Casual Friday Presents

Fine-Tuning Mitochondrial Function Pt. 3

A BIOGENETIX CLINICAL PRESENTATION

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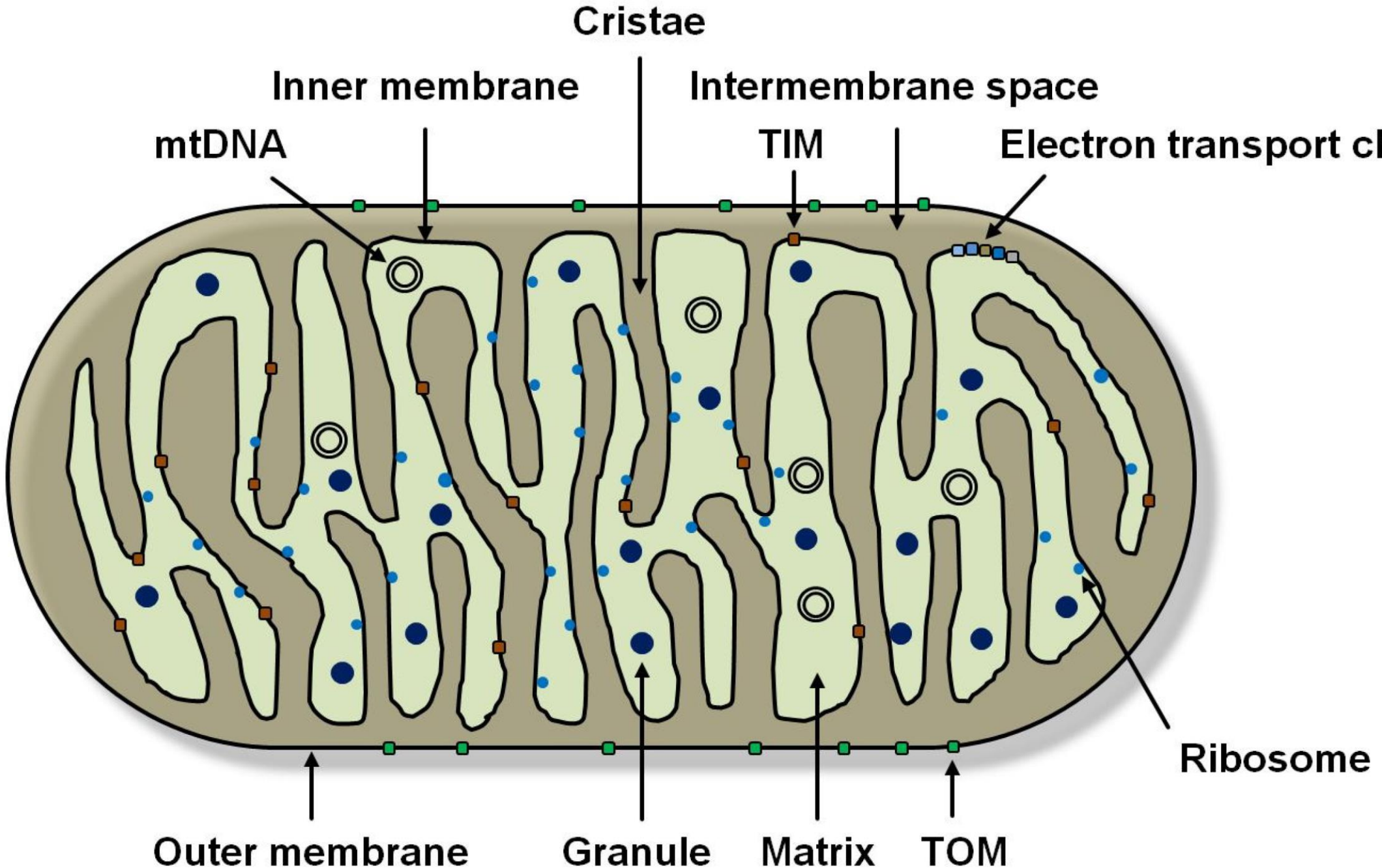

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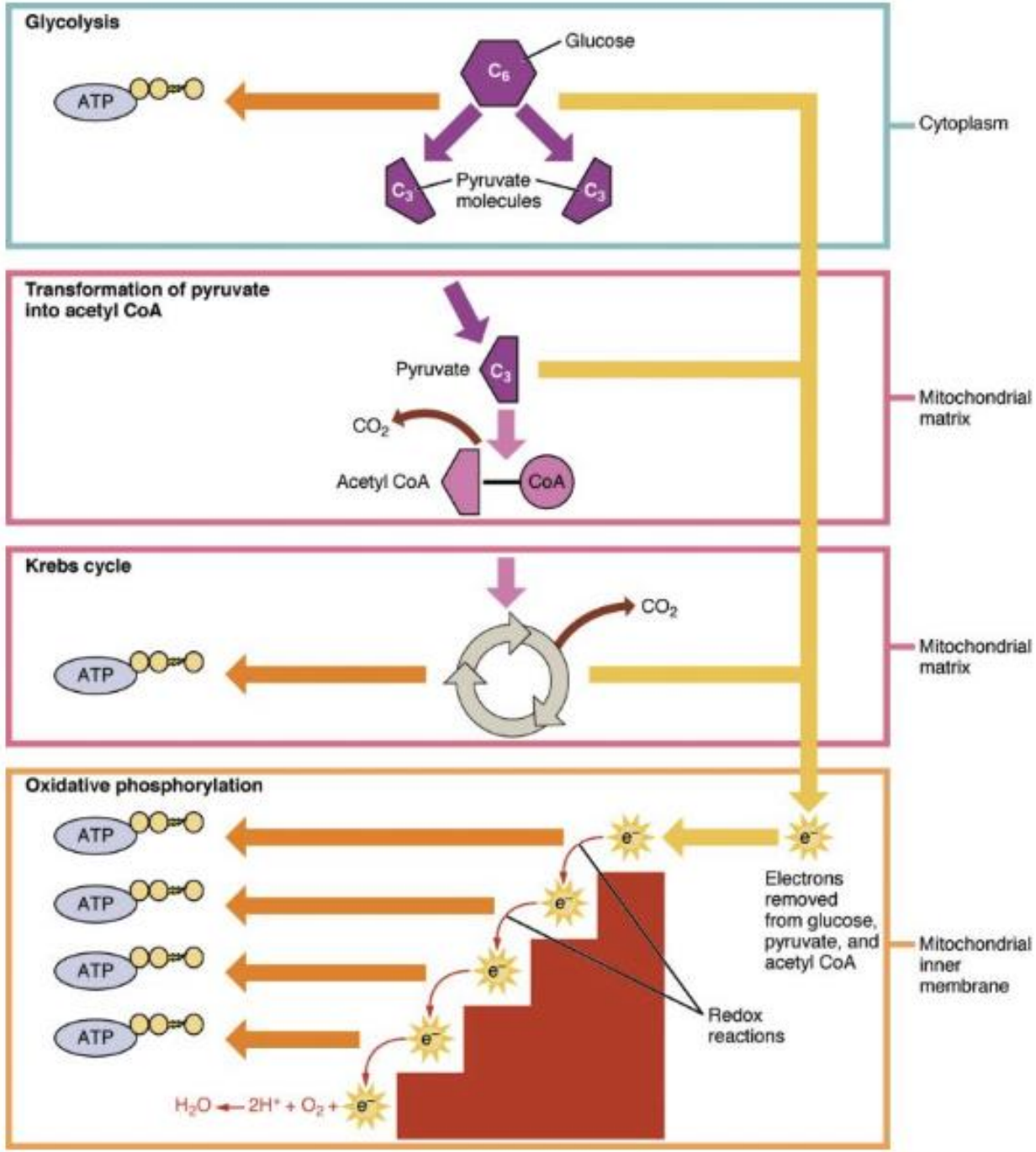
Glycolysis
Glucose
C_6
ATP
Cytoplasm
C_3
Pyruvate molecules
C_3
Transformation of pyruvate into acetyl CoA
Pyruvate
C_3
Mitochondrial matrix
CO_2
Acetyl CoA
CoA
Krebs cycle
CO_2
ATP
Mitochondrial matrix
Oxidative phosphorylation
ATP
ATP
ATP
ATP
e^-
e^-
e^-
e^-
e^-
Electrons removed from glucose, pyruvate, and acetyl CoA
Mitochondrial inner membrane
Redox reactions
$H_2O \leftarrow 2H^+ + O_2 + e^-$

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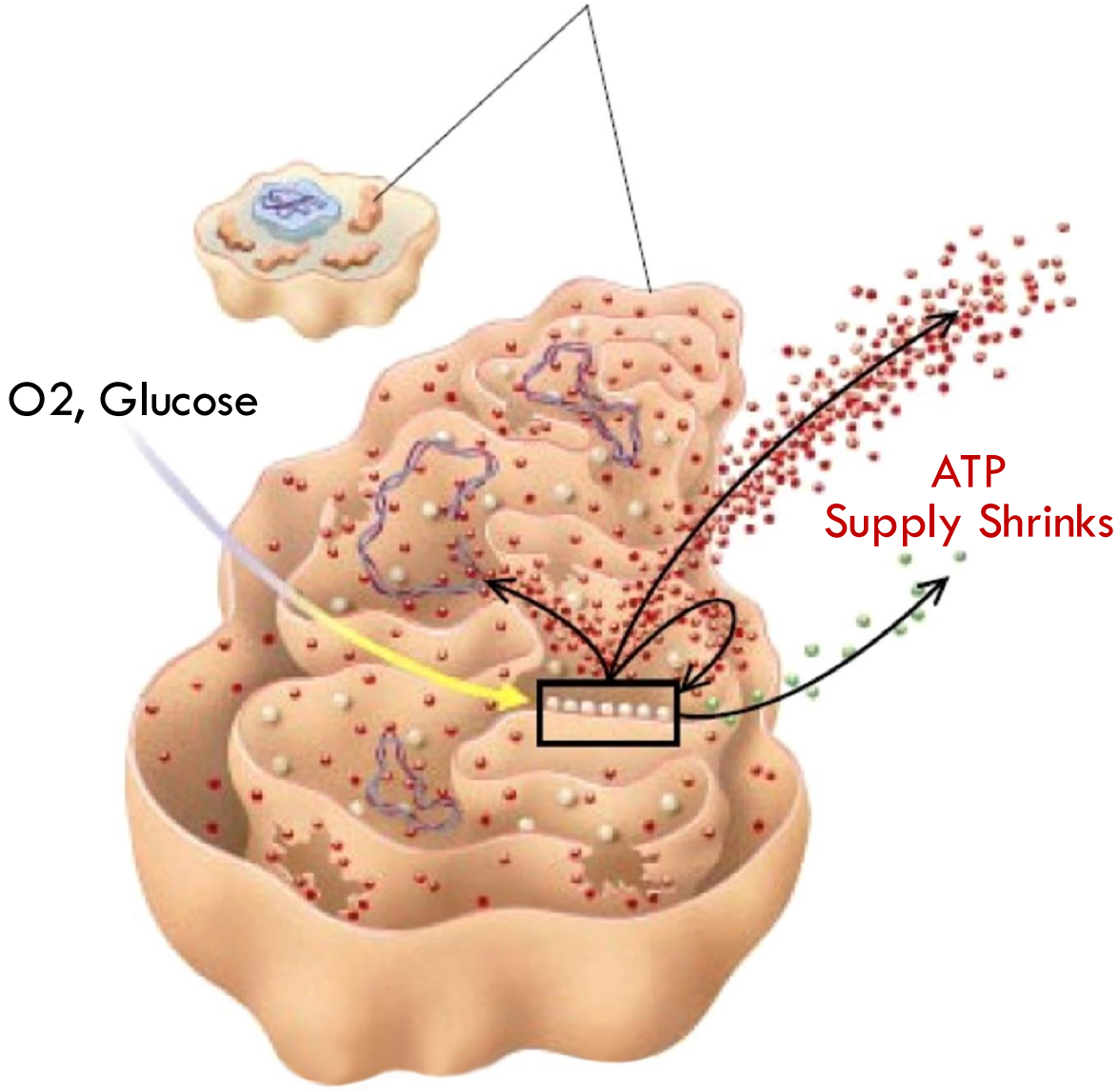
Damaged Mitochondria in
Distressed Old Cell



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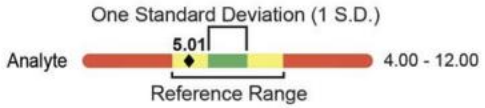
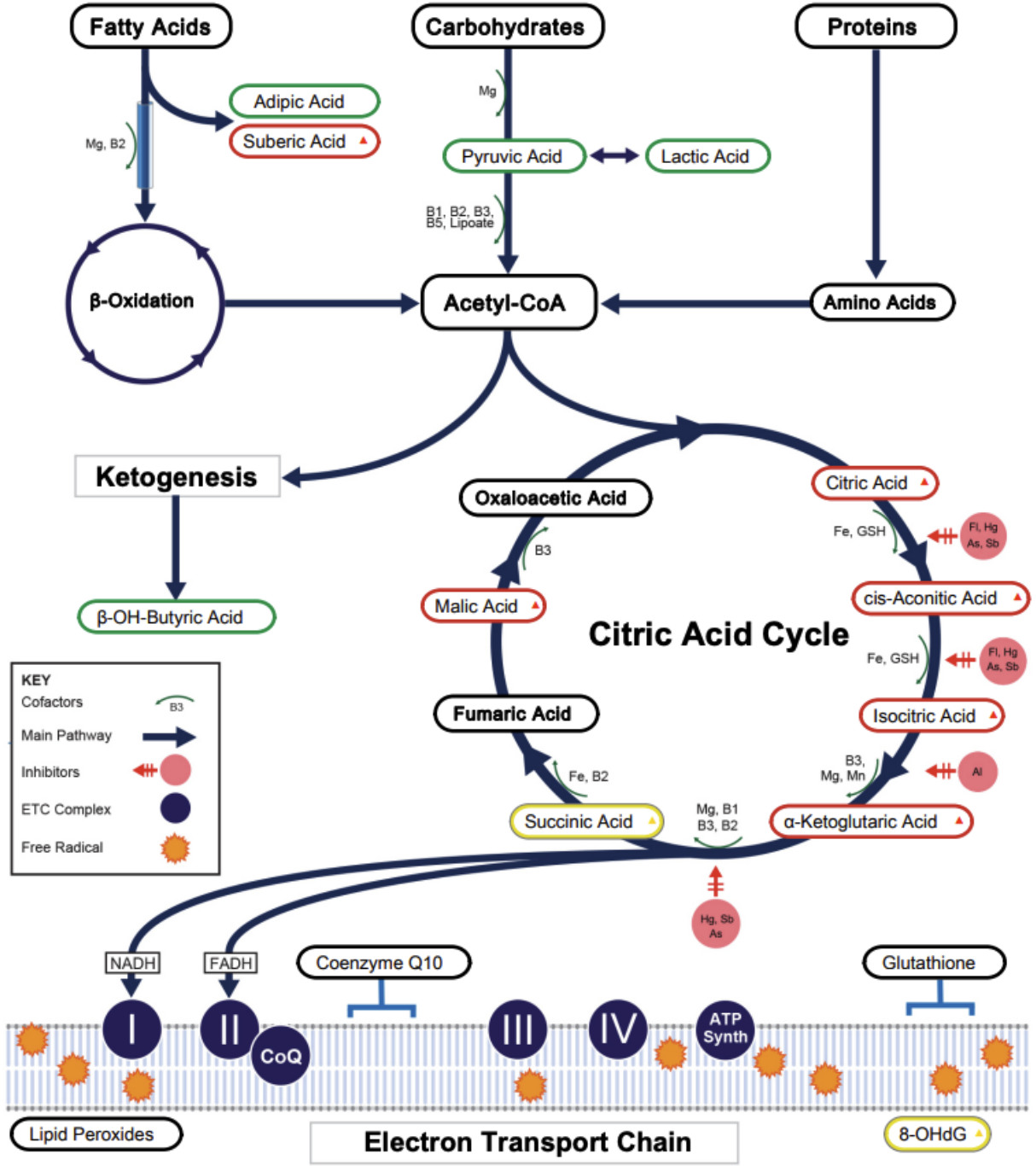

One Standard Deviation (1 S.D.)
Analyte
5.01
4.00 - 12.00
Reference Range


Fatty Acids
Carbohydrates
Proteins
Adipic Acid
Suberic Acid
Mg, B2
Mg
Pyruvic Acid
Lactic Acid
B1, B2, B3, B5, Lipoate
β-Oxidation
Acetyl-CoA
Amino Acids
Ketogenesis
β-OH-Butyric Acid
Oxaloacetic Acid
B3
Malic Acid
Citric Acid
Fe, GSH
Fl, Hg As, Sb
cis-Aconitic Acid
Citric Acid Cycle
Isocitric Acid
B3, Mg, Mn
Al
α-Ketoglutaric Acid
Mg, B1 B3, B2
Succinic Acid
Fe, B2
Fumaric Acid
KEY
Cofactors
Main Pathway
Inhibitors
ETC Complex
Free Radical
Hg, Sb As
NADH
FADH
Coenzyme Q10
Glutathione
I
II
CoQ
III
IV
ATP Synth
Lipid Peroxides
Electron Transport Chain
8-OHdG

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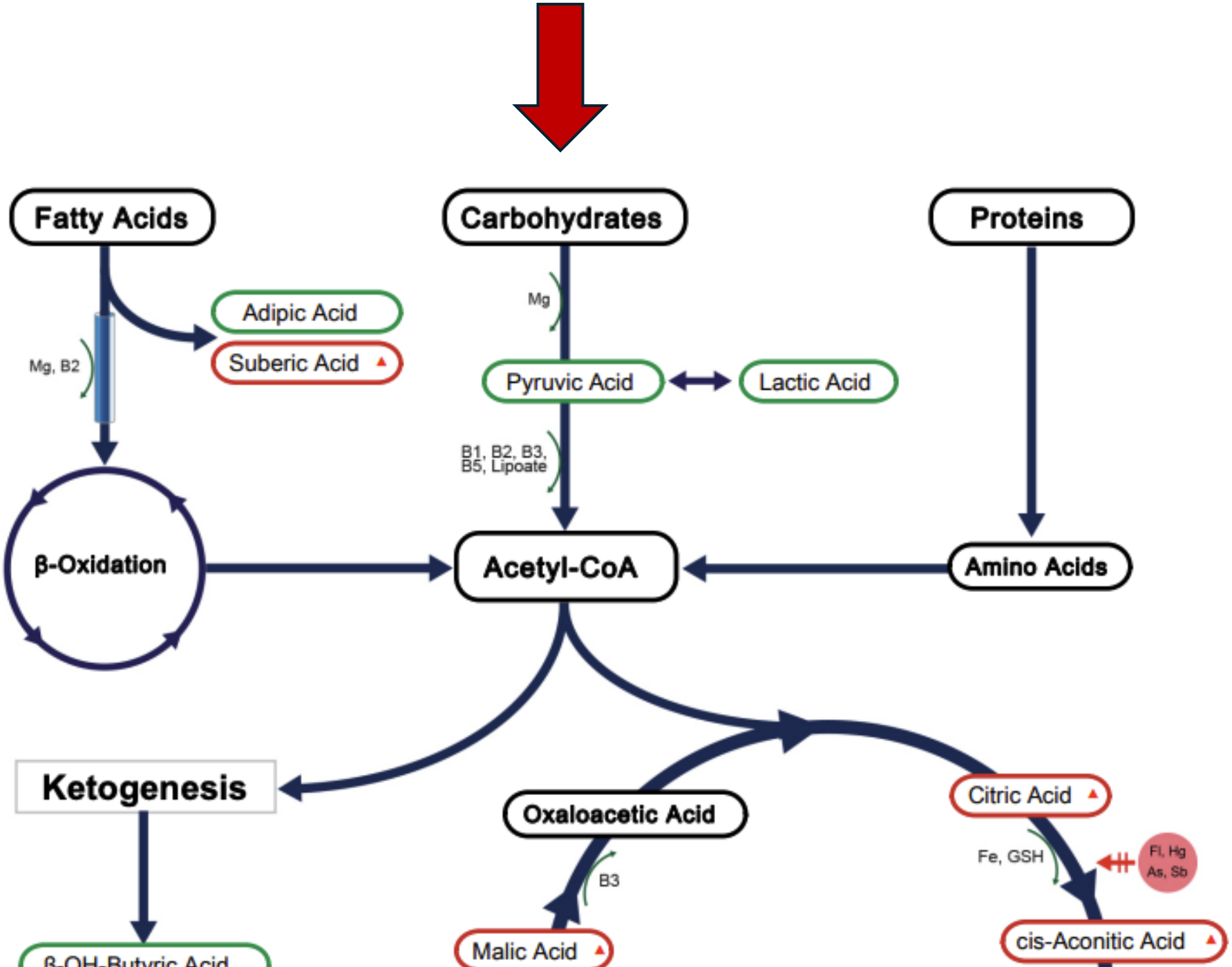
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Fl, Hg As, Sb
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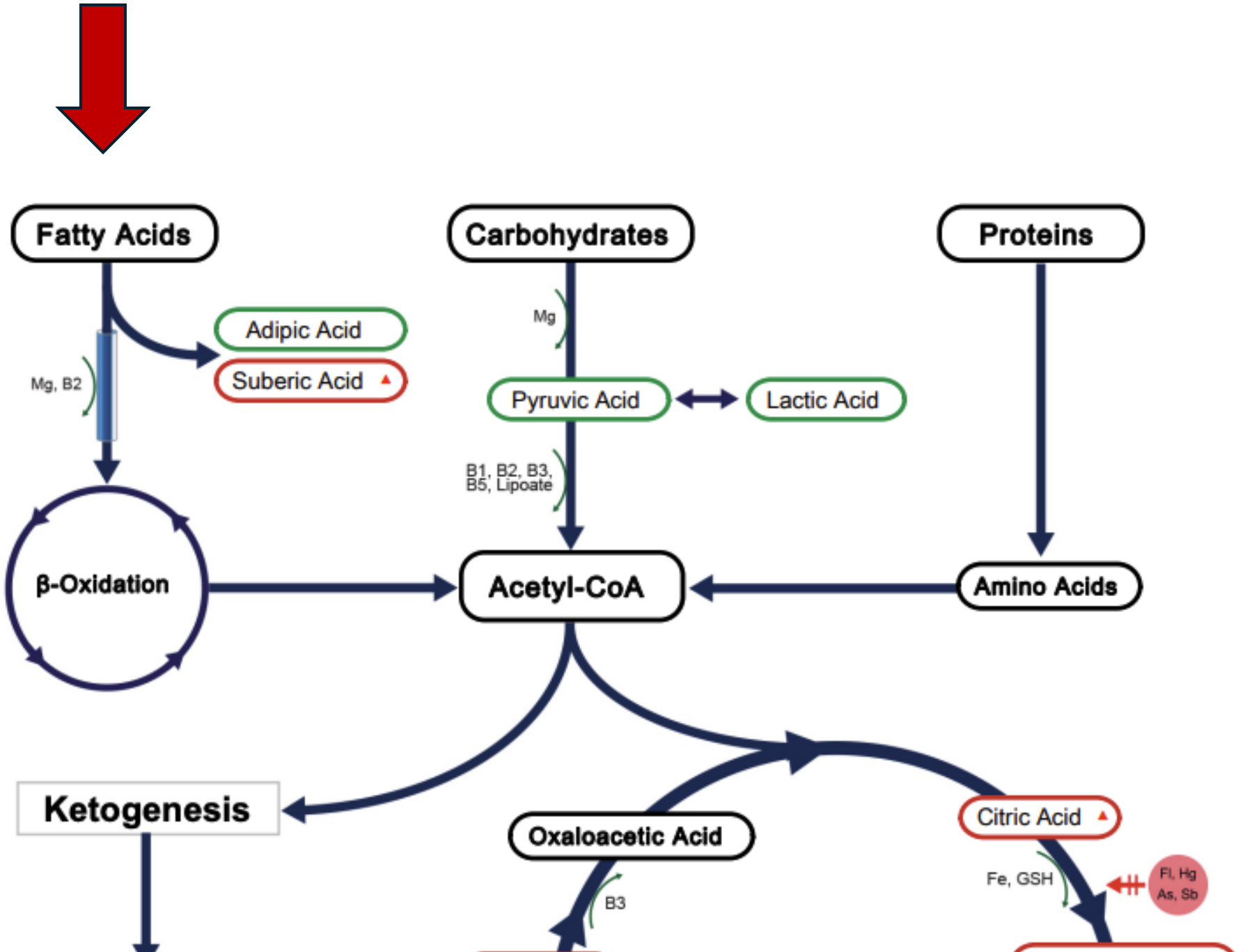
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Acetyl-CoA
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Ketogenesis
Oxaloacetic Acid
B3
Citric Acid
Fe, GSH
Fl, Hg
As, Sb

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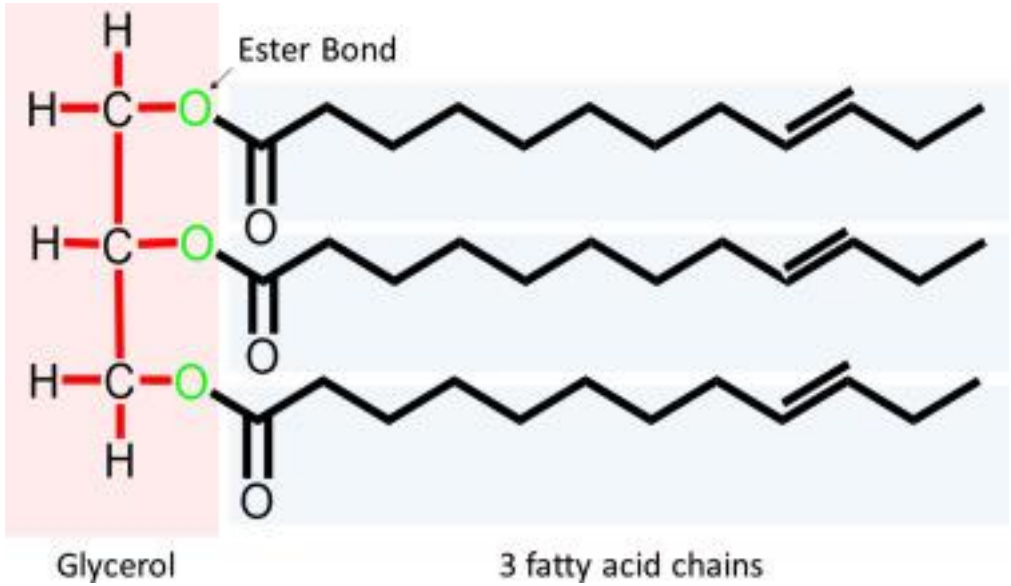
Triglyceride



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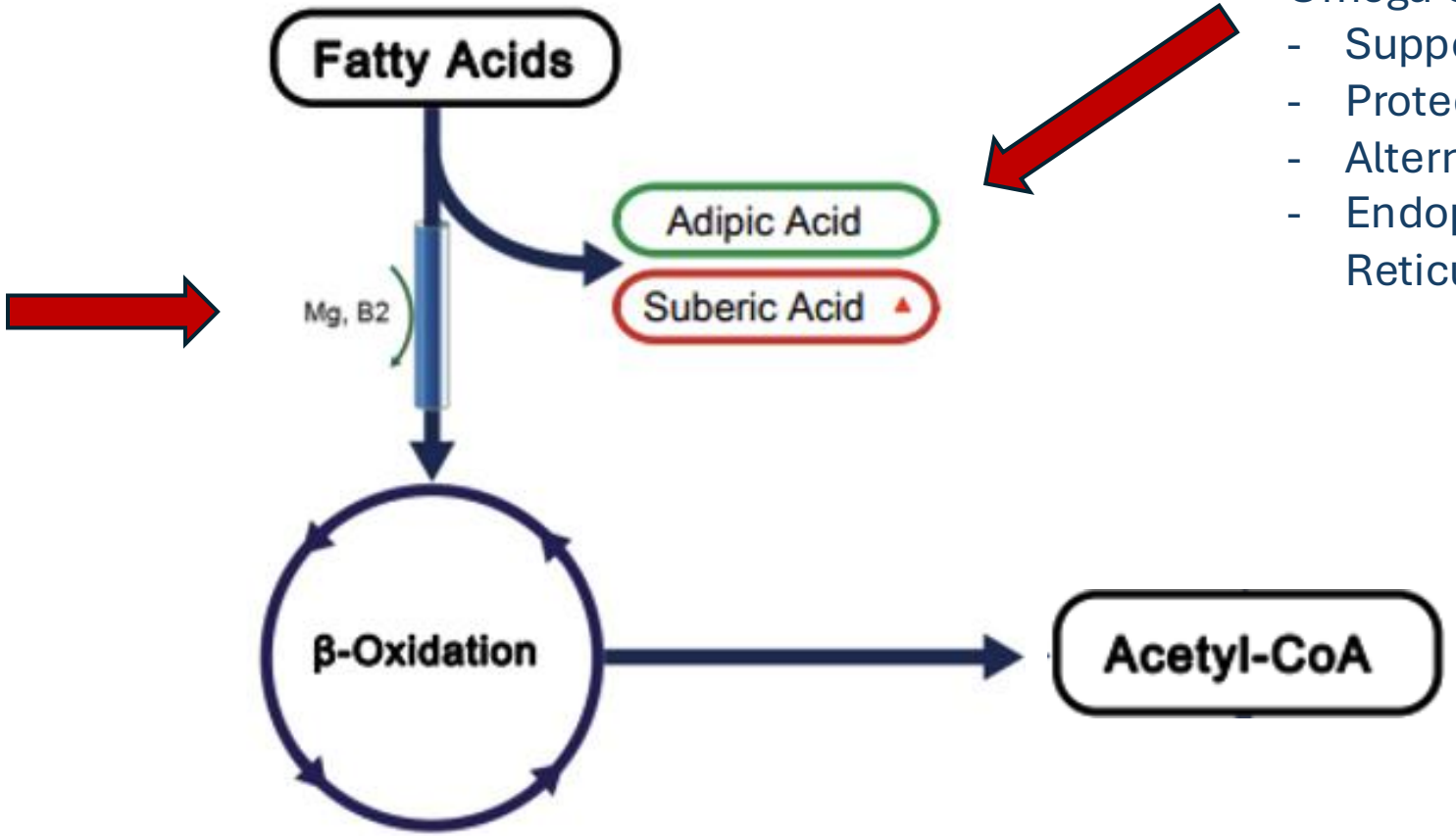
Magnesium
Riboflavin



Omega Oxidation
- Supportive
- Protective
- Alternative
- Endoplasmic Reticulum

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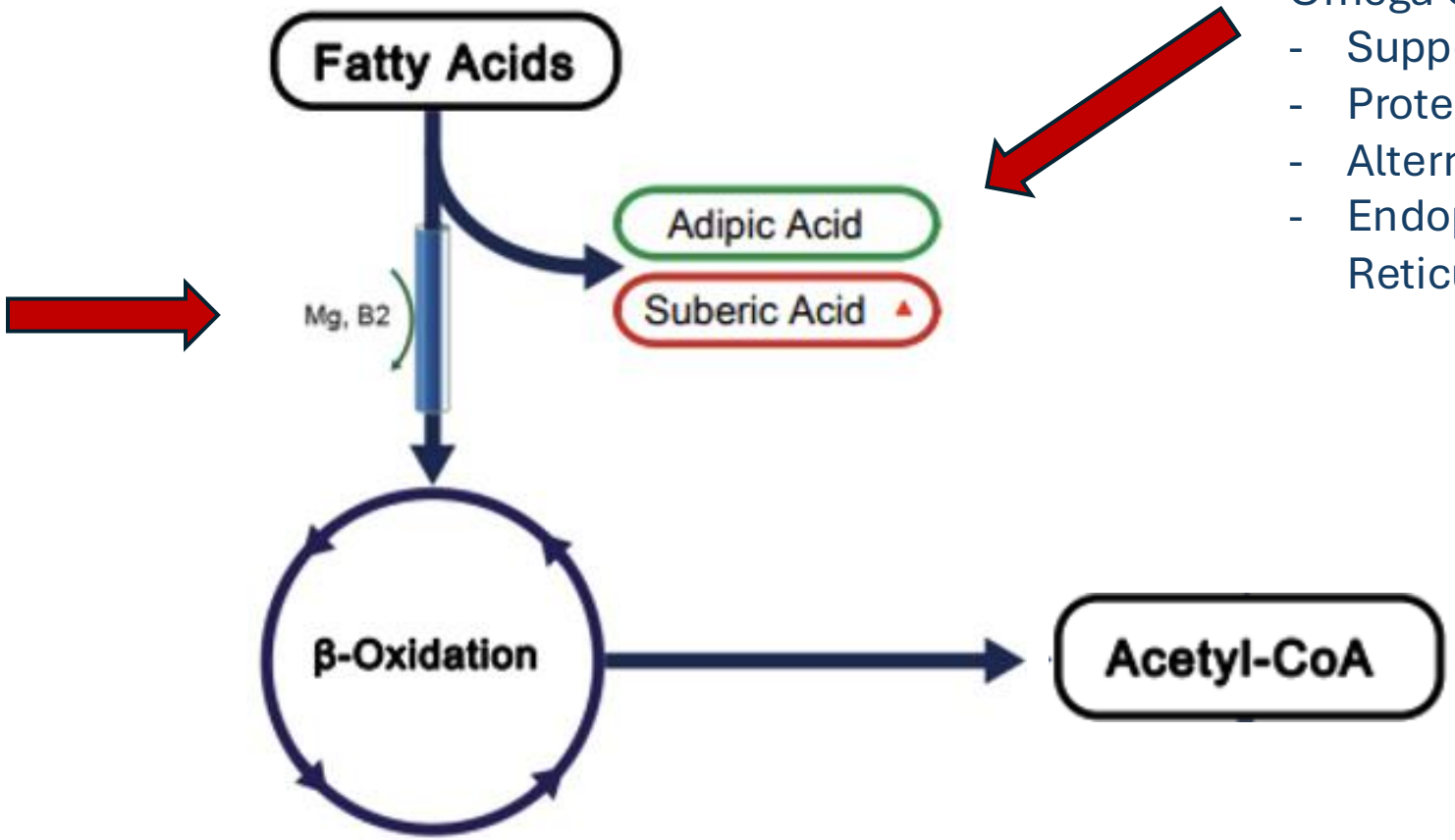
Magnesium
Riboflavin
*Carnitine Shuttle



Omega Oxidation
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*Omega Fatty Acid Oxidation generally occurs when B-Oxidation is defective, or Fatty acid concentrations are very high. Generally, Insulin Resistance, Fasting, Ketosis, Diabetes, or extremely low carb dietary patterns.

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Magnesium
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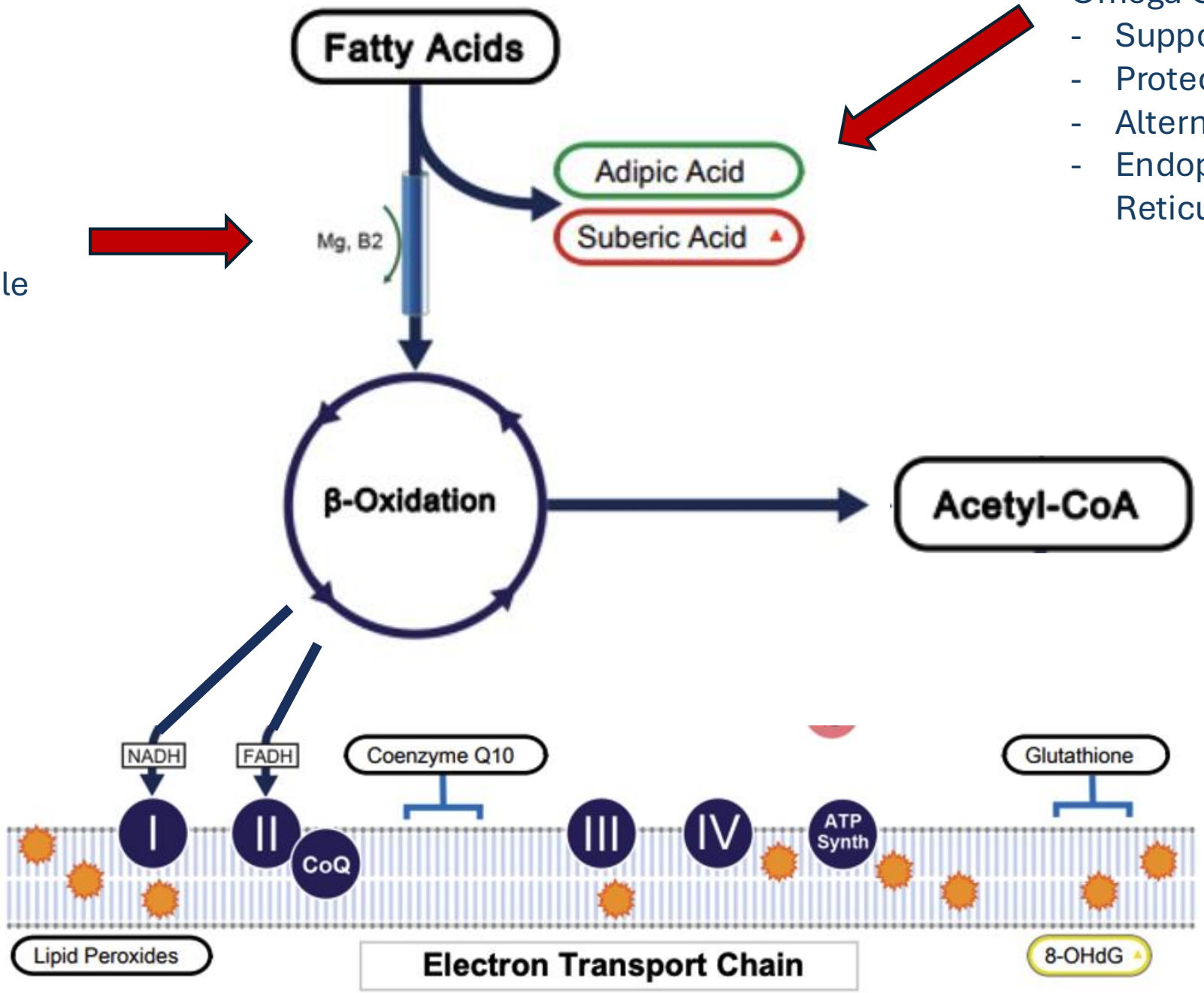

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Carnitine (beta-hydroxy-gamma-trimethylammonium butyrate) is an indispensable water-soluble molecule derived from amino acids.[1][2] In non-vegetarians, dietary intake is the primary source of carnitine and accounts for almost three-fourths of the total body stores.[3] The main dietary source of carnitine is red meat, poultry, and dairy products.[4] The bioavailability of dietary carnitine is between 54% to 87%.[5] The remaining one-fourth of the carnitine pool can be produced endogenously from lysine and methionine mostly by the liver and kidneys.[3][6] Vegetarians have a relatively lower plasma carnitine level than non-vegetarians.[7] In strict vegetarians, most of the carnitine (>90%) is produced endogenously.[3] Despite variabilities in dietary carnitine intake, the plasma carnitine level is maintained within the normal range by an efficient renal reabsorption system while excessive carnitine is promptly excreted in the urine.[8] About 90% to 99% of the filtered carnitine is usually reabsorbed by the renal tubules.[3]

Carnitine plays a substantial physiological role in lipid metabolism and intermediary metabolic pathways.[5] Through the carnitine shuttle, carnitine helps in transporting the long-chain fatty acids from the cytoplasm to the mitochondrial matrix for subsequent degradation for beta-oxidation, which is detailed in the pathophysiology section (figure).[3] Plasma carnitine accounts for approximately 0.5% of the total body stores, and the remaining vast majority is found within the cells.[3][5] As carnitine is essential for fueling the exercising muscle through fatty acid oxidation and energy production via the Krebs's cycle, more than 95% of total body carnitine is found in skeletal muscle.[5][7][9] The liver, heart, and kidneys have the rest of the carnitine stores.[5]

https://www.ncbi.nlm.nih.gov/books/NBK559041/

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Under normal physiological conditions, fatty acids are the main source of energy during fasting.[6] Energy production from fatty acids occurs via beta-oxidation of fatty acids in the liver, heart, and skeletal muscles.[6] Beta oxidation of the long-chain fatty acid (LCFAs) occurs exclusively in the mitochondrial matrix. The mitochondrial membrane is impermeable to LCFAs and requires the obligatory carnitine shuttle (Figure). To be transported across the mitochondrial membrane, LCFAs are activated in the cytoplasm by conversion to long-chain fatty acyl-CoAs (LCFA-CoAs). This reaction is catalyzed by long-chain fatty acyl-CoA synthetase.[5] LCFA-CoAs then can diffuse through the outer mitochondrial membrane where they are converted to acylcarnitine in a presence of carnitine by the enzyme carnitine palmitoyltransferase-1 (CPT-I). In normal states, acylcarnitine formation reduces the proportion of acyl residues combined with coenzyme A (CoA) and improves the ratio between free CoA and acyl-CoAs.
[6] Acylcarnitine crosses the inner mitochondrial membrane by the carnitine-acylcarnitine translocase (CACT) via the carnitine shuttle. In the mitochondrial matrix, acylcarnitine is converted back to LCFA-CoAs and free carnitine by the carnitine palmitoyltransferase-2 (CPT-II). When acylcarnitine crosses the inner mitochondrial membrane, simultaneously the free carnitine released by the CPT-II leaves the mitochondrial matrix by the action of CACT and this termed as the carnitine shuttle. Once they are inside the mitochondrial matrix, LCFA-CoAs are readily oxidized and results in acetyl-CoA production. Acetyl-CoA is subsequently used for energy and ketone bodies production. Acetyl-CoA is also an allosteric activator of pyruvate carboxylase that catalyzes the gluconeogenesis pathway which is active during catabolic states such as fasting.[6][15][16]

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In carnitine deficient states, LCFAs cannot be effectively transported to the mitochondria matrix for oxidation and subsequent utilization in Kreb's cycle and ketone body production. During periods of fasting, improper utilization of fatty acids impairs gluconeogenesis and characteristically leads to nonketotic or hypoketotic (no or minimal ketone body production respectively) hypoglycemia.[3] When fatty acid oxidation is impaired, glucose is readily consumed without replenishment from gluconeogenesis.[6] In carnitine deficiency states, various intermediary metabolic pathways such as Kreb's cycle, amino acid metabolism, and beta-oxidation of fatty acids are also affected. Fatty acids released from adipose tissues during fasting accumulate in various organs predisposing to their impaired function.[5][6] Accumulation of fat in the liver causes steatosis and impairment of ketone body production.[5][6][8] In the heart and skeletal muscles, this abnormal accumulation results in cardiomyopathy and myopathy respectively.[5][6] Heart derives two-thirds of its energy from free fatty acids and this predisposes patients with impaired carnitine metabolism to the development of cardiomyopathy.[6] Additionally, impaired lipid metabolism can affect the electrical rhythm of the heart resulting in arrhythmias.[6] The brain utilizes ketone bodies as an alternate energy source in fasting states. These ketones are derived from acetyl-CoA from fatty acid oxidation and in carnitine deficiency, this is defective.[6] Unstable energy and metabolic abnormalities can impair brain function with loss of consciousness and metabolic encephalopathy.[6][17]

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Secondary carnitine deficiency (SCD) could result from multiple causes, either from a decrease in carnitine intake or more commonly from an increase in renal excretion. SCD may result from severe malnutrition, ketogenic diet, severe malabsorptive states, extremely preterm infants, and prolonged parenteral nutrition without adequate L-carnitine supplementation.[4][6] In conditions with renal tubular dysfunction (e.g., Fanconi syndrome), renal losses of carnitine are accentuated. Medications such as valproic acid, cyclosporine, pivampicillin, and some anti-cancer drugs (e.g., etoposide, vinblastine) can also contribute to carnitine deficiency.[6] Valproic acid therapy may deplete carnitine stores by various mechanisms such as increased urinary excretion as valproylcarnitine, decreased renal tubular reabsorption, and decreased endogenous production.[19] Similarly, pivampicillin antibiotic usage may cause reduce carnitine levels due to the formation of pivaloyl-carnitine ester, which is excreted in the urine.[5] The severity of SCD is generally less when compared to PCD as the plasma carnitine levels are relatively higher and hence easier to manage.[3][8]Patients with SCD, in general, do not have hepatic or cardiac involvement. However, they may have a moderate degree of skeletal muscular dysfunction.[20]

Similarly to PCD, hypoketotic hypoglycemia is highly suggestive for mitochondrial fatty acid oxidation (FAO) disorders (e.g., very long-chain acyl-CoA dehydrogenase or VLCAD, medium-chain acyl-CoA dehydrogenase or MCAD, etc.), or disorders of a defective mitochondrial carnitine-acylcarnitine cycle or simply referred to as disorders of carnitine shuttle (due to defects in enzymes, CPT-I, or CPT-II or CACT).[6][15] In most of the aforementioned SCD disorders with impaired fatty acid oxidation, the accumulation of acylcarnitine esters occurs.[5] These excessive acylcarnitines can inhibit carnitine reabsorption in the kidneys and are subsequently excreted in the urine resulting in SCD.[6][5] The accumulating acyl-carnitine in cardiac tissue can also induce damage.[6]

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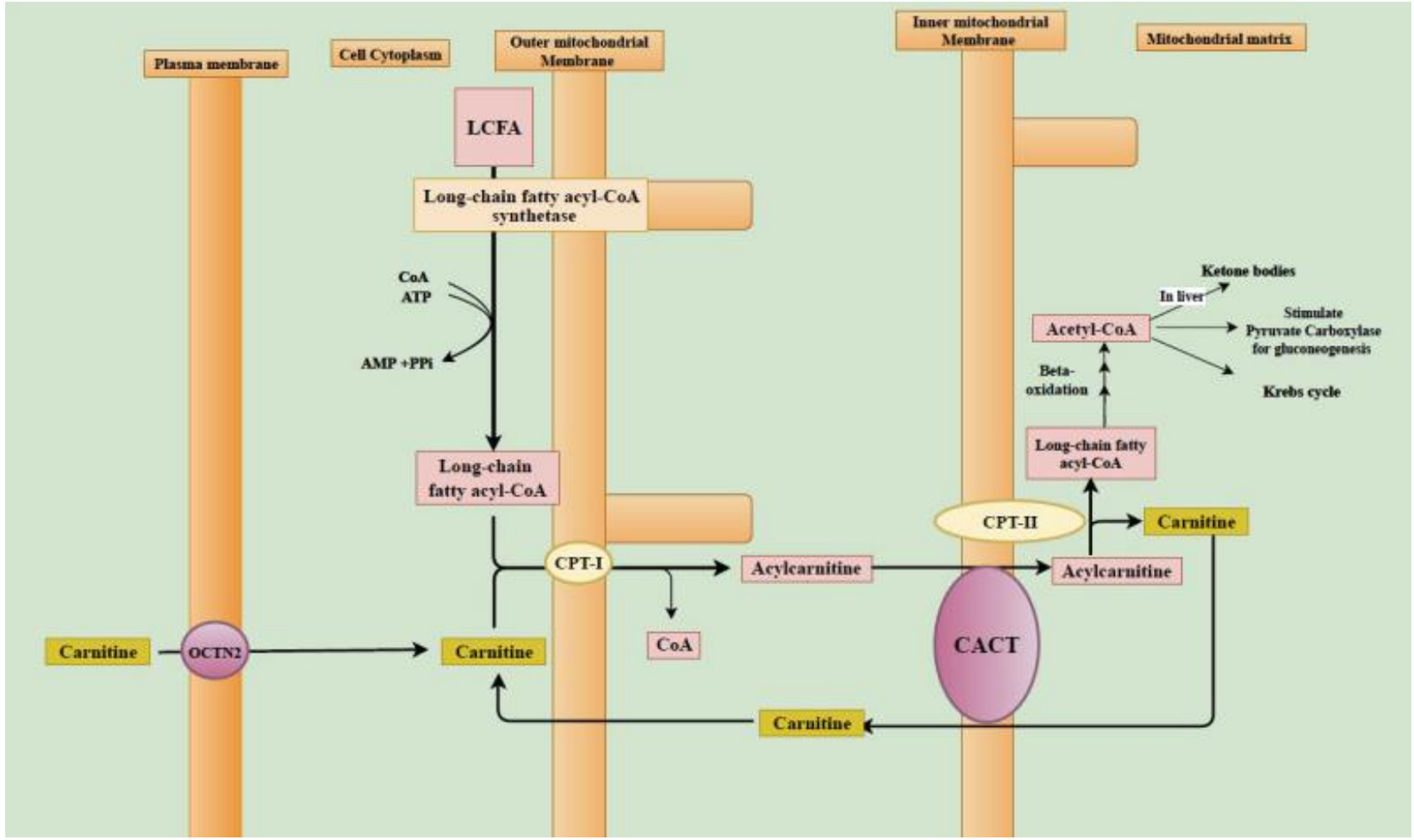

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CMP14+LP+TP+TSH+5AC+CBC/D/P...

	Test	Current Result and Flag		Previous Result and Date		Units	Reference Interval
	Chemistries [01]						
	Glucose [01]	83		97	04/23/2025	mg/dL	70-99
▼	**Hemoglobin A1c** [01]	**4.6**	**Low**	**4.7**	04/23/2025	%	4.8-5.6
	Please Note: [01]	Prediabetes: 5.7 - 6.4 Diabetes: >6.4 Glycemic control for adults with diabetes: <7.0					
	Uric Acid [01]	6.0		7.0	04/23/2025	mg/dL	3.8-8.4
				Therapeutic target for gout patients: <6.0			
	BUN [01]	19		14	04/23/2025	mg/dL	6-20
▲	**Creatinine** [01]	**1.33**	**High**	1.25	04/23/2025	mg/dL	0.76-1.27
	eGFR	76		82	04/23/2025	mL/min/1.73	>59
	BUN/Creatinine Ratio	14		11	04/23/2025		9-20
	Sodium [01]	139		139	04/23/2025	mmol/L	134-144
	Potassium [01]	4.6		5.1	04/23/2025	mmol/L	3.5-5.2
	Chloride [01]	102		103	04/23/2025	mmol/L	96-106
	Carbon Dioxide, Total [01]	24		23	04/23/2025	mmol/L	20-29
	Calcium [01]	9.6		9.6	04/23/2025	mg/dL	8.7-10.2
	Phosphorus [01]	3.1		3.0	04/23/2025	mg/dL	2.8-4.1
	Magnesium [01]	2.2		2.2	04/23/2025	mg/dL	1.6-2.3
	Protein, Total [01]	6.8		7.0	04/23/2025	g/dL	6.0-8.5
	Albumin [01]	4.6		4.5	04/23/2025	g/dL	4.3-5.2
	Globulin, Total	2.2		2.5	04/23/2025	g/dL	1.5-4.5
	Bilirubin, Total [01]	0.9		0.7	04/23/2025	mg/dL	0.0-1.2
	Alkaline Phosphatase [01]	86		66	04/23/2025	IU/L	44-121
	LDH [01]	170		208	04/23/2025	IU/L	121-224
	AST (SGOT) [01]	32		30	04/23/2025	IU/L	0-40
	ALT (SGPT) [01]	38		39	04/23/2025	IU/L	0-44
	GGT [01]	13		17	04/23/2025	IU/L	0-65
	Iron Bind.Cap.(TIBC)	344		275	04/23/2025	ug/dL	250-450
	UIBC [01]	263		185	04/23/2025	ug/dL	111-343
	Iron [01]	81		90	04/23/2025	ug/dL	38-169
	Iron Saturation	24		33	04/23/2025	%	15-55
	Ferritin [01]	104		107	04/23/2025	ng/mL	30-400

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	Homocyst(e)ine [01]	7.7		6.0	04/23/2025	umol/L	0.0-14.5
	TSH [01]	3.050		2.230	06/10/2025	uIU/mL	0.450-4.500
	Thyroxine (T4) [01]	8.9		9.5	06/10/2025	ug/dL	4.5-12.0
	T3 Uptake [01]	27		32	04/23/2025	%	24-39
	Free Thyroxine Index	2.4		2.9	04/23/2025		1.2-4.9
	Triiodothyronine (T3) [01]	160		114	06/10/2025	ng/dL	71-180
	Triiodothyronine (T3), Free [01]	4.2		3.4	06/10/2025	pg/mL	2.0-4.4
	Reverse T3, Serum [A, 02]	18.0		**24.6**	06/10/2025	ng/dL	9.2-24.1
	T4,Free(Direct) [01]	1.40		1.61	06/10/2025	ng/dL	0.82-1.77
▲	**Thyroid Peroxidase (TPO) Ab** [01]	**165**	**High**	**191**	06/10/2025	IU/mL	0-34
▲	**Thyroglobulin Antibody** [01]	**1.2**	**High**	**1.1**	06/10/2025	IU/mL	0.0-0.9

Insulin

Test	Current Result and Flag		Previous Result and Date		Units	Reference Interval
Insulin [01]	6.6		9.0	04/23/2025	uIU/mL	2.6-24.9

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High

Mycotoxins | Heavy Metals

Test Name	Current	Previous	Result (75th / 95th)	Reference
Tellurium (ug/g)	1.25		0.42 / 0.89	≤0.89
Enniatin B1(ENN B1) (ng/g)	0.24		0.13 / 0.22	≤0.22
Fumonisins B2 (ng/g)	25.11		4.05 / 7.2	≤7.2
Fumonisins B3 (ng/g)	29.21		6.08 / 10.8	≤10.8
Zearalenone (ZEN) (ng/g)	1.19		0.38 / 0.67	≤0.67

Suboptimal

Mycotoxins | Heavy Metals | Environmental Toxins

Test Name	Current	Previous	Result (75th / 95th)	Reference
Atrazine mercapturate^ (ug/g)	0.03		0.02 / 0.05	≤0.05
Butylparaben^ (ug/g)	0.29		0.25 / 4.39	≤4.39
Dimethylthiophosphate (DMTP)^ (ug/g)	17.11		5.91 / 33.7	≤33.7
Barium^ (ug/g)	2.67		2.33 / 5.59	≤5.59
Nickel (ug/g)	8.81		6.37 / 12.13	≤12.13
Tungsten^ (ug/g)	0.25		0.12 / 0.33	≤0.33
Ochratoxin A (OTA) (ng/g)	4.71		3.83 / 6.8	≤6.8

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