Functional Medicine University's Functional Diagnostic Medicine Training Program

INSIDER'S GUIDE

Interpretation and treatment: Organic acid – Energy and oxidative markers and treatment

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Table of Contents

A Very Brief Didactic Overview

Summary of the Citric Acid Cycle and the Significance of Organic Acid

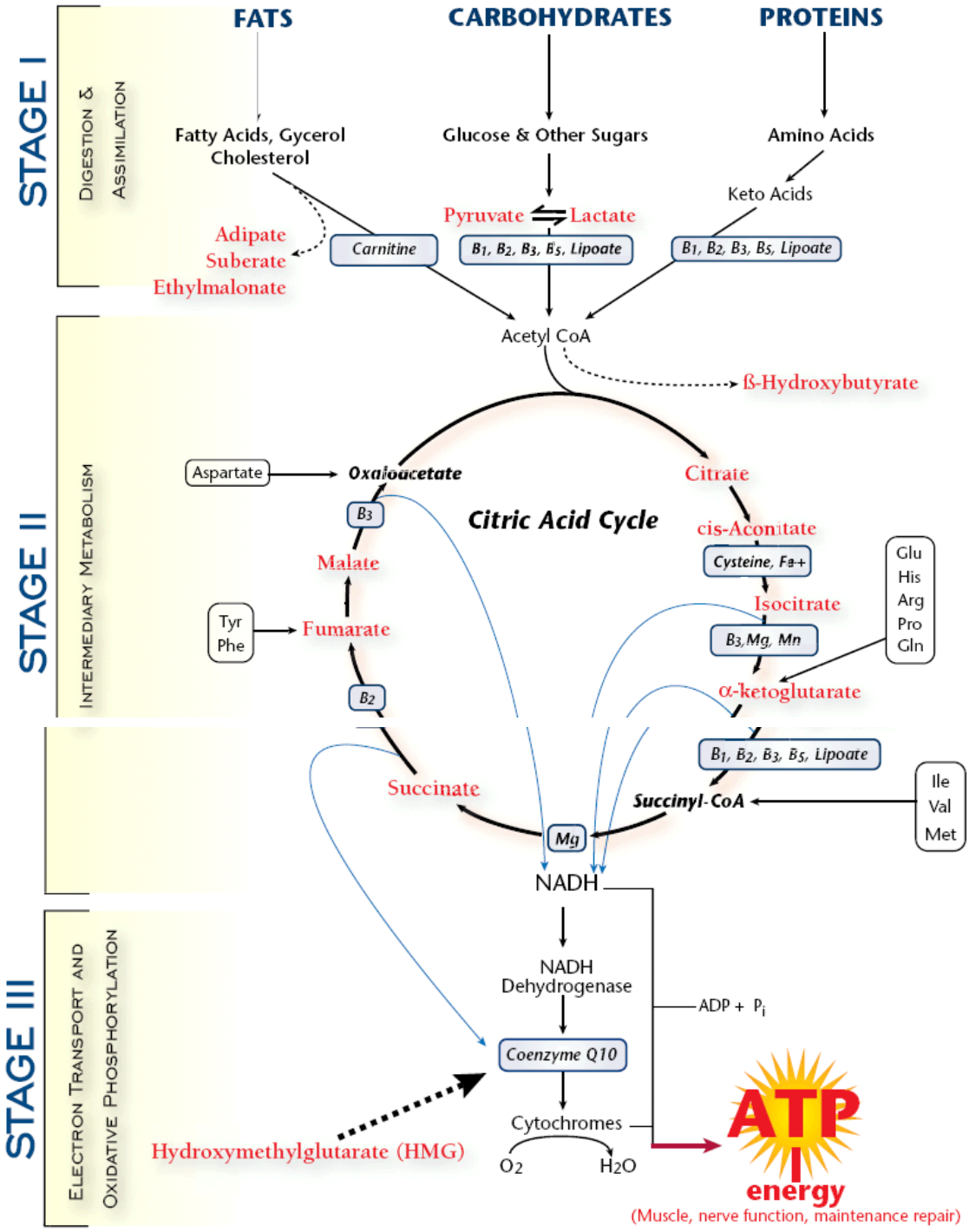


Diagram by MetaMetrix- www.metametrix.com

The citric acid cycle, also known as the tricarboxylic acid cycle (TCA cycle) or the Krebs cycle occurs in the matrix of the mitochondrion.

The citric acid cycle is the all important metabolic pathway which uses a series of enzyme-catalysed chemical reactions involved in the conversion of carbohydrates, fats and proteins into carbon dioxide and water to generate a form of usable energy.

Other relevant reactions in the pathway include those in glycolysis and pyruvate oxidation before the citric acid cycle, and oxidative phosphorylation after it.

Glycolysis is the sequence of reactions that converts glucose into pyruvate with the concomitant production of a relatively small amount of adenosine triphosphate (ATP).

Pyruvate decarboxylation is the biochemical reaction that uses pyruvate to form acetyl-CoA, releasing reducing equivalents and carbon dioxide.

Oxidative phosphorylation is a metabolic pathway that uses energy released by the oxidation of nutrients to produce adenosine triphosphate (ATP).

Adenosine-5'-triphosphate (ATP) has been coined the "molecular currency" of intracellular energy transfer. ATP is considered by biologists to be the energy currency of life.
It is the high-energy molecule that stores the energy we need to do just about everything we do.

As food in the cells is gradually oxidized, the released energy is used to re-form the ATP so that the cell always maintains a supply of this essential molecule

In short, the Citric Acid Cycle supplies the body with its primary energy needs. Any metabolic glitches or blocks in the citric acid cycle or impairments in any of these processes may lead to chronic fatigue, muscle pain and fatigue, accelerated cell breakdown, and unhealthy aging.

Because enzyme cofactors are involved in virtually every system in the body, insufficiencies in these vitamins or minerals can affect a wide range of functions, including immunologic, endocrine, musculoskeletal, and metabolic.

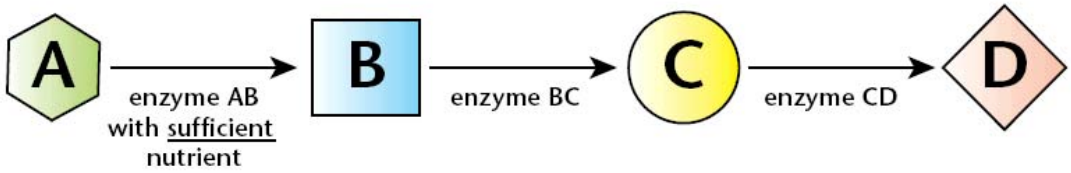
Organic Acids Simplified

The Organic Acid Profile is like an emission test performed on your car. The exhaust is examined to see how efficiently the engine is burning fuel. Similarly, certain compounds called “organic acids” in your urine reveal the efficiency of your body’s machinery.

Many organic acids result from the metabolic pathways, or chemical reactions, your body uses to transform food into energy, growth, maintenance, and repair of body tissue. Like spark plugs that ignite fuel in a car engine, vitamins and other essential nutrients are necessary for these

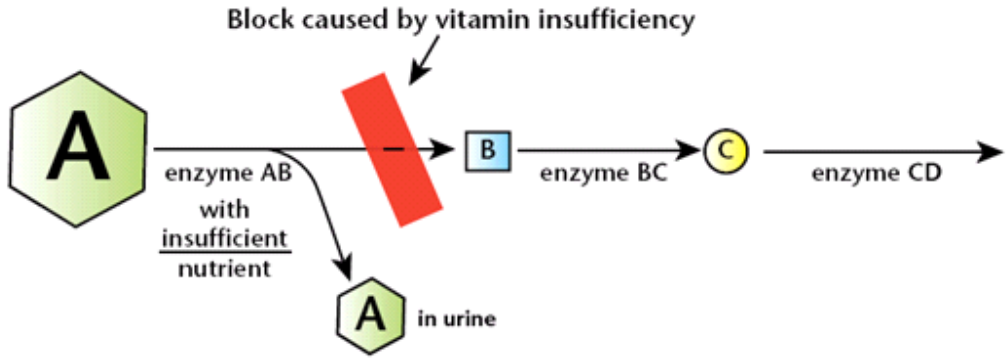
chemical reactions that power your metabolic machinery. Thousands of these reactions occur in your body every second and are the basis of your level of health and vitality.

The figure below illustrates a well-functioning metabolic pathway. Molecule A is converted to Molecule B by the enzyme AB. Molecule B is converted to Molecule C by the enzyme BC and so on all the way down the metabolic pathway. Many enzymes require nutrients such as specific vitamins and minerals in order to perform their functions in converting one molecule to another.



Adapted from Metametrix interpretation guide for Organic Acids- metametrix.com

If specific nutrients are not available in adequate amounts, important reactions cannot occur as well as they should. The illustration below shows what happens when the nutrient is not present in adequate amounts so that enzyme AB functions inefficiently. A small amount of Molecule A is converted to Molecule B and the remainder builds up and spills into the urine. Notice that Molecules B through D downstream are also affected.



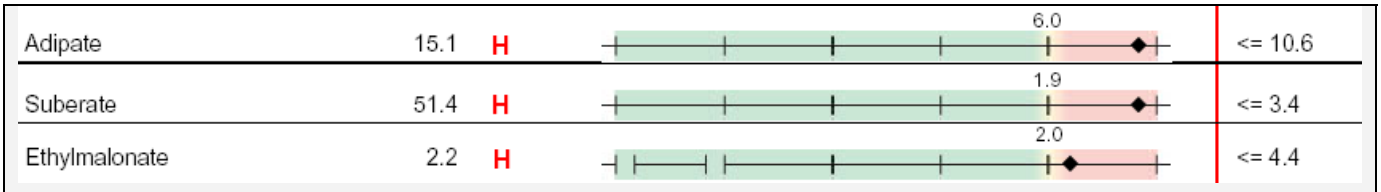
Adapted from Metametrix interpretation guide for Organic Acids- metametrix.com

Visualize this process as a dam blocking a stream — very little water flowing downstream and an overflow occuring upstream. The Organic Acid test measures the overflow of certain organic acids in the urine to determine what blockages may be occurring in the metabolic pathways due to nutrient insufficiencies or other issues.

High levels of many organic acids can indicate which nutrient insufficiencies may be affecting your patient's health.

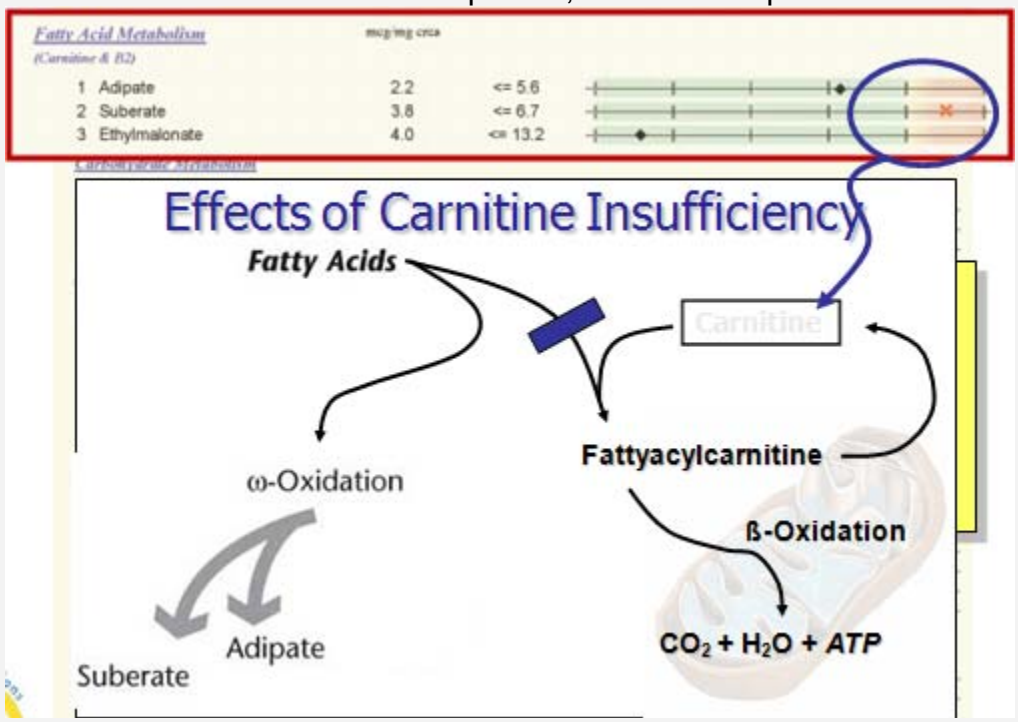
Detailed Explanation of Organic Acids

Deficiency of Carnitine and CoQ10



Adipate, Suberate, and Ethylmalonate are all functional markers for deficiency of carnitine Carnitine is needed to move fatty acids into the mitochondria where they are converted to energy using vitamin B2. When insufficient levels of carnitine or vitamin B2 slow down this process, other parts of the cellular machinery take over and make adipate and suberate. A similar block in another pathway causes high ethylmalonate. Since most of your body's energy is produced from the burning of fatty acids, your muscles and brain suffer when this cellular energy pathway is blocked.

Anything that interferes with the normal fatty acid oxidation may reveal high levels of these metabolites. Rule out environmental toxin exposure, excessive aspirin use

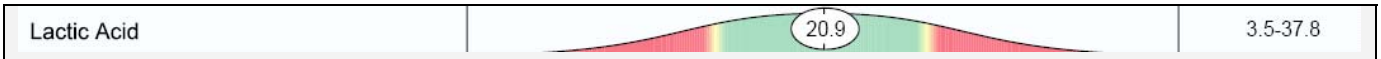


Adapted from Metametrix interpretation guide for Organic Acids- metametrix.com

If HIGH

Consider supplementing with carnitine and vitamin B2. Lysine being a precursor of carnitine, it may also be of value. Carnitine supplementation has been documented to improve Alzheimer's, age-related cognitive decline, and cardiac function.

Lactate and Pyruvate

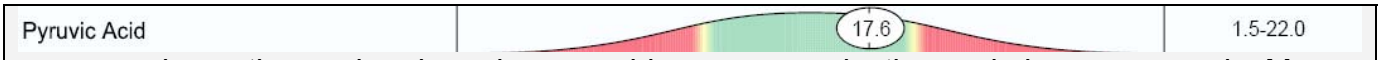


Lactate is the principal product of glucose metabolism in skeletal muscle and is a major player in anaerobic energy production and gluconeogenesis. High levels are commonly associated with coenzyme Q10, biotin and lipoic acid deficiencies. The following should be ruled in or out to determine the underlying reason why lactic acid is elevated: overwhelming infection, hypoxia, high intake of acetaminophen, increased consumption of alcohol, cocaine, increased iron levels, drug side effects (metformin). Rule out diabetes. High lactate can cause muscle cramping, fatigue and brain fog.

If HIGH

Consider supplementing with CoQ10, Vitamin B1, B2, B3, B5, Lipoic acid and Biotin.

Gluconeogenesis is a metabolic pathway that results in the generation of glucose from non-carbohydrate carbon substrates such as pyruvate, lactate, glycerol, and glucogenic amino acids.



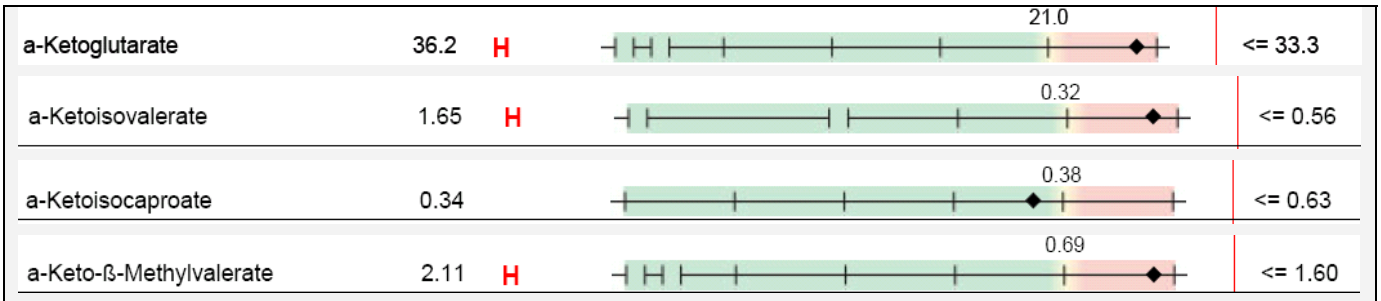
Pyruvate is another major player in anaerobic energy production and gluconeogenesis. May be elevated when B1, B5 and lipoic acid are insufficient.

Suspect **lipoic acid deficiency** when the combination of lactate and pyruvate are high. Many studies have shown that lipoic acid is helpful in treating diabetes and for assisting the liver with removing toxins from the body.

When the pyruvate marker is high, it is important to quickly scan to see if **alpha-ketoglutarate, alpha-ketoisovalerate, alpha-ketoisocaproate, and alpha-keto-beta-methylvalerate** are also high. All of these analytes share a common enzyme complex – all relying on the same coenzymes: **Vitamin B1, B5, lipoic acid, B2, and B3**. (in descending order of significance).

Lactate elevations, alone (meaning, not in combination with elevated Pyruvate) suggests **CoQ10 deficiency.**

Ketoglutarate, a-Ketoisovalerate, a-Ketoisocaproate, and a-Keto-ß-methylvalerate



Vitamins B1 (thiamin), B3 (niacin), and B5 (pantothenic acid) are necessary for energy pathways of all of the cells in your body. As your food is broken down, specific compounds are formed at steps that require B vitamin assistance. **Ketoglutarate, a-Ketoisovalerate, a-Ketoisocaproate, and a-Keto-ß-methylvalerate** are some these compounds. Alpha-ketoisovaleric Acid, Alpha-ketoisocaproic Acid and Alpha-keto-betamethylvaline Acid are metabolites of amino acids valine, leucine, & isoleucine, respectively. The production of these metabolites require vitamins **B1, B3, B5 and lipoic acid.**

If HIGH

Impaired metabolism due to cofactor insufficiencies or toxic metals; OR "maple syrup urine disease" (if markedly elevated).

Supplement cofactors (**vitamins B1, B2, B3, B5, Mg, cysteine, or lipoic acid**); remove toxic metals (As, Hg, Sb, Cd)

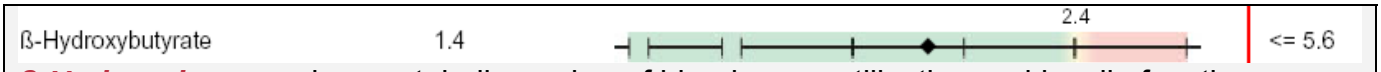
If LOW

Possible low B6; OR secondary to low branched-chain amino acids.

Clinical Note: If patient is on Clofibrate (Clofibrate is a lipid lowering agent used for controlling the high cholesterol) this marker might have diminished sensitivity.

Acetyl-CoA is an important molecule in metabolism, used in many biochemical reactions. Its main use is to convey the carbon atoms within the acetyl group to the citric acid cycle to be oxidized for energy production. In chemical structure, acetyl-CoA is the thioester between coenzyme A (a thiol) and acetic acid (an acyl group carrier). Acetyl-CoA is produced during the second step of aerobic cellular respiration, pyruvate decarboxylation, which occurs in the matrix of the mitochondria. Acetyl-CoA then enters the citric acid cycle.

ß-Hydroxybutyrate



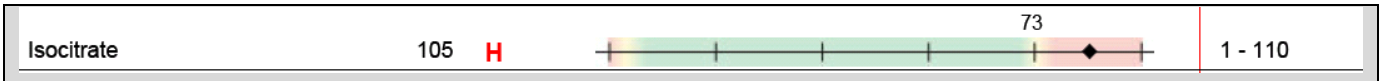
ß-Hydroxybutyrate is a metabolic marker of blood sugar utilization and insulin function. Elevated **β-Hydroxybutyrate** is a sign that extra chromium and vanadium may be warranted. It is also a byproduct of ketosis. Ketosis occurs when cells do not get a steady supply of sugar from dietary carbohydrate, so they burn fat instead. If you do not eat carbohydrate-rich foods or if your insulin is not working, then you can have metabolic ketosis. It is not necessarily a serious matter, but your doctor may need to find out just what the cause is. Beta-hydroxymethylbutyrate is a ketone body.

If HIGH
Consider supplementing with chromium, vanadium, and lipoic acid.

Citrate, Cis-Aconitate and Isocitrate

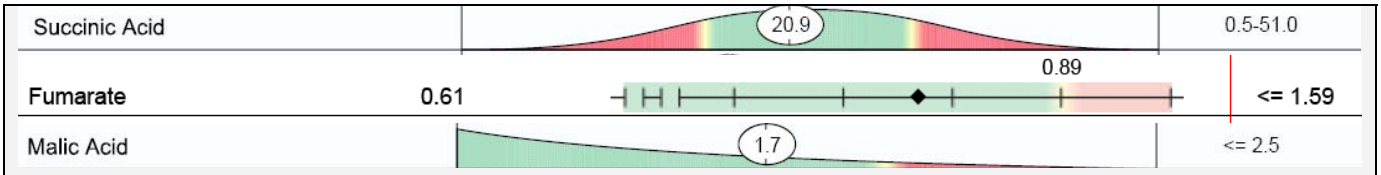
If HIGH
Impaired metabolism due to toxic metals (Fl, Hg, As, Sb) OR low cofactors (Fe, GSH—depleted in oxidative stress); OR high amounts of dietary citric acid; OR metabolic acidosis (if mildly increased cisaconitic acid but markedly increased citric acid).
High Citrate and Cis-aconitate can indicate **arginine insufficiency** for ammonia clearance through the Urea Cycle
Consider supplementing with arginine
Rule out toxic metals; glutathione, N-acetylcysteine, Mg, or L-glutamine; consider anti-oxidants; rule out pancreatic insufficiency (can lead to metabolic acidosis from deficient bicarbonate).
If LOW
Low or high pyruvic acid or low acetyl CoA (from fatty acid oxidation)

Arginine is a conditionally essential amino acid that is critical for your cardiovascular health and detoxification functions. The amino acid, arginine, is used to make the powerful blood vessel regulator, nitric oxide. Nitric oxide acts to lower blood pressure. Too little arginine can lead to high blood pressure.



If HIGH
Impaired metabolism due to low cofactors (B3, Mg, Mn) or inhibition by aluminum.
High Isocitrate can indicate arginine insufficiency for ammonia clearance through the Urea Cycle
Consider supplementing with arginine
Rule out Al toxicity; consider vitamin B3, Mg, Mn supplementation.
If LOW
2° to subnormal upstream metabolites; OR same causes of high cisaconitic acid

Succinate, Fumarate, and Malate



Succinate, Fumarate, and Malate are used in the body's metabolic pathway that generates cellular energy – the Citric Acid Cycle. Higher levels of these compounds in urine indicate inefficiencies in energy production. If ketoglutarate is elevated along with succinate, malate, and fumarate, you may need additional CoQ10.

Succinate, Fumarate, and Malate are all involved in mitochondrial oxidation. Succinate, Fumarate are metabolites of the amino acids leucine & isoleucine and phenylalanine & tyrosine respectively.

Common symptoms of high levels of the above may include: fatigue, weakness, myocardial degeneration, neurological degeneration.

If HIGH

Consider supplementing with CoQ10, riboflavin (B2) and magnesium.

SPECIAL CONSIDERATION

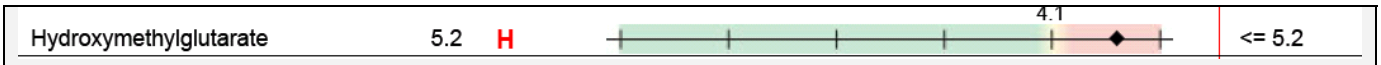
Succinate metabolism may be impaired due to low cofactors (Fe or B2); OR bacterial degradation of glutamine.

If LOW

Consider over-utilization of the Citric Acid Cycle. Fatigue and weakness are common symptoms.

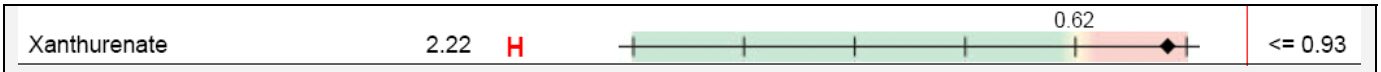
Consider supplementing with L-Leucine, L-Isoleucine and Vitamin B12 with low succinate, tyrosine & phenylalanine with low fumarate and balanced amino acid blend with low malate.

Hydroxymethylglutarate (HMG)



Hydroxymethylglutarate (HMG) is a metabolic precursor of cholesterol used by your cells to make CoQ10, a nutrient that enables the body to use oxygen to generate large amounts of energy. Cholesterol-lowering statin drugs block this process, causing HMG to become elevated and inhibiting the production by the cells of CoQ10. While there can be other causes for this metabolic block, high levels of HMG generally indicate need for CoQ10 supplementation. Since your body can make coenzyme Q10, it is not called a vitamin. If you are making enough to meet the demands of your tissues, you do not need to take any extra. However, many people do not make enough coenzyme Q10. Elevation of **Hydroxymethylglutarate** can reveal a block in your body's synthesis of coenzyme Q10. Other functional markers such as **Lactate, Succinate, Fumarate, and Malate,** indicate whether your body is able to produce energy efficiently by utilizing coenzyme Q10.

Xanthurenate



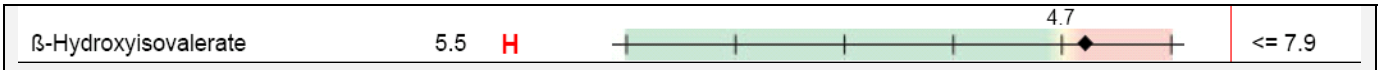
Xanthurenate is a functional marker of B6 (Pyridoxine) and is a metabolite of the amino acid tryptophan. High levels can indicate an insufficiency of B6, a vitamin critical for all protein metabolism. Use of medications such as oral contraceptives, anti-hypertensives, and bronchodilators and exposure to tobacco smoke as well as pesticides and other agricultural products can all contribute to insufficiency of vitamin B6. Problems with balance, fatigue, and mental/emotional stability (such as PMS and ADHD), high homocysteine, peripheral neuropathy, lymphopenia are frequently found in patients with inadequate vitamin B6.

Research has shown that symptoms of autism can be ameliorated with vitamin B6 supplementation. Additionally, xanthurenate can prevent insulin from performing its vital role in blood sugar regulation, which can contribute to diabetes.

If HIGH

Low B6; may also indicate low vitamin B3 and/or picolinic acid.
Supplement vitamin B6, possibly also B3 and picolinic acid

ß-Hydroxyisovalerate



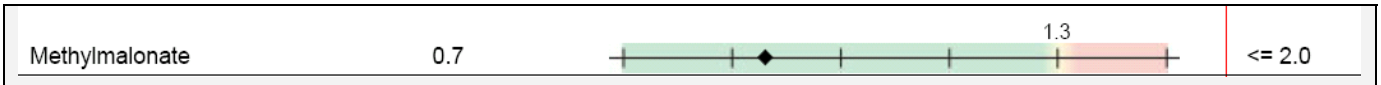
ß-Hydroxyisovalerate is a sensitive indicator of biotin deficiency and is a metabolite of the amino acid isoleucine. Until recently, biotin deficiency was very difficult to determine in humans because this vitamin deficiency affects health in ways that mimic many other conditions. Doctors were likely to overlook biotin deficiency until this test was discovered. Beta(ß)-hydroxyisovalerate is a specific and sensitive metabolic marker for functional biotin deficiency. As your biotin intake decreases, your ß-hydroxyisovalerate excretion increases.Biotin deficiencies develop for a number of reasons, including pregnancy, antibiotic use, dysbiosis and anticonvulsant therapy. It is important to remember that raw egg whites are rich in the glycoprotein, avidin which binds with biotin leading to a deficiency. Symptoms can include hair loss, skin rash, dermatitis, immune deficiencies, gait disturbances, tremors and muscle weakness.

If HIGH:

Consider supplementing with biotin. Include biotin rich foods such as cooked eggs, fish, dairy products, legumes, cruciferous vegetables, sweet potatoes and lean beef.

Address dysbiosis

Methylmalonate



Methylmalonate is a functional marker of vitamin B12 and a metabolite of the amino acid valine. High levels indicate insufficient vitamin B12. Increased alcohol consumption, dysbiosis, aging and HIV infection will all have a detrimental impact on B12 absorption.
Common symptoms may include: Anemia, fatigue, elevated homocysteine, ischemic heart disease, stroke, deep vein thrombosis, paresthesias and GI disorders
Consider supplementing with B12 sublingual or IV B12 (if oral is ineffective). Stop alcohol and address dysbiosis.

Formiminoglutamate (FIGLU)

Formiminoglutamate (FIGLU) is a functional marker of insufficiency of folic acid and is a compound made from the amino acid histidine. High levels indicate insufficient folic acid. Increased alcohol consumption, excessive consumption of processed foods, oral contraception, smoking and pregnancy will all have a detrimental impact on folic acid absorption.

Common symptoms may include: Anemia, fatigue, elevated homocysteine, ischemic heart disease, stroke and deep vein thrombosis. Pregnant women especially need to have adequate folic acid to prevent birth defects. Folic acid insufficiency can play a role in childhood development problems, depression, immune function, and is a risk factor for cardiovascular disease.

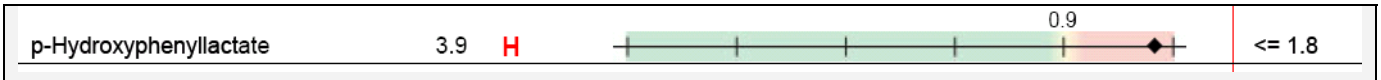
If HIGH

Consider supplementing with folic acid. Stop alcohol. If homocysteine is elevated, consider using 5-methyltetrahydrofolate.

Elevations of homocysteine, methylmalonate and formiminoglutamate are the most sensitive markers and indicators for megaloblastic anemia

Vitamins C and E and coenzyme Q10 are grouped together because they are all involved in antioxidant protection. The special role of antioxidant vitamins is to protect your cells from damage. Without them, your rate of aging and risk of chronic disease are increased.

p-Hydroxyphenyllactate

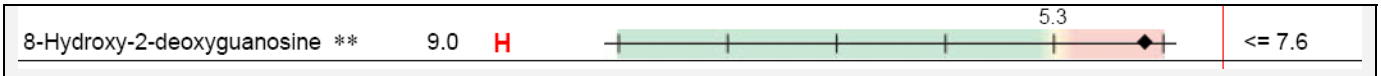


p-Hydroxyphenyllactate is a metabolite of the amino acid Tyrosine. It is a sensitive marker for the depletion of methyl- p-hydroxyphenyllactate which is an important cell growth inhibiting agent. Due to its pro-oxidative character high levels are associated with carcinogenesis.

If HIGH

Consider supplementing with Vitamin C. Vitamin C is easily lost from the body and must be replaced frequently. Most experts agree that the average healthy person needs a minimum of 100-150 mg of vitamin C per day to stay healthy.

8-Hydroxy-2-deoxyguanosine



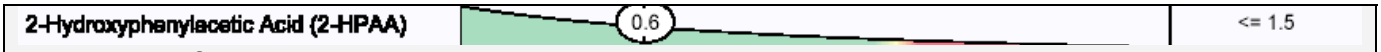
8-Hydroxy-2-deoxyguanosine is marker for oxidative damage to DNA**.** Causes of increased levels of 8-Hydroxy-2-deoxyguanosine may be due to stress, smoking, chronic inflammation, diabetes, air pollution, high polyunsaturated fat intake, irradiation, thermal injury, heavy metal and pesticide toxic exposure.

If HIGH

Consider supplementing with Vitamin C, E, lipoic acid and NAC. Also consider using green tea, grapes and berries. Although an increase consumption of alcohol will have a detrimental impact on this marker, an occasional glass of red wine may be of value due to its high level of flavonoids.

High levels of **p-Hydroxyphenyllactate, 8-Hydroxy-2'-deoxyguanosine, Glucarate, and Quinolinate** are associated with increased oxidative stress. Significant elevations in one or more of these compounds could indicate a strong need for other antioxidants as well.

2-Hydroxphenylacetic Acid



Metabolite of phenylalanine

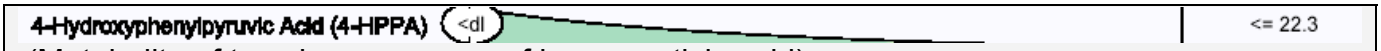
If HIGH

Excessive phenylalanine (dietary or PKU) or tyrosine; OR reduced oxygenation (e.g., iron deficiency anemia, pulmonary disorder); OR low tetrahydrobiopterin (BH4), which may result in low neurotransmitters and/or nitric oxide

CONSIDER

Amino Acid Analysis is recommended to rule out excessive phenylalanine &/or tyrosine.
Correct oxygenation if relevant.
Supplement vitamin C (increases BH4 levels in body).
5-MTHF (from folic acid) may help nitric oxide production when BH4 is low

4-Hydroxphenylpyruvic Acid

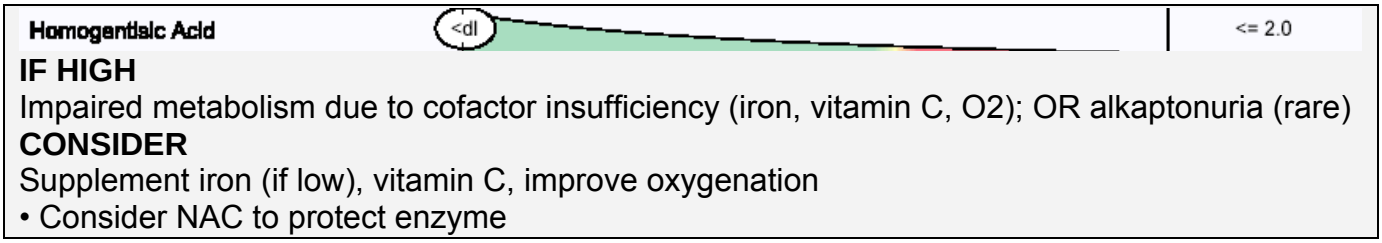


(Metabolite of tyrosine, precursor of homogentisic acid)

If HIGH

Impaired metabolism to homogentisic acid due to cofactor insufficiencies (copper, vitamin C, O2); OR possible low iron (if homogentisic acid is markedly elevated);
Supplement vitamin C or Cu, improve oxygenation
(e.g., correct anemia, pulmonary problems, cardiac insufficiency, etc.)

Homogentisic acid

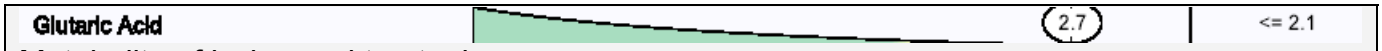


IF HIGH
Impaired metabolism due to cofactor insufficiency (iron, vitamin C, O2); OR alkaptonuria (rare)
CONSIDER
Supplement iron (if low), vitamin C, improve oxygenation
• Consider NAC to protect enzyme

a-Ketoadipic Acid (AKAA)

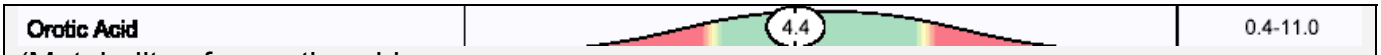
(Made from tryptophan and lysine via alpha-aminoadipic acid, also a byproduct of yeast; precursor of glutaric acid)
If HIGH
May be secondary to high glutaric acid (check glutaric level); OR impaired metabolism due to cofactor insufficiencies OR toxic metals (As, Hg, Sb, Cd); OR may be secondary to yeast or fungal infection (derives from alphaaminoadipic acid)—see yeast markers.
CONSIDER
Supplement cofactors (vitamins B1, B2, B3, B5, Mg, cysteine, or lipoic acid); remove toxic metals (As, Hg, Sb, Cd)
Antifungals, anti-yeast diet, probiotics, if relevant Alpha-ketoadipic Acid (AKAA)

Glutaric Acid



Metabolite of lysine and tryptophan.
If HIGH
Possible low FAD (riboflavin) (cofactor for alternative metabolism of one of glutaric acid's precursors); OR inborn error of metabolism; may be associated with CETP genetic polymorphism.
CONSIDER
Supplement vitamin B2, consider mitochondrial support nutrients (e.g. CoQ10)

Orotic Acid



(Metabolite of aspartic acid.

If HIGH

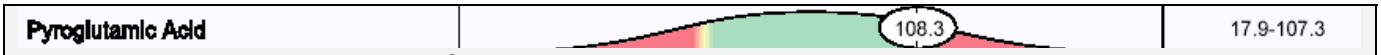
Possible liver damage (e.g., from alcohol), urea cycle dysfunction, ammonia excess OR; barbiturates; OR impaired metabolism due to cofactor insufficiencies (vitamins B3, B6, folate, Mg, glutamine, glycine, serine); OR use of allopurinol or chemotherapy

CONSIDER

Supplement vitamins B3, B6, folic acid, Mg, glutamine, glycine, serine

Consider alpha-ketoglutarate and arginine for ammonia excess, support liver

Pyroglutamic Acid



Intermediate in the recycling of glutathione)

If HIGH

Impaired recycling to glutathione due to cofactor insufficiencies (Mg, cysteine, glycine, glutamic acid); consistent with deficient GSH

Supplement Mg, N-acetylcysteine (NAC), possible glycine, L-glutamine, &/or GSH

If LOW

Low glutathione (insufficient precursors, toxicity, or oxidant stress)

CONSIDER

Supplement NAC, possible Mg, glycine, L-glutamine, &/or GSH

Identify and correct toxicity

Adipic Acid

(Formed from “omega” oxidation of fats when beta oxidation is impaired)

If HIGH

Impaired mitochondrial beta oxidation of fats; may be secondary to insufficient carnitine, B2, or acetyl CoA, or to insulin excess; OR may be secondary to ketosis.

Consider supplementing with L-carnitine or acetyl-L-carnitine, riboflavin, acetyl CoA precursors (cysteine, B5, Mg)

b-OH-b-Methyglutaric Acid (HMG)

(Formed from acetyl CoA, precursor of cholesterol and CoQ10)

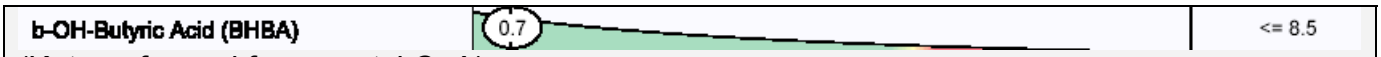
If HIGH

Citric acid cycle impairment (anaerobic glycolysis); OR
carbohydrate unavailability (e.g., high-protein diet, fasting, diabetes); OR inhibited utilization of HMG (e.g., from high cholesterol diet, yeast overgrowth, glucocorticoid excess, statins)

CONSIDER

Identify and correct specific underlying imbalance (e.g., remove yeast overgrowth, reduce dietary cholesterol, remove blocks in citric acid cycle)

b-OH-Butyric (BHBA)



(Ketone formed from acetyl CoA)

If HIGH

Ketosis from carbohydrate unavailability (e.g., fasting, diabetes, strenuous exercise, ketogenic diet)

CONSIDER

See comments above for HMG)

Credit is contributed to the following labs for their advancement in the field of functional medicine:

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