METABOLIC TERRAIN INSTITUTE OF HEALTH

Genes and Biomarkers Associated with Metabolic Therapies and Mitochondrial Function

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Introduction:

This is a case preesentation of metabolic lifestyle intervention by a 60-year-old female with an end stage cancer diagnosis. Urine Organic Acids was followed for three years. The focus of this poster will be Lactate:Pyruvate (Lac:Pyr) and Acetoacetate:β-hydroxybutyrate (AcAc:BHB) ratios as surrogate markers of NAD^+:NADH ratio as a marker of cellular redox state. The data presented here suggests the Lac:Pyr is inversely proportional to mitochondrial function and directly proportional to severity of disease state and AcAc:BHB is directly proportional to mitochondrial function and inversely proportional to severity of disease state.
The primary interventions were mistletoe, ketogenic diet, fasting, exercise, sauna, cold plunge and breathing exercises. Results of organic acids suggest significant improvements in mitochondrial function as expressed by Lactate:Pyruvate and AcAc:BHB ratios. Gene polymorphisms associated with ketogenesis are noted.

Ketogenisis/Ketolysis

BDH1	BHB Dehydrogenase 1	
OXCT1	SCOT aka 3-Oxoacid CoA-Transferase 1	
HMGCS2	HMG CoA Synthase	
ACAT1	Acetyl-CoA Acyl Transferase	GG
SLC22A5	Organic Cation/Carnitine Transporter 2	AC
PPAR*A*	Peroxisome Proliferator Activated Receptor Alpha	
ACSL1	Acyl-CoA Synthetase Long Chain Family Member 1	GG

Case presentation:

The patient presented with invasive ductal carcinoma right breast and DCIS in 2018. The patient underwent 2xLumpectomy, Mastectomy and reconstruction, and reconstruction in 2018. Previous health history includes benign lumpectomy 1988, and detection of toxic levels of Mercury, Lead, Arsenic and Copper in 1997.

CBC/CMP: In 2020 the patient presented with high Anion Gap (17), Low Total Protein (63), High Fating Glucose (5.6), and thyroid dysfunction.

Tox Screen: in 2020 the patient presented with elevated Ochratoxin A, Mycophenolic Acid, and Enniatin B, later learning in 2023 her house was infested with mold. The patient also presented with elevations in Phenylglyoxalic acid, Perchlorate, N-Acetyl(propyl)cysteine, *N*-acetyl(2-hydroxypropyl)cysteine, N-acetyl(3,4-dihydroxybutyl)cysteine indicating exposures to toxic substances.

Discussion:

Plasma or CSF lac:pyr has been suggested to be a biomarker of severity of mitochondrial diseases[1]. Four months prior the patients Anion Gap was 17, Total protein was low (64-63)two of the previous 8 months and was experiencing loss of muscle mass. The lab reference for Lac:Pyr was 5.3 for a "healthy" population not in a state of therapeutic ketosis. From 2020 to 2023 the observed lactate:pyruvate ratio dropped from 600 to 56, indicating a marked improvement in mitochondrial function and a reflection of metabolic adaptation. This decrease in Lac:Pyr suggests a proportional change in cytosolic NAD^+:NADH ratio and an improvement in disease prognosis.

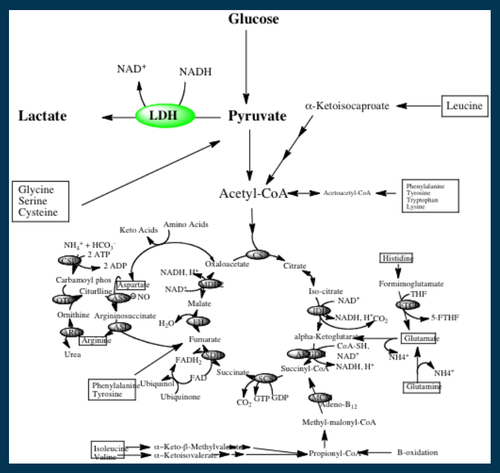
Arterial AcAc:BHB ratio has been used as a prognostic marker in liver dysfunction[2]. The urinary levels of AcAc and BHB were extremely high in 2020 urinary measurements relative to a patient population not in therapeutic ketosis. The lab reference value of AcAc:BHB was 3.3 for a "healthy" population. The patients AcAc:BHB ratio was 0.21 at baseline and increased to 2.3 in 2023. This increase in AcAc:BHB ratio suggests an inversely proportional change in mitochondrial NAD^+:NADH theoretically representing an improvement in cellular redox state and a departure from oxidative stress and chronic disease state.

As an oversimplification of the significance of individual TCA cycle intermediates and the true meaning of composite elevations of TCA cycle intermediates, this poster is suggesting that The greater the number of elevated TCA cycle intermediates in urine is an indication of poor mitochondrial function. What was observed was 6 elevated TCA Cycle biomarkers at baseline and three elevated biomarkers at year three, this combined with the changes in Lac:Pyr and AcAc:BHB, decrease in plasma fasting glucose, and LDH all suggest an improvement in mitochondrial function.

Results

1. Lactate:Pyruvate Ratio

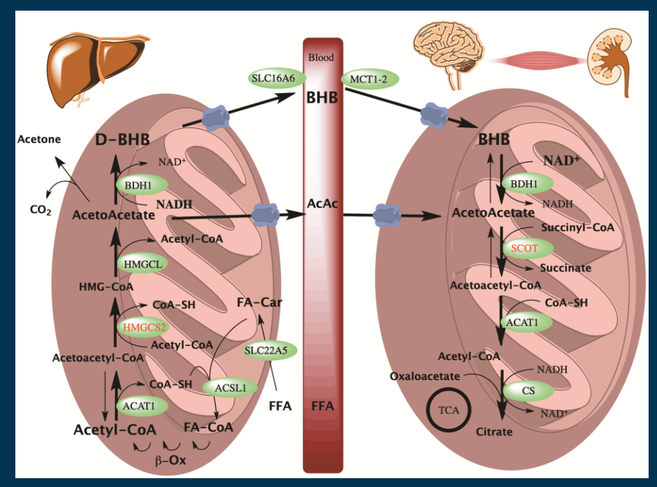
	11/09/2020	Ratio	06/13/2022	Ratio	10/09/23	Ratio
Lab Ref = 5.3						
Lactate	54	600				
Pyruvate	0.09					
Lactate			15	37		
Pyruvate			0.41			
Lactate					27	56
Pyruvate					0.48	



Results (cont.)

2. AcAC:BHB Ratio

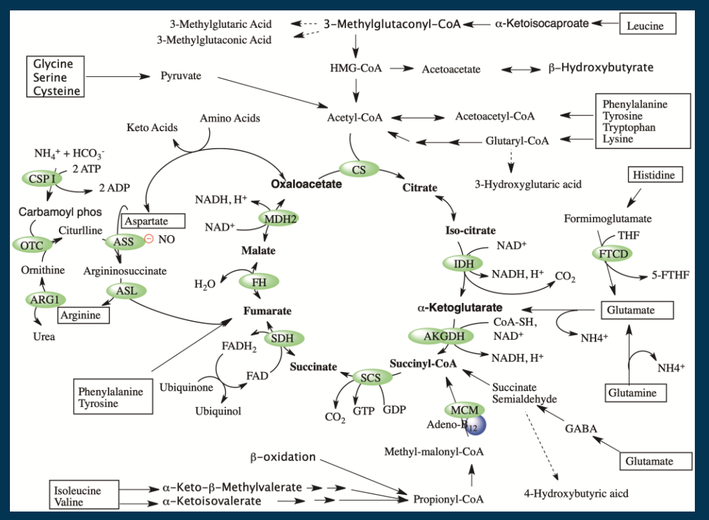
	11/09/2020	Ratio	06/13/2022	Ratio	10/09/23	Ratio
Lab Ref = 3.2						
AcAc	647	0.21				
BHB	3,091					
AcAc			212	1.6		
BHB			129			
AcAc					413	2.3
BHB					182	



Results (con.)

3. TCA Cycle intermediates

	11/09/2020	06/13/2022	10/09/23
Succinic	12	26	11
Fumaric	6.2	2.6	2.9
Malic	7.7	2.6	0.68
2-Oxoglutaric	25	1.7	18
Aconitic	30	15	16
Citric	266	406	344
3-Methylglutaric	1.2	0.37	0.46
3-Hydroxyglutaric	8.5	5.5	7.5
3-Methylglutaconic	2.0	1.3	1.3



Conclusion:

In this case, urinary biomarkers were followed over a three-year period following a breast cancer diagnosis. The baseline set of markers presented here clearly indicate patterns of impaired mitochondrial function which expressed as advanced disease state, muscle wasting.

Over the course of three years the patient reported significant improvement in lean muscle mass (not quantified), increased strength and energy (qualitative assessment), appetite, with a positive change in multiple QOL parameters. In addition, the changes in Lac:Pyr, AcAc:BHB, may indicate a dramatic improvement in mitochondrial function. Fasting Glucose, LDH and Total Protein, suggest possible correlation with disease severity with markers of mitochondrial function. This case presentation indicates the need to conduct a more rigorous clinical trial to validate the relation ship between plasma biomarkers, urinary biomarkers and disease progression.