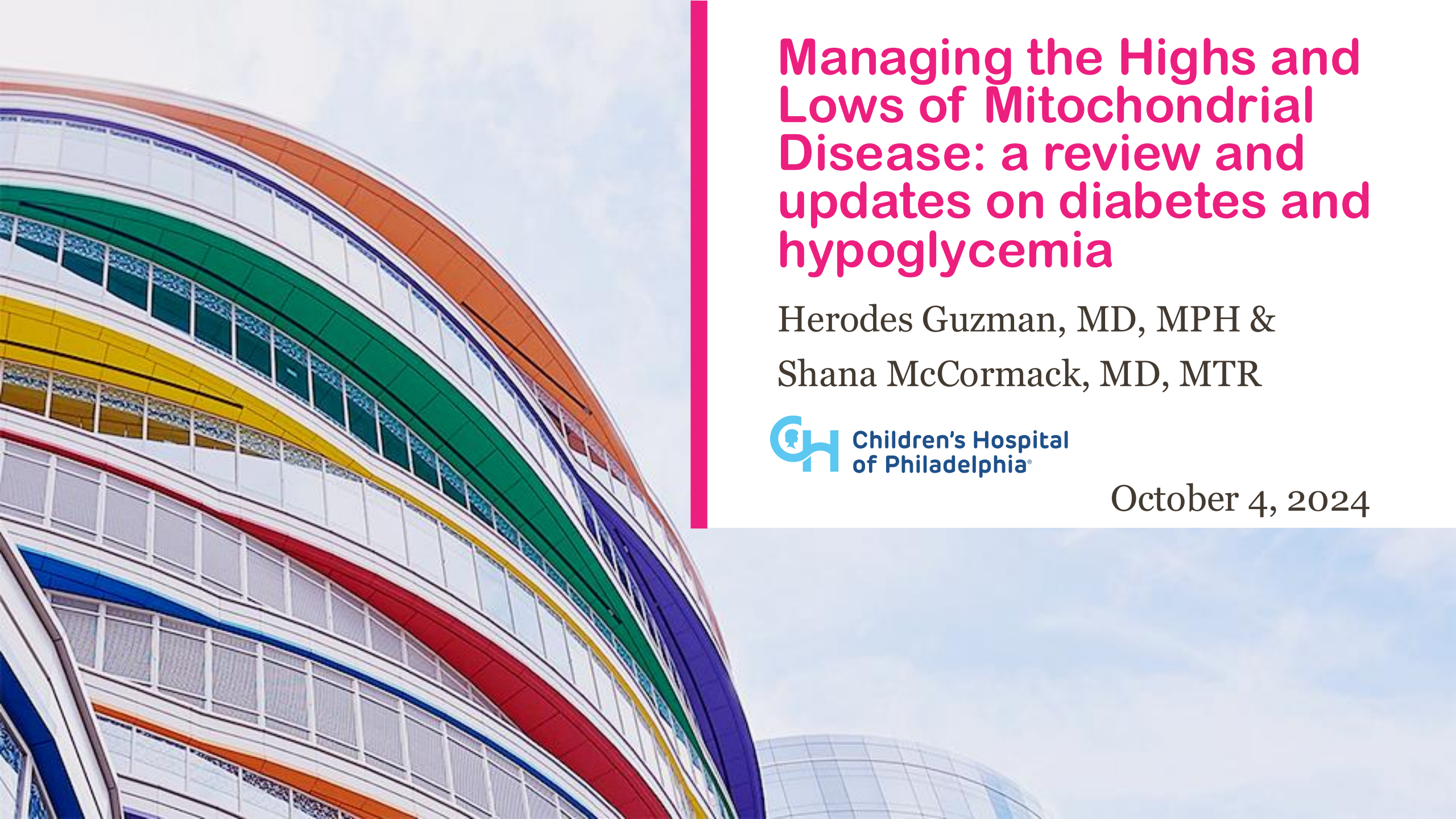

Managing the Highs and Lows of Mitochondrial Disease: a review and updates on diabetes and hypoglycemia

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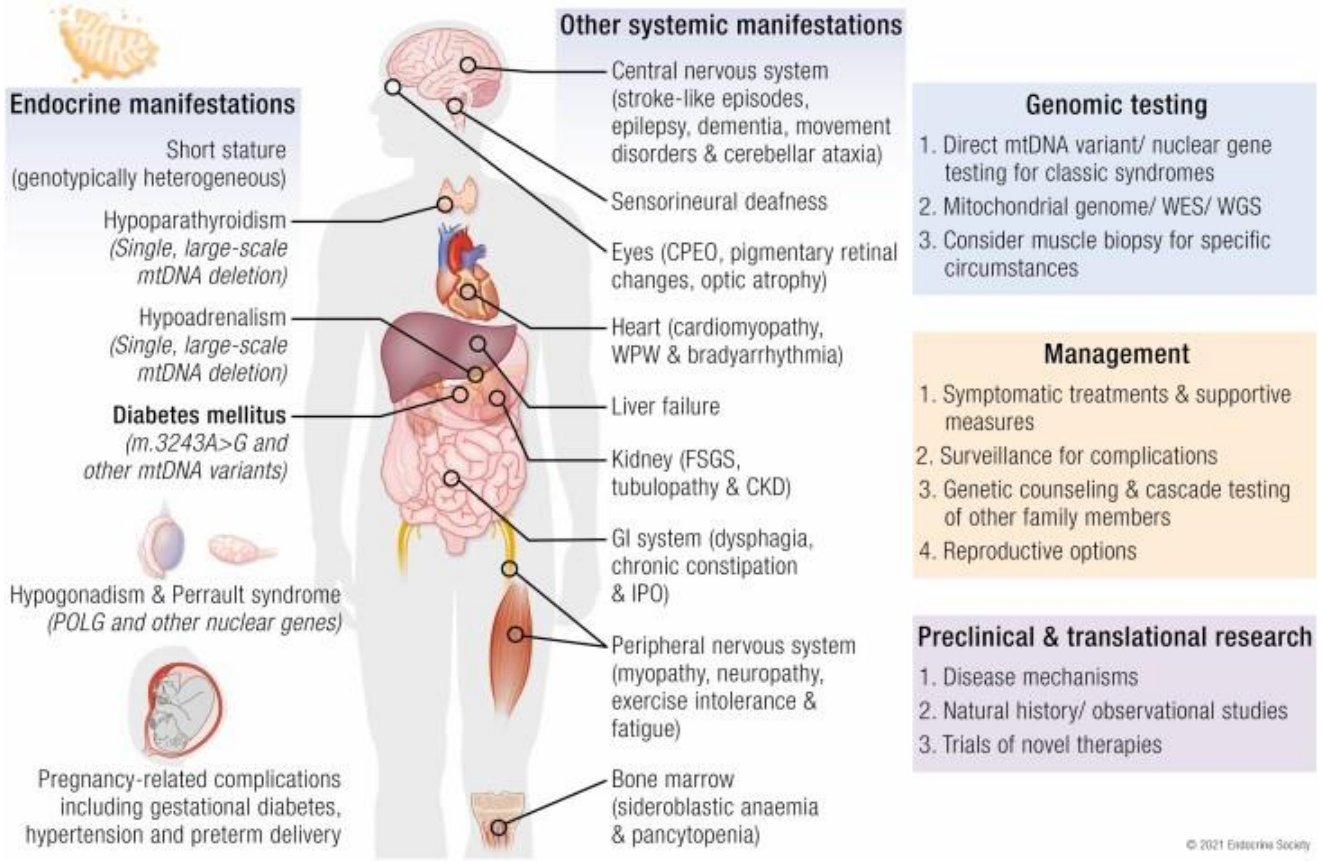
Children's Hospital of Philadelphia®

October 4, 2024

Mitochondrial disease affects endocrine function

- **Mitochondrial diabetes** is the most common endocrine disorder

- **Hypoglycemia** or low blood sugar is also seen in mitochondrial disease, affecting diabetes management



Reference PMID: 34644386

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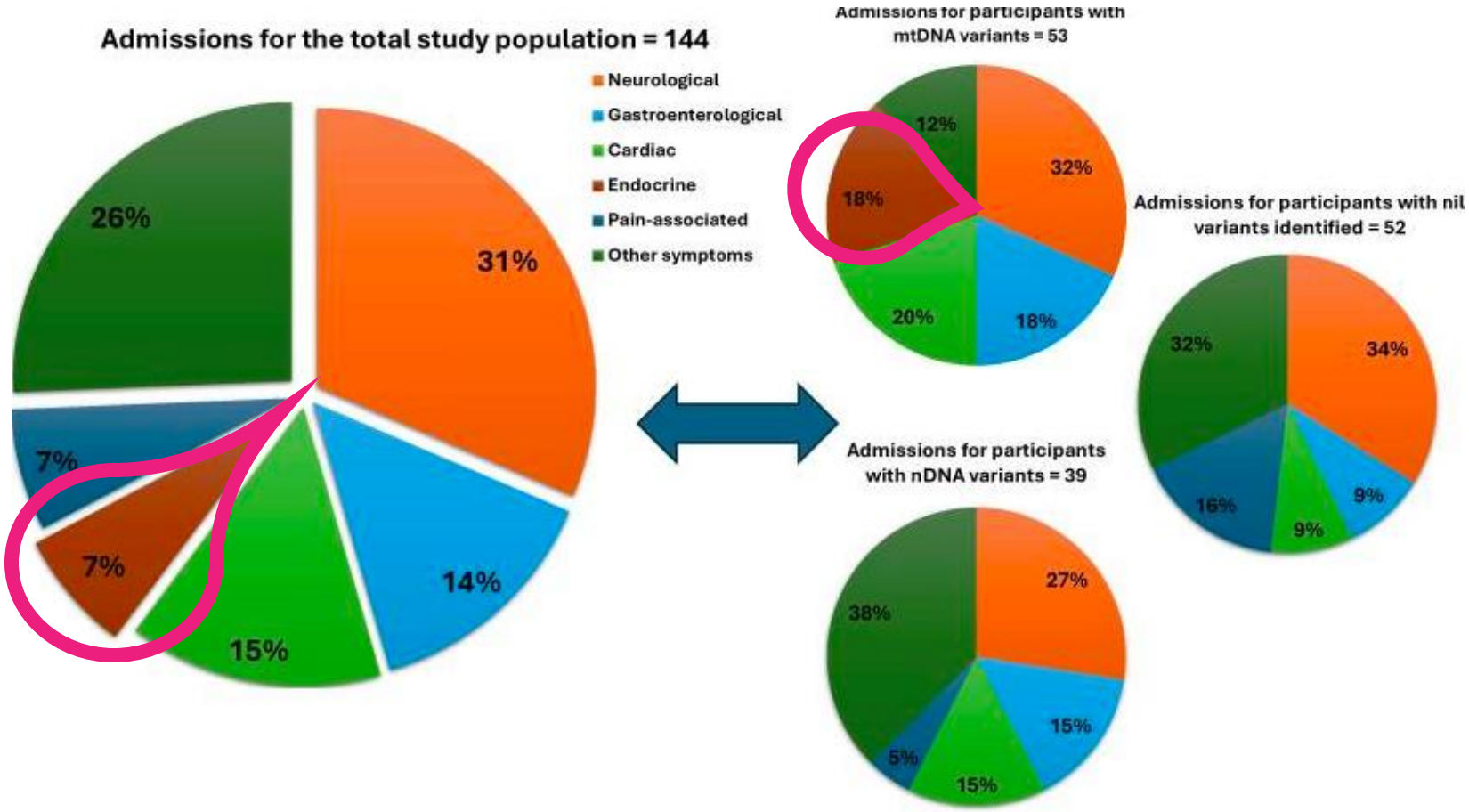
Endocrine-related hospitalizations

- In one study, 7% of hospital admissions were due to endocrine disease (**all blood sugar related**)



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Reference PMID: 38868460

Mitochondrial Diabetes

The most common mitochondrial endocrine disorder

- Mitochondrial diabetes affects 2% of children with mitochondrial disease
- Affects 24% of adults with mitochondrial disease

Mitochondrial disease (genotype)	Prevalence estimates (all ages)
OVERALL	**15%**
m.3243A>G (MELAS, MIDD)	~40%
m.14709T>C	50%
SLSMDS	10-15%
m.8344A>G (MERRF)	~10%
m.11778G>A	7%
Multiple mtDNA mutations	7%
RRM2B (AR, AD)	3-5%
OPA1 (AR, AD)	4%
POLG (AR, AD)	3-11%
Others	-

Among genotype; from small studies; AR: autosomal recessive; AD: autosomal dominant

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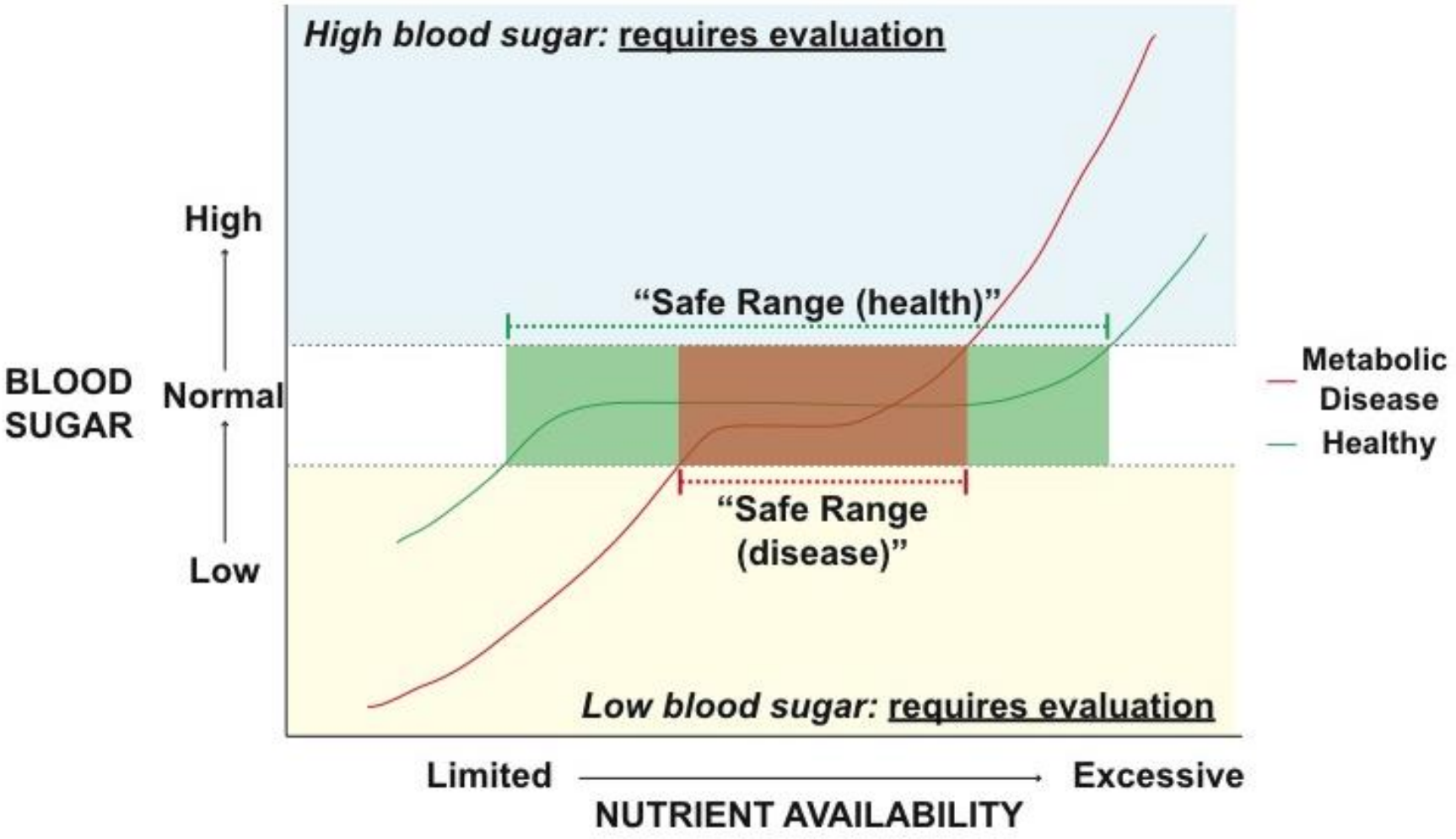
Reference PMIDs: 35552684, 29594260, 25330715, 27716753

What is a normal blood sugar?



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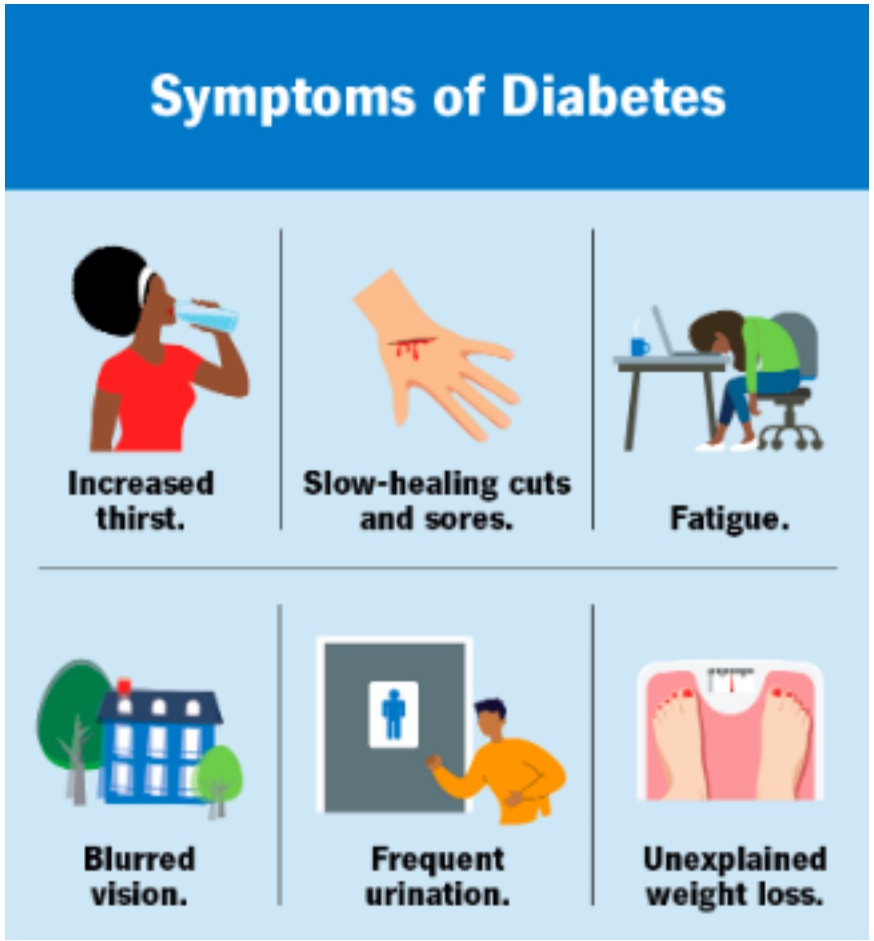
Mitochondrial diabetes symptoms*



- **Emergencies**:
  - Diabetic ketoacidosis
  - Hyperosmolar hyperglycemia

Cleveland Clinic. Diabetes.

Mitochondrial diabetes is different

- **Type 1 Diabetes**
  - Autoimmune injury leads to insulin deficiency
- **Type 2 Diabetes**
  - Increased insulin resistance leads to beta cell failure and eventual insulin deficiency

- **Mitochondrial diabetes**
  - Thought to be due to a combination of both insulin deficiency and insulin resistance

Reference PMIDs: 35552684, 25330715, 34320286

There are no evidence-supported practices specific to mitochondrial diabetes

Our Approach: for those at risk

- Yearly surveillance
  - Hemoglobin A1c
  - Fructosamine
  - Blood sugar checks (for 3 days prior to visit)
    - First thing in the morning
    - 2 hours after the largest meal of the day

If there is ketosis/dehydration/weight loss…

- Start insulin therapy

If there is none of the above…

- Consider oral therapies

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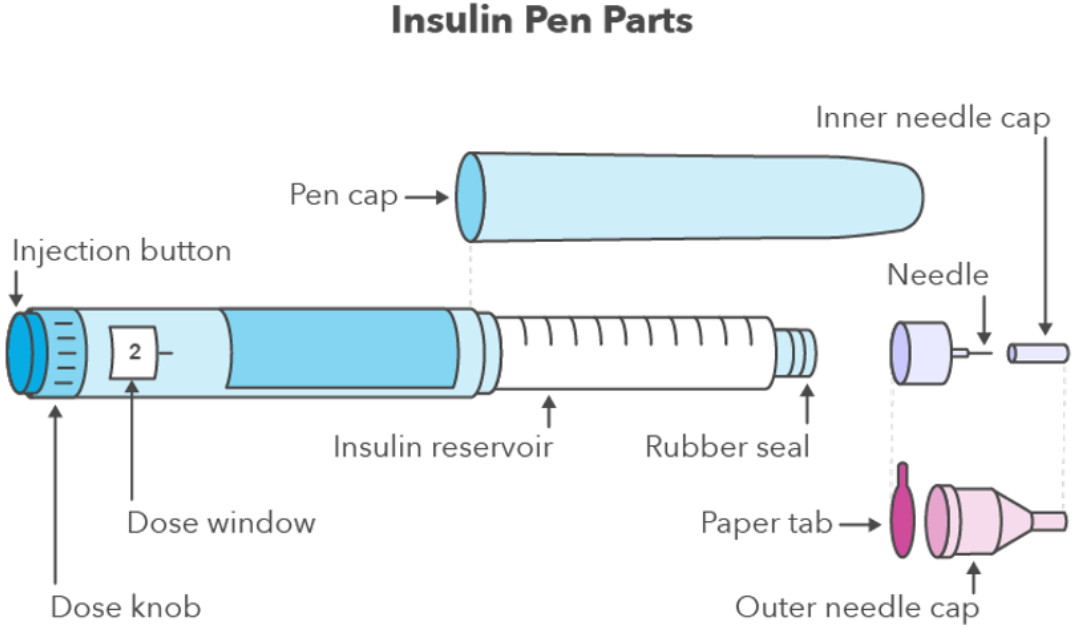
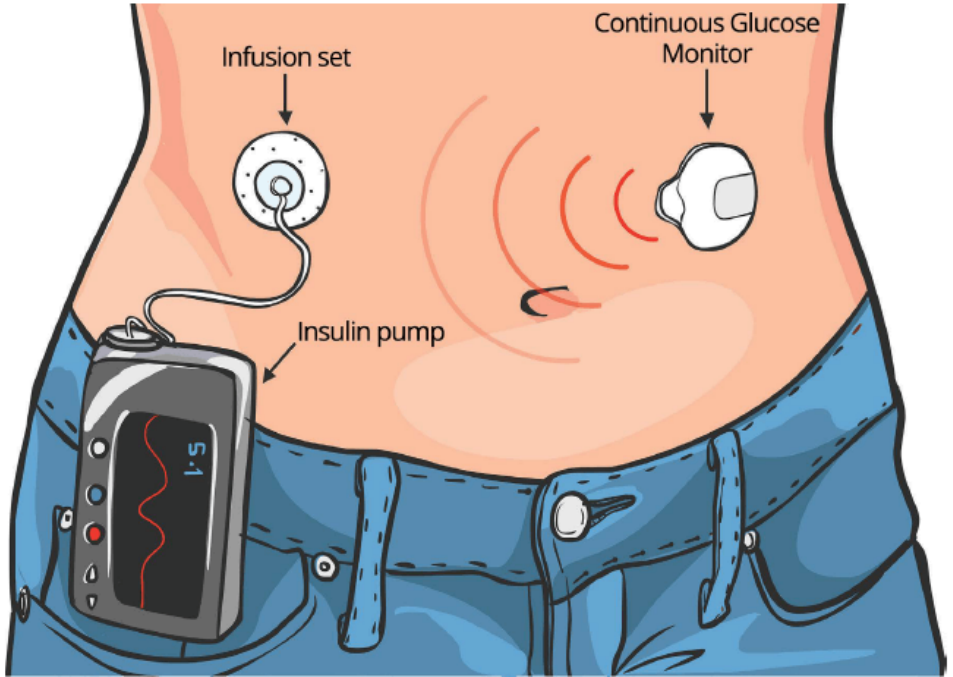
Our Approach: management considerations

- Insulin therapy
  - Multiple daily injections (basal/bolus vs. 70/30)





- Insulin pumps

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Our Approach: management considerations

- Oral medications
  - Sulfonylureas (hypoglycemia risk)
  - GLP-1 receptor agonists (can present a problem for gut dysmotility and pancreatitis)
  - Tirzepatide (dual GIP and GLP-1 receptor agonist)

  - Consider metformin (lactic acidosis risk)
  - Consider SGLT2 inhibitors (ketoacidosis risk)
  - Consider DPP4 inhibitors (in adults)

  - Under study:
    - Imeglimin

Reference PMIDs: 38061447, 37715448

Our Approach: management considerations

- Blood sugar monitoring
  - Finger stick blood sugars

- Continuous glucose monitors

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Our Approach: management considerations

- Hypoglycemia rescue
  - Premixed, intranasal, injectable glucagon

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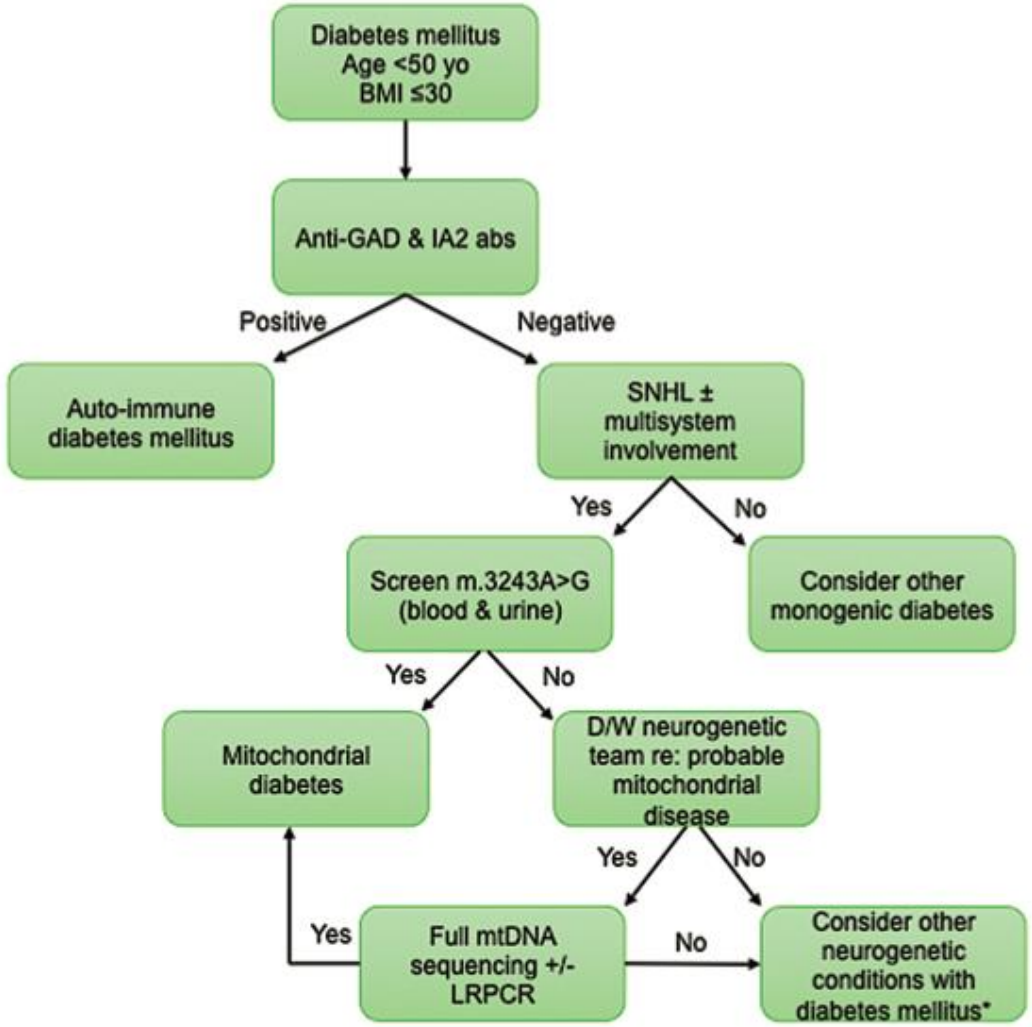
Summary

- *Insulin secretion* requires mitochondrial ATP production
- *Insulin resistance* (e.g., in muscle) can occur
- **Educate** regarding symptoms
- **Screen** annually
- **Manage** based on physiology, including blood ketones
- Select medications based on **comorbidities** and risk for off-target effects
- Use **technology** (CGM, pumps) where possible



*Wolfram syndrome, Friedreich ataxia, myotonic dystrophy type I

Reference PMID: 35552684

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Hypoglycemia

Hypoglycemia in mitochondrial disease

- Overall estimated prevalence of ~19% among patients with mitochondrial disease <u>without</u> diabetes

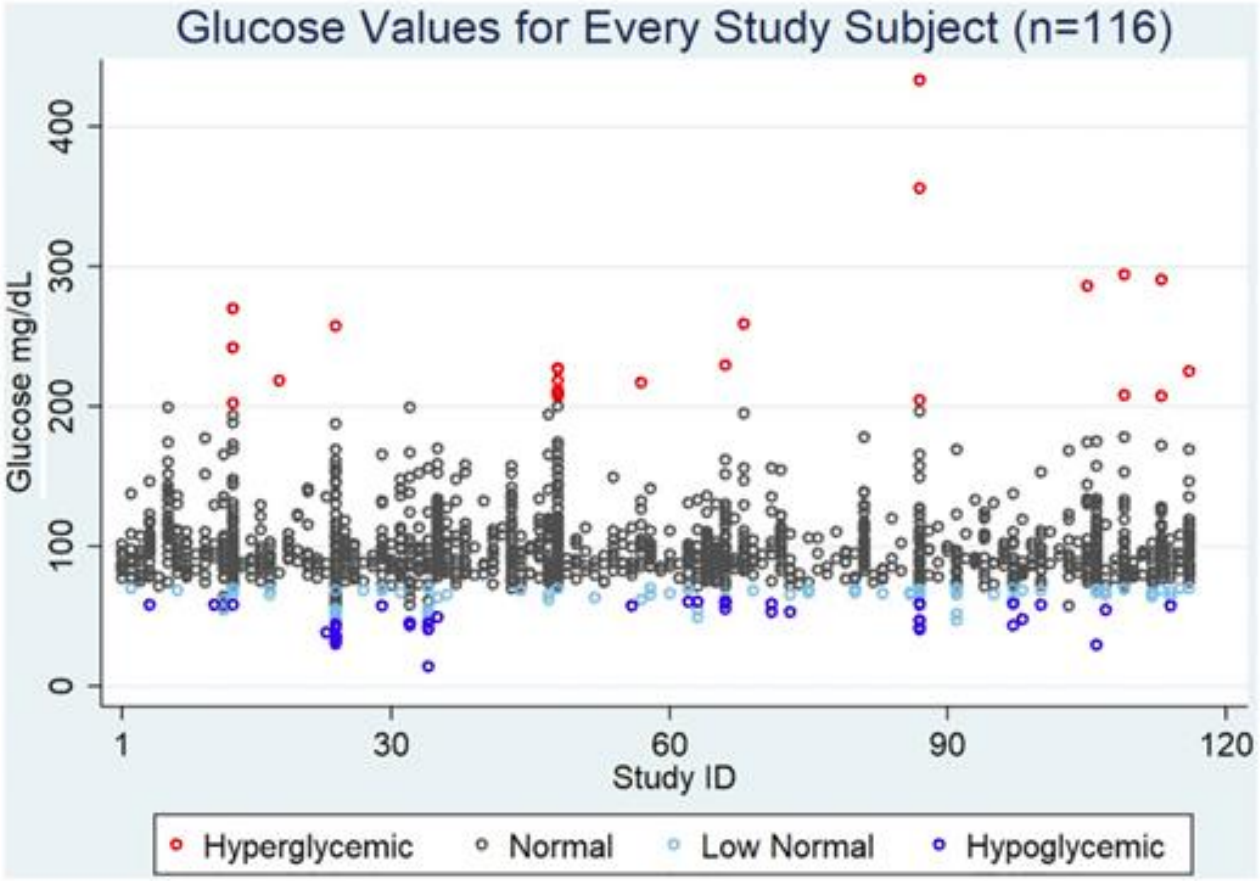

Fig. 1. Glucose values for every study subject (n = 116).

Reference PMID: 33737013

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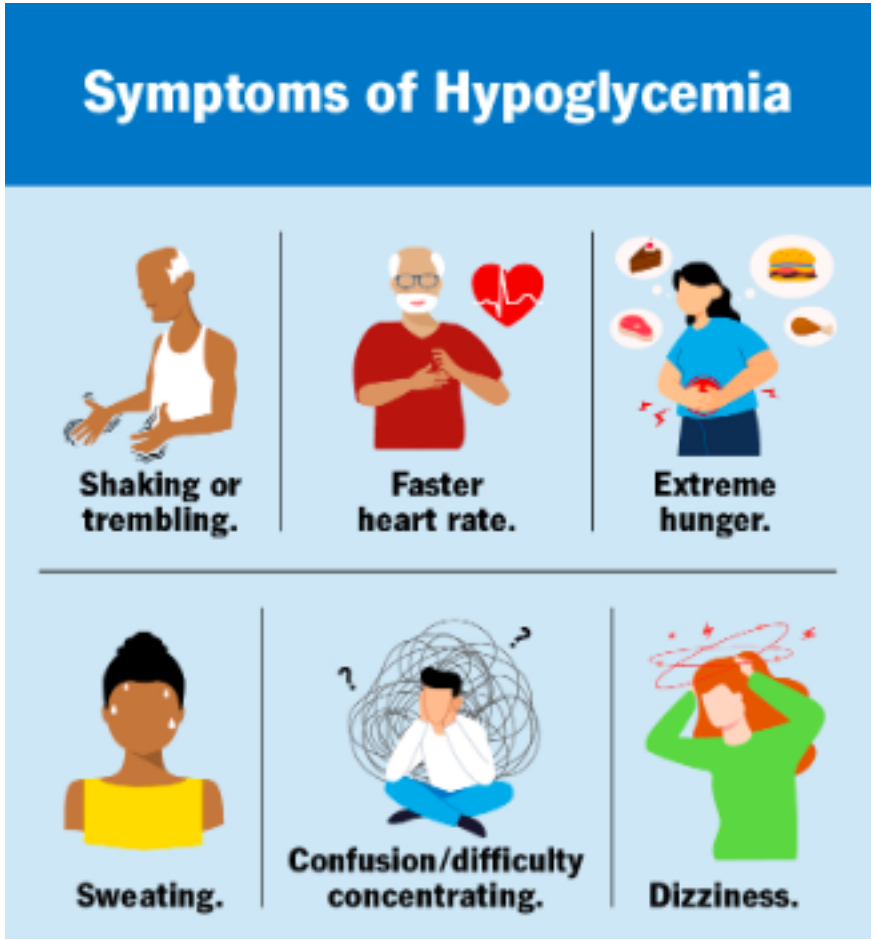
Hypoglycemia symptoms*



- Can progress to seizures and unresponsiveness

[Cleveland Clinic. Hypoglycemia.]

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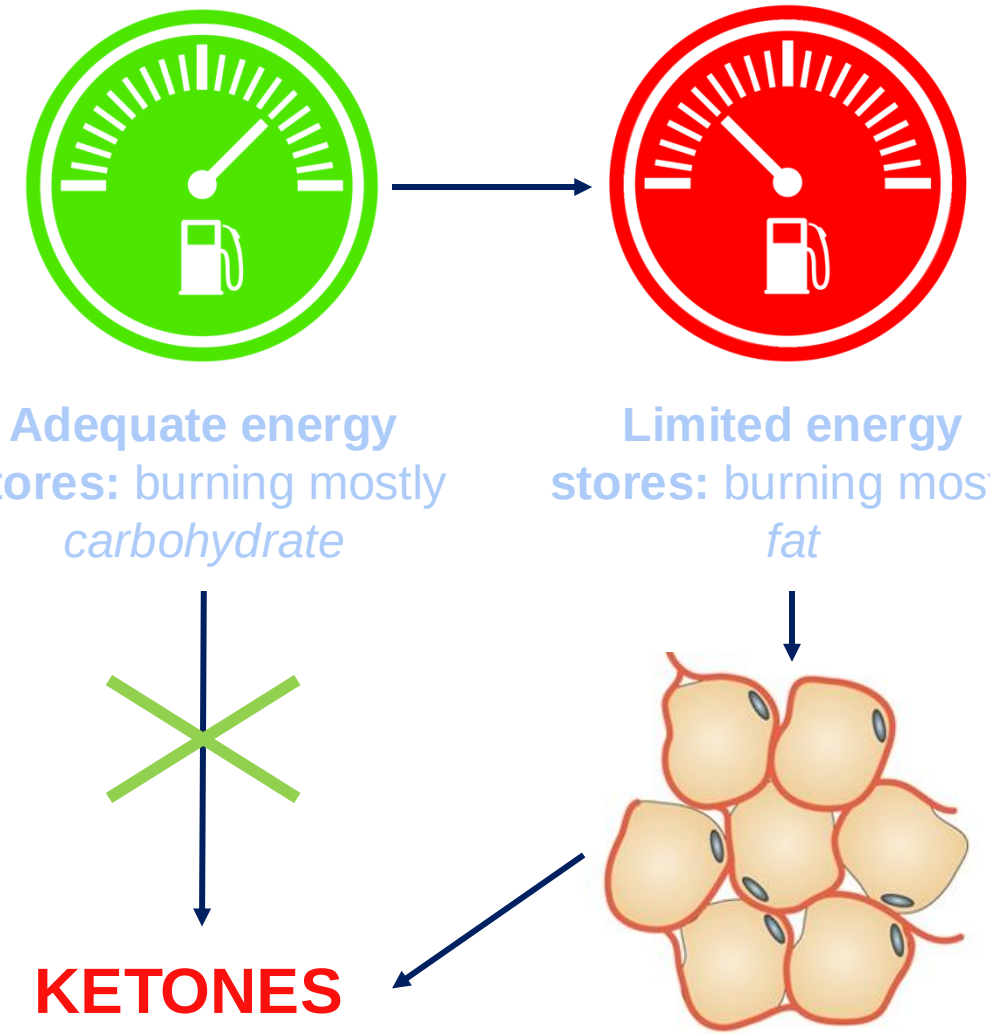
Hypoglycemia types

- When evaluating, we divide into **ketotic** and **non-ketotic hypoglycemia**
- Often, **“fasting”** hypoglycemia is **ketotic**
- Often, **“reactive”** hypoglycemia is **non-ketotic**
- Some individuals with metabolic disorders **cannot produce ketones**



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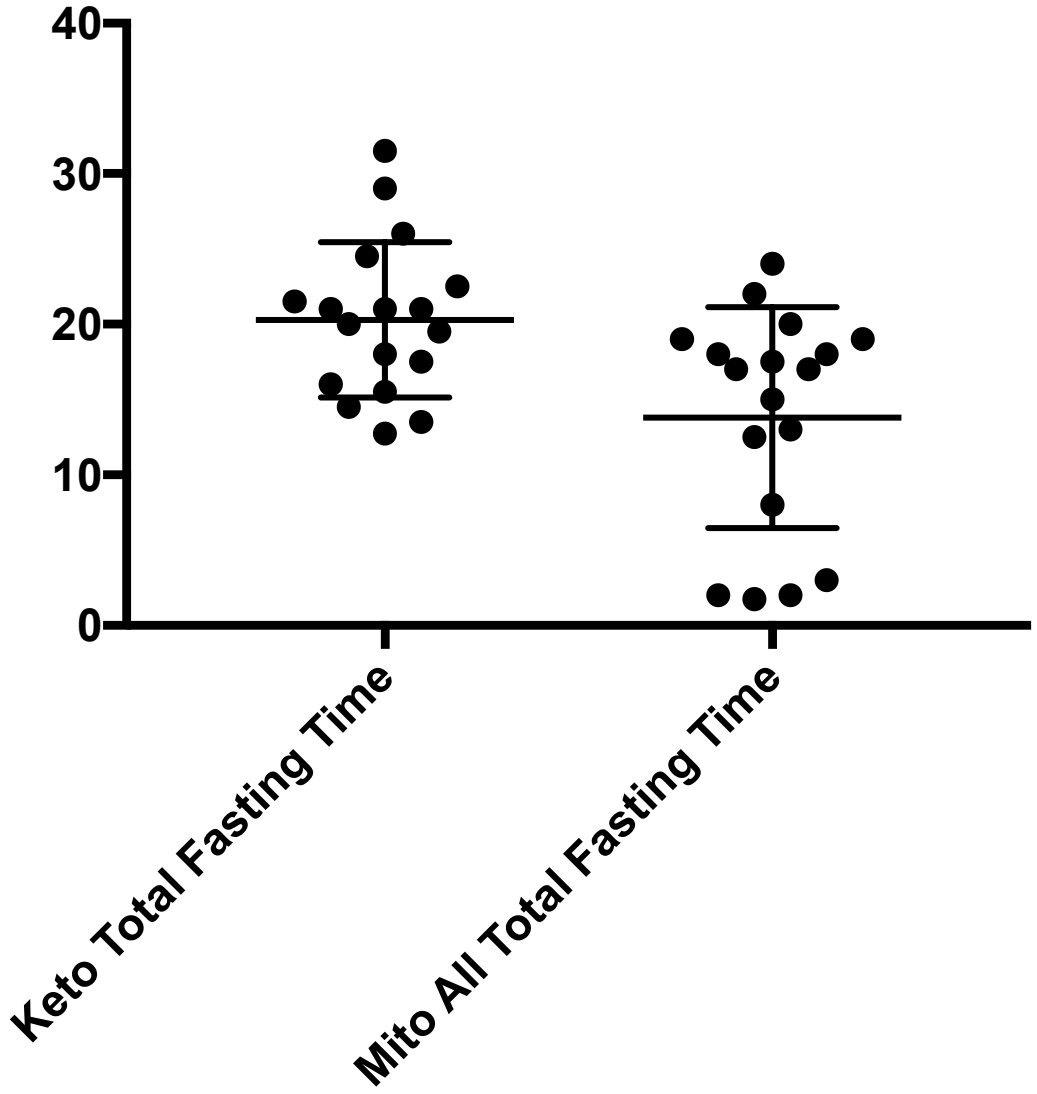
Hypoglycemia evaluation

- Inpatient diagnostic fasting studies (controlled monitoring)
- Compare mitochondrial disease (suspected, confirmed) to idiopathic ketotic hypoglycemia
- **Fasting time was shorter, and ketone production was less**



Patrick Hanley, CHOP/Nemours

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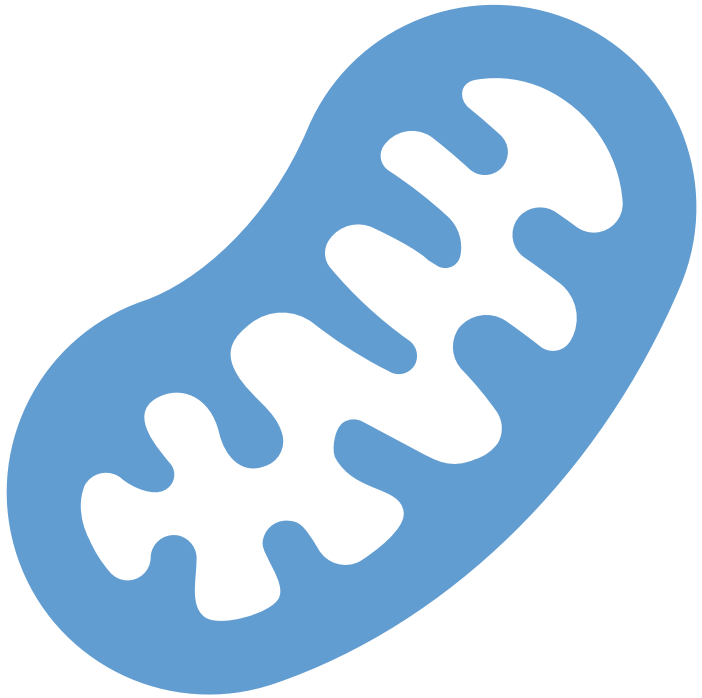
Causes of hypoglycemia in mitochondrial disease

- Inherent to mitochondrial disease
- Liver dysfunction
- Malnutrition
- Reactive hypoglycemia
- Adrenal insufficiency
- Growth hormone deficiency
- Diabetes management (i.e., from insulin overdose or oral hypoglycemics)



Reference PMID: 33737013

Hypoglycemia management

Emergency

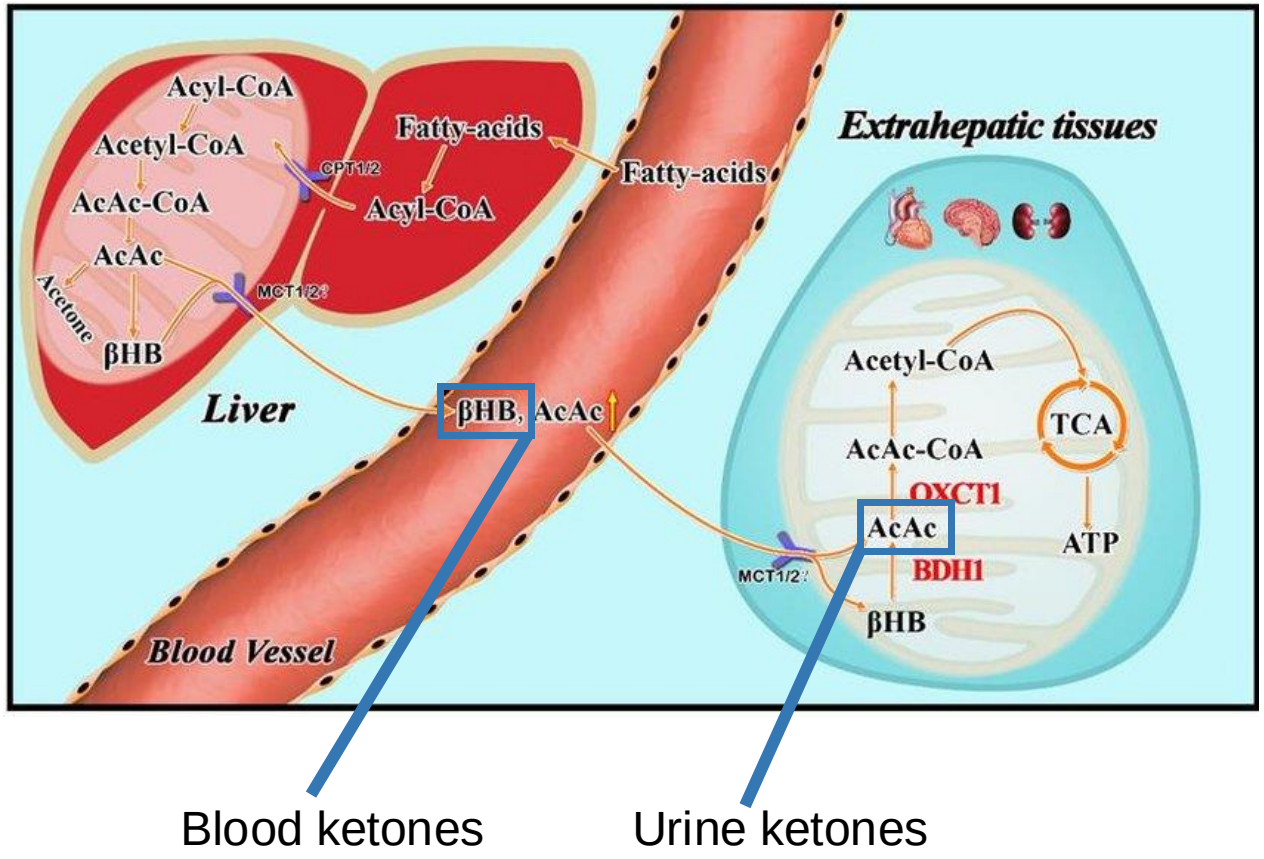
- Push dextrose fluids (D10)
- Avoid hyperglycemia (lactate risk)
- May need dextrose + insulin drip

Have an emergency plan and letter

- **Maintenance**
  - Use D5 maintenance fluids until tolerating regular diet
  - Avoid prolonged fasting
  - Restart complete nutrition as soon as possible

Hypoglycemia management

- **Check blood sugar** when
  - symptomatic
  - after longest usual fasting period
- Goal blood sugar at least 70 mg/dL
  - <50 mg/dL is an **emergency**
- **Check blood ketones (BHB)**
- Next steps are based on findings
  - Surveillance
  - Rescue
  - Support
- **Watch out for NPO status!**



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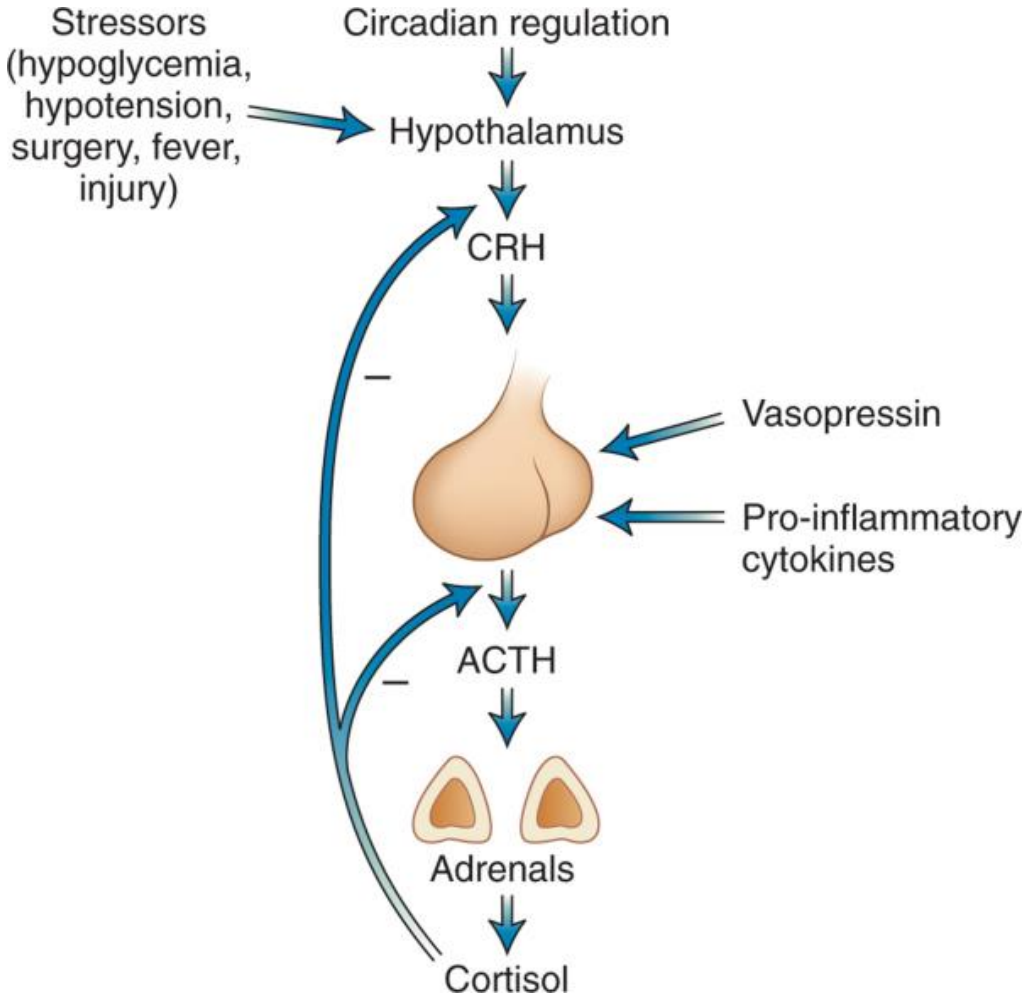
Reference PMID: 29414764

Adrenal insufficiency

- Mitochondria are critical for **steroid synthesis**
- Symptoms of adrenal insufficiency (especially with critical illness)
  - Low blood sugar
  - Low blood pressure
  - Low sodium levels
  - High potassium levels



Williams, 12th edition

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Adrenal insufficiency: who needs testing?

- History of having received steroid medications (e.g., prednisone)
- Individuals with suggestive symptoms warrant testing
- Empiric "stress dose steroids" are sometimes given in ICU settings

Table 1. Descriptive statistics of clinical characteristics in pediatric intensive care unit (PICU) patients with and without mitochondrial disease.

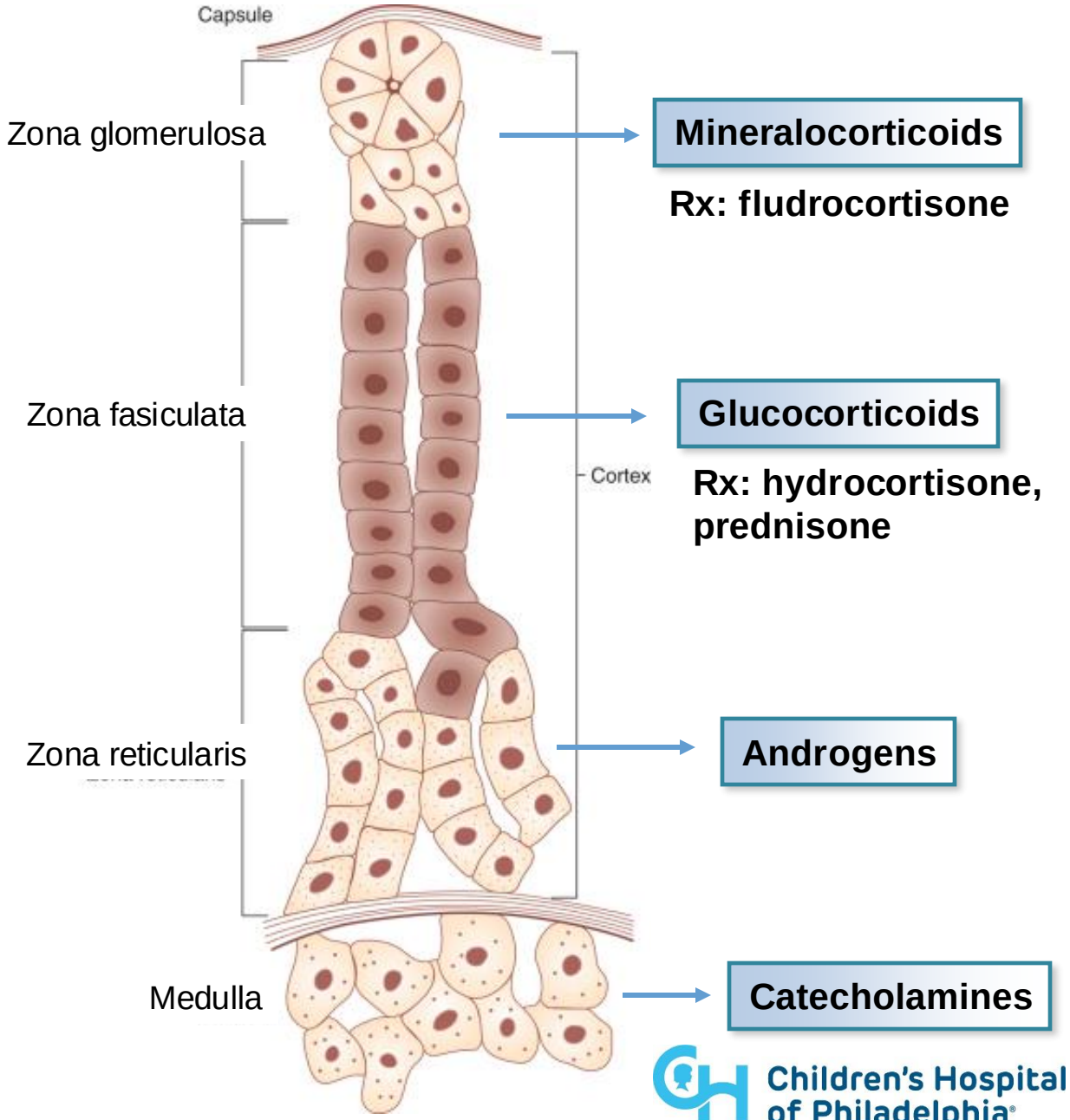
Factor	Mitochondrial disease	Other diagnoses
Age in years, median (IQR)	7.6 (9.0)	4.6 (11.6)
Length of stay in days, median (IQR)	2.9 (5.6)	1.7 (2.9)
Mortality, % deceased	5.2%	2.4%
PRISM score median (IQR)	3 (6)	2 (5)
PIM2 score (IQR)	−3.38 (1.88)	−4.74 (2.02)
Hours on ventilator, median (IQR)	71.5 (187.7)	14.0 (49.5)

IQR interquartile range.

PMID: 33627817

Adrenal insufficiency

- **Screening**
  - 8a ACTH
  - cortisol
  - *PRA/aldosterone, DHEAS*
- **Provocative testing**
- **Steroid replacement**
  - Glucocorticoid/mineralocorticoid
  - Formulation
  - Daily
  - Stress-dose
- **Adverse effects (iatrogenic Cushing's)**



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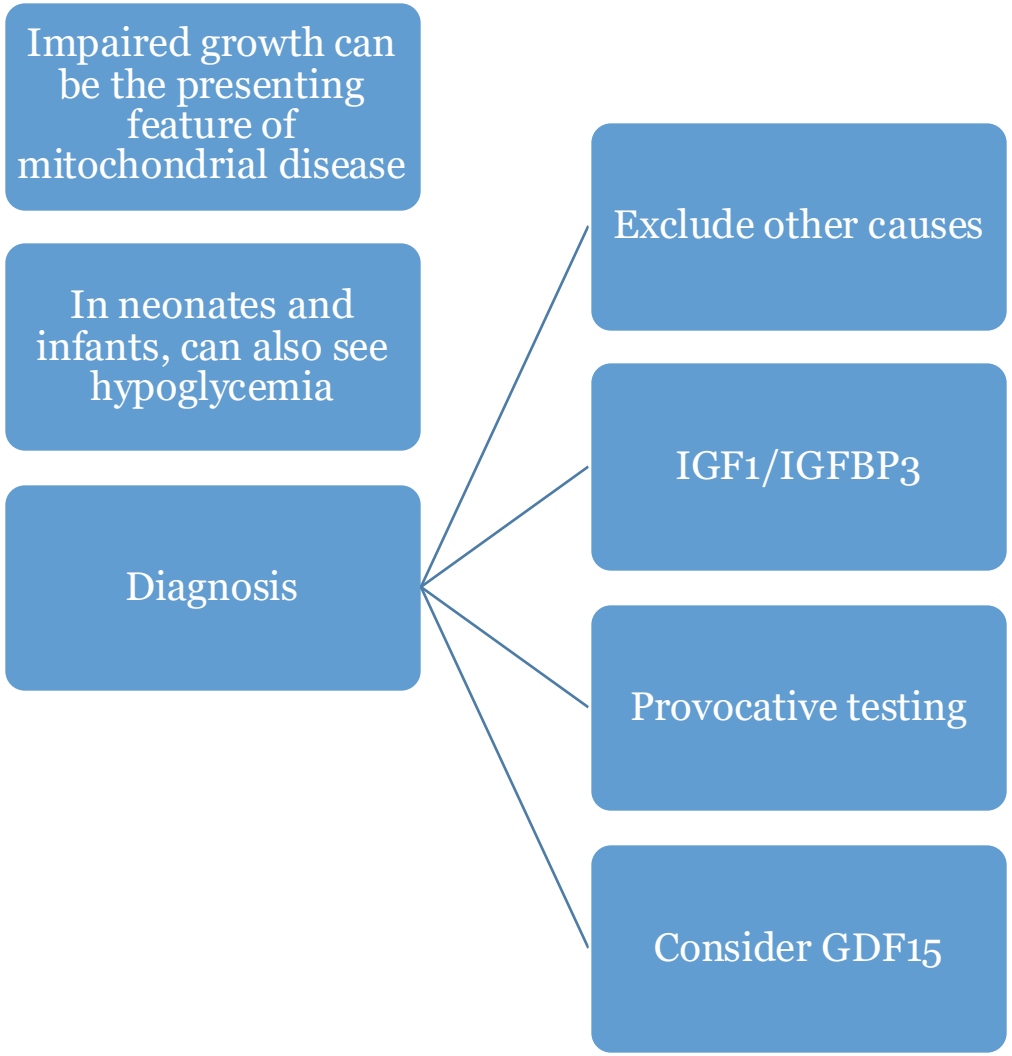
Growth hormone deficiency



- **Management**
  - Growth hormone injections (daily vs weekly)
- **Risks**
  - Diabetes development

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Summary

- Endocrine disorders are prevalent in individuals with mitochondrial disease
- Evidence-supported and symptom-directed patient screening is appropriate
- Identify opportunities for effective interventions

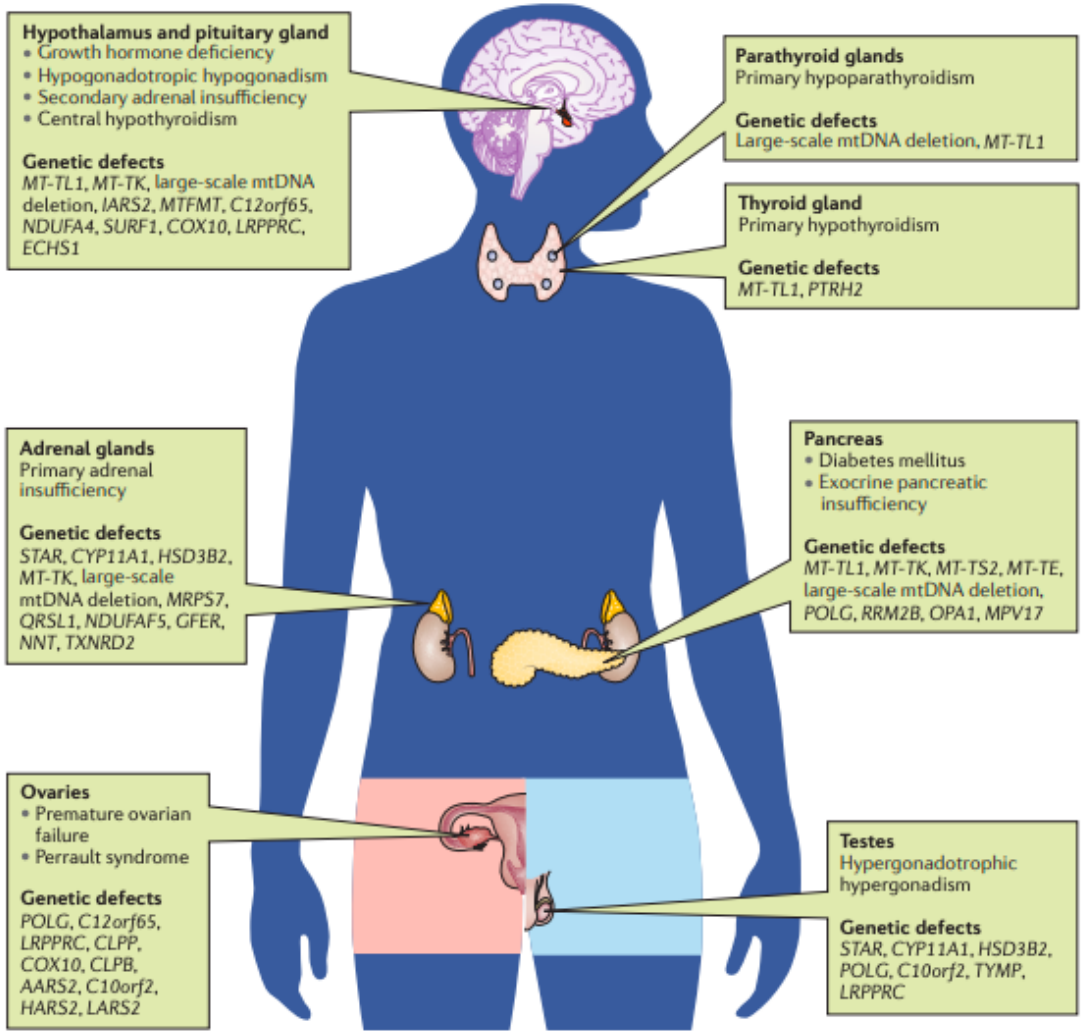

Figure 2 | **Endocrine dysfunction in mitochondrial disease and their associated gene defects.** Endocrine dysfunction associated with primary mitochondrial disease. Genes with mutations reported in patients with dysfunction of the illustrated endocrine gland are included. mtDNA, mitochondrial DNA.

Reference PMID: 27716753

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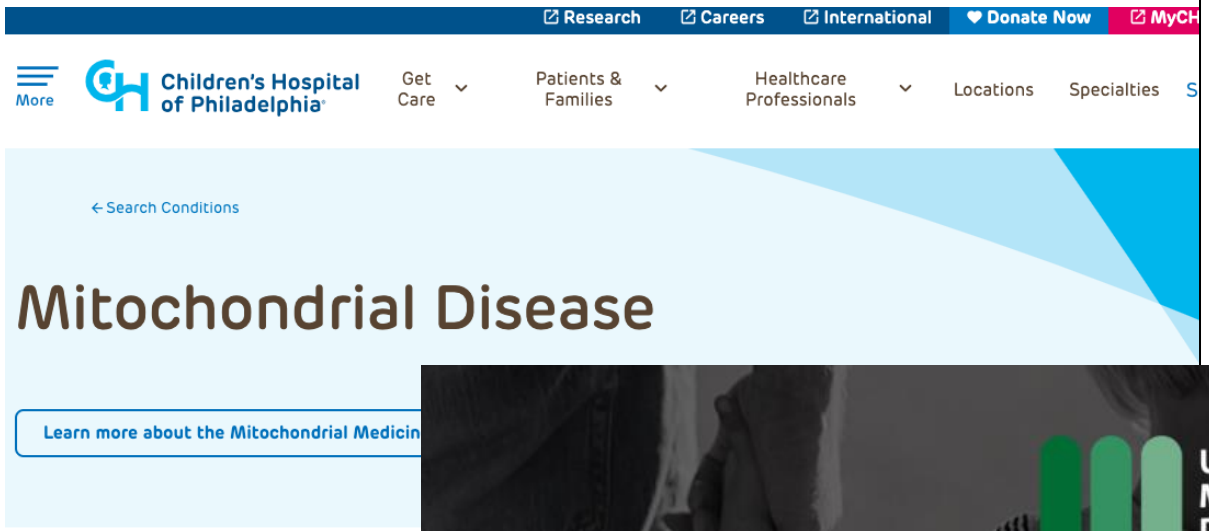
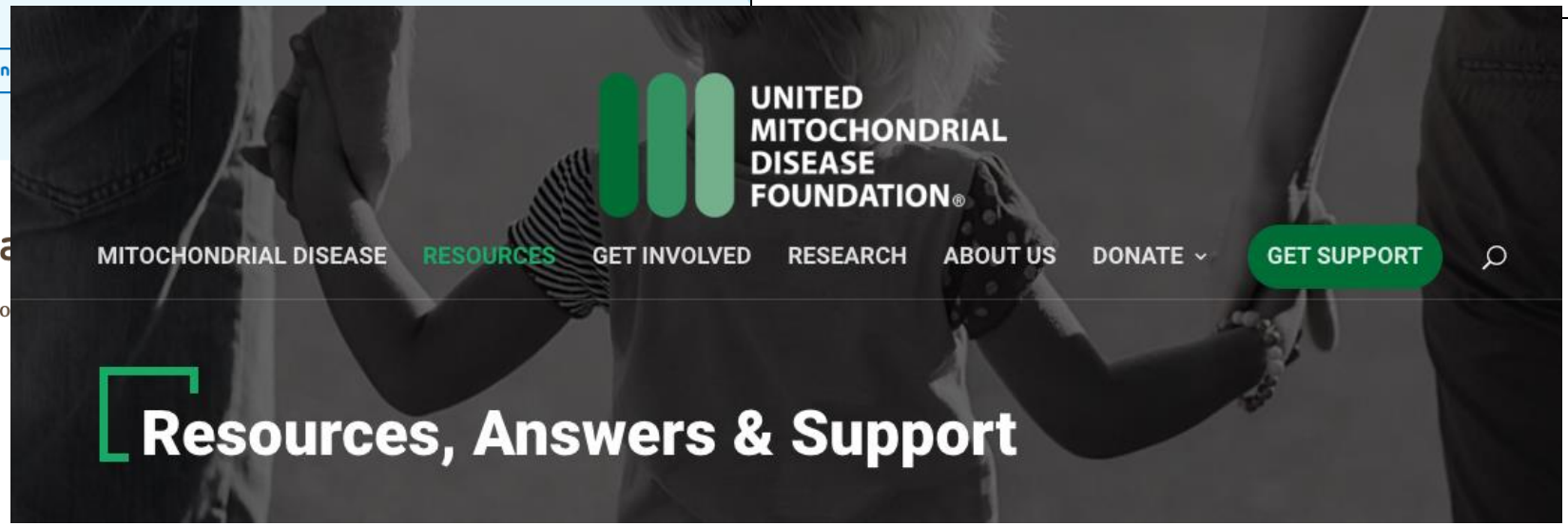
Resources





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Thank you!