Casual Friday Series

Functional Blood Chemistry Series
Pt. V: Glucose (2)

A Biogenetix Clinical Presentation

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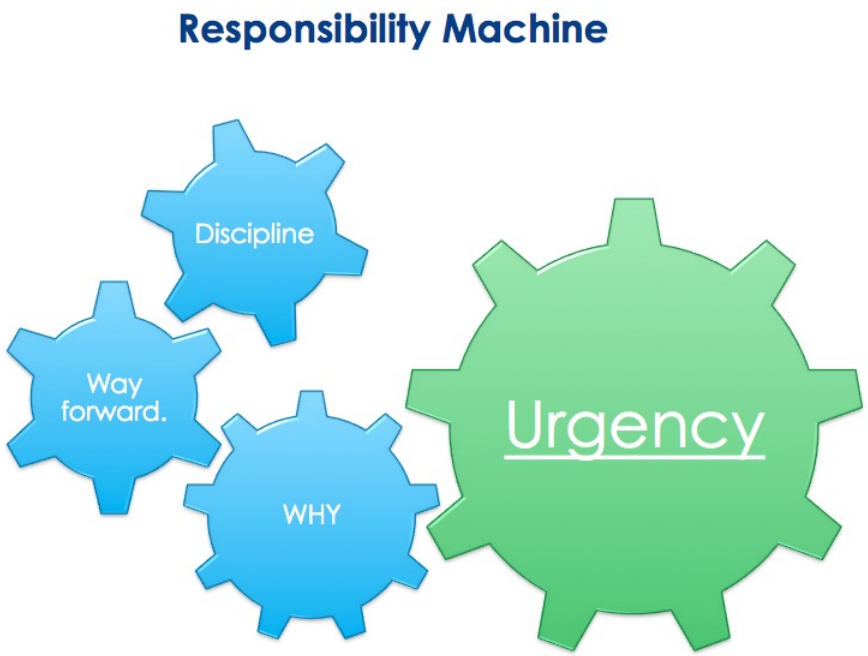
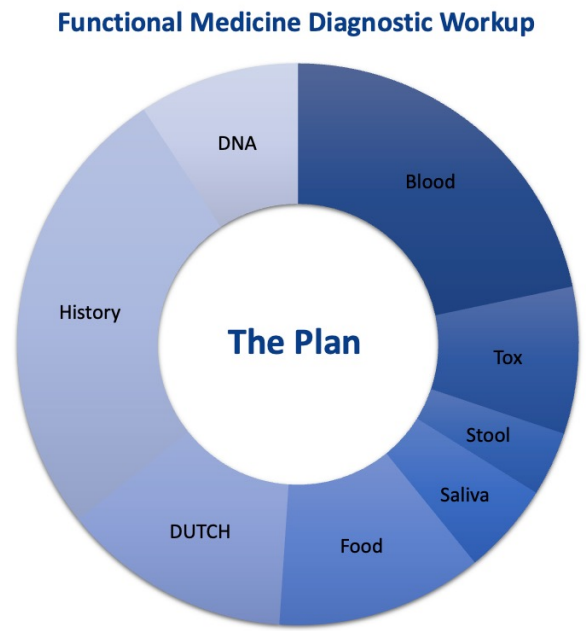
- *Information in this presentation is not intended to diagnose, treat, reverse, cure, or prevent any disease. While this presentation is based on medical literature, findings, and text, The following statements have not been evaluated by the FDA.*
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*

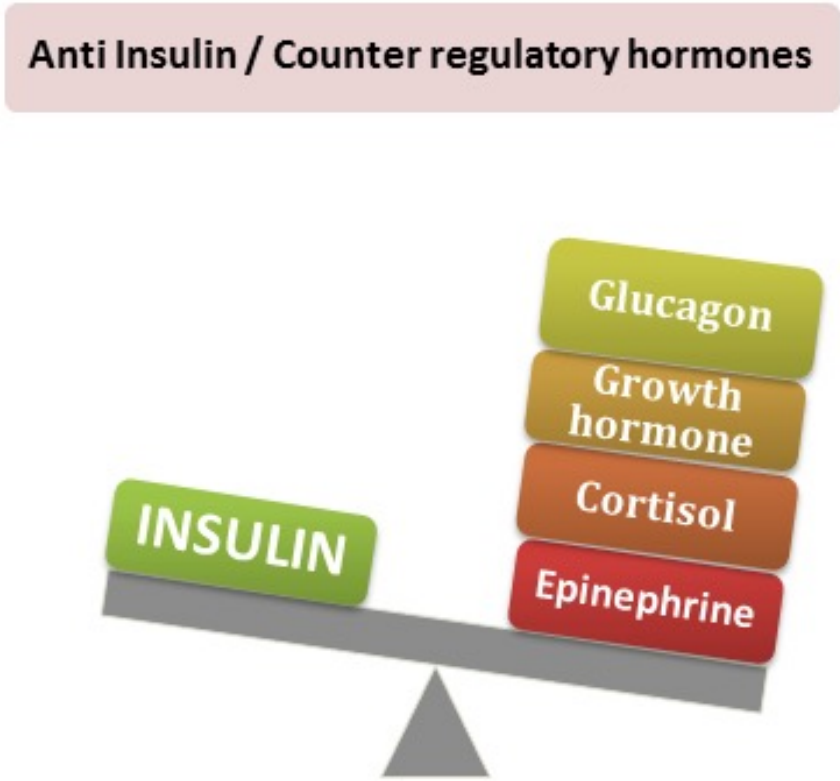
Applied FM





Progress.

Other glucose regulatory hormones



Digestion and Absorption

When glucose enters circulation, pancreatic beta cells synthesize and release insulin.

First phase insulin response – *preformed* insulin stored within the beta cells is released.

- Limits post-prandial glucose elevation
- Suppresses hepatic glucose production (gluconeogenesis)
- Begins within 2 minutes of nutrient ingestion, continues for 10-15 minutes

Second phase insulin response – insulin synthesis and release continues until serum glucose levels are normalized; longer process due to need to synthesize new insulin.

Lab Testing – Glucose related markers

- Fasting glucose
- Fasting insulin
- Hemoglobin A1C
- C-Peptide (Insulin)
- Glycomark

Fasting Glucose

Traditional Reference range:

65-100 mg/dL

Optimal Reference Range:

82 - 88 mg/dL

85-99 mg/dL

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE

Normal Fasting Plasma Glucose and Risk of Type 2 Diabetes Diagnosis

Gregory A. Nichols, PhD, Teresa A. Hillier, MD, MS, Jonathan B. Brown, PhD, MPP
Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon.

ABSTRACT

PURPOSE: The study compares the risk of incident diabetes associated with fasting plasma glucose levels in the normal range, controlling for other risk factors.

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46,578 members of Kaiser Permanente Northwest who had fasting plasma glucose levels less than 100 mg/dL.

Assigned subjects to 1 of 4 categories (<85, 85-89, 90-94, or 95-99 mg/dL)

We followed them until they developed diabetes, died, or left the health plan, or until April 30, 2007.

betes development.[4]

The reduction of the impaired fasting glucose cut-point generated international controversy, in part because the re-

of other risk factors (family history of diabetes, smoking, hypertension, physical activity levels, triglycerides, and the ratio of total to high-density lipoprotein cholesterol) found that fasting plasma glucose levels significantly increased diabetes risk among young men (aged 26-45 years) with fasting plasma glucose levels less than 100 mg/dL.[7] We recently reported that fasting plasma glucose independently increased diabetes risk among a community-based sample

Requests for reprints should be addressed to Gregory A. Nichols, PhD, Center for Health Research, 3800 N. Interstate Avenue, Portland, OR 97227-1098.

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Compared with those with fasting plasma glucose levels less than 85 mg/dL, subjects with glucose levels of 95 to 99 mg/dL were 233% more likely to develop diabetes. Subjects in the 90 to 94 mg/dL group were 49% more likely to progress to diabetes.

Each milligram per deciliter of fasting plasma glucose increased diabetes risk by 6%.

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More recently, an Israeli study that adjusted for a number of other risk factors (family history of diabetes, smoking, hypertension, physical activity levels, triglycerides, and the ratio of total to high-density lipoprotein cholesterol) found that fasting plasma glucose levels significantly increased diabetes risk among young men (aged 26-45 years) with fasting plasma glucose levels less than 100 mg/dL.[7] We recently reported that fasting plasma glucose independently increased diabetes risk among a community-based sample

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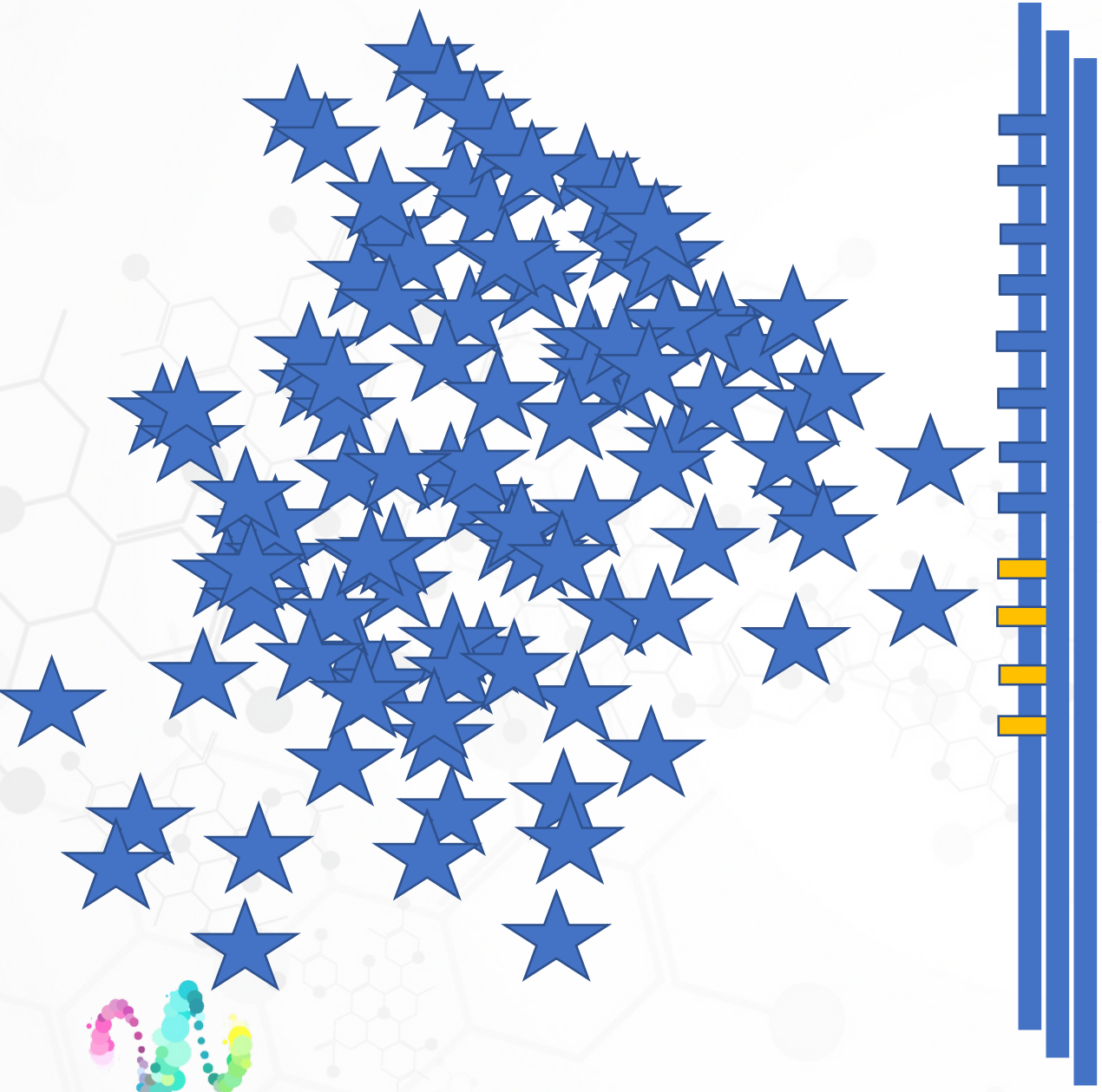
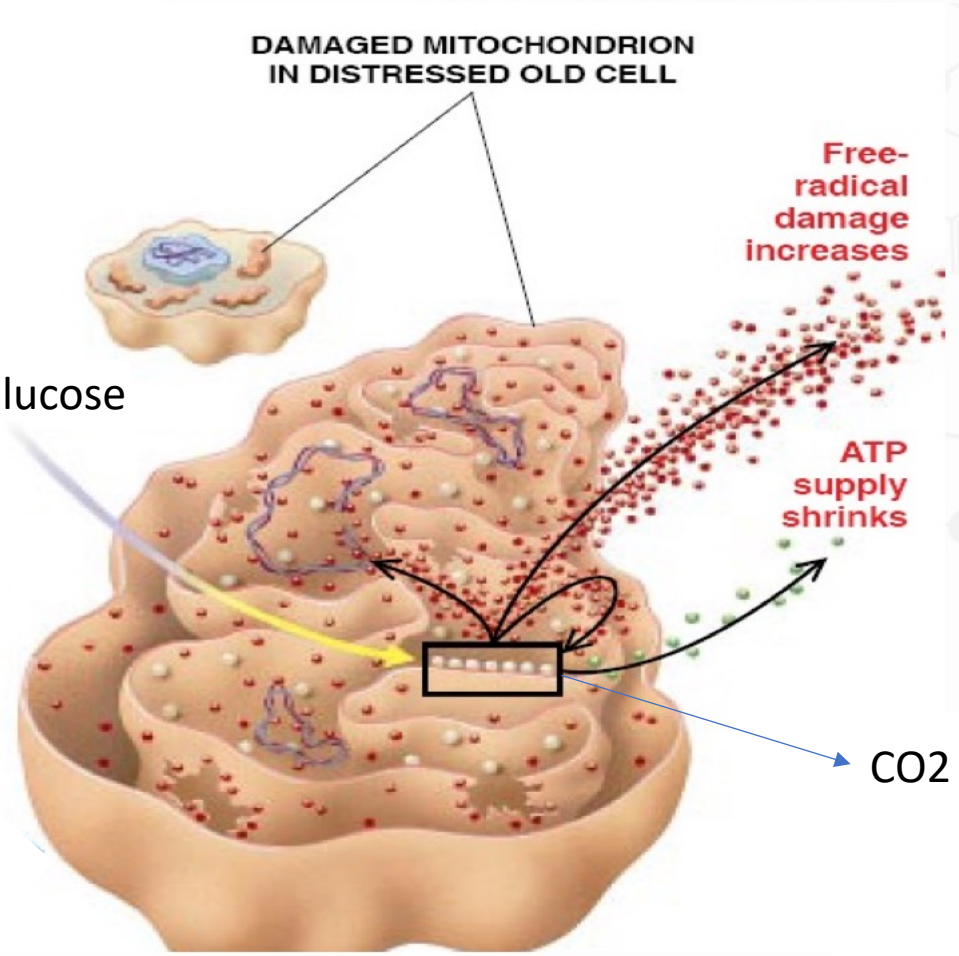
Glucose – Elevated

Cause	Reason	Additional Inquiry
Insulin resistance (increased glucagon)	Dysfunctional insulin signaling (eg receptors) causing glucose to remain elevated in the blood.	Fatigue after meals, sweets cravings even after carbohydrate ingestion; evaluate c-peptide, hemoglobin A1C
Pancreatic dysfunction	Poor insulin production	Evaluate c-peptide.
Hyperthyroidism	Shorter half-life of insulin, increased intestinal glucose absorption, increased FFA and thus hepatic gluconeogenesis, excess lactate leading to increased hepatic gluconeogenesis (Cori cycle), increase in GH, glucagon and catecholamines all promote hyperglycemia	Evaluate thyroid markers.
Hyperadrenal function	Increased cortisol and/or catecholamine increase glucose levels	Consider evaluating cortisol levels.

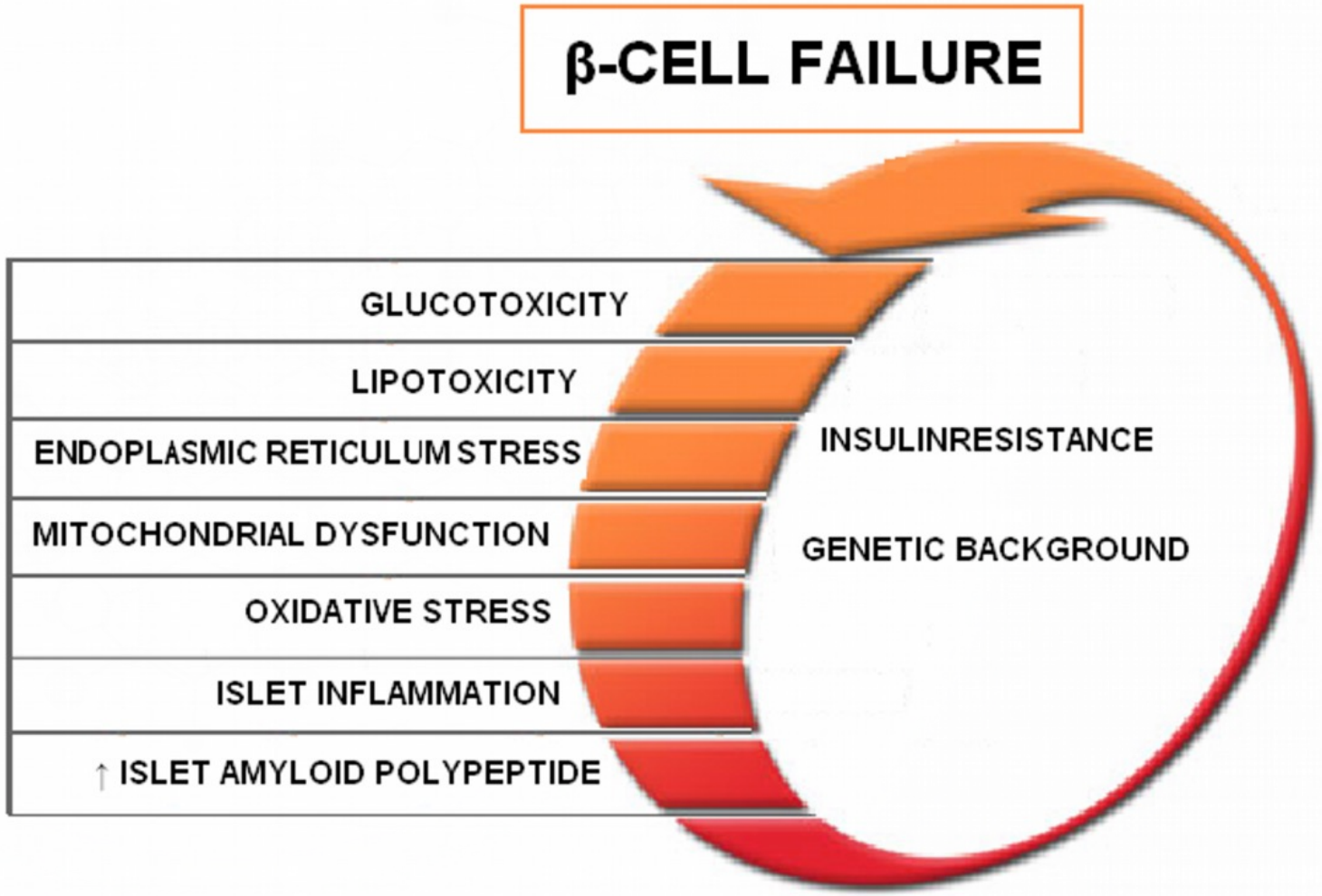


O2, Glucose


DAMAGED MITOCHONDRION
IN DISTRESSED OLD CELL
Free-
radical
damage
increases
ATP
supply
shrinks
CO2

Glucose – Elevated

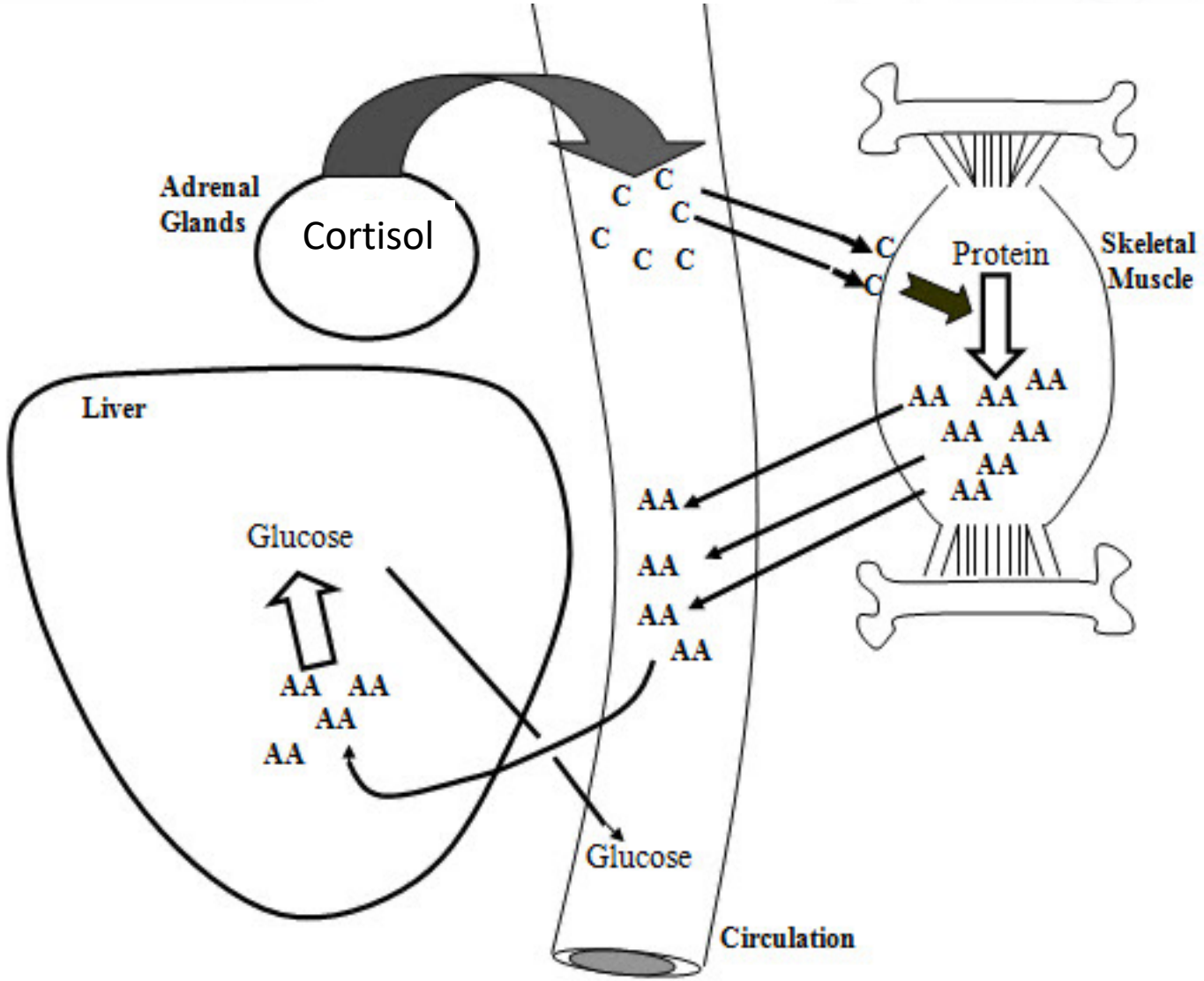
- Glucotoxicity
- Lipotoxicity



Glucose toxicity and Lipotoxicity in Beta Cells

- Either appear to negatively impact beta cell function
- Excess ROS production is a major theory behind glucose toxicity
- High glucose levels increase intraislet peroxide levels and observed low levels of antioxidant enzymes
- Lipotoxicity thought to be due to hyperlipidemia, especially of saturated long chain fatty acids
  - Therapeutic ketogenic diet may be helpful at reducing toxicity (personal opinion)

Hyper Adrenal Function (cortisol)



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Hyperadrenal function	Increased cortisol and/or catecholamine increase glucose levels	Consider evaluating cortisol levels.

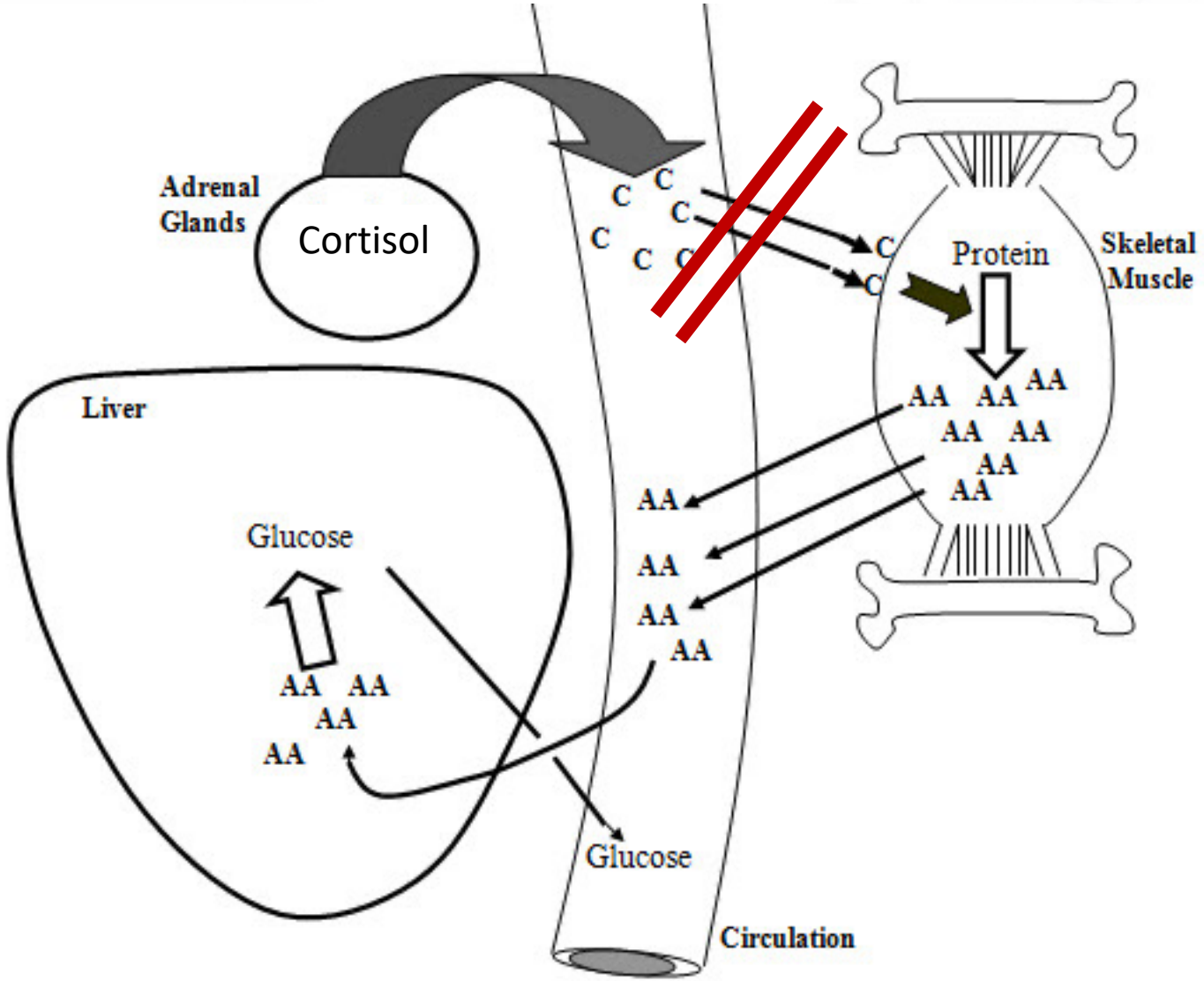
Glucose - Decreased

Cause	Reason	Additional Inquiry
Hypoadrenal function	Low cortisol levels leading to an inability to maintain stable glucose levels	Evaluate Na and K on blood chemistry; evaluate cortisol levels
Hypopituitary	Low TSH, low ACTH and low GH can all lead to hypoglycemia.	
Hypothyroidism	Decreased intestinal glucose absorption, decreased gastric emptying, decreased gluconeogenesis and glycogenolysis, decreased cortisol response, decreased glucagon production, blunted growth hormone response	Evaluate thyroid markers
Vitamin B6 deficiency	Pyridoxine (B6) is required for glycogen phosphorylase, the first and rate limiting step in glycogenolysis	Evaluate low AST and/or ALT levels; diet journal for B6 intake
Carnitine deficiency	See above – carnitine is important for the initial step of gluconeogenesis (pyruvate carboxylase)	Consider lysine and or methionine deficiency (key amino acid in carnitine synthesis, often deficiency in vegetarians), poor carnitine intake, or other deficiencies (eg vitamin C)

Glucose - Decreased

Vitamin C deficiency	Vitamin C is required for synthesis of carnitine, which is required to bring long-chain fatty acids into the mitochondria; high levels of Acetyl CoA in the mitochondria stimulate gluconeogenesis. Thus, low carnitine -> low acetyl CoA -> poor gluconeogenesis -> low glucose.	Evaluate low alkaline phosphatase; bleeding gums; easy bruising
H. Pylori infection	There is growing evidence between H.Pylori and insulin resistance. It may be that reactive hypoglycemia may precede insulin resistance and have an H. Pylori connection.	
Biotin deficiency	Biotin is required for the initial enzyme of gluconeogenesis, pyruvate carboxylase and thus, may lead to hypoglycemia. On the other hand, it must be noted that biotin has other roles in glucose metabolism including the synthesis of glucokinase, PFK-1, and in allowing the pancreas to sense glucose and thus produce insulin.	
High-dose vitamin C	Vitamin C, specifically dehydroascorbic acid, competes with glucose across cell membranes and thus may slow intestinal glucose absorption. (Conversely, high serum glucose may cause a relative vitamin C deficiency within cells.)	

Hypo Adrenal Function (cortisol)



Hypopituitary function

- The anterior pituitary releases three hormones that could relate to glucose levels
  - TSH – Thyroid
  - ACTH – Cortisol
  - Growth Hormone
- If the pituitary is dysfunctional, all three of these hormones may be low, thus contributing to periods of low blood sugar

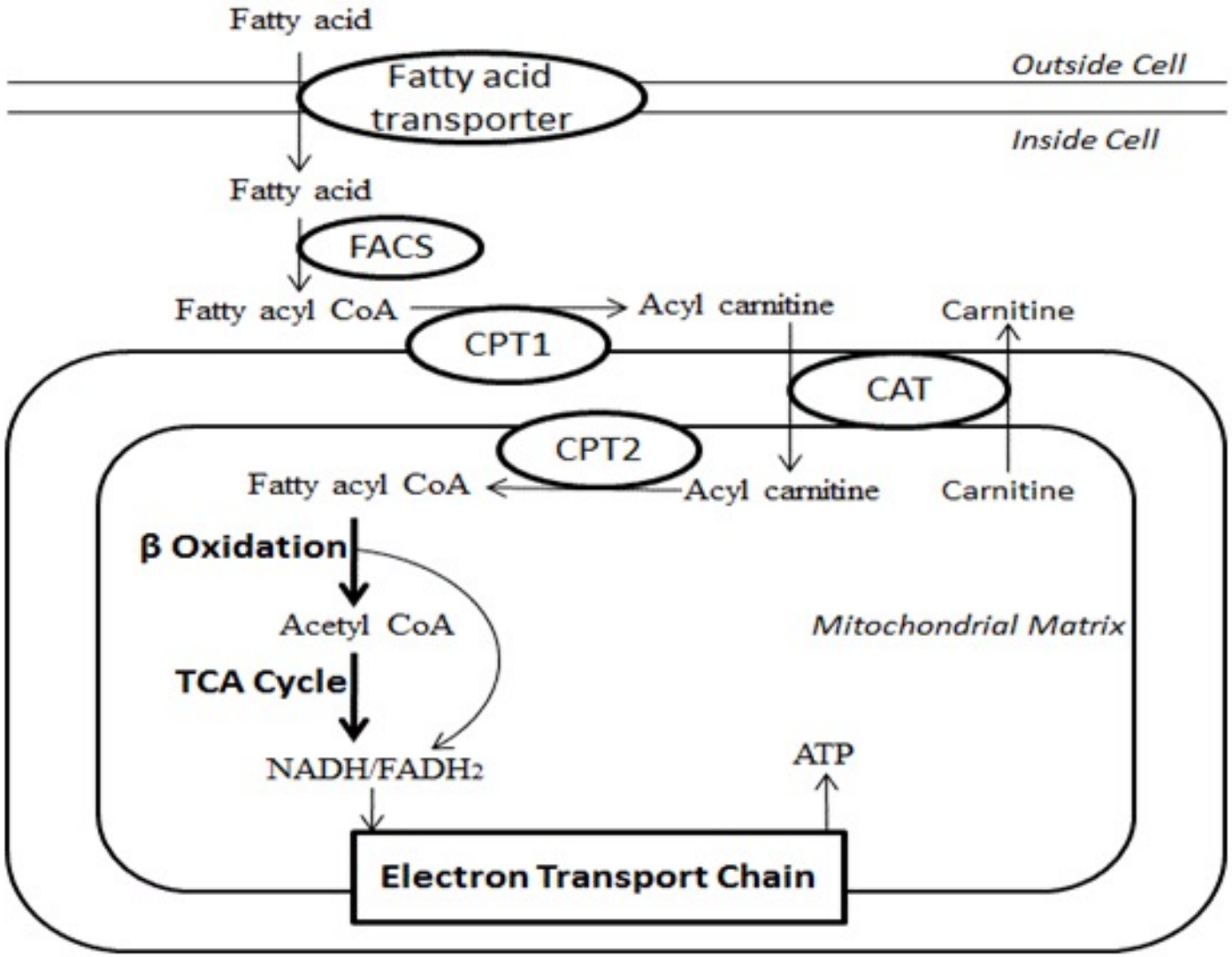
Hypothyroidism

- Decreased intestinal glucose absorption
- Decreased gastric emptying
- Decreased gluconeogenesis and glycogenolysis
- Decreased cortisol response
- Decreased glucagon production
- Blunted GH response

Vitamin B6 (pyridoxine) deficiency

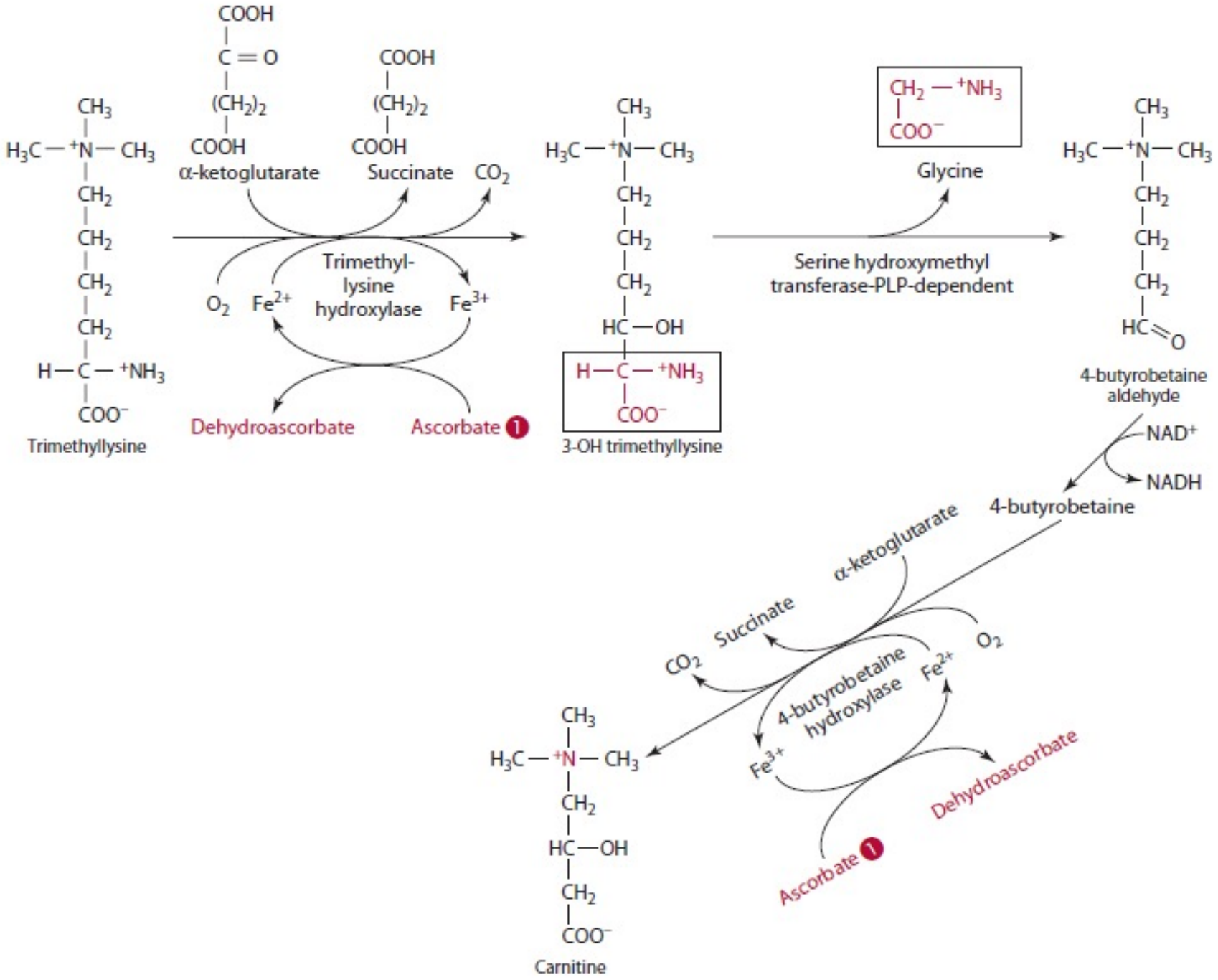
- Glycogen phosphorylase – the rate limiting enzyme of glycogenolysis – is a B6 dependent enzyme
- Low B6 may lead to hypoglycemic tendencies

Carnitine and/or vitamin C deficiency



Nutritional requirements for carnitine synthesis:

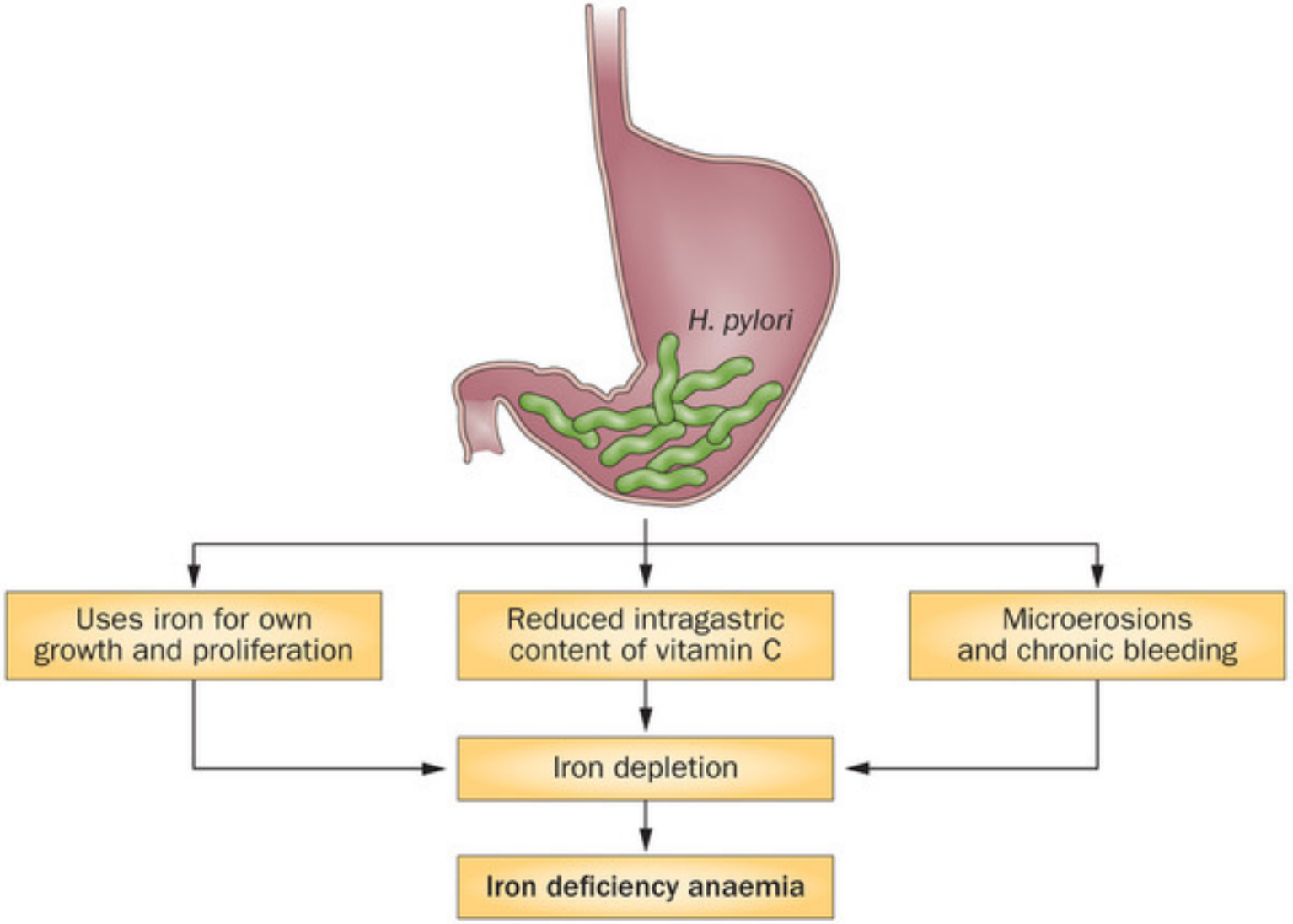
- Lysine
- Vitamin C
- Iron
- Oxygen
- Vitamin B6



H. Pylori Infection

- There is growing evidence between H.Pylori and insulin resistance.
- If reactive hypoglycemia precedes insulin resistance, then it is possible that hypoglycemic symptoms may be caused in part by a concomitant H. pylori infection.

H. Pylori/Carnitine connection?



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Glucose – Interfering Factors

Interfering Factors	
Elevated	Decreased
Non-fasting	Stress response before test
Medications - **Corticosteroids**	Medications
	Intense exercise

Reactive Hypoglycemia - Symptoms

- Shaky, light-headed, irritable, especially between meals
- May crave salt
- Craves sweets, but corrected after sweets are consumed
- Food provides energy
- Consistently wakes up during the night

Reactive Hypoglycemia

- Periods of low glucose causing primarily neurological symptoms
- Could be due to excess insulin
- Counter regulatory hormones (glucagon and cortisol) may not be working correctly
  - Often find low cortisol in these individuals
- The question is, why are they not able to maintain healthy glucose levels – glycogenolysis and gluconeogenesis
- Due to increased GLP-1

Reactive Hypoglycemia

- Glycogenolysis requires vitamin B6
- Low insulin levels should simulate free fatty acid release for use in beta-oxidation within mitochondria
  - Requires carnitine to shuttle long chain fatty acids into mitochondria
  - Without carnitine fatty acids are not brought into the mitochondria
  - When acetyl CoA levels are elevated (eg beta-oxidation), pyruvate carboxylase (biotin dependent enzyme) is upregulated, and gluconeogenesis proceeds. When acetyl CoA is low, pyruvate carboxylase is inhibited, and gluconeogenesis decreases.
- Therefore, for hypoglycemia, consider B6, biotin, carnitine and vitamin C (required for carnitine synthesis)

Reactive Hypolycemia – The Short Version

- Hyperinsulinemia
- Excess GLP-1 production
- Low counter regulatory hormones
- Glucagon resistance
- Carnitine deficiency

Lactate Dehydrogenase (LDH)

- Lactate Dehydrogenase (LDH) is a widely-distributed, intracellular enzyme found in skeletal and cardiac muscle, kidney, liver, lungs, and red blood cells.
- As an intracellular enzyme, when LDH is elevated on a blood chemistry it suggests tissue damage. But due to its wide distribution in tissues, by itself is impossible to know where the damage is located.
  - LDH isoenzymes can better pinpoint the type of tissue being damaged

❖ **There are many possible reasons for elevated LDH, but *low* LDH can indicate poor glucose metabolism, aka hypoglycemic tendencies**

Lactate Dehydrogenase (LDH)

Traditional Reference range:

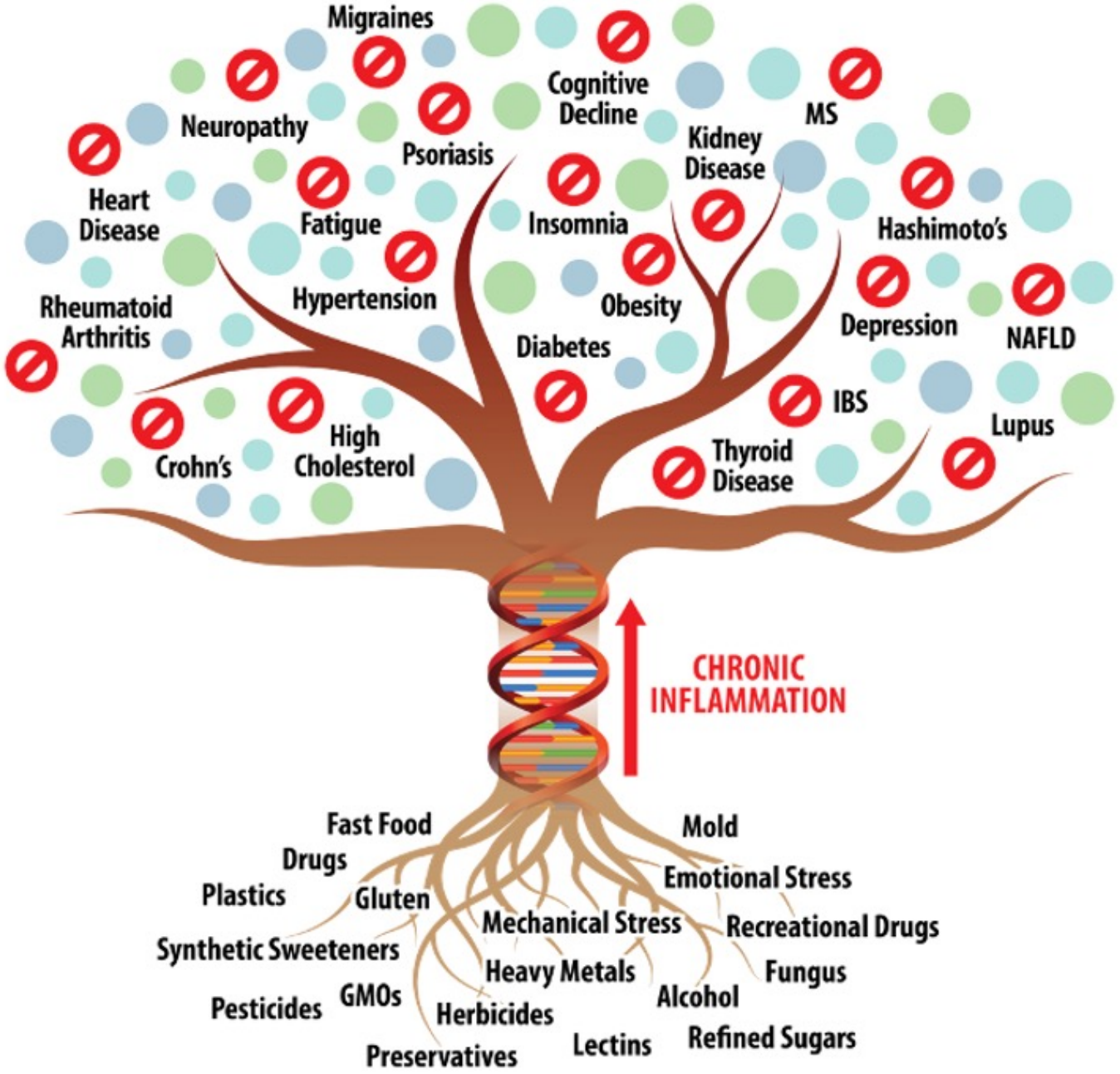
100–280 U/L

Optimal Reference Range:

140–170 U/L

LDH - Decreased

Cause	Reason	Additional Inquiry
Hypoglycemia	Poor glucose entry into a cell downregulates LDH enzyme production intracellularly, thus leading to low levels of LDH. (NADH/NAD ratio?)	Evaluate glucose levels and hypoglycemic symptoms.
Diabetes	Poor glucose entry into cells can decrease LDH production leading to low levels.	Evaluate hyperglycemic markers and symptoms.
Ketosis	Due to the utilization of ketones over glucose molecules during ketosis, it is possible someone following a ketogenic diet will have low LDH levels.	Client history. Presence of ketones.


Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Herbicides
Alcohol
Preservatives
Lectins
Refined Sugars

The Wedge Protocol