Casual Friday Presents

Fine-Tuning Mitochondrial Function Pt. 4

A BIOGENETIX CLINICAL PRESENTATION

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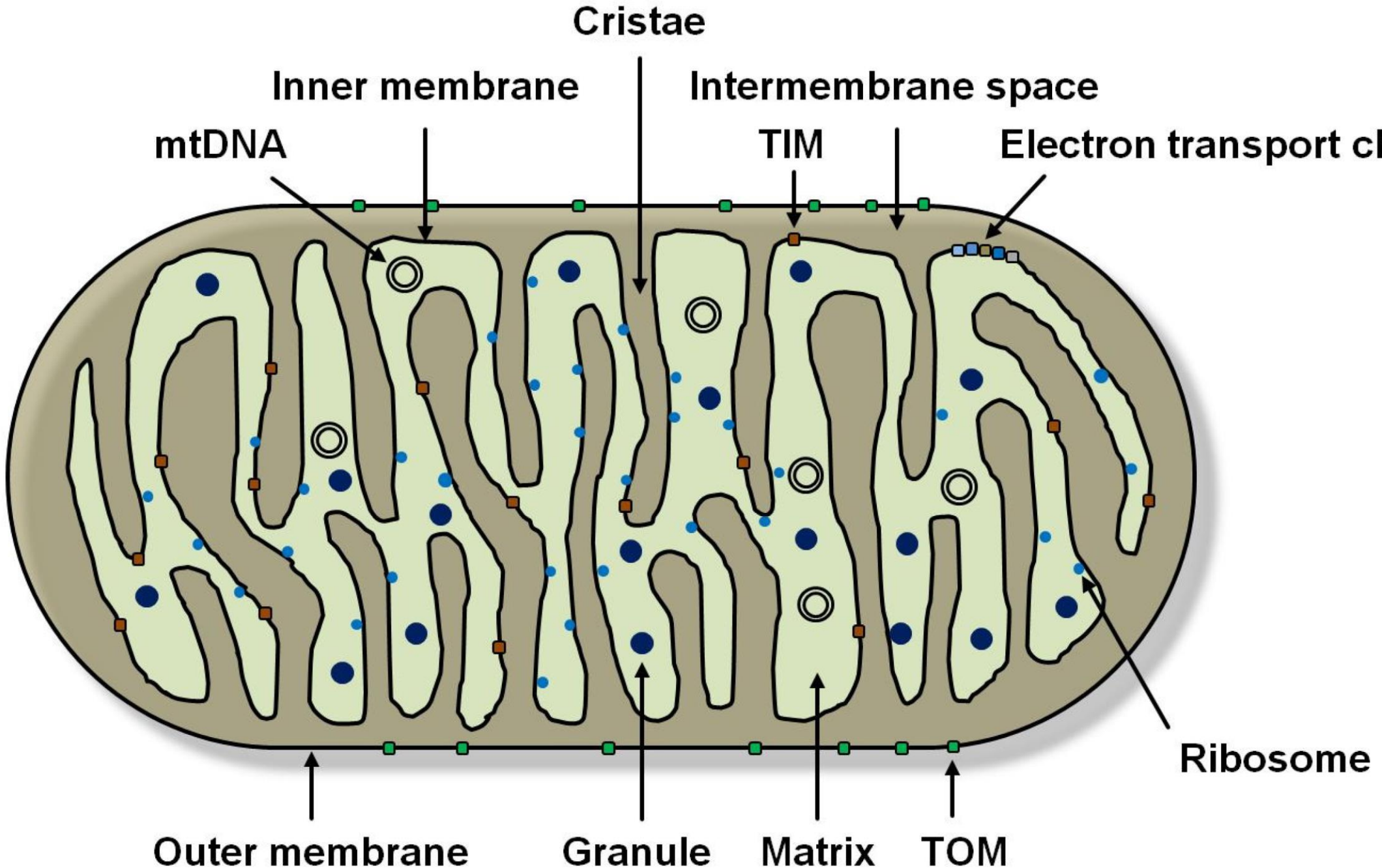

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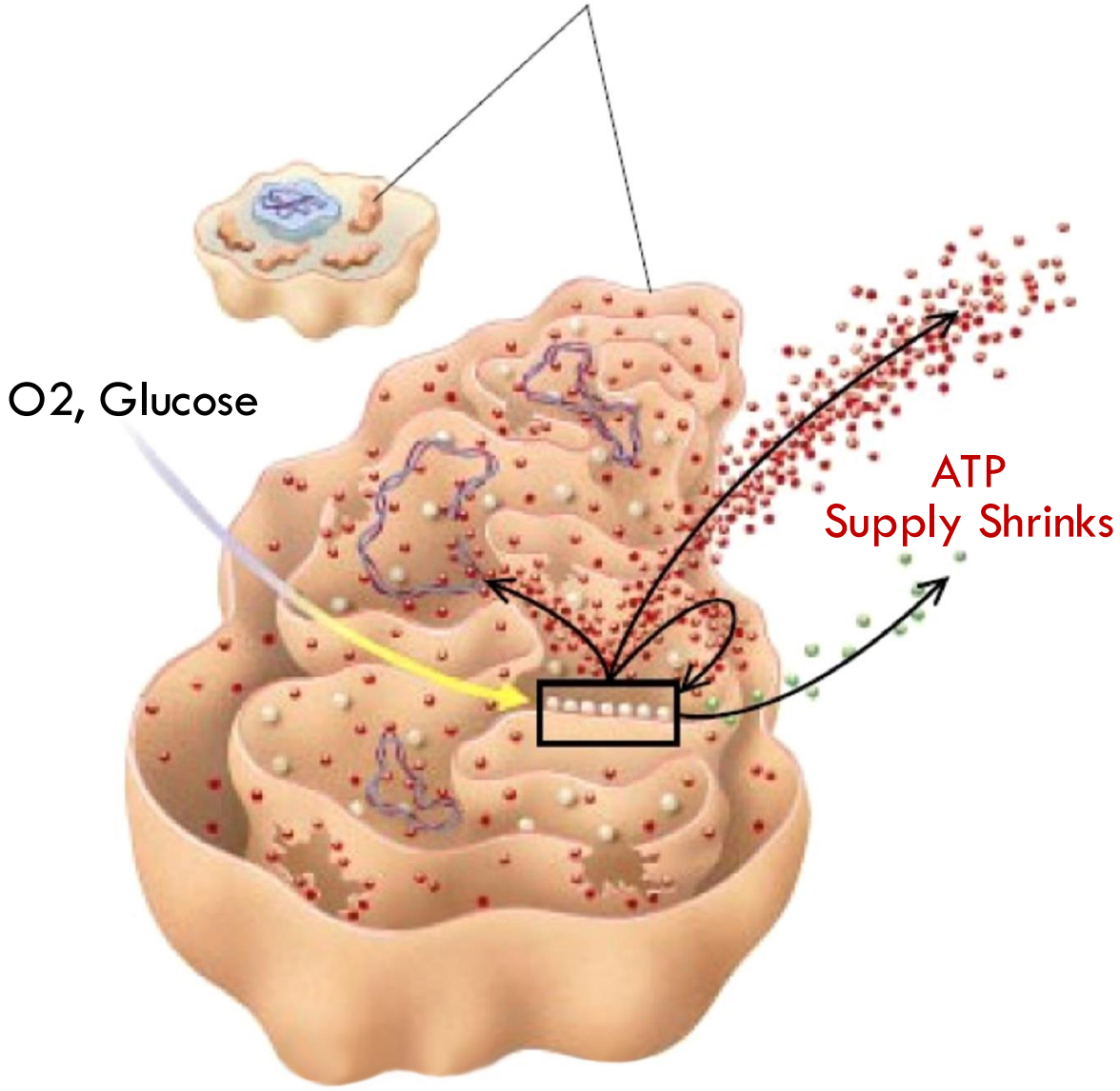
Damaged Mitochondria in
Distressed Old Cell



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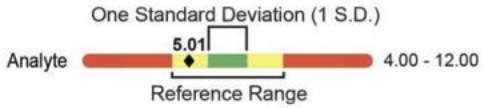
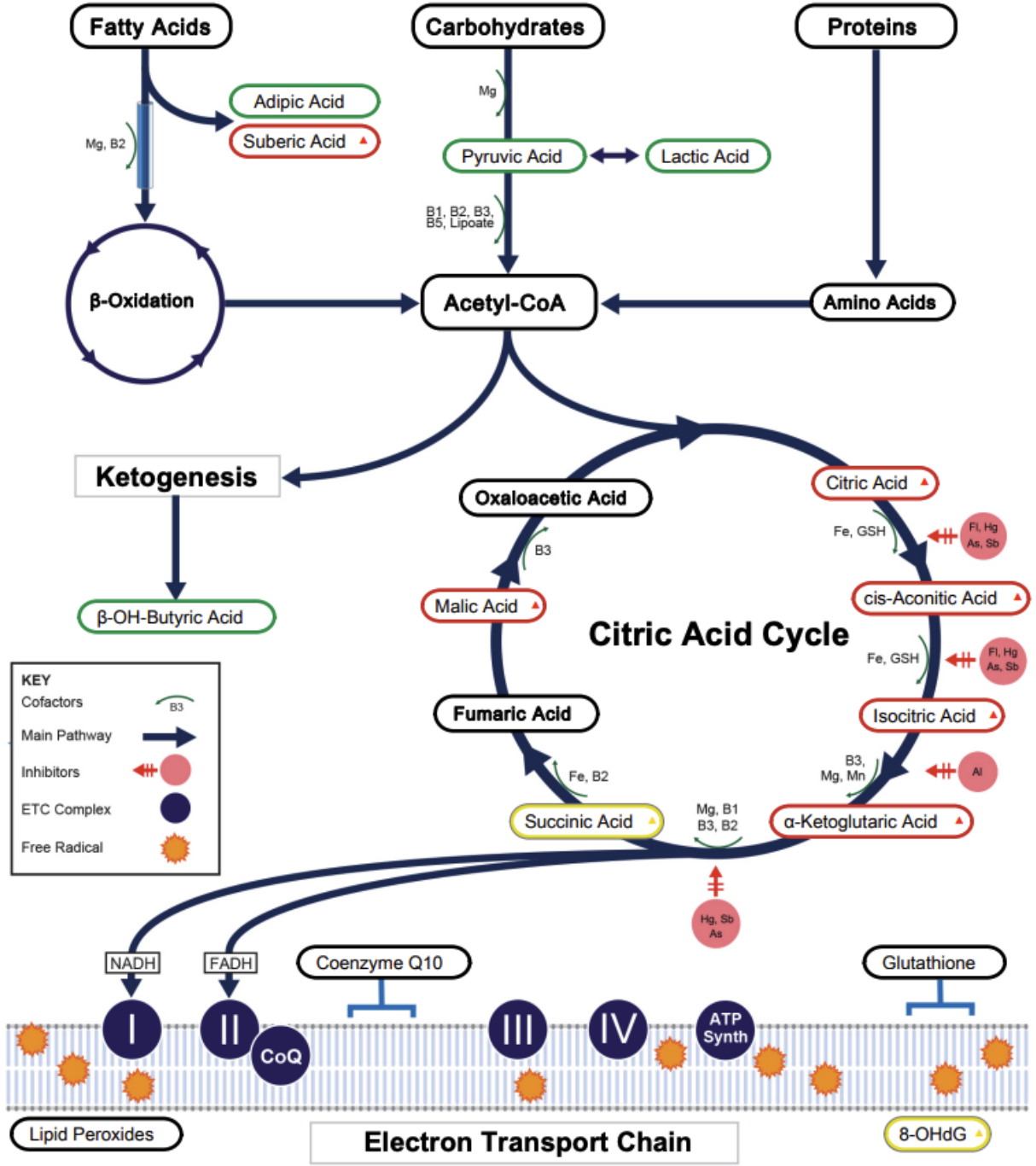

One Standard Deviation (1 S.D.)
Analyte
5.01
4.00 - 12.00
Reference Range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Carbohydrates
Proteins
Adipic Acid
Suberic Acid
Mg, B2
Mg
Pyruvic Acid
Lactic Acid
B1, B2, B3, B5, Lipoate
β-Oxidation
Acetyl-CoA
Amino Acids
Ketogenesis
β-OH-Butyric Acid
Oxaloacetic 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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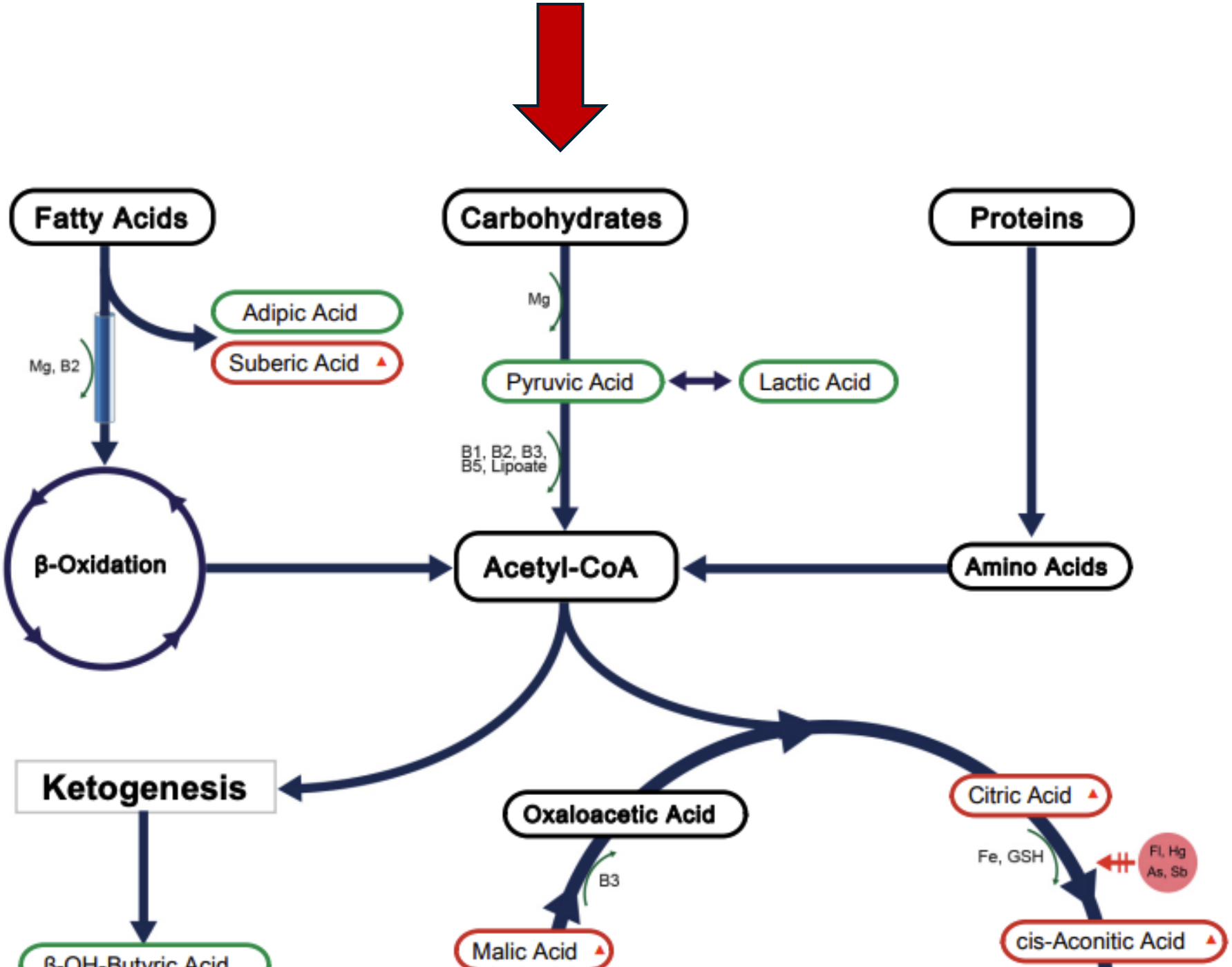
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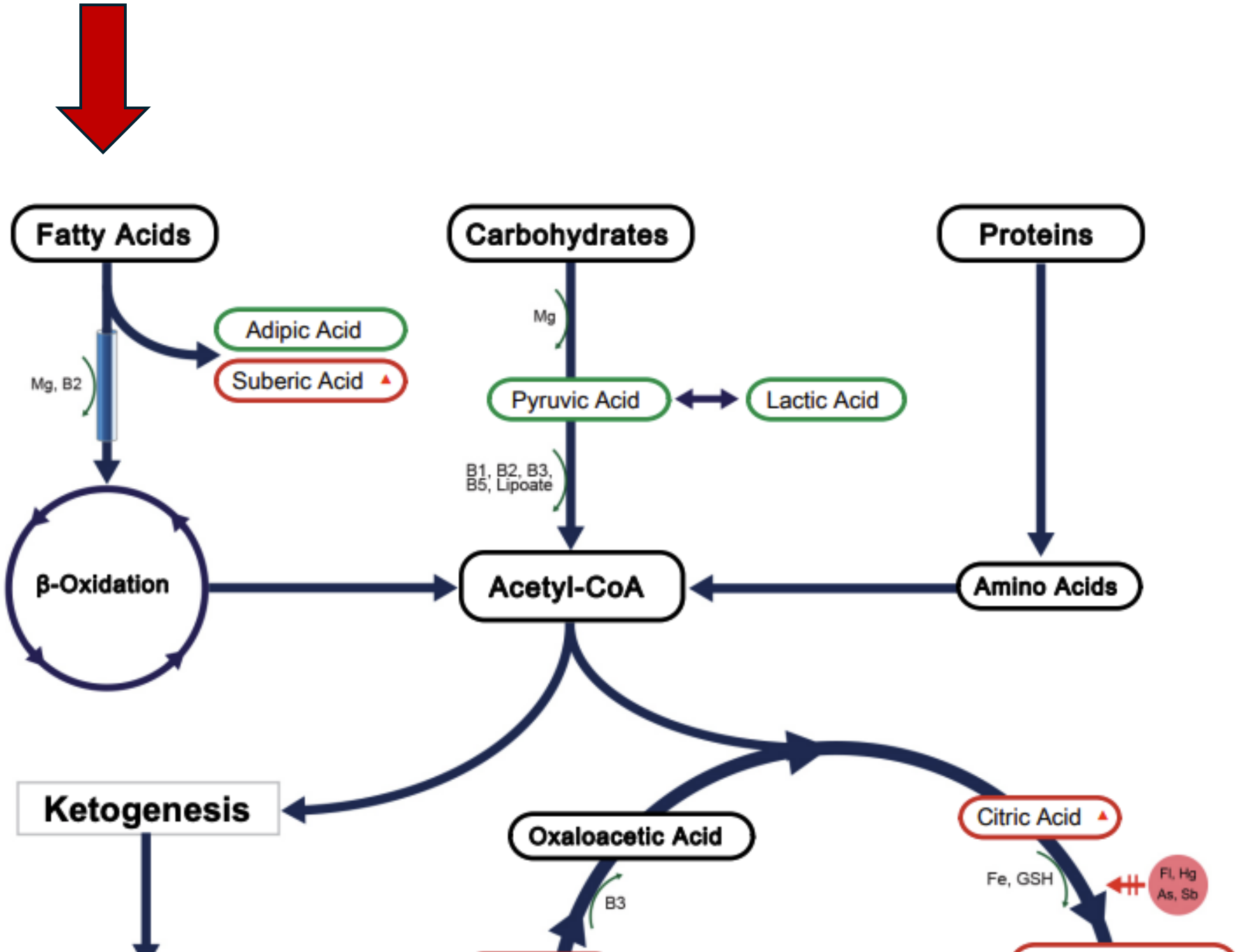
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B3
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Fe, GSH
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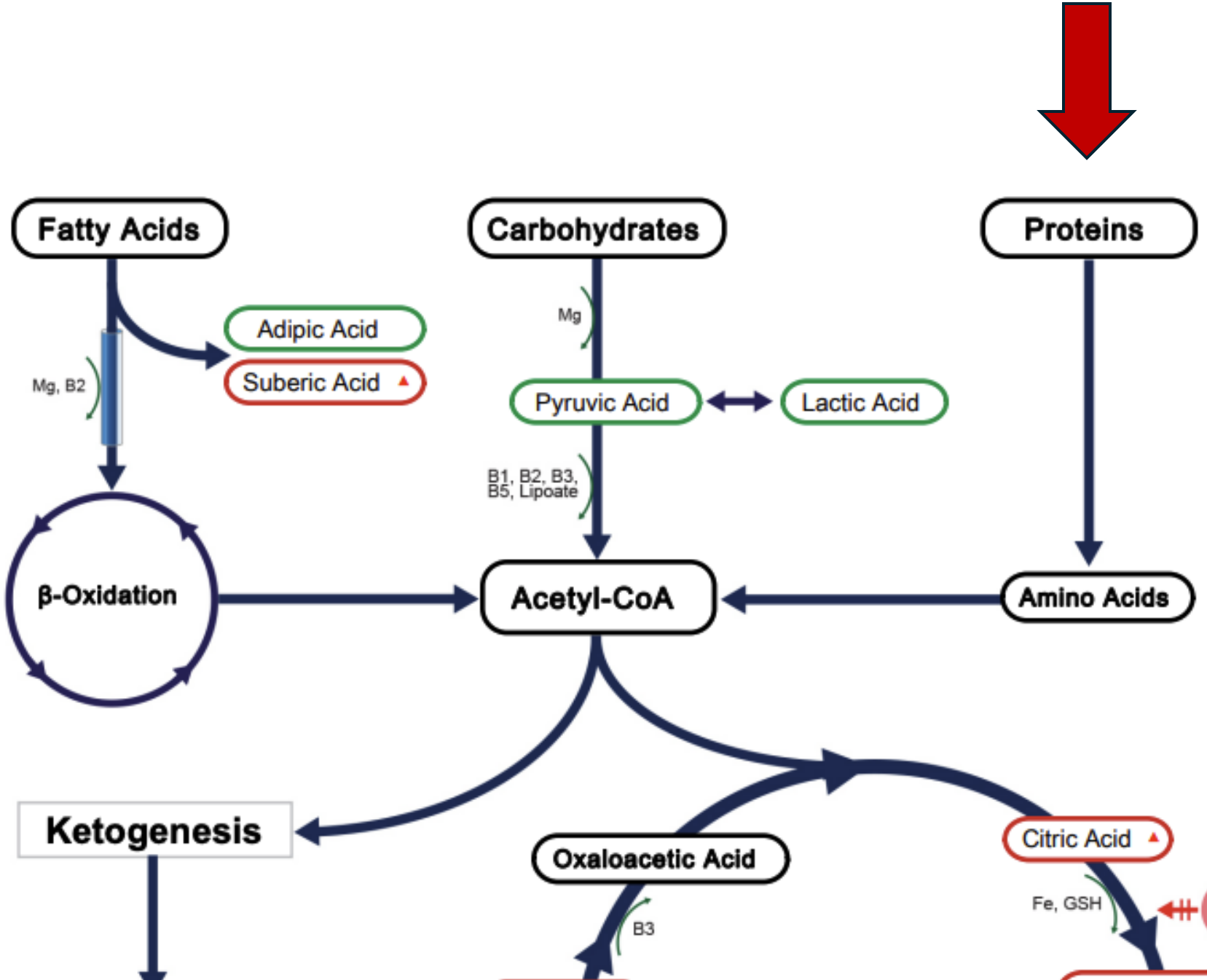
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B3
Citric Acid
Fe, GSH
Fl, Hg
As, Sb

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National Library of Medicine
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The body uses protein catabolism for ATP production by breaking proteins into amino acids, removing their nitrogenous groups to form ammonia, and feeding the remaining carbon skeletons into the Krebs cycle as acetyl-CoA or other intermediates. These intermediates are then fully oxidized in the Krebs cycle and oxidative phosphorylation, generating NADH and FADH2, which subsequently power the electron transport chain to synthesize large amounts of ATP. This pathway is a less preferred energy source for ATP production compared to carbohydrates or fats, primarily used during prolonged fasting or low-energy states.

~2-3 ATP per carbon in the Amino Acid
~15-20 ATP per gram of Protein

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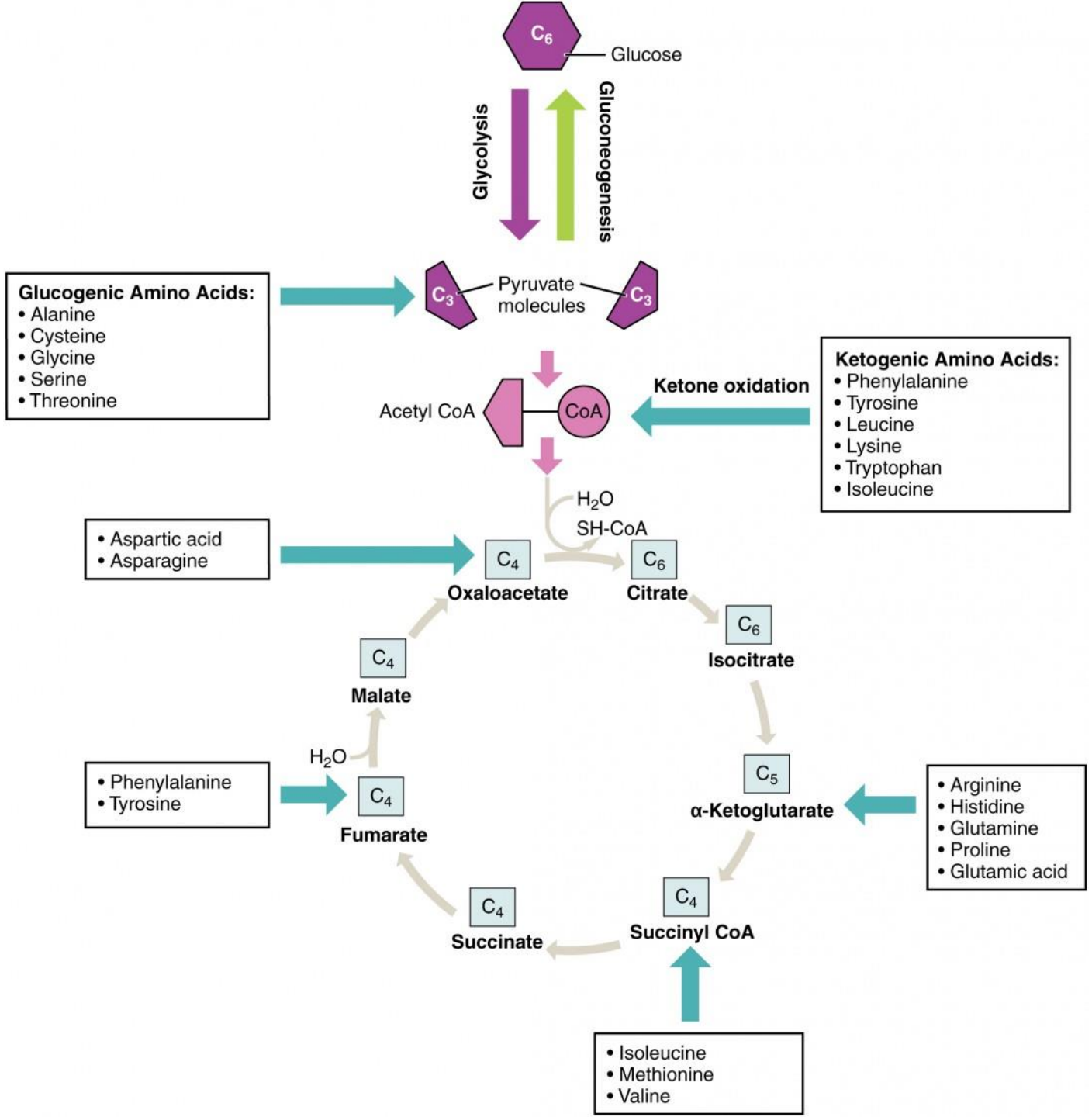
C6
Glucose
Glycolysis
Gluconeogenesis
Glucogenic Amino Acids:
• Alanine
• Cysteine
• Glycine
• Serine
• Threonine
C3
Pyruvate molecules
C3
Acetyl CoA
CoA
Ketone oxidation
Ketogenic Amino Acids:
• Phenylalanine
• Tyrosine
• Leucine
• Lysine
• Tryptophan
• Isoleucine
H2O
SH-CoA
• Aspartic acid
• Asparagine
C4
Oxaloacetate
C6
Citrate
C6
Isocitrate
C4
Malate
H2O
• Phenylalanine
• Tyrosine
C4
Fumarate
C5
α-Ketoglutarate
• Arginine
• Histidine
• Glutamine
• Proline
• Glutamic acid
C4
Succinate
C4
Succinyl CoA
• Isoleucine
• Methionine
• Valine

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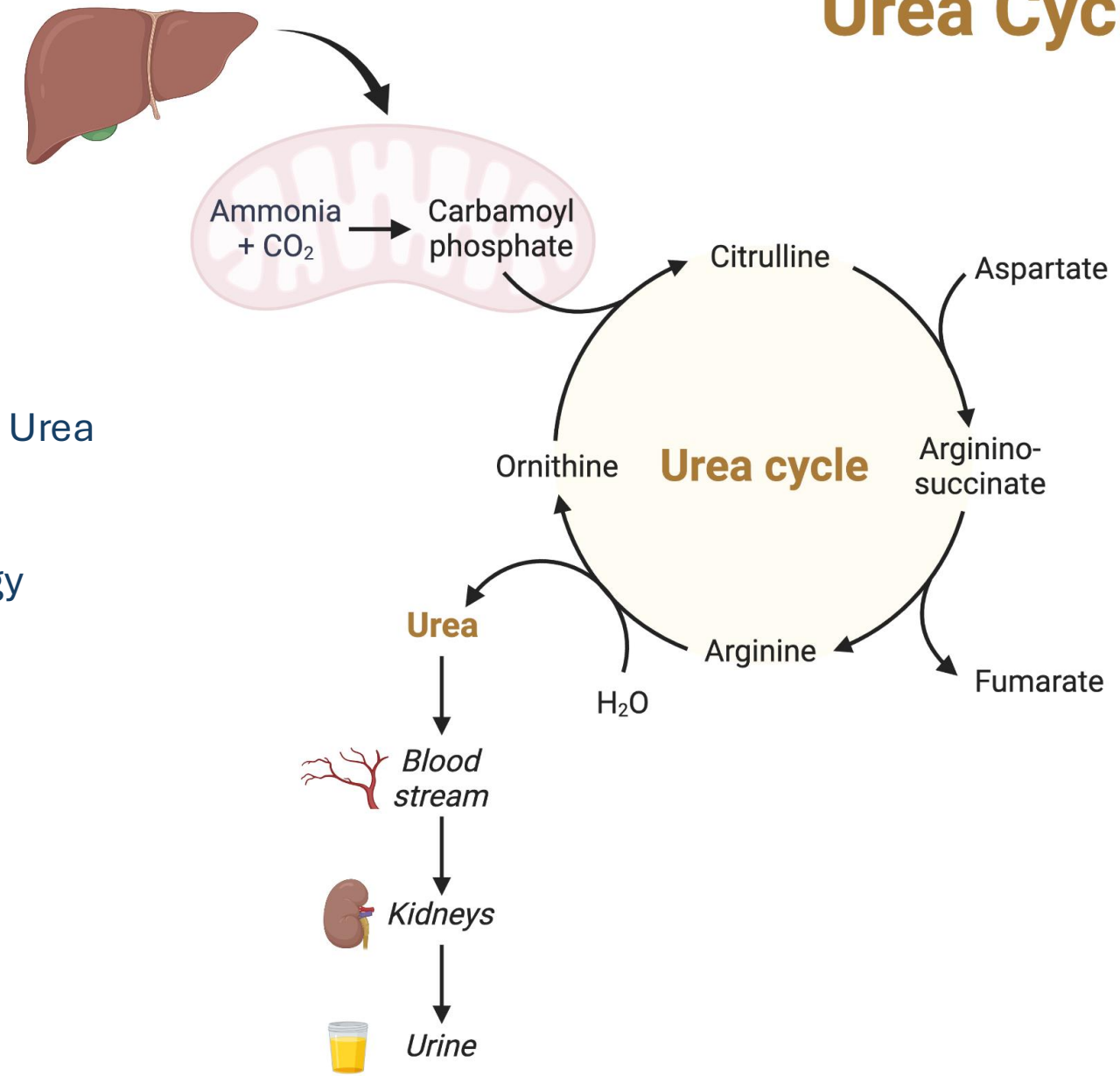
Urea Cycle

Ammonia is toxic – detox pathway is Urea Cycle.

We can use BUN to determine energy source preference/prevalence.



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Comp. Metabolic Panel (14)

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
▲	**Glucose** [01]	**210**	**High**		mg/dL	70-99
▲	**BUN** [01]	**37**	**High**		mg/dL	8-27
▲	**Creatinine** [01]	**1.17**	**High**		mg/dL	0.57-1.00
▼	**eGFR**	**49**	**Low**		mL/min/1.73	>59
▲	**BUN/Creatinine Ratio**	**32**	**High**			12-28
	Sodium [01]	137			mmol/L	134-144
	Potassium [01]	4.6			mmol/L	3.5-5.2
	Chloride [01]	101			mmol/L	96-106
	Carbon Dioxide, Total [01]	20			mmol/L	20-29
▲	**Calcium** [01]	**10.7**	**High**		mg/dL	8.7-10.3
		Verified by repeat analysis				
	Protein, Total [01]	7.1			g/dL	6.0-8.5
	Albumin [01]	4.5			g/dL	3.8-4.8
	Globulin, Total	2.6			g/dL	1.5-4.5
	Bilirubin, Total [01]	0.2			mg/dL	0.0-1.2
	Alkaline Phosphatase [01]	78			IU/L	44-121
	AST (SGOT) [01]	17			IU/L	0-40
	ALT (SGPT) [01]	14			IU/L	0-32

LP+Chol/HDL+LDL/HDL+CHD Risk

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
	Lipids [03]					
▲	**Cholesterol, Total** [01]	**217**	**High**		mg/dL	100-199
▲	**Triglycerides** [01]	**150**	**High**		mg/dL	0-149
	HDL Cholesterol [01]	83			mg/dL	>39
	VLDL Cholesterol Cal	26			mg/dL	5-40
▲	**LDL Chol Calc (NIH)**	**108**	**High**		mg/dL	0-99

Hgb A1c with eAG Estimation

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
▲	**Hemoglobin A1c** [01]	**9.8**	**High**		%	4.8-5.6
	Please Note: [01]					
		Prediabetes: 5.7 - 6.4 Diabetes: >6.4 Glycemic control for adults with diabetes: <7.0				
	Estim. Avg Glu (eAG)	235			mg/dL	

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J Hepatol. 2018 Oct;69(4):905-915. doi: 10.1016/j.jhep.2018.06.023. Epub 2018 Jul 5.

Urea cycle dysregulation in non-alcoholic fatty liver disease

Francesco De Chiara [1], Sara Heebøll [2], Giusi Marrone [1], Carmina Montoliu [3], Stephen Hamilton-Dutoit [4], Antonio Ferrandez [5], Fausto Andreola [1], Krista Rombouts [1], Henning Grønbæk [2], Vicente Felipo [6], Jordi Gracia-Sancho [7], Rajeshwar P Mookerjee [1], Hendrik Vilstrup [2], Rajiv Jalan [8], Karen Louise Thomsen [9]

Affiliations + expand

PMID: 29981428 DOI: 10.1016/j.jhep.2018.06.023

NASH is associated with a reduction in the gene and protein expression, and activity, of UCEs. This results in hyperammonemia, possibly through hypermethylation of UCE genes and impairment of urea synthesis. Our investigations are the first to describe a link between NASH, the function of UCEs, and hyperammonemia, providing a novel therapeutic target.

In patients with fatty liver disease, the enzymes that convert nitrogen waste into urea may be affected, leading to the accumulation of ammonia, which is toxic. This accumulation of ammonia can lead to scar tissue development, increasing the risk of disease progression. In this study, we show that fat accumulation in the liver produces a reversible reduction in the function of the enzymes that are involved in detoxification of ammonia. These data provide potential new targets for the treatment of fatty liver disease.

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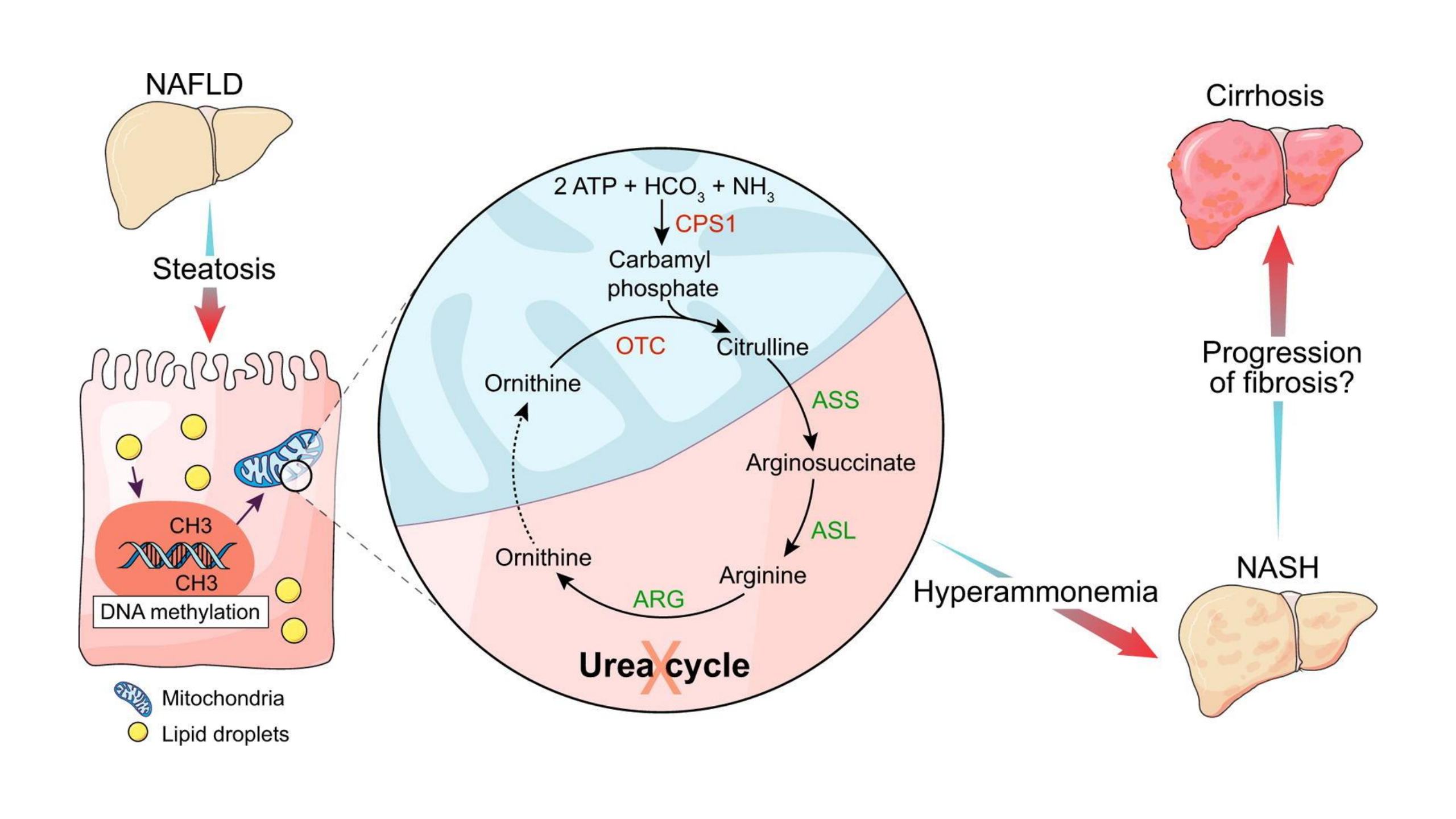
NAFLD
Steatosis
CH3
CH3
DNA methylation
Mitochondria
Lipid droplets
2 ATP + HCO3 + NH3
CPS1
Carbamyl phosphate
OTC
Citrulline
ASS
Arginosuccinate
ASL
Arginine
ARG
Ornithine
Ornithine
Urea cycle
Hyperammonemia
NASH
Progression of fibrosis?
Cirrhosis

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
	Chemistries [01]					
▲	**Glucose** [01]	**281**	**High**		mg/dL	70-99
▲	**Hemoglobin A1c** [01]	**9.4**	**High**		%	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]	6.5			mg/dL	3.8-8.4
				Therapeutic target for gout patients: <6.0		
▲	**BUN** [01]	**53**	**High**		mg/dL	8-27
▲	**Creatinine** [01]	**2.64**	**High**		mg/dL	0.76-1.27
▼	**eGFR**	**26**	**Low**		mL/min/1.73	>59
	BUN/Creatinine Ratio	20				10-24
	Sodium [01]	139			mmol/L	134-144
	Potassium [01]	4.9			mmol/L	3.5-5.2
	Chloride [01]	103			mmol/L	96-106
	Carbon Dioxide, Total [01]	22			mmol/L	20-29
	Calcium [01]	9.6			mg/dL	8.6-10.2
	Phosphorus [01]	3.4			mg/dL	2.8-4.1
	Magnesium [01]	2.1			mg/dL	1.6-2.3
	Protein, Total [01]	7.3			g/dL	6.0-8.5
	Albumin [01]	4.8			g/dL	3.9-4.9
	Globulin, Total	2.5			g/dL	1.5-4.5
	Bilirubin, Total [01]	0.5			mg/dL	0.0-1.2
	Alkaline Phosphatase [01]	73			IU/L	44-121
	LDH [01]	213			IU/L	121-224
	AST (SGOT) [01]	17			IU/L	0-40
	ALT (SGPT) [01]	29			IU/L	0-44
	GGT [01]	32			IU/L	0-65
	Iron Bind.Cap.(TIBC)	303			ug/dL	250-450
	UIBC [01]	212			ug/dL	111-343

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	Iron [01]	91			ug/dL	38-169
	Iron Saturation	30			%	15-55
▲	**Ferritin** [01]	**640**	**High**		ng/mL	30-400
	Cholesterol, Total [01]	175			mg/dL	100-199
▲	**Triglycerides** [01]	**170**	**High**		mg/dL	0-149
▼	**HDL Cholesterol** [01]	**35**	**Low**		mg/dL	>39
	VLDL Cholesterol Cal	30			mg/dL	5-40
▲	**LDL Chol Calc (NIH)**	**110**	**High**		mg/dL	0-99

▲	**C-Reactive Protein, Cardiac** [01]	**3.88**	**High**		mg/L	0.00-3.00
				Relative Risk for Future Cardiovascular Event		
				Low	<1.00	
				Average	1.00 - 3.00	
				High	>3.00	
▲	**Homocyst(e)ine** [01]	**17.9**	**High**		umol/L	0.0-17.2
	TSH [01]	0.883			uIU/mL	0.450-4.500
	Thyroxine (T4) [01]	7.1			ug/dL	4.5-12.0
	T3 Uptake [01]	31			%	24-39
	Free Thyroxine Index	2.2				1.2-4.9
	Triiodothyronine (T3) [01]	84			ng/dL	71-180
	Triiodothyronine (T3), Free [01]	2.8			pg/mL	2.0-4.4
▲	**Reverse T3, Serum** [A, 02]	**26.8**	**High**		ng/dL	9.2-24.1

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> Sci Rep. 2022 Mar 1;12(1):3418. doi: 10.1038/s41598-022-06614-9.

Liver injury in non-alcoholic fatty liver disease is associated with urea cycle enzyme dysregulation

Rocío Gallego-Durán [# 1 2], Javier Ampuero [# 3 4 5], Helena Pastor-Ramírez [3 4], Leticia Álvarez-Amor [6 7], Jose Antonio Del Campo [8], Douglas Maya-Miles [3 4], Rocío Montero-Vallejo [3 4], Antonio Cárdenas-García [6 7], Mª Jesús Pareja [9], Sheila Gato-Zambrano [3 4], Raquel Millán [3 4], María Del Carmen Rico [3 4],

The main aim was to evaluate changes in urea cycle enzymes in NAFLD patients and in two preclinical animal models mimicking this entity. Seventeen liver specimens from NAFLD patients were included for immunohistochemistry and gene expression analyses. Three-hundred-and-eighty-two biopsy-proven NAFLD patients were genotyped for rs1047891, a functional variant located in carbamoyl phosphate synthetase-1 (CPS1) gene. Two preclinical models were employed to analyse CPS1 by immunohistochemistry, a choline deficient high-fat diet model (CDA-HFD) and a high fat diet LDLr knockout model (LDLr -/-). A significant downregulation in mRNA was observed in CPS1 and ornithine transcarbamylase (OTC1) in simple steatosis and NASH-fibrosis patients versus controls. Further, age, obesity (BMI > 30 kg/m^2), diabetes mellitus and ALT were found to be risk factors whereas A-allele from CPS1 was a protective factor from liver fibrosis. CPS1 hepatic expression was diminished in parallel with the increase of fibrosis, and its levels reverted up to normality after changing diet in CDA-HFD mice. In conclusion, liver fibrosis and steatosis were associated with a reduction in both gene and protein expression patterns of mitochondrial urea cycle enzymes. A-allele from a variant on CPS1 may protect from fibrosis development. CPS1 expression is restored in a preclinical model when the main trigger of the liver damage disappears.

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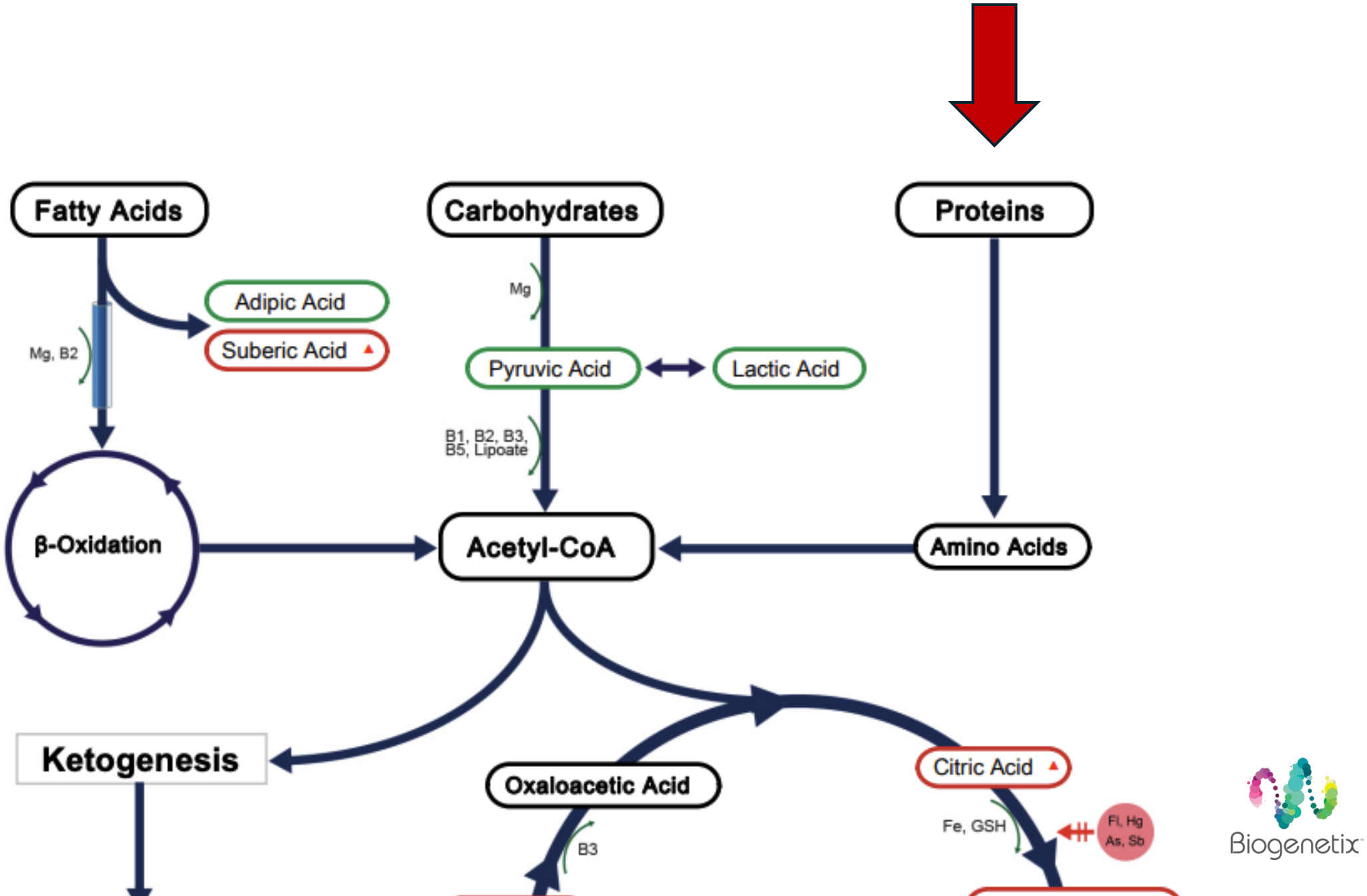
Fatty Acids
Carbohydrates
Proteins
Adipic Acid
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Mg, B2
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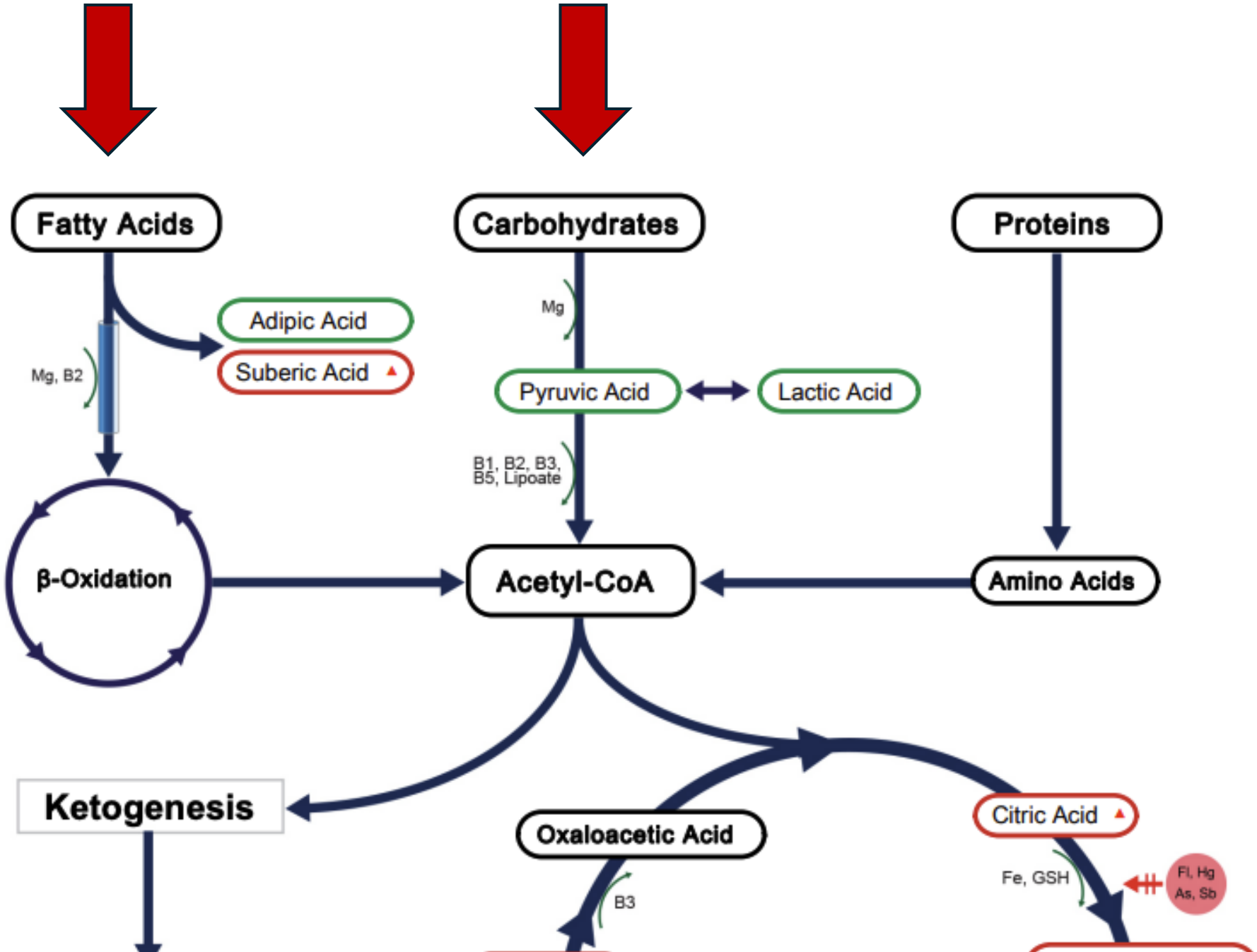
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B3
Citric Acid
Fe, GSH
Fl, Hg
As, Sb

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Comp. Metabolic Panel (14)

	Test	Current Result and Flag		Previous Result and Date		Units	Reference Interval
▲	**Glucose** [01]	**177**	**High**	**103**	07/02/2025	mg/dL	70-99
	BUN [01]	17		15	07/02/2025	mg/dL	8-27
	Creatinine [01]	0.90		0.85	07/02/2025	mg/dL	0.76-1.27
	eGFR	91		93	07/02/2025	mL/min/1.73	>59
	BUN/Creatinine Ratio	19		18	07/02/2025		10-24
	Sodium [01]	140		142	07/02/2025	mmol/L	134-144
	Potassium [01]	4.3		4.5	07/02/2025	mmol/L	3.5-5.2
	Chloride [01]	104		105	07/02/2025	mmol/L	96-106
▼	**Carbon Dioxide, Total** [01]	**19**	**Low**	21	07/02/2025	mmol/L	20-29
▲	**Calcium** [01]	**10.3**	**High**	9.7	07/02/2025	mg/dL	8.6-10.2
	Protein, Total [01]	7.1		6.5	07/02/2025	g/dL	6.0-8.5
	Albumin [01]	4.7		4.5	07/02/2025	g/dL	3.8-4.8
	Globulin, Total	2.4		2.0	07/02/2025	g/dL	1.5-4.5
▲	**Bilirubin, Total** [01]	**1.8**	**High**	**1.7**	07/02/2025	mg/dL	0.0-1.2
	Alkaline Phosphatase [01]	78		68	07/02/2025	IU/L	44-121
	AST (SGOT) [01]	15		13	07/02/2025	IU/L	0-40
	ALT (SGPT) [01]	22		26	07/02/2025	IU/L	0-44

	Test	Current Result and Flag		Previous Result and Date		Units	Reference Interval
	TSH [01]	1.560		1.540	03/19/2025	uIU/mL	0.450-4.500
	Thyroxine (T4) [01]	6.8				ug/dL	4.5-12.0
▼	**T3 Uptake** [01]	**22**	**Low**			%	24-39
	Free Thyroxine Index	1.5					1.2-4.9

Hgb A1c with eAG Estimation

	Test	Current Result and Flag		Previous Result and Date		Units	Reference Interval
▲	**Hemoglobin A1c** [01]	**7.3**	**High**	**7.1**	07/02/2025	%	4.8-5.6
	Please Note: [01]						
	Estim. Avg Glu (eAG)	163		157	07/02/2025	mg/dL	

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Prediabetes: 5.7 - 6.4
Diabetes: >6.4
Glycemic control for adults with diabetes: <7.0
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