

How to Assess Patient Biochemical and Nutritional Individuality through Organic Acid Testing

Cheryl K. Burdette, ND

Metamatrix Clinical Laboratory
Department of Science and Education

J. Alexander Bralley, PhD, CCN Medical Sciences

Richard S. Lord, PhD Biochemistry

Robert M. David, PhD Clinical Chemistry

Reprinted with permission from
Townsend Letter for Doctors and Patients

How to Assess Patient Biochemical and Nutritional Individuality through Organic Acid Testing

Organic acid testing is used to detect devastating pathology which is why it is the first test that is run on most all of us at birth. Before a newborn is able to leave the hospital, “Inborn Errors Of Metabolism” (IEOM) are universally screened for. If these inborn errors of metabolism are present, they are often fatal or highly morbid if not detected at the earliest possible moment.

An example of an inborn error of metabolism is citrullinemia. This is a urea cycle defect that will present with lethargy, vomiting, seizures, and possible coma due to ammonia toxicity. In citrullinemia there is an accumulation of citrulline due to an enzymatic defect allowing for conversion of citrulline to argininosuccinate in the urea cycle. Genetic mutations result in an inability to drive the urea cycle leading to ammonia toxicity. The degree of neurologic dysfunction and chance of coma is dependent on the length of time the enzyme defect is left untreated.

While absolute omissions or dysfunction of enzymes are rare, and consequently there is a low occurrence of different IEOM, slight defects or polymorphisms are more common. Each individual has variant enzymatic activity driving metabolic pathways. These slight shifts in activity of our biochemical reactions that take place in our body drive our individual need for nutrients. Mild enzymatic defects exist in most individuals and will manifest as symptoms only when the system is challenged. While a mild hyperammonia state due to a slight polymorphism of argininosuccinate synthetase will not result in symptoms such as seizures and coma, even slight elevations of ammonia are enough to cause headaches, fatigue and difficulty concentrating. [1] Slight increases in ammonia are all that are necessary for irritation to the central nervous system. This biochemical presentation directs the nutritional intervention of increasing specific cofactor availability to push a “sluggish” pathway.

While the FDA establishes limits for preventing deficiency for a population, organic acid testing demonstrates an individual’s need for a nutrient. Just as a comprehensive metabolic panel gives a snapshot of potential pathology, organic acid testing gives a snapshot of potential biochemical disturbances. A standard panel can be used to evaluate the following areas simultaneously:

1. Fatty Acid Metabolism and Energy Production by the Mitochondria
2. Carbohydrate metabolism
3. Toxicant assessment/Detoxification capacity
4. B-complex deficiency/Methylation inadequacy
5. Neurotransmitter turnover
6. Oxidative stress
7. Bacterial and Yeast overgrowth

Consider the following case study of a 43 year old female:

Case Study I: Chronic Fatigue

NUTRIENT MARKERS

Fatty Acid Metabolism

(Carnitine & B2)

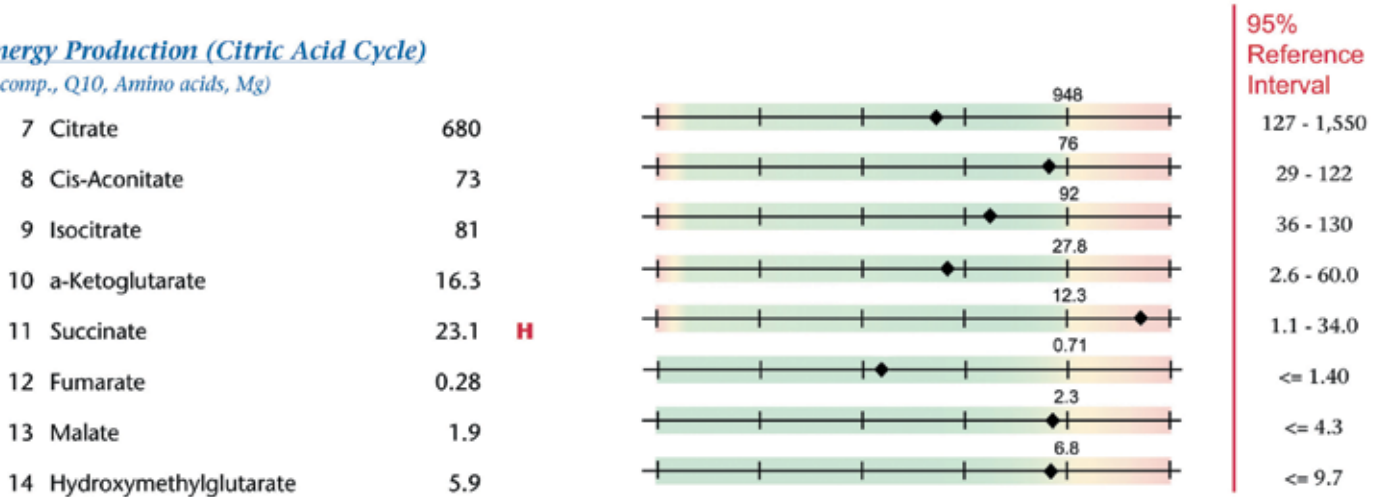


Carnitine and B₂ are necessary for adipate, suberate, and ethylmalonate to enter the mitochondria. An increase in these intermediates in the urine demonstrates enzymatic variability and individuality in ones ability to complete the process of Beta-oxidation, compromising the ability of the mitochondria to generate ATP. Supplementing with carnitine and B₂ will decrease gamma-oxidation, and will improve the mitochondrial ability to generate ATP. This may explain the positive outcomes in clinical trials of chronic fatigue syndrome and fibromyalgia with carnitine and B₂. [2] Fibromyalgia and other conditions of chronic fatigue are often hypothesized to be an inability of the mitochondria to generate ATP or energy. [3]

Further demonstration of mitochondrial dysfunction is seen by looking at Kreb cycle intermediates. In the process of energy generation,

Energy Production (Citric Acid Cycle)

(B comp., Q10, Amino acids, Mg)



Kreb cycle intermediate succinate must be converted to fumarate in a step that is highly sensitive to CoQ10 sufficiency. Biochemical individuality will demand differing levels of CoQ10 for appropriate shuttling. CoQ10 is a nutrient deficiency that is commonly associated with fatigue, and this is one major role CoQ10 plays that explains why a deficiency is responsible for fatigue. Organic acid testing explains the biochemistry of the association of a decrease CoQ10 with fatigue.[4]

Mitochondria function is also evaluated by measuring Krebs or Citric Acid Cycle intermediates. Utilization of energy from food components is demonstrated by the ability of the body to make basic molecules to support organ function. Measurement allows for evaluation of an individual from the cellular level up. Abnormal spilling of Citric acid cycle intermediates into the urine reveal dysfunction of regulatory enzymes. These functions can be modulated by nutrient co-factors.

Another patient that presents with the same chief complaint of chronic fatigue has a different biochemical issue at play.

How to Assess Patient Biochemical and Nutritional Individuality through Organic Acid Testing

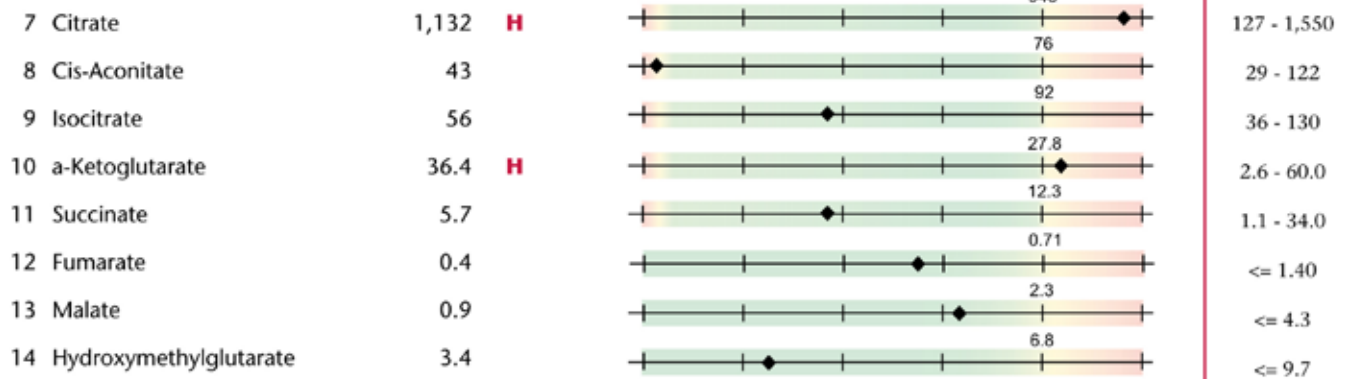
In this case the following 42 year old female presented with these abnormal lab results:

Case Study II: Chronic Fatigue

Here we see a citric acid cycle (CAC) intermediate, citrate, high in the urine. Citrate will flux out of the CAC and into the urine to buffer excess ammonia. [5] This leaves the cycle compromised. Further blocks in the cycle are seen with an elevation of alpha-Ketoglutarate.

Energy Production (Citric Acid Cycle)

(B comp., Q10, Amino acids, Mg)

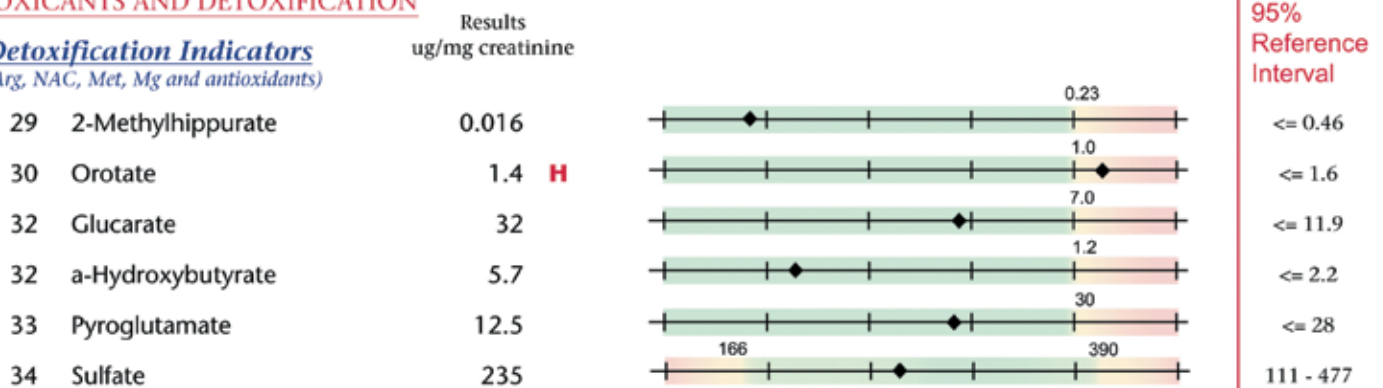


Lack of cofactor availability, including B₁, B₂, B₃, and lipoic acid drive alpha-Ketoglutarate up, compounding the problem of energy production. Renal threshold has been exceeded in terms of ability to clear ammonia. To gauge if this is a true toxicity, hepatic threshold must be assessed. Orotate goes up as the liver is challenged with ammonia toxicity. [6] Orotate is also elevated, demonstrating true toxicity. Ammonia toxicity presents with fatigue, head-aches, inability to concentrate. Elimination of ammonia will improve with supplemental arginine to drive the urea cycle, as well as adequate cofactor availability including manganese and magnesium.

TOXICANTS AND DETOXIFICATION

Detoxification Indicators

(Arg, NAC, Met, Mg and antioxidants)



A third case of chronic fatigue presents with the following in this 43 year old female:

Case Study III: Chronic Fatigue

Carbohydrate Metabolism

(B1, B3, Cr, Lipoic acid, CoQ10)

4	Pyruvate	7.1	H	4.1
5	Lactate	6.3		10.7
6	β-Hydroxybutyrate	1.0		2.8

95%
Reference
Interval

<= 7.1
1.4 - 41.4
<= 12.8

Energy Production (Citric Acid Cycle)

(B comp., Q10, Amino acids, Mg)

7	Citrate	869		948
8	Cis-Aconitate	44		76
9	Isocitrate	87		92
10	α-Ketoglutarate	53.8	H	27.8
11	Succinate	4.6		12.3
12	Fumarate	0.78		0.71
13	Malate	1.4		2.3
14	Hydroxymethylglutarate	6.0		6.8

127 - 1,550
29 - 122
36 - 130
2.6 - 60.0
1.1 - 34.0
<= 1.40
<= 4.3
<= 9.7

An elevation of Pyruvate, the entry point into the CAC, will limit energy production. Cofactors helping to move pyruvate are both B1 and B5. Corroborative evidence of this pattern is seen with a concomitant elevation of alpha-Ketoglutarate, which also increases in the urine with B vitamin deficiencies. Using multiple markers that require similar cofactors allows the clinician to discriminate the magnitude of the problem. Even though multiple markers may have the same co-factor requirement, the degree to which the cofactors bind will result in enzymes that have a unique sensitivity to a particular level of nutrient sufficiency. That is, an enzyme that tightly binds to a cofactor will be less affected by lower levels than an enzyme that binds loosely. Multiple markers allows for assessment of degree of deficiency.

Yeast / Fungal

45	D-Arabinitol	124		32
----	--------------	-----	--	----

<= 59

In addition to B vitamins contributing to fatigue, this female presents with a concomitant yeast infection. Overgrowth of yeast in the GI tract is a well-known etiology of fatigue. While treatment of the yeast infection may give some improvement, it is not the only factor playing a role in her fatigue. A more complete understanding of etiology allows for better outcomes.

In addition to the areas mentioned in the previous case study, the following areas are also evaluated through organic acid testing and could be contributors to a complaint as multifaceted as chronic fatigue.

Carbohydrate Metabolism markers:

B-hydroxybutyrate is a classic ketone body found alongside acetone and acetoacetate. A failure of glucose utilization as with diabetes will result in the formation and urinary elevation of these 3 ketone bodies. Conditions like diabetes and obesity are overtaking smoking as the leading cause of preventable death.[7] Screening for a failure to utilize glucose appropriately is an important part of most people's healthcare.

Toxicant/Detoxification Evaluation

Byproducts of detoxification are measured in the urine as part of the organic acid profile. This gives clinical evidence of type of exposure as well as how well the liver is handling the exposure. Markers such as 2-Methylhippurate can be measured which is the byproduct of detoxification of a common solvent, xylene. Xylene is oxidized via hepatic p450 oxidase enzymes following exposure to compounds such as paint thinners, building products, fuel, exhaust fumes, industrial degreasers, and solvents.

Just as important as exposure is how the liver handles the assault. A number of markers can be looked at in the liver to gage the liver's activity. Glucarate is a by-product of Phase I reactions that is used for Phase II conjugation reactions. Low glucarate is an indication of reduced hepatic function.

Glutathione is the main intercellular antioxidant of the liver. Evaluation of the use of glutathione is of great utility when judging liver function. A number of urine markers can help make this evaluation. A low sulfate reveals a need to replenish sulfur containing amino acids. Glutathione administration with oral cysteine, taurine and salts of sulfate, or methionine are used in combination to replenish sulfur pathways and increase sulfation.

B Vitamins/Methylation

Many biochemical pathways are reliant on nutrient cofactors. When a cofactor is insufficient, the pathway will become sluggish and "back-up" will occur, resulting in compounds being spilled in the urine. For example, the catabolism of the amino acid isoleucine is a high-flux process that requires biotin. If biotin is deficient, B-hydroxyisovalerate will accumulate and spill in the urine. Biotin is used in so many processes, that signs and symptoms of a biotin deficiency are near impossible to detect from history alone. Testing reveals a subclinical biotin deficiency. Processes that involve methylation can also be evaluated by measuring deficiencies in nutrients such as B6, B12 and folate. An organic acid profile shows a "functional" need for B vitamins, rather than just a deficiency. This allows the individuals personal biochemistry to be treated, rather than population based dosing.

Neurotransmitter Turnover

A urine sample can also be used to gage neurotransmitter levels. Metabolites of neurotransmitters are present in the urine. Research confirms that levels of urinary metabolites mirror levels of central nervous system production. For example, when serotonin production is low, its metabolite 5-Hydroxyindoleacetate is also low. Organic acid testing can be used to evaluate serotonin, epinephrine, norepinephrine, dopamine and NMDA antagonists and agonists.

Oxidative stress

Degenerative disease has an ever-increasing impact on society. Tied to the process of degeneration is oxidative stress. 8-Hydroxy-2-deoxyguanosine is a marker of DNA repair that goes up as DNA repair accelerates post insult. P-Hydroxyphenyllactate (HPLA) is a metabolite of tyrosine that acts as part of the cell signaling mechanism for apoptosis. HPLA is an important marker for normal and malignant cell growth. Elevated levels of HPLA result in a dramatic need of ascorbic acid, which may explain Vitamin C's role in treating or preventing cancers. Both markers are seen in the urine when there is an oxidative burden on the system.

Bacteria and Yeast overgrowth

Critical to nutritional evaluation and treatment is assessment of digestive process. Appropriate balance of flora is associated with a healthy digestive process. By measuring compounds in the urine made by microbes judgment can be made as to how much the local growth of bacteria in the gut is causing systemic effect. Toxic byproducts that are absorbed can only be measured in the urine. Additionally many species that cause dysbiosis are anaerobic. They only grow in an oxygen free environment, which means as soon as a stool specimen is collected it is exposed to oxygen, resulting in loss of species, and therefore an inability to culture them.

Organic Acid testing gives a broad view of the body. One urine sample can be used to evaluate gut, liver, and nervous system health as well as energy metabolism and nutrient deficiencies. Knowing how these areas are functioning at any one time, allows for analysis of system interaction, rather than a more reductionist approach. Evaluating multiple organ systems and biochemical pathways allows for treatment of the whole person. An organic acid profile can be used as an effective screen for areas of abnormality that may not be able to be ascertained from history alone. By using multiple metabolic markers in conjunction with one another a sophisticated, targeted and individualized treatment plan can be more easily developed.

REFERENCES

1. Butterworth, R.F, Effects of hyperammonaemia on brain function. *J Inherit Metab Dis*, 1998. 21 Suppl 1: p. 6-20.
2. Okada, T., et al., Mechanisms underlying fatigue: a voxel-based morphometric study of chronic fatigue syndrome. *BMC Neurol*, 2004. 4(1): p. 14.
3. Park, J.H., K.J. Niernann, and N. Olsen, Evidence for metabolic abnormalities in the muscles of patients with fibromyalgia. *Curr Rheumatol Rep*, 2000. 2(2): p. 131-40.
4. Bentler, S.E., A.J. Hartz, and E.M. Kuhn, Prospective observational study of treatments for unexplained chronic fatigue. *J Clin Psychiatry*, 2005. 66(5): p. 625-32.
5. Simpson, D.P, Citrate excretion: a window on renal metabolism. *Am J Physiol*, 1983. 244(3): p. F223-34.
6. Vissek, W.J., Nitrogen-stimulated orotic acid synthesis and nucleotide imbalance. *Cancer Res*, 1992. 52(7 Suppl): p. 2082s-2084s.
7. Beebe, R., Size matters. Understanding morbid obesity & its associated complications. *Jems*, 2002. 27(1): p. 22-8, 30-3.