5 Organic Acids

Contents

The ***Organix™ Comprehensive Profile*** provides a view into the several metabolic processes and the efficiency of metabolic function. Identifying metabolic blocks that can be treated nutritionally allows individual tailoring of interventions that maximize patient responses and lead to improved patient outcomes.

Organic acids are metabolic intermediates that are produced in pathways of central energy production, detoxification and biotransformation, neurotransmitter breakdown, or intestinal microbial activity. Marked accumulation of specific organic acids detected in urine often signals a metabolic inhibition or blockage. The abnormality may be due to a nutrient deficiency, an inherited enzyme deficit, toxic interference, or

drug effect. Several analytes provide insight into gastrointestinal bacterial or fungal imbalance.

- Elevations in any organic acids can contribute to metabolic acidosis
- Symptoms from mild, chronic acidurias may not manifest until adulthood
- **The mitochondrial function markers include:**
  - » Fatty Acid Metabolism
  - » Carbohydrate Metabolism
  - » Citric Acid Cycle Intermediates

Fatty Acid Metabolism

- Needed for energy
- Supplements:
  - » Carnitine, a metabolic cofactor synthesized from L-lysine and L-methionine (as SAMe)
    - Conditionally essential nutrient
    - Fatty acid transport carrier from cytosol into mitochondria for beta-oxidation
  - » Vitamin B_2 (riboflavin)
    - Aids oxidative metabolism of fats within the mitochondria

Adipate (Adipic Acid), and Suberate (Suberic Acid)

- Functional markers of carnitine insufficiency
- Six and eight carbon dicarboxylic acids, respectively
- Products of peroxisomal fatty acid oxidation
- Increased when carnitine insufficiency limits long chain fatty acid entry into mitochondria

IF ADIPATE AND SUBERATE HIGH:

- Causes:
  - » Incomplete fatty acid oxidation
  - » Carnitine deficiency
  - » Environmental toxin exposure—alters lipid metabolism
  - » Adipate elevation alone: consider exogenous adipate ingestion (gelling and flavoring agent)
- Symptoms/Conditions:
  - » Periodic mild weakness
  - » Mitochondrial dysfunction
  - » Nausea
  - » Fatigue
  - » Hypoglycemia
  - » Recurrent infections
  - » "Sweaty feet" odor
  - » Attention deficit in children (association noted)
  - » Metabolic acidosis
  - » Reye syndrome (inhibition of fatty acid oxidation likely caused by aspirin in presence of a genetic mutation given for viral infection—viral toxins also implicated)
- Treatment:
  - » L-Carnitine, 500–1000 mg TID
  - » May be contraindicated in certain patients on thyroid medications

- » Vitamin B_2 (riboflavin), 100 mg BID
- » L-Lysine (if low), 1000 mg QD–TID—a precursor for carnitine
- » Other nutrients involved in carnitine synthesis include SAMe, B_6, magnesium, ascorbate, iron, niacin
- » Ensure optimal protein intake, digestion and absorption

Ethylmalonate (Ethylmalonic Acid)

- Five carbon branched dicarboxylic acid formed in isoleucine catabolism
- Functional marker of carnitine insufficiency
- May be formed when short chain fatty acid oxidation is compromised, which causes an elevation of butyrate, some of which is converted to ethylmalonate
- Oxidation dependent on formation of acylcarnitine

IF ETHYLMALONATE HIGH:

- Causes:
  - » Carnitine deficiency
  - » Riboflavin deficiency
  - » Failure in formation or oxidation of butyrylcarnitine
  - » Genetic mutations (short-chain acyl-CoA dehydrogenase, multiple acyl-CoA dehyrdrogenase)
  - » Isoleucine loading
- Symptoms/Conditions:
  - » See above: Adipate and Suberate
- Treatment:
  - » Same as above for Adipate and Suberate
  - » Also:
    - Glycine, 250 mg/kg/day
    - Avoid medium chain fatty acids such as coconut oil

Carbohydrate Metabolism

Pyruvate

- Three carbon keto-acid (α-ketopropionate)
- Breakdown product of glucose oxidation—energy production
- Under aerobic conditions, oxidized to acetyl-CoA
- Under anaerobic conditions, reduced to lactate (skeletal muscle)
- Stimulates gluconeogenesis and inhibits fatty acid synthesis
- Substrate of pyruvate dehydrogenase complex (PDC) that requires coenzymes produced from vitamins B_1, B_2, B_3, B_5, and lipoic acid

IF PYRUVATE HIGH:

- Causes:
  - » Vitamin B deficiencies, especially B_1 and B_5
  - » Lipoic acid insufficiency
  - » Under eating
- Symptoms/Conditions:
  - » Thiamine-deficiency encephalopathy associated

with alcohol use (Wernicke-Korsakoff syndrome)
  - » Fatty liver associated with alcohol use
  - » Metabolic acidosis
- Treatment:
  - » Vitamin B_1 (thiamine), up to 100 mg TID with B complex support; for concurrent L-lactate elevation: lipoic acid, 500 mg TID

L-Lactate (L-Lactic Acid)

- Chiral center of lactic acid generates 2 enantiomers, D and L
- Human metabolic product is always L-lactate (D-lactate is discussed under "intestinal dysbiosis")
- Three carbon hydroxy acid
- Anaerobic energy production
- Principal product of glucose oxidation in skeletal muscle
- Gluconeogenesis substrate
- NADH-dependent oxidation to pyruvate prior to mitochondrial entry

IF L-LACTATE HIGH:

- Causes:
  - » Block in final oxidative phosphorylation stage of energy production—inactivation of citric acid cycle
  - » Coenzyme Q10 deficiency
  - » Biotin deficiency
  - » Lipoic acid deficiency
  - » Temporary increase due to alcohol consumption
  - » Metabolic acidosis from:
    - Hypoxia
    - Poor perfusion, induced by various shock states
    - Overwhelming infection
  - » Medicinal and toxic causes:
    - Acetaminophen
    - Alcohols and glycols (ethanol, ethylene glycol, methanol, propylene glycol)
    - Antiretroviral nucleoside analogs (zidovudine, delavirdine, didanosine, lamivudine, stavudine, zalcitabine)
    - Beta-adrenergic agents (e.g., epinephrine, ritodrine, terbutaline), biguanides (phenformin, metformin)
    - Cocaine
    - Cyanogenic compounds (e.g., cyanide, aliphatic nitriles, nitroprusside)
    - Diethyl ether
    - 5-fluorouracil
    - Halothane
    - Isoniazid
    - Nalidixic acid
    - Propofol
    - Sugars and sugar alcohols (fructose, sorbitol, and xylitol)
    - Salicylates (e.g., Reye syndrome)
    - Strychnine
    - Sulfasalazine
    - Valproic acid