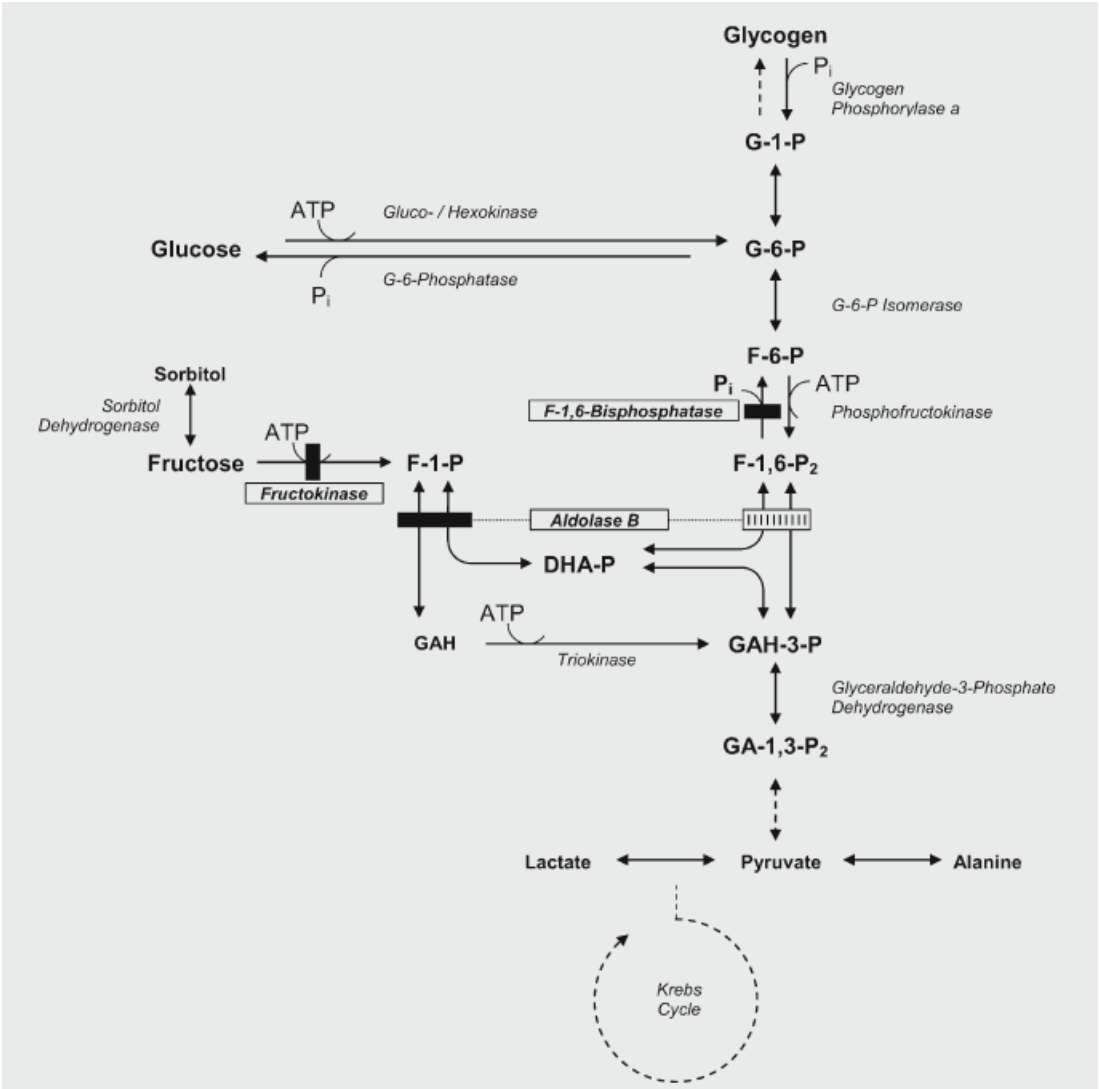


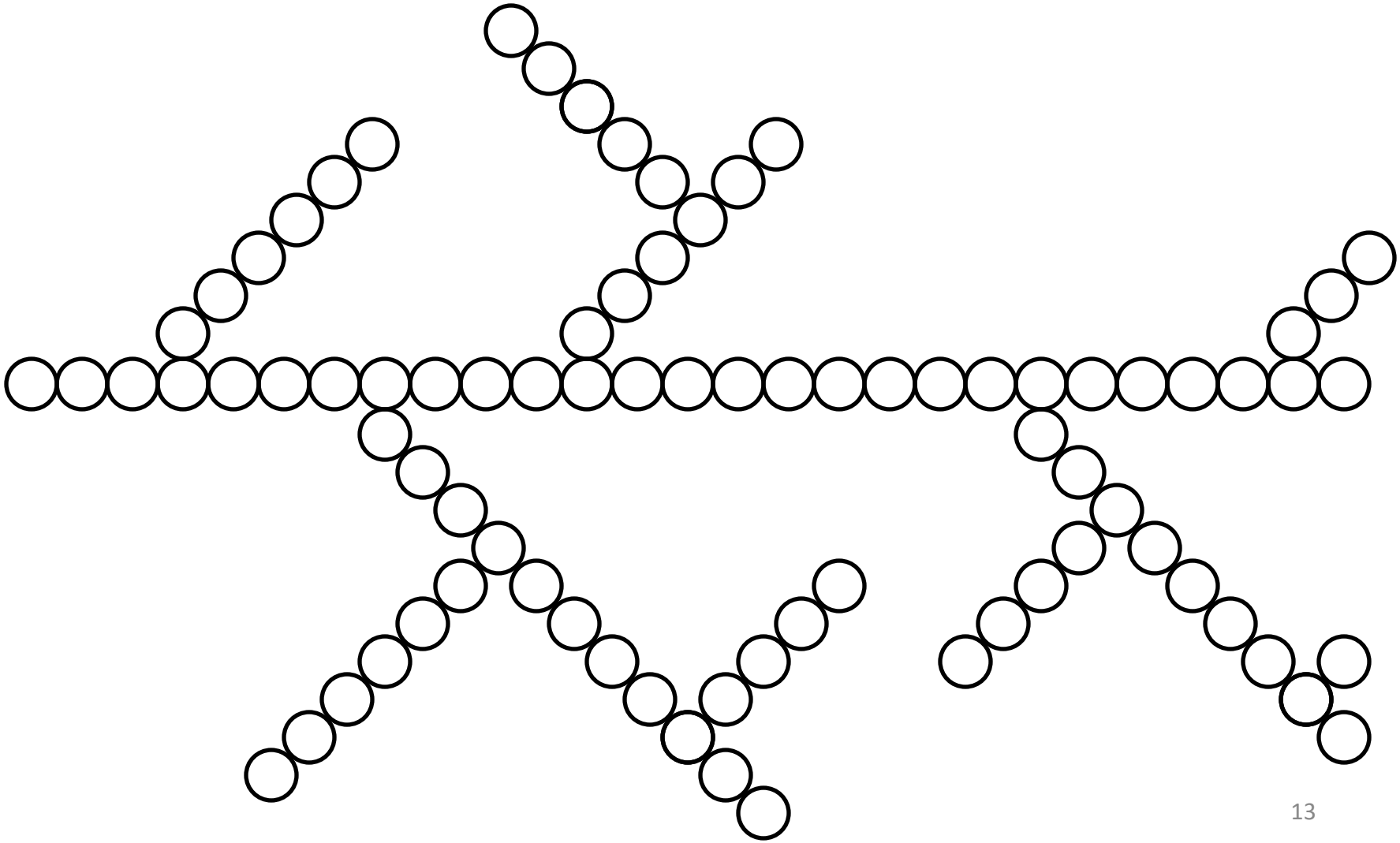
Fig. 9.1. Fructose metabolism. *DHA-P*, Dihydroxyacetone phosphate; *F*, fructose; *G*, glucose; *GA*, glycerate; *GAH*, glyceraldehyde; *P*, phosphate; *Pi*, inorganic phosphate. The three enzyme defects in fructose metabolism are boxed and depicted by *solid bars* across the *arrows*; the diminished activity of aldolase B toward fructose-1,6-bisphosphate is depicted by a *broken bar*

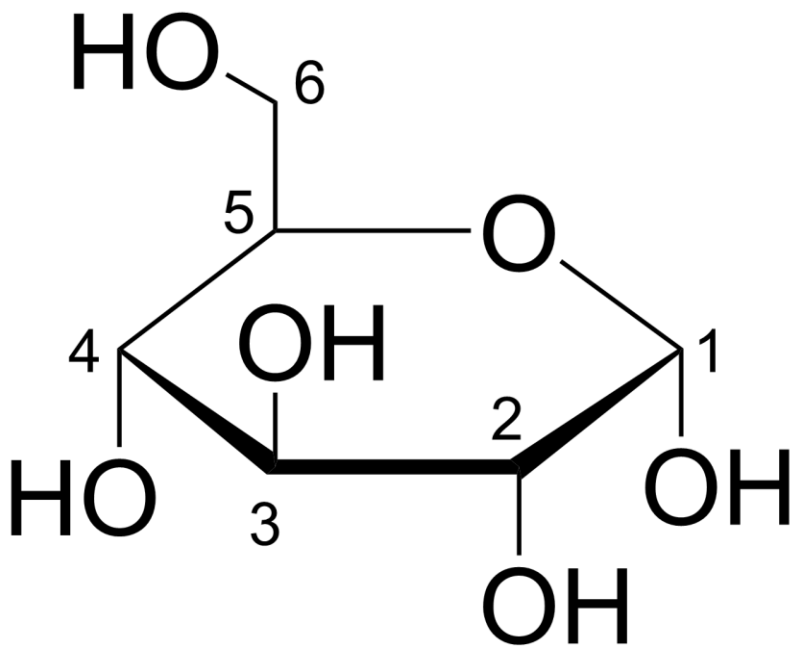
Fructose-1,6-Bisphosphatase Deficiency

- Deficiency of FBPase, a key enzyme in gluconeogenesis, impairs the formation of glucose from all gluconeogenic precursors, including dietary fructose.
- Infants with FBPase deficiency can present with:
  - Lactic acidosis, hypoglycemia, ketosis
  - Hepatomegaly
  - Seizures, irritability, lethargy, hypotonia, apnea, and coma.

- Diagnosis is confirmed by enzyme assay and *FBP1* gene sequencing.
- Management
  - The acute presentation can be treated with glucose infusion and bicarbonate to control hypoglycemia and acidosis.
  - Maintenance therapy aims at avoiding fasting by frequent feeding and uncooked starch use.
  - Restriction of fructose and sucrose is also recommended.

Glycogen storage diseases





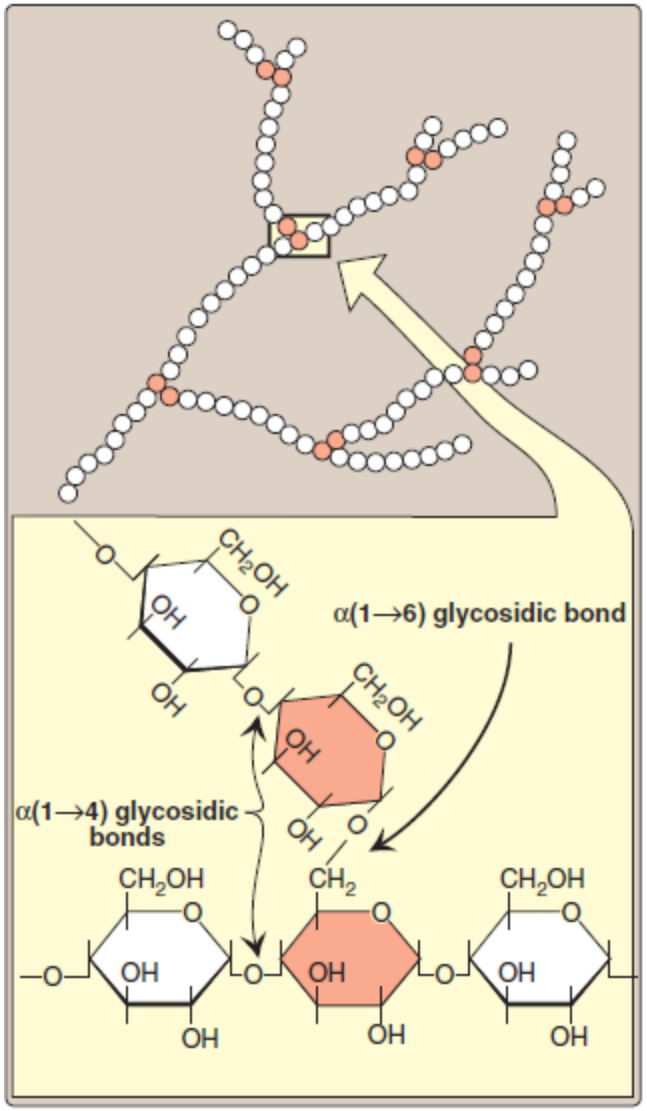


Figure 11.3
Branched structure of glycogen, showing α(1→4) and α(1→6) glycosidic bonds.

- 400 g glycogen in muscle (1-2% of muscle weight)
- 100 g glycogen in liver (10% of liver weight)
- Function of liver glycogen vs muscle glycogen

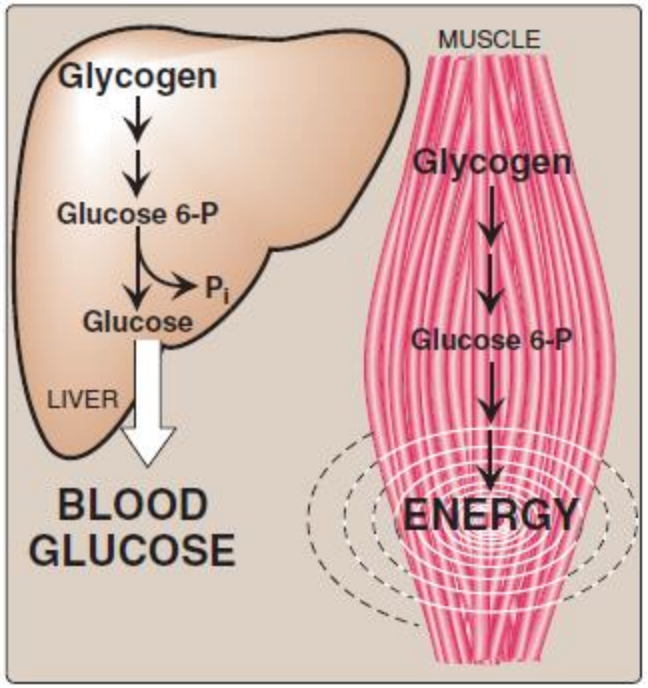
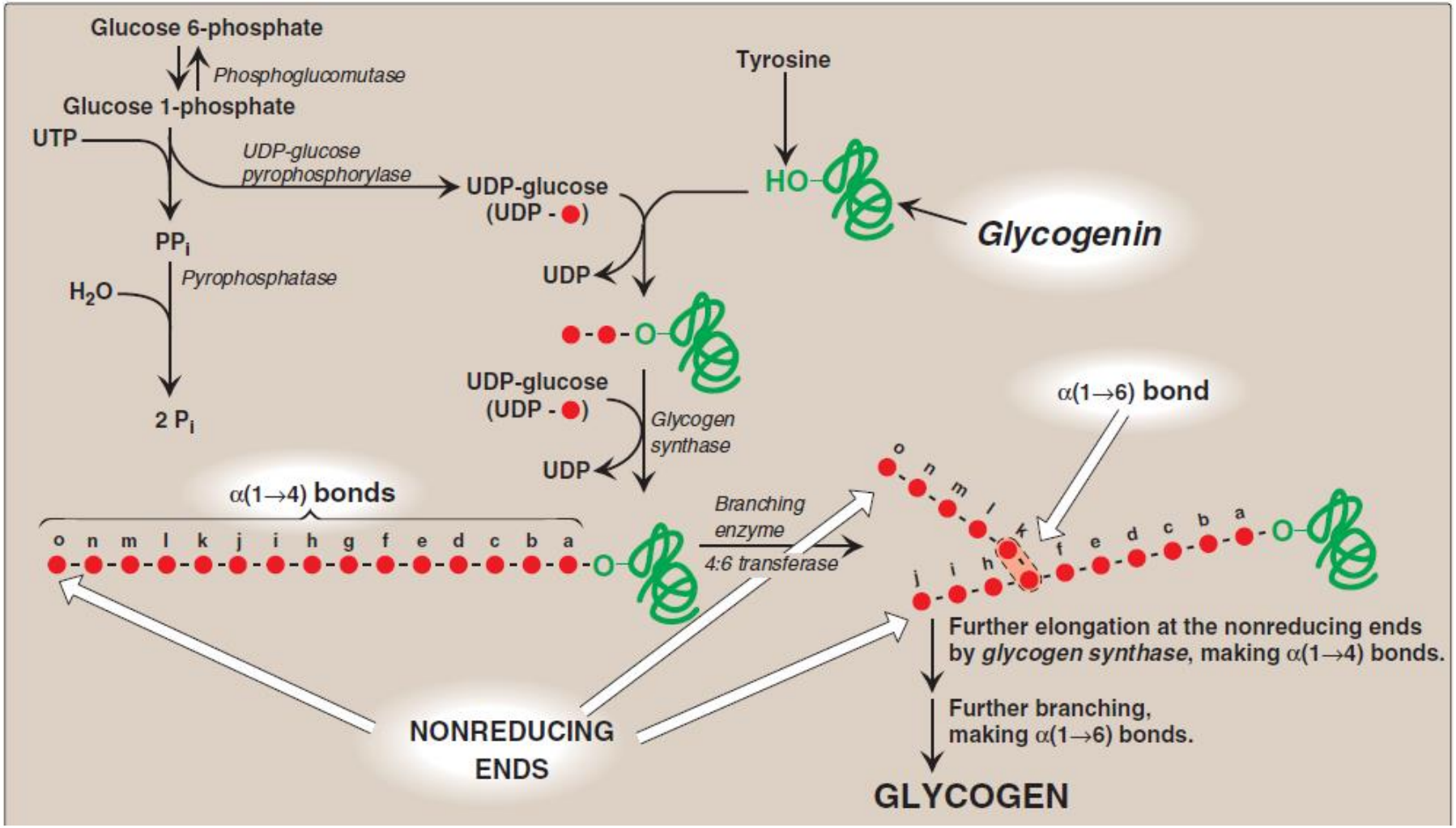


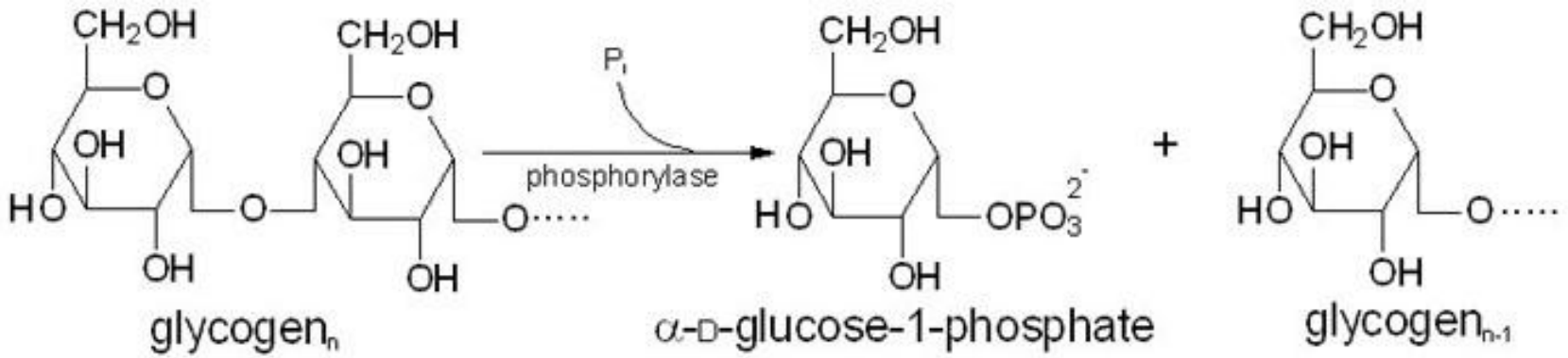
Figure 11.2
Functions of muscle and liver glycogen.

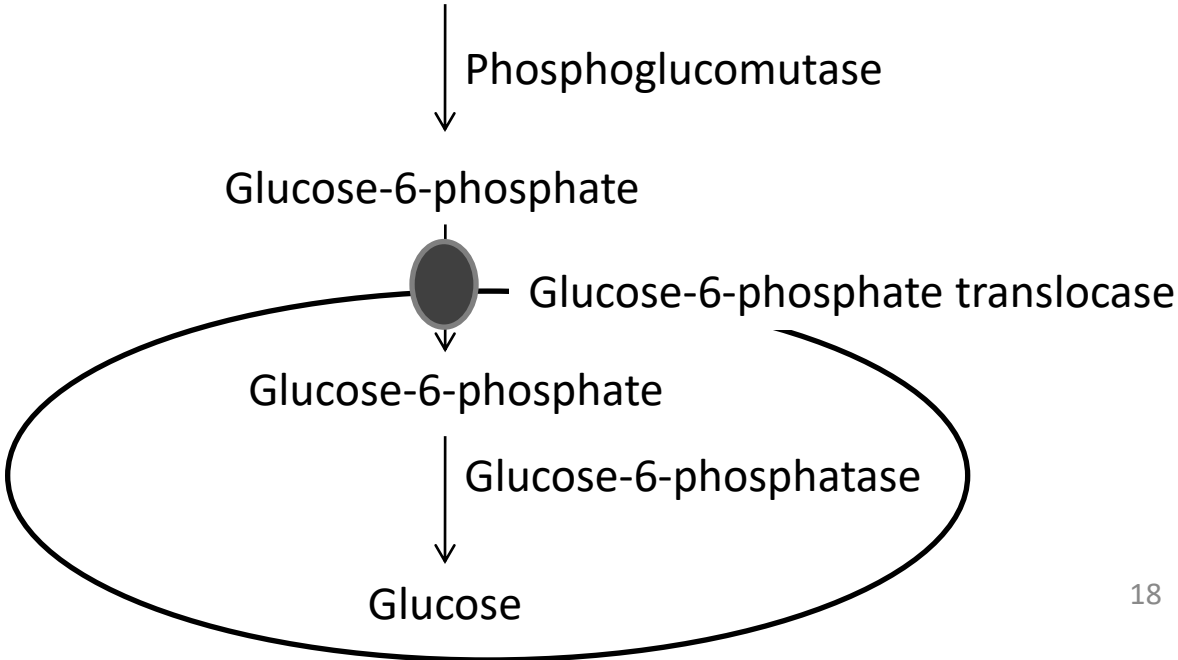
- Glycogen in branched molecule:
  - More soluble
  - High number of ends to which glucose molecule can be added or removed increasing the rate of glycogen synthesis and degradation.

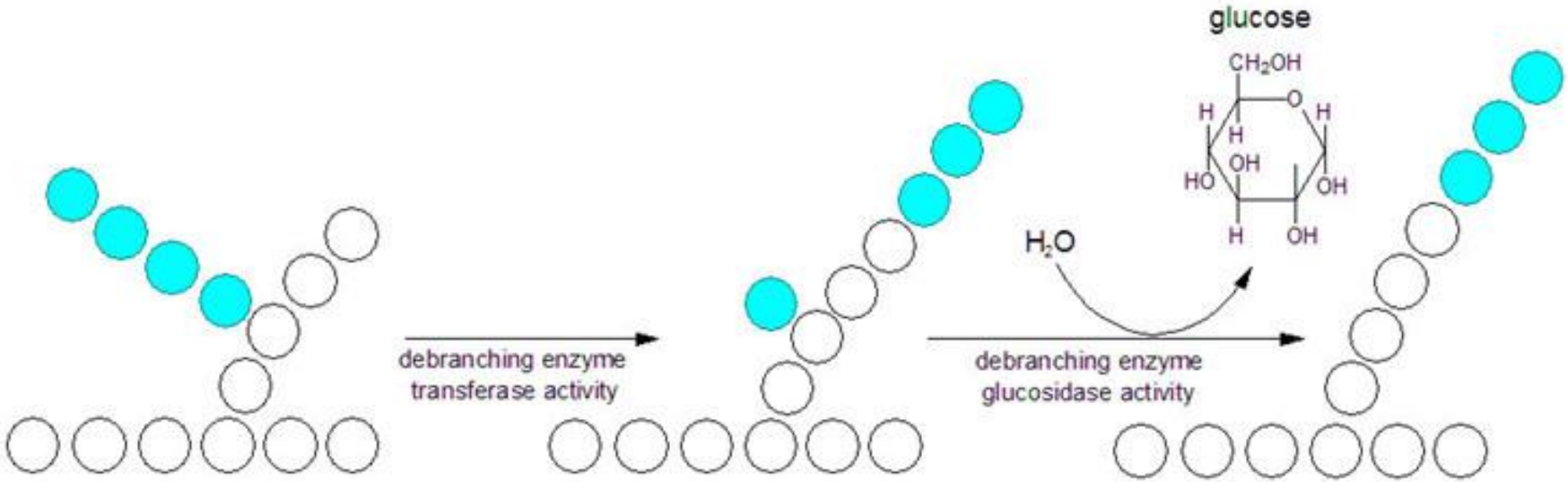
Glycogen synthesis



Glycogen degradation






glucose
CH2OH
O
H
H
H
OH
HO
OH
H
OH
H2O
debranching enzyme
transferase activity
debranching enzyme
glucosidase activity

Lysosomal degradation of glycogen

- 1-3% of glycogen is continuously degraded by the lysosomal enzyme α(1→4)-glucosidase (acid maltase)

- Liver GSD (0B, **I**, IIIb, **VI**, **IXa**, IXc):
  - Hypoglycemia
  - Hepatomegaly
  - Growth failure
  - Metabolic derangements: hyperlipidemia, lactic acidosis, hyperuricemia.
- Muscle GSD (0A, **V**, IXd, IXe):
  - Exercise intolerance, easy fatigability, weakness
  - Myalgia
  - Rhabdomyolysis
- Heart GSD (0A, **II**, IXf)
- Combined liver and muscle (**IIIa**, IXb)

- Treatment of GSD:
  - Liver: avoid fasting, cornstarch
  - Muscle: exercise, oral sucrose
  - Pompe: enzyme replacement therapy (Alglucosidase alfa (Myozyme)).

Complications of hepatic glycogenoses:

- Seizure, developmental delay, growth failure (hypoglycemia)
- Renal impairment: tubulopathy (hypercalciuria) and glomerular disease (microalbuminuria and hypertension, renal failure).
- Delayed puberty and osteoporosis (chronic ketosis)
- Hepatic adenoma
- Anemia
- Polycystic ovaries
- Complications of hyperlipidemia: pancreatitis

- Complications of muscle glycogenoses:
  - Renal failure because of rhabdomyolysis
  - Muscle weakness and wasting
  - Cardiomyopathy

Case scenario 2

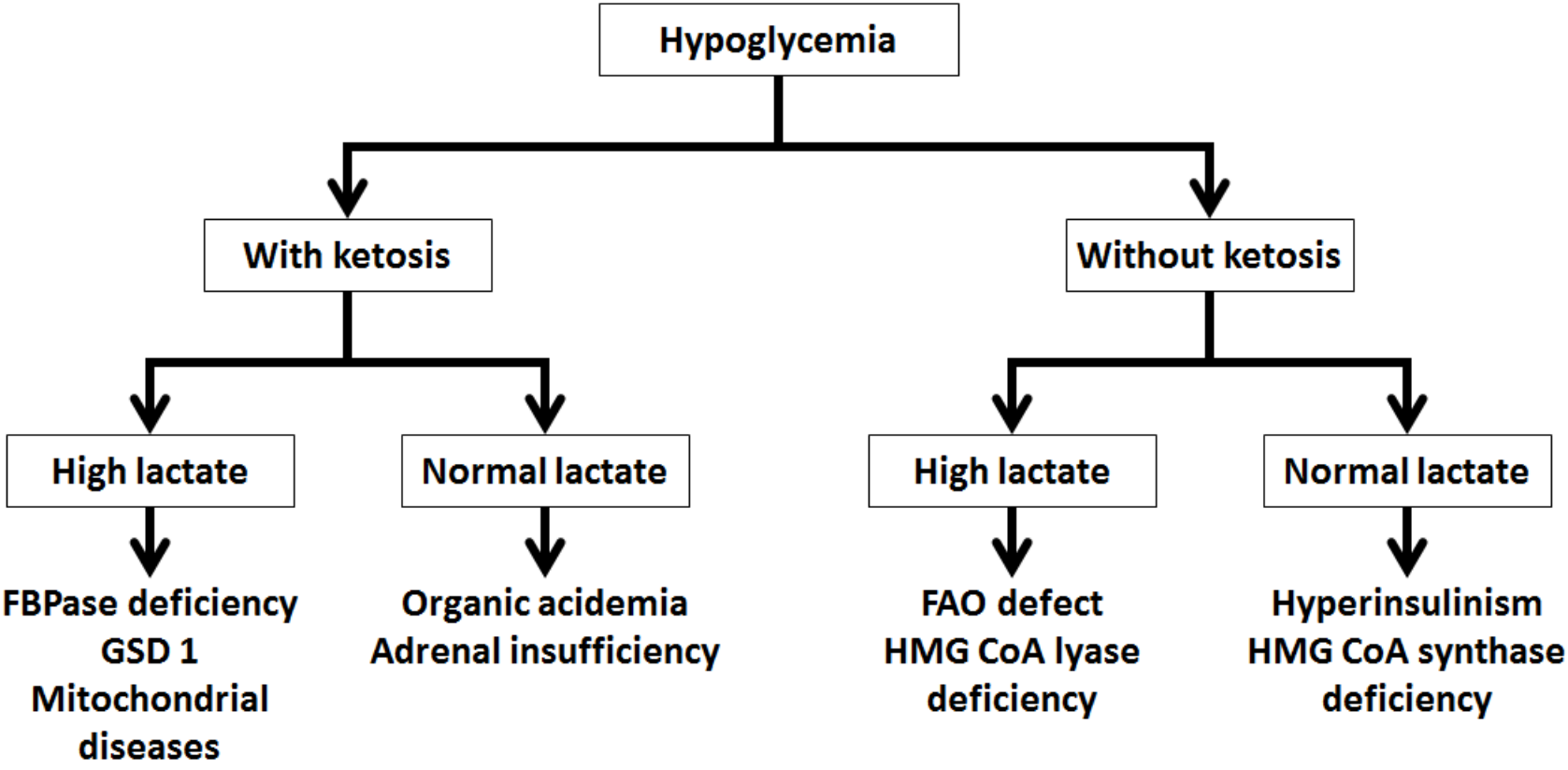
- 4 year old girl presented to the ER with 2 day history of runny nose and decreased appetite. This morning, the mother noticed that she is very tired and does not want to leave the bed.
- Mild cough, runny nose, felt worm to touch.
- Her brother has cold
- Normal development
- Fully vaccinated

- Regular diet, but decreased appetite for the past two days. Last meal was yesterday 6 pm.
- No significant past medical or surgical histories.
- Parents are cousins. She has a younger brother.

- O/E:
- VS: tachypnia, tachycardia, febrile (38.5)
- Lethargic and pale
- Chest/CVS: normal
- Abdomen: liver felt 2 cm BCM
- MSS: normal
- Neuro: lethargic

- ER lab:
- U&E: CO2 16
- Glucose: 2 mmol/l (35 mg/dl)
- CBC: normal
- UA: normal (negative ketones)

- Most likely diagnosis?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GSD 1
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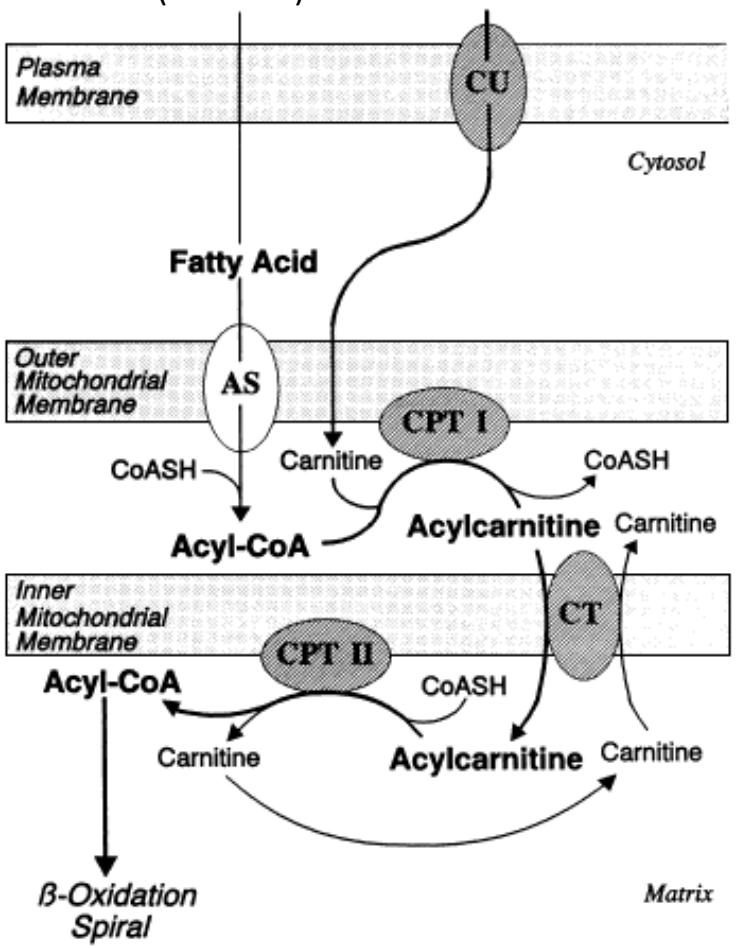
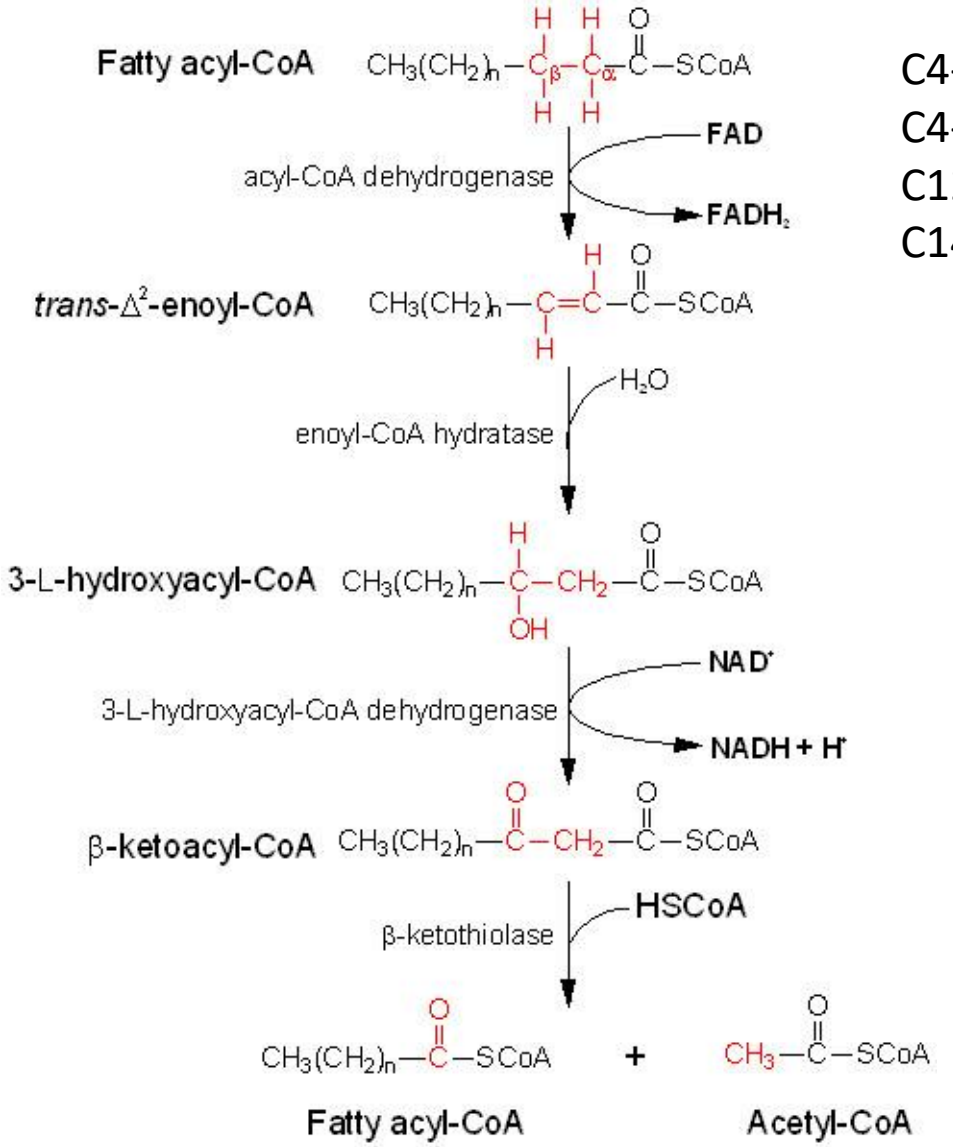
Hyperinsulinism
HMG CoA synthase deficiency

Fatty acids

Medium and short fatty acids (C4-C12)

Long chain fatty acids (C14-C18)

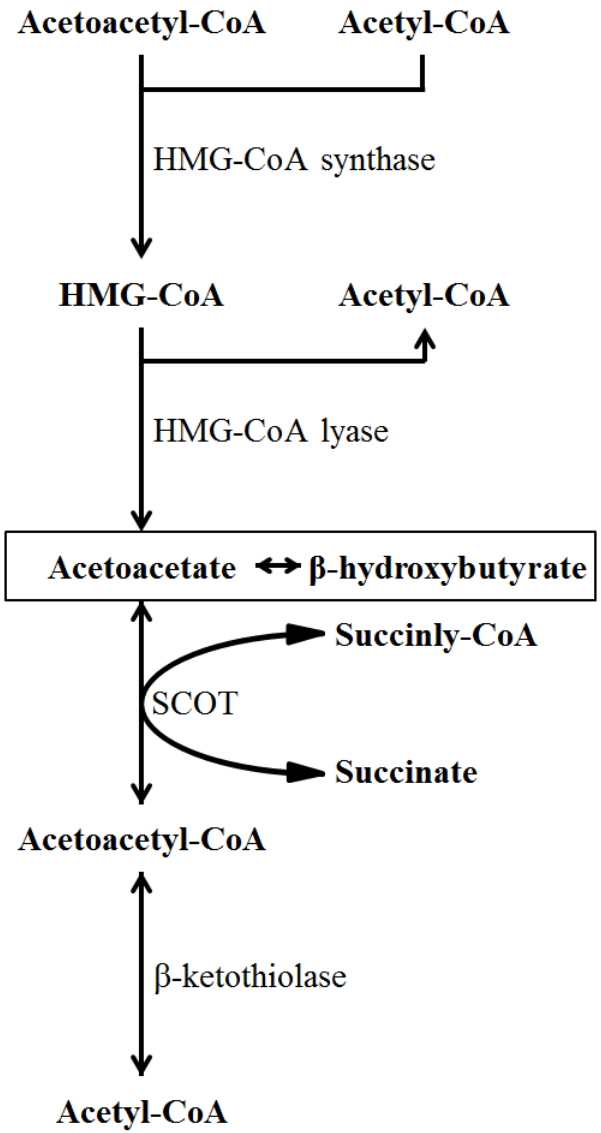




C4-C6: SCAD
C4-C12: MCAD
C12-C18: LCAD
C14-C20: VLCAD

- Fatty acid oxidation defects:
  - Hypoglycemia
  - Hepatopathy
  - Myopathy
  - Cardiomyopathy

- Management:
  - Fat restriction
  - Avoid fasting
  - MCT for long chain fatty acid oxidation defects


Acetoacetyl-CoA
Acetyl-CoA
HMG-CoA synthase
HMG-CoA
Acetyl-CoA
HMG-CoA lyase
Acetoacetate ↔ β-hydroxybutyrate
Succinly-CoA
SCOT
Succinate
Acetoacetyl-CoA
β-ketothiolase
Acetyl-CoA

- HMG CoA synthase deficiency:
  - Hypoglycemia with acute illness
  - Hepatomegaly
  - Low ketones

- HMG CoA lyase deficiency
  - Hypoglycemia
  - Acidosis
  - Low ketones
  - High lactate
  - High ammonia
  - Hepatomegaly and abnormal LFT
  - Pancreatitis and cardiomyopathy

- Rx:
  - Avoid fasting
  - High carbohydrate intake during stress
  - IV dextrose
  - Restrict protein and fat

Case scenario 3

- 6 years old presented to your clinic for regular follow up visit.
- Her past medical history was significant for recurrent episodes of hypoglycemia that typically triggered by common illnesses or prolonged fasting.
- Otherwise she has been healthy.
- Metabolic and endocrine work up have been normal (positive ketones during the hypoglycemia episodes).
- Episodes were more frequent, but last episode was 6 months ago.

- Ketotic hypoglycemia