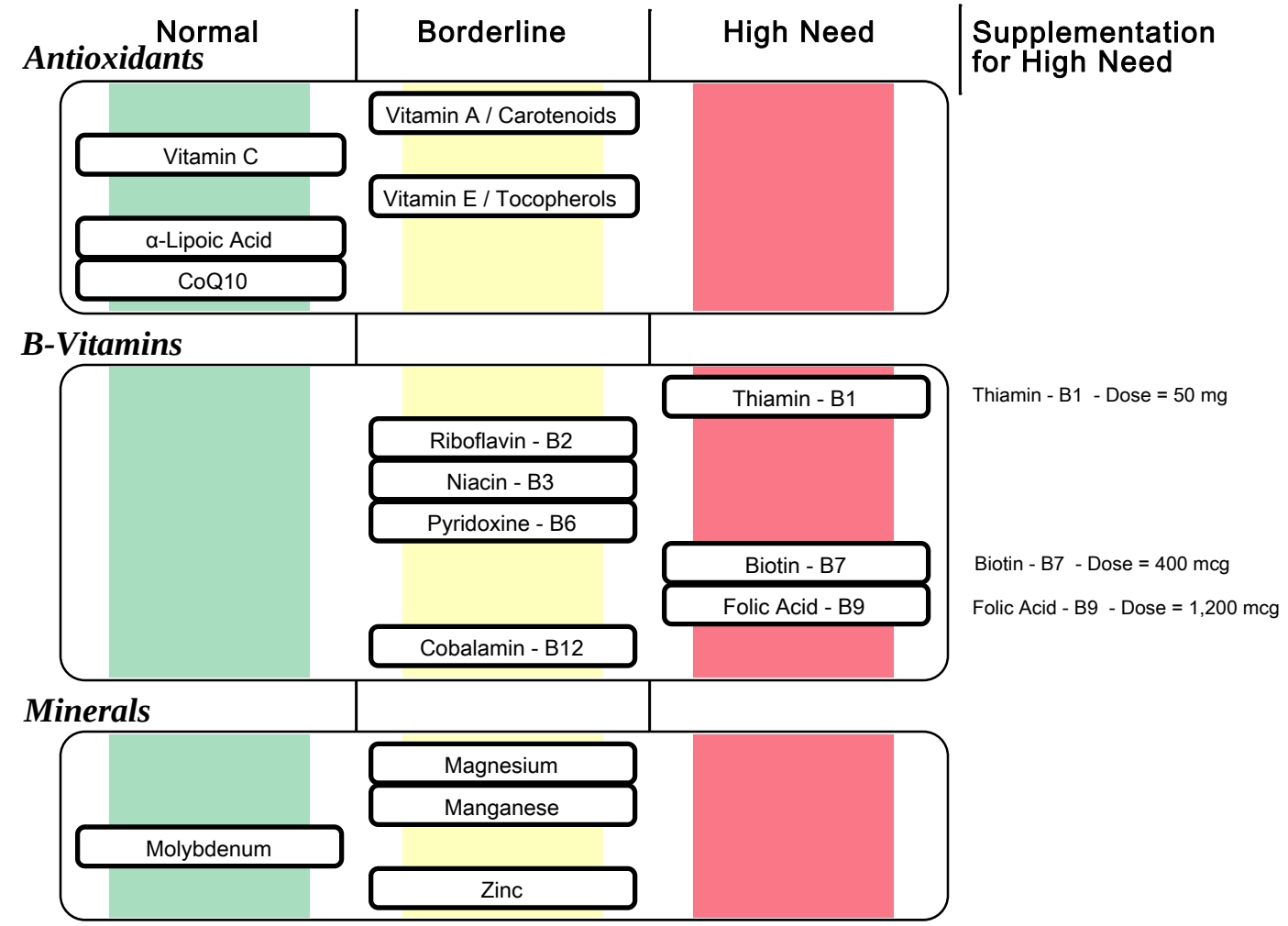
GENOVA DIAGNOSTICS

63 Zillicoa Street
Asheville, NC 28801

ONE FMV®
OPTIMAL NUTRITION EVALUATION

Patient: **FEMALE TEST**
DOB: January 01, 1940
Sex: F
MRN: 1232590242

ONE Results Overview



SUGGESTED SUPPLEMENT SCHEDULE

Supplements	Daily Recommended Intake (DRI)	Patient's Daily Recommendations	Provider Daily Recommendations
Antioxidants			
Vitamin A / Carotenoids	2,333 IU	5,000 IU	
Vitamin C	75 mg	250 mg	
Vitamin E / Tocopherols	22 IU	200 IU	
α-Lipoic Acid		50 mg	
CoQ10		30 mg	
B-Vitamins			
Thiamin - B1	1.1 mg	50 mg	
Riboflavin - B2	1.1 mg	25 mg	
Niacin - B3	14 mg	30 mg	
Pyridoxine - B6	1.5 mg	25 mg	
Biotin - B7	30 mcg	400 mcg	
Folic Acid - B9	400 mcg	1,200 mcg	
Cobalamin - B12	2.4 mcg	500 mcg	
Minerals			
Magnesium	320 mg	600 mg	
Manganese	1.8 mg	5.0 mg	
Molybdenum	45 mcg	75 mcg	
Zinc	8 mg	20 mg	
Digestive Support			
Probiotics		50 billion CFU	
Pancreatic Enzymes		5,000 IU	
Other Vitamins			
Vitamin D	800 IU		

Amino Acid	mg/day	Amino Acid	mg/day
Arginine	0	Methionine	0
Asparagine	0	Phenylalanine	0
Cysteine	0	Serine	0
Glutamine	0	Taurine	0
Glycine	0	Threonine	0
Histidine	0	Tryptophan	0
Isoleucine	0	Tyrosine	0
Leucine	0	Valine	0
Lysine	0		

Recommendations for age and gender-specific supplementation are set by comparing levels of nutrient functional need to optimal levels as described in the peer-reviewed literature. They are provided as guidance for short-term support of nutritional deficiencies only.

The Suggested Supplemental Schedule is provided at the request of the ordering practitioner. Any application of it as a therapeutic intervention is to be determined by the ordering practitioner.

Key

Normal **Borderline** **High Need**

Interpretation At-A-Glance

Nutritional Needs

Antioxidants

Vitamin A / Carotenoids

- Beta-carotene & other carotenoids are converted to vitamin A (retinol), involved in vision, antioxidant & immune function, gene expression & cell growth.
- Vitamin A deficiency may occur with chronic alcoholism, zinc deficiency, hypothyroidism, or oral contraceptives containing estrogen & progestin.
- Deficiency may result in night blindness, impaired immunity, healing & tissue regeneration, increased risk of infection, leukoplakia or keratosis.
- Food sources include cod liver oil, fortified cereals & milk, eggs, sweet potato, pumpkin, carrot, cantaloupe, mango, spinach, broccoli, kale & butternut squash.

Vitamin C

- Vitamin C is an antioxidant (also used in the regeneration of other antioxidants). It is involved in cholesterol metabolism, the production & function of WBCs and antibodies, and the synthesis of collagen, norepinephrine and carnitine.
- Deficiency may occur with oral contraceptives, aspirin, diuretics or NSAIDs.
- Deficiency can result in scurvy, swollen gingiva, periodontal destruction, loose teeth, sore mouth, soft tissue ulcerations, or increased risk of infection.
- Food sources include oranges, grapefruit, strawberries, tomato, sweet red pepper, broccoli and potato.

Vitamin E / Tocopherols

- Alpha-tocopherol (body's main form of vitamin E) functions as an antioxidant, regulates cell signaling, influences immune function and inhibits coagulation.
- Deficiency may occur with malabsorption, cholestyramine, colestipol, isoniazid, orlistat, olestra and certain anti-convulsants (e.g., phenobarbital, phenytoin).
- Deficiency may result in peripheral neuropathy, ataxia, muscle weakness, retinopathy, and increased risk of CVD, prostate cancer and cataracts.
- Food sources include oils (olive, soy, corn, canola, safflower, sunflower), eggs, nuts, seeds, spinach, carrots, avocado, dark leafy greens and wheat germ.

α-Lipoic Acid

- Lipoic acid plays an important role in energy production, antioxidant activity (including the regeneration of vitamin C and glutathione), insulin signaling, cell signaling and the catabolism of α-keto acids and amino acids.
- High biotin intake can compete with lipoic acid for cell membrane entry.
- Optimal levels of lipoic acid may improve glucose utilization and protect against diabetic neuropathy, vascular disease and age-related cognitive decline.
- Main food sources include organ meats, spinach and broccoli. Lesser sources include tomato, peas, Brussels sprouts and brewer's yeast.

CoQ10

- CoQ10 is a powerful antioxidant that is synthesized in the body and contained in cell membranes. CoQ10 is also essential for energy production & pH regulation.
- CoQ10 deficiency may occur with HMG-CoA reductase inhibitors (statins), several anti-diabetic medication classes (biguanides, sulfonylureas) or beta-blockers.
- Low levels may aggravate oxidative stress, diabetes, cancer, congestive heart failure, cardiac arrhythmias, gingivitis and neurologic diseases.
- Main food sources include meat, poultry, fish, soybean, canola oil, nuts and whole grains. Moderate sources include fruits, vegetables, eggs and dairy.

Glutathione

- Glutathione (GSH) is composed of cysteine, glutamine & glycine. GSH is a source of sulfate and plays a key role in antioxidant activity and detoxification of toxins.
- GSH requirement is increased with high-fat diets, cigarette smoke, cystinuria, chronic alcoholism, chronic acetaminophen use, infection, inflammation and toxic exposure.
- Deficiency may result in oxidative stress & damage, impaired detoxification, altered immunity, macular degeneration and increased risk of chronic illness.
- Food sources of GSH precursors include meats, poultry, fish, soy, corn, nuts, seeds, wheat germ, milk and cheese.

Plant-based Antioxidants

- Oxidative stress is the imbalance between the production of free radicals and the body's ability to readily detoxify these reactive species and/or repair the resulting damage with anti-oxidants.
- Oxidative stress can be endogenous (energy production and inflammation) or exogenous (exercise, exposure to environmental toxins).
- Oxidative stress has been implicated clinically in the development of neurodegenerative diseases, cardiovascular diseases and chronic fatigue syndrome.
- Antioxidants may be found in whole food sources (e.g., brightly colored fruits & vegetables, green tea, turmeric) as well as nutriceuticals (e.g., resveratrol, EGCG, lutein, lycopene, ginkgo, milk thistle, etc.).

Key

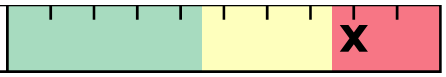
- Function
- Causes of Deficiency
- Complications of Deficiency
- Food Sources

Interpretation At-A-Glance

Nutritional Needs

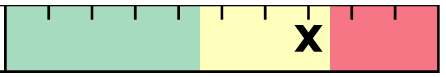
B-Vitamins

Thiamin - B1



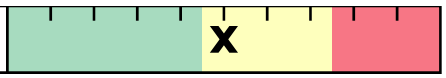
- B1 is a required cofactor for enzymes involved in energy production from food, and for the synthesis of ATP, GTP, DNA, RNA and NADPH.
- Low B1 can result from chronic alcoholism, diuretics, digoxin, oral contraceptives and HRT, or large amounts of tea & coffee (contain anti-B1 factors).
- B1 deficiency may lead to dry beriberi (e.g., neuropathy, muscle weakness), wet beriberi (e.g., cardiac problems, edema), encephalopathy or dementia.
- Food sources include lentils, whole grains, wheat germ, Brazil nuts, peas, organ meats, brewer's yeast, blackstrap molasses, spinach, milk & eggs.

Pyridoxine - B6



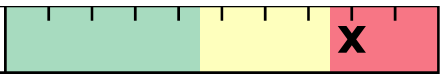
- B6 (as P5P) is a cofactor for enzymes involved in glycogenolysis & gluconeogenesis, and synthesis of neurotransmitters, heme, B3, RBCs and nucleic acids.
- Low B6 may result from chronic alcoholism, long-term diuretics, estrogens (oral contraceptives and HRT), anti-TB meds, penicillamine, L-DOPA or digoxin.
- B6 deficiency may result in neurologic symptoms (e.g., irritability, depression, seizures), oral inflammation, impaired immunity or increased homocysteine.
- Food sources include poultry, beef, beef liver, fish, whole grains, wheat germ, soybean, lentils, nuts & seeds, potato, spinach and carrots.

Riboflavin - B2



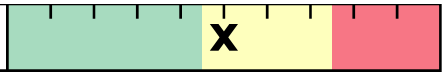
- B2 is a key component of enzymes involved in antioxidant function, energy production, detoxification, methionine metabolism and vitamin activation.
- Low B2 may result from chronic alcoholism, some anti-psychotic medications, oral contraceptives, tricyclic antidepressants, quinacrine or adriamycin.
- B2 deficiency may result in oxidative stress, mitochondrial dysfunction, low uric acid, low B3 or B6, high homocysteine, anemia or oral & throat inflammation.
- Food sources include milk, cheese, eggs, whole grains, beef, chicken, wheat germ, fish, broccoli, asparagus, spinach, mushrooms and almonds.

Biotin - B7



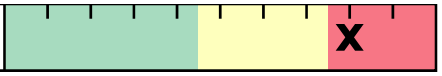
- Biotin is a cofactor for enzymes involved in functions such as fatty acid (FA) synthesis, mitochondrial FA oxidation, gluconeogenesis, and DNA replication & transcription.
- Deficiency may result from certain inborn errors, chronic intake of raw egg whites, long-term TPN use, anticonvulsants, high-dose B5, sulfa drugs & other antibiotics.
- Low levels may result in neurologic symptoms (e.g., paresthesias, depression), hair loss, scaly rash on face or genitals or impaired immunity.
- Food sources include yeast, whole grains, wheat germ, eggs, cheese, liver, meats, fish, wheat, nuts & seeds, avocado, raspberries, sweet potato and cauliflower.

Niacin - B3



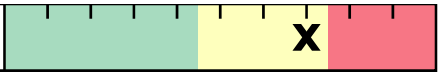
- B3 is used to form NAD and NADP, involved in energy production from food, fatty acid & cholesterol synthesis, cell signaling, DNA repair & cell differentiation.
- Low B3 may result from deficiencies of tryptophan (B3 precursor), B6, B2 or Fe (cofactors in B3 production), or from long-term isoniazid or oral contraceptive use.
- B3 deficiency may result in pellagra (dermatitis, diarrhea, dementia), neurologic symptoms (e.g., depression, memory loss), bright red tongue or fatigue.
- Food sources include poultry, beef, organ meats, fish, whole grains, peanuts, seeds, lentils, brewer's yeast and lima beans.

Folic Acid - B9



- Folic acid plays a key role in coenzymes involved in DNA and SAMe synthesis, methylation, nucleic acids & amino acid metabolism and RBC production.
- Low folate may result from alcoholism, high-dose NSAIDs, diabetic meds, H2 blockers, some diuretics and anti-convulsants, SSRIs, methotrexate, trimethoprim, pyrimethamine, triamterene, sulfasalazine or cholestyramine.
- Folate deficiency can result in anemia, fatigue, low methionine, increased homocysteine, impaired immunity, heart disease, birth defects and CA risk.
- Food sources include fortified grains, green vegetables, beans & legumes.

Cobalamin - B12



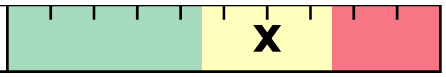
- B12 plays important roles in energy production from fats & proteins, methylation, synthesis of hemoglobin & RBCs, and maintenance of nerve cells, DNA & RNA.
- Low B12 may result from alcoholism, malabsorption, hypochlorhydria (e.g., from atrophic gastritis, H. pylori infection, pernicious anemia, H2 blockers, PPIs), vegan diets, diabetic meds, cholestyramine, chloramphenicol, neomycin or colchicine.
- B12 deficiency can lead to anemia, fatigue, neurologic symptoms (e.g., paresthesias, memory loss, depression, dementia), methylation defects or chromosome breaks.
- Food sources include shellfish, red meat poultry, fish, eggs, milk and cheese.

Interpretation At-A-Glance

Nutritional Needs

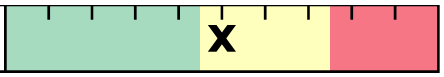
Minerals

Manganese



- Manganese plays an important role in antioxidant function, gluconeogenesis, the urea cycle, cartilage & bone formation, energy production and digestion.
- Impaired absorption of Mn may occur with excess intake of Fe, Ca, Cu, folic acid, or phosphorous compounds, or use of long-term TPN, Mg-containing antacids or laxatives.
- Deficiency may result in impaired bone/connective tissue growth, glucose & lipid dysregulation, infertility, oxidative stress, inflammation or hyperammonemia.
- Food sources include whole grains, legumes, dried fruits, nuts, dark green leafy vegetables, liver, kidney and tea.

Magnesium

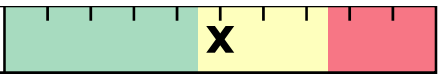


- Magnesium is involved in >300 metabolic reactions. Key areas include energy production, bone & ATP formation, muscle & nerve conduction and cell signaling.
- Deficiency may occur with malabsorption, alcoholism, hyperparathyroidism, renal disorders (wasting), diabetes, diuretics, digoxin or high doses of zinc.
- Low Mg may result in muscle weakness/spasm, constipation, depression, hypertension, arrhythmias, hypocalcemia, hypokalemia or personality changes.
- Food sources include dark leafy greens, oatmeal, buckwheat, unpolished grains, chocolate, milk, nuts & seeds, lima beans and molasses.

Molybdenum

- Molybdenum is a cofactor for enzymes that convert sulfites to sulfate, and nucleotides to uric acid, and that help metabolize aldehydes & other toxins.
- Low Mo levels may result from long-term TPN that does not include Mo.
- Mo deficiency may result in increased sulfite, decreased plasma uric acid (and antioxidant function), deficient sulfate, impaired sulfation (detoxification), neurologic disorders or brain damage (if severe deficiency).
- Food sources include buckwheat, beans, grains, nuts, beans, lentils, meats and vegetables (although Mo content of plants depends on soil content).

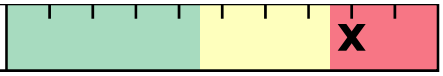
Zinc



- Zinc plays a vital role in immunity, protein metabolism, heme synthesis, growth & development, reproduction, digestion and antioxidant function.
- Low levels may occur with malabsorption, alcoholism, chronic diarrhea, diabetes, excess Cu or Fe, diuretics, ACE inhibitors, H2 blockers or digoxin.
- Deficiency can result in hair loss and skin rashes, also impairments in growth & healing, immunity, sexual function, taste & smell and digestion.
- Food sources include oysters, organ meats, soybean, wheat germ, seeds, nuts, red meat, chicken, herring, milk, yeast, leafy and root vegetables.

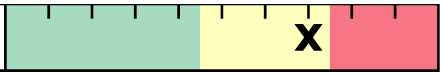
Digestive Support

Need for Probiotics



- Probiotics have many functions. These include: production of some B vitamins and vitamin K; enhancement of digestion & absorption; decreasing severity of diarrheal illness; modulation of immune function & intestinal permeability.
- Alterations of gastrointestinal microflora may result from C-section delivery, antibiotic use, improved sanitation, decreased consumption of fermented foods, and use of certain drugs.
- Some of the diseases associated with microflora imbalances include: IBS, IBD, fibromyalgia, chronic fatigue syndrome, obesity, atopic illness, colic and cancer.
- Food sources rich in probiotics are yogurt, kefir and fermented foods.

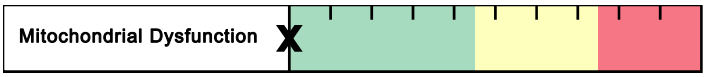
Need for Pancreatic Enzymes



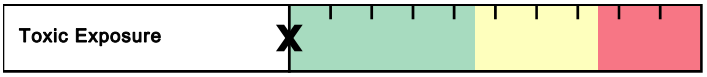
- Pancreatic enzymes are secreted by the exocrine glands of the pancreas and include protease/peptidase, lipase and amylase.
- Pancreatic exocrine insufficiency may be primary or secondary in nature. Any indication of insufficiency warrants further evaluation for underlying cause (i.e., celiac disease, small intestine villous atrophy, small bowel bacterial overgrowth).
- A high functional need for digestive enzymes suggests that there is an impairment related to digestive capacity.
- Determining the strength of the pancreatic enzyme support depends on the degree of functional impairment. Supplement potency is based on the lipase units present in both prescriptive and non-prescriptive agents.

Interpretation At-A-Glance

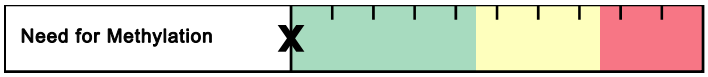
Functional Imbalances



- Mitochondria are a primary site of generation of reactive oxygen species. Oxidative damage is considered an important factor in decline of physiologic function that occurs with aging and stress.
- Mitochondrial defects have been identified in cardiovascular disease, fatigue syndromes, neurologic disorders such as Parkinson's and Alzheimer's disease, as well as a variety of genetic conditions. Common nutritional deficiencies can impair mitochondrial efficiency.

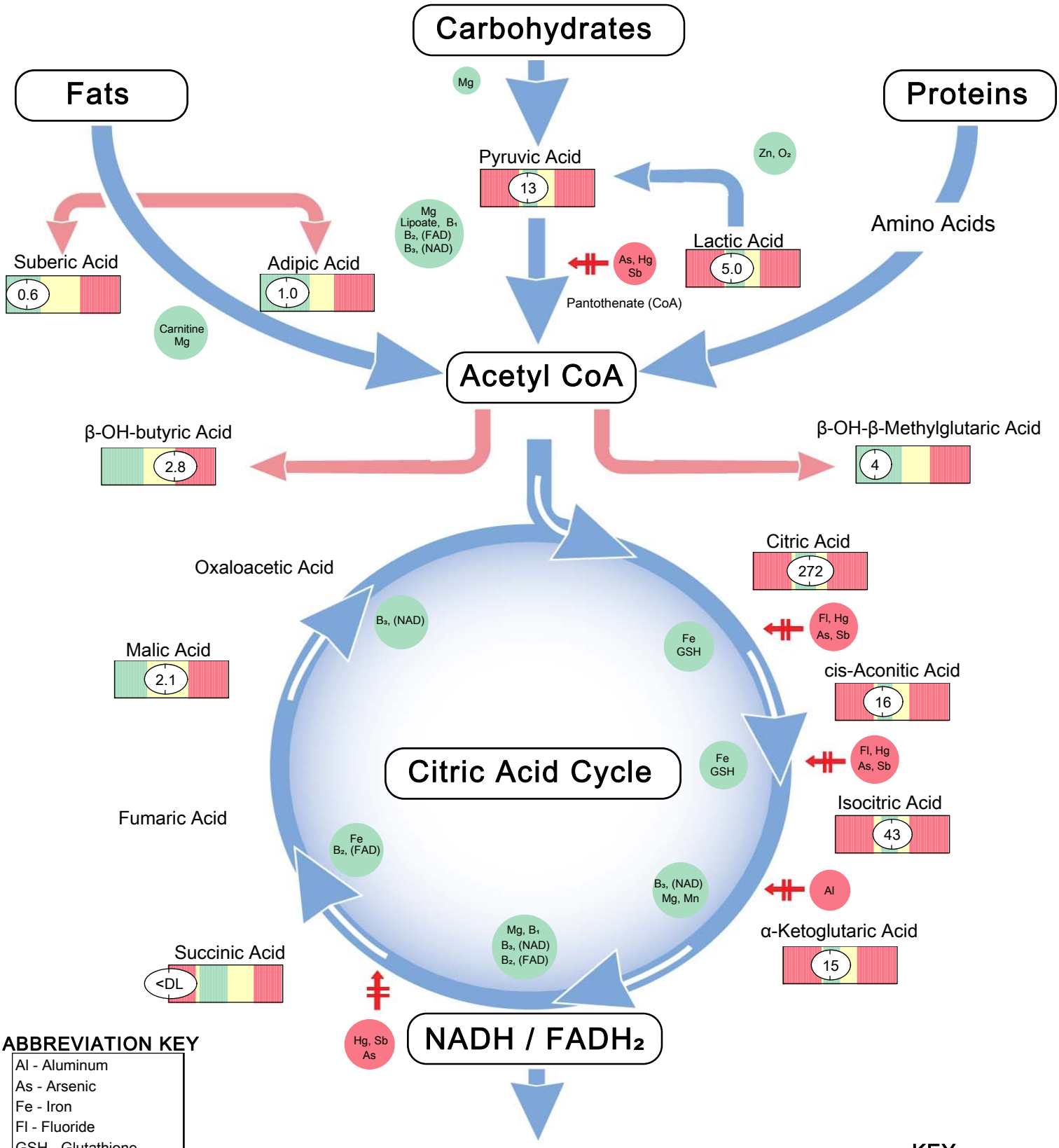


- Methyl tert-Butyl Ether (MTBE) is a common gasoline additive used to increase octane ratings, and has been found to contaminate ground water supplies where gasoline is stored. Inhalation of MTBE may cause nose and throat irritation, as well as headaches, nausea, dizziness and mental confusion. Animal studies suggest that drinking MTBE may cause gastrointestinal irritation, liver and kidney damage and nervous system effects.
- Styrene is classified by the US EPA as a "potential human carcinogen," and is found widely distributed in commercial products such as rubber, plastic, insulation, fiberglass, pipes, food containers and carpet backing.
- Levels of these toxic substances should be examined within the context of the body's functional capacity for methylation and need for glutathione.



- Methylation is an enzymatic process that is critical for both synthesis and inactivation. DNA, estrogen and neurotransmitter metabolism are all dependent on appropriate methylation activity.
- B vitamins and other nutrients (methionine, magnesium, selenium) functionally support catechol-O-methyltransferase (COMT), the enzyme responsible for methylation.

Krebs Cycle At-A-Glance



ABBREVIATION KEY

Al - Aluminum
As - Arsenic
Fe - Iron
Fl - Fluoride
GSH - Glutathione
Hg - Mercury
Mg - Magnesium
Mn - Manganese
Sb - Antimony
Zn - Zinc

KEY

Green = cofactor

Red = inhibitor

All biomarkers reported in mmol/mol creatinine unless otherwise noted.

Metabolic Analysis Markers (Urine)

Malabsorption and Dysbiosis Markers

Malabsorption Markers

		Reference Range
Indoleacetic Acid (IAA)	2.6	<= 4.2
Phenylacetic Acid (PAA)	0.14	<= 0.12

Bacterial Dysbiosis Markers

		Reference Range
Dihydroxyphenylpropionic Acid (DHPPA)	0.5	<= 5.3
3-Hydroxyphenylacetic Acid	6.7	<= 8.1
4-Hydroxyphenylacetic Acid	13	<= 29
Benzoic Acid	0.07	<= 0.05
Hippuric Acid	178	<= 603

Yeast / Fungal Dysbiosis Markers

		Reference Range
Arabinose	35	<= 96
Citramalic Acid	1.9	<= 5.8
Tartaric Acid	<DL	<= 15

Cellular Energy & Mitochondrial Metabolites

Carbohydrate Metabolism

		Reference Range
Lactic Acid	5.0	1.9-19.8
Pyruvic Acid	13	7-32
β-OH-Butyric Acid (BHBA)	2.8	<= 2.8

Energy Metabolism

		Reference Range
Citric Acid	272	40-520
Cis-Aconitic Acid	16	10-36
Isocitric Acid	43	22-65
α-Ketoglutaric Acid (AKG)	15	4-52
Succinic Acid	<DL	0.4-4.6
Malic Acid	2.1	<= 3.0
β-OH-β-Methylglutaric Acid (HMG)	4	<= 15

Fatty Acid Metabolism

		Reference Range
Adipic Acid	1.0	<= 2.8
Suberic Acid	0.6	<= 2.1

Creatinine Concentration

		Reference Range
Creatinine ◆	6.1	3.1-19.5 mmol/L

Methodology: GCMS, LC/MS/MS, Alkaline Picrate

Neurotransmitter Metabolites

		Reference Range
Vanilmandelic Acid	1.2	0.4-3.6
Homovanillic Acid	1.8	1.2-5.3
5-OH-indoleacetic Acid	13.5	3.8-12.1
3-Methyl-4-OH-phenylglycol	0.06	0.02-0.22
Kynurenic Acid	4.9	<= 7.1
Quinolinic Acid	3.9	<= 9.1
Kynurenic / Quinolinic Ratio	1.26	>= 0.44

Vitamin Markers

		Reference Range
α-Ketoadipic Acid	0.6	<= 1.7
α-Ketoisovaleric Acid	0.57	<= 0.97
α-Ketoisocaproic Acid	0.58	<= 0.89
α-Keto-β-Methylvaleric Acid	2.3	<= 2.1
Formiminoglutamic Acid (FIGlu)	1.3	<= 1.5
Glutaric Acid	0.18	<= 0.51
Isovalerylglycine	4.1	<= 3.7
Methylmalonic Acid	1.4	<= 1.9
Xanthurenic Acid	0.45	<= 0.96
3-Hydroxypropionic Acid	22	5-22
3-Hydroxyisovaleric Acid	22	<= 29

Toxin & Detoxification Markers

		Reference Range
α-Ketophenylacetic Acid (from Styrene)	0.40	<= 0.46
α-Hydroxyisobutyric Acid (from MTBE)	5.0	<= 6.7
Orotic Acid	0.63	0.33-1.01
Pyroglutamic Acid	24	16-34

Tyrosine Metabolism

		Reference Range
Homogentisic Acid	5	<= 19
2-Hydroxyphenylacetic Acid	0.73	<= 0.76

Metabolic Analysis Reference Ranges are Age Specific

The performance characteristics of all assays have been verified by Genova Diagnostics, Inc. Unless otherwise noted with ◆, the assay has not been cleared by the U.S. Food and Drug Administration.

Amino Acids (Urine FMV)

All biomarkers reported in micromol/g creatinine unless otherwise noted.

Nutritionally Essential Amino Acids

Amino Acid		Reference Range
Arginine	15	3-43
Histidine	462	124-894
Isoleucine	25	3-28
Leucine	64	4-46
Lysine	88	11-175
Methionine	15	2-18
Phenylalanine	85	8-71
Taurine	905	21-424
Threonine	90	17-135
Tryptophan	49	5-53
Valine	44	7-49

Nonessential Protein Amino Acids

Amino Acid		Reference Range
Alanine	220	63-356
Asparagine	88	25-166
Aspartic Acid	<DL	<= 14
Cysteine (FMV urine)	33	8-74
Cystine (FMV Urine)	72	10-104
γ-Aminobutyric Acid	1	<= 5
Glutamic Acid	12	4-27
Glutamine	545	110-632
Proline	7	1-13
Tyrosine	113	11-135

Creatinine Concentration

		Reference Range
Creatinine ◆	5.8	3.1-19.5 mmol/L

Amino Acid reference ranges are age specific.

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Methodology: LC/MS/MS, Alkaline Picrate

Intermediary Metabolites

B Vitamin Markers

		Reference Range
α-Aminoadipic	54	2-47
α-Amino-N-butyric Acid	17	2-25
β-Aminoisobutyric Acid	133	11-160
Cystathionine	85	2-68
3-Methylhistidine	301	44-281

Urea Cycle Markers

Citrulline	2.4	0.6-3.9
Ornithine	12	2-21
Urea ◆	448	168-465 mmol/g creatinine

Glycine/Serine Metabolites

Glycine	561	95-683
Serine	159	40-163
Ethanolamine	147	50-235
Phosphoethanolamine	18	1-13
Phosphoserine	13	3-13
Sarcosine	<DL	<= 1.1

Dietary Peptide Related Markers

		Reference Range
Anserine (dipeptide)	48.1	0.4-105.1
Carnosine (dipeptide)	21	1-28
1-Methylhistidine	1,740	38-988
β-Alanine	53	<= 22

Oxidative Stress Markers

Oxidative Stress Markers

Reference Range

Methodology: thiobarbituric acid reactive substances (TBARS), Alkaline Picrate, Hexokinase/G-6-PDH, LC/MS/MS

Lipid Peroxides (urine)	7.0	<=10.0 micromol/g Creat.
8-OHdG (urine)	7	<=15 mcg/g Creat.

Lab Comments

Please note the reference range for 8-OHdG (urine) has been updated.

The performance characteristics of all assays have been verified by Genova Diagnostics, Inc. Unless otherwise noted with ◆, the assay has not been cleared by the U.S. Food and Drug Administration.

Interpretation At-A-Glance Details

Antioxidants

Vitamin A / Carotenoids

Contributing Biomarkers:
β-Alanine
Cystine
Cysteine
Taurine

Vitamin E / Tocopherols

Contributing Biomarkers:
β-Alanine
Cystine
Cysteine
Taurine

Plant-based Antioxidants

Contributing Biomarkers:
Cystine
Cysteine
Taurine

B-Vitamins

Thiamin - B1

Contributing Biomarkers:
5-OH-Indoleacetic Acid
α-Keto-β-Methylvaleric Acid
α-Ketoisocaproic Acid
α-Ketoisovaleric Acid
Leucine
Phenylalanine
Taurine

Riboflavin - B2

Contributing Biomarkers:
α-Keto-β-Methylvaleric Acid
α-Aminoadipic Acid

Niacin - B3

Contributing Biomarkers:
5-OH-Indoleacetic Acid
α-Keto-β-Methylvaleric Acid

Interpretation At-A-Glance Details

Pyridoxine - B6

Contributing Biomarkers:
α-Aminoadipic Acid
β-Alanine
Cystathionine
Leucine
Methionine

Biotin - B7

Contributing Biomarkers:
3-Hydroxyisovaleric Acid
3-Hydroxypropionic Acid
Phenylalanine

Folic Acid - B9

Contributing Biomarkers:
α-Aminoadipic Acid
Cystathionine
Formiminoglutamic Acid
Phenylalanine

Cobalamin - B12

Contributing Biomarkers:
α-Aminoadipic Acid
Cystathionine
Formiminoglutamic Acid
Leucine
Phenylalanine
Succinic Acid

Minerals

Manganese

Contributing Biomarkers:
5-OH-Indoleacetic Acid

Molybdenum

Contributing Biomarkers:
Taurine

Magnesium

Contributing Biomarkers:
Ethanolamine
Phosphoethanolamine
Phenylalanine

Interpretation At-A-Glance Details

Zinc

Contributing Biomarkers:
Phosphoethanolamine

Digestive Support

Need for Probiotics

Contributing Biomarkers:
Benzoic Acid
β-Alanine
Phenylacetic Acid
Phosphoethanolamine

Need for Pancreatic Enzymes

Contributing Biomarkers:
1-Methylhistidine
Phenylacetic Acid

Metabolic Analysis Commentary

Commentary is provided to the practitioner for educational purposes, and should not be interpreted as diagnostic or treatment recommendations. Diagnosis and treatment decisions are the responsibility of the practitioner.

Phenylacetic Acid (PAA) is elevated. If the essential amino acid phenylalanine is not sufficiently digested and absorbed in the small intestine, it is carried to the large bowel where anaerobic bacteria convert it to phenylethylamine. This is then absorbed, and in body tissues such as the liver, it is converted by deamination to PAA, which is excreted in the urine. Some species of Clostridia can produce PAA directly from aromatic amino acids. Its presence at elevated levels indicates one or more of the following: gastric hypochlorhydria or pepsin inactivity, impaired digestive peptidase function in the small intestine, rate-limited or insufficient absorption or mucosal transport in the small intestine, abnormal intestinal motility (partly regulated by cholecystokinin and secretin), or presence of colonic or other bacteria in the small intestine (dysbiosis).

Additionally, some elevation of PAA may occur in the uncommon instances of phenylketonuria and with Type I tyrosinemia (tyrosinosis). With phenylketonuria, 2-hydroxyphenylacetate (2-HPAA) would be significantly elevated. An amino acid analysis also is helpful in diagnosing such conditions.

Benzoic acid is a common food component, especially in fruits and in particular berries/cranberries. It is also a common food additive/preservative. Benzoic acid is also formed by gut microflora metabolism of phenylalanine and dietary polyphenols. Elevated levels may thus reflect dietary intake (for example strawberries), imbalanced gut flora or a high intake of polyphenols or phenylalanine. Older studies note a relationship between decreased cognitive function and increased BA in the urine.

5-Hydroxyindoleacetic Acid (5-HIAA) is elevated. 5-HIAA is a normal urine metabolite of the neurotransmitter serotonin, which is formed from the essential amino acid, tryptophan. Virtually all blood serotonin and most urine 5-HIAA comes from serotonin formation outside of the CNS. This occurs primarily in tissues in the abdominal cavity, especially the gastrointestinal tract, pancreas and spleen.

Slightly or moderately elevated 5-HIAA may result from increased formation of serotonin, a vasoconstrictor and smooth-muscle contractor, in the small intestine. Secondary inflammatory responses may be present. Slightly or moderately increased 5-HIAA may also be a dietary artifact from consumption of relatively large amounts of bananas, plantain, pineapple, kiwi fruit, plums, avocado, walnuts or pecans. Similarly, the medications acetaminophen and guaifenesin can elevate urinary 5-HIAA. Elevated 5-HIAA may also occur if methylation by S-adenosylmethionine (SAM) is impaired, as methylation of serotonin is needed to produce other products of serotonin: melatonin and 5-methoxy-3-indoleacetic acid (a waste metabolite like 5-HIAA). Notably high levels of 5-HIAA (and serotonin) are found in carcinoid disease, where malignant cells in the intestine, particularly the ileum, produce excess serotonin.

Succinic acid participates in the citric acid cycle, acting to donate electrons to the mitochondrial electron transport and leading to formation of fumaric acid. Common in foods such as cantaloupe, it is also a food additive, providing flow-altering effects and a tart flavor. It appears that lacto-ovo vegetarians may show decreased levels in the urine and chronic fatigue patients may also show low levels, although studies on this topic are mixed. Low levels may also be an indicator of B12 or folate deficiency.

Alpha-keto-beta-methylvaleric Acid (AKBM) is measured to be elevated. AKBM comes from the essential amino acid isoleucine via transamination. Moderate elevations of AKBM usually mean that AKBM's further metabolism to the compound, alpha-methylbutyryl-CoA, is impaired either by coenzyme/cofactor insufficiency or by (genetic) weakness in

Commentary

the enzyme complex. The dehydrogenase enzyme complex that accomplishes this requires lipoic acid, vitamin B1 as thiamin pyrophosphate and vitamin B2 as FAD. Vitamin B3 as NAD is a necessary cofactor, which removes hydrogen to become NADH. The other necessary cofactor is coenzyme A, requiring pantothenic acid, cysteine, and magnesium. Elevated levels of AKBM may indicate low levels of any of these nutrients.

The toxic elements arsenic, antimony, mercury and cadmium may also weaken lipoic acid and dehydrogenase activity. Very high elevation of AKBM and its sister keto acids (alpha-ketoisovaleric, alpha-ketoisocaproic) constitute a rare disorder called "maple syrup urine disease". When AKBM is elevated, isoleucine may also be elevated per urine or plasma amino acid analysis.

Isovalerylglycine (IVG) is a product of leucine catabolism, and has been observed to be elevated in the urine with increased leucine intake, anorexia nervosa or an enzyme defect. There are numerous variants of the enzyme errors, some of which respond to combined treatment with carnitine and glycine by increasing the excretion (detoxification) of the IVG. There are additional cases where riboflavin appears to be an important way to correct the metabolic difficulties. High levels could be due to high leucine intake, dramatic dietary issues such as anorexia or potential enzyme defect, which are often accompanied by significant muscular symptoms such as weakness or hypotonia. High levels of IVG benefit therapeutically from carnitine, glycine, and riboflavin.

Amino Acid Commentary

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Beta-alanine is measured to be high in the urine. Often this amino acid is elevated when the dietary peptides anserine and carnosine are elevated because they contain beta-alanine. Beta-alanine also is a breakdown product of the pyrimidine bases cytosine and uracil. Catabolism of damaged or diseased body tissue, tumors and malignancy feature increased production and urinary disposal of beta-alanine. Besides elevated anserine or carnosine and accelerated catabolism of unwanted body tissue, the next most likely source of beta-alanine is imbalanced gut flora. Some beta-alanine is produced by normal gut flora which also make pantothenic acid from it. Elevated levels of staphylococcus or streptococcus, use of antibiotics, and breakdown of yeast or fungi in the body can result in increased levels of urinary beta-alanine. Continuously elevated beta-alanine can be detrimental by impairing renal conservation of taurine.

Taurine is measured to be elevated in the urine, which is consistent with excess dietary intake, or with urinary wasting due to poor renal conservation. Excessive dietary intake of taurine-rich sources like seafood (especially shellfish), and from liver and organ meats may elevate plasma blood levels, as may consumption of taurine-supplemented sports and stimulant drinks. Urinary wasting can be secondary to generally increased renal clearance or nephrotic syndromes. Wasting can also occur when the similarly-structured amino acid beta-alanine is elevated or is present in kidney tubules. In molybdenum deficiency or sulfite oxidase impairment, elevated urine taurine results as a mode of sulfur excretion.

Renal wasting of taurine can be medically significant if it affects one or more of taurine's many important functions -

- Conjugation of cholesterol (as cholyl-coenzyme A) to form taurocholic acid, an important component of bile and a major utilization of cholesterol.
- Mediation of the flux of electrolyte elements at the plasma membrane of cells. Deficient taurine may result in increased cellular calcium and sodium and reduced magnesium.
- Increased resistance to aggregation of blood platelets and decreased thromboxane release if aggregation does occur.
- Sparing of magnesium - globally. Urinary magnesium wasting can result from taurine insufficiency. Magnesium deficiency may cause fatigue, depression, muscle tremor and hypertension.
- Antioxidant functions. Taurine scavenges excess hypochlorite ion, OCl-, in leukocytes and facilitates effective phagocytosis by enhancing survival of leukocytes. Deficient taurine may lead to increased inflammatory response to: toxins, foreign proteins, and xenobiotic chamicals including aldehydes, alcohols, amines, petroleum solvents, and chlorine or chlorite (bleach).
- Neurotransmitter functions. Taurine strongly influences neuronal concentrations and activities of GABA and glutamic acid. Taurine can have anti-convulsant and anti-epileptic effects.

Pathologies attributed to taurine insufficiency include: biliary insufficiency, fat malabsorption (steatorrhea), cardiac arrhythmia, congestive heart failure, poor vision, retinal degeneration, granulomatous disorder of neutrophils, immune dysfunction, enhanced inflammatory response to xenobiotics, convulsions and seizures.

The uncommon condition of overall taurine excess (hypertaurinuria with hypertaurinemia) usually is insufficiency of sulfite oxidase activity, possibly due to molybdenum deficiency. In this condition there is increased urinary sulfites and decreased sulfates. If molybdenum is deficient, uric acid levels are reduced, xanthine is increased and aldehyde detoxication is impaired (aldehyde intolerance).

1-Methylhistidine is found to be elevated; it is a component of the dietary peptide anserine. Anserine is beta-alanyl-1-methyl-L-histidine, and it is known to come from chicken, turkey, duck, rabbit, tuna and salmon. Other food sources (especially trout and fowl) also are likely but are not documented. The peptidase enzyme that hydrolyzes anserine is present in the small intestine and also present in liver, spleen, and kidney tissues and in blood serum. Some direct uptake of dietary anserine is normal, and moderate levels of urinary 1-methylhistidine are normal.

Commentary

However, high levels suggest increased uptake of short-chain peptides, possibly increased gut permeability, and increased hydrolysis of short-chain dietary peptides by peptidases in blood, liver and spleen. Elevated 1-methylhistidine suggests one or more of: dietary overload of anserine-source foods, increased gut permeability, and decreased activity of digestive peptidases in the small intestine. There may or may not be associated symptomatology. 1-Methylhistidine itself is not known to be detrimental.

3-Methylhistidine is elevated. This methylated form of histidine comes from muscle tissue, both dietary and endogenous, where it is part of the muscle proteins actin and myosin. A moderate level of urine 3-methylhistidine is normal. Elevated levels suggest either an inordinately high intake of dietary actin/myosin or accelerated catabolism of muscle tissue in this individual. 3-Methylhistidine excretion is increased after strenuous physical exercise and also occurs in muscle wasting conditions - dystrophies, lack of exercise, extended bed rest, terminal stages of severe illness. Convulsions and seizures also feature increased urinary 3-methylhistidine. There is some correlation between elevated 3-methylhistidine and increased need for vitamin B12, folic acid, methionine and perhaps histidine if it is marginal or low.

Phenylalanine , a nutritionally essential amino acid, is measured to be elevated. Tyrosine, a direct metabolite of phenylalanine, is not elevated, and generalized hyperaminoaciduria is not presented. This suggests a rate limitation in phenylalanine-to-tyrosine metabolism which involves the enzyme phenylalanine monooxygenase (also called phenylalanine hydroxylase) and several cofactors: oxygen, reduced and probably phosphorylated NAD, biopterin, and iron. Iron is bound to the monooxygenase as an activator. NADPH donates hydrogen to form tetrahydrobiopterin (BH4); and the BH4 and oxygen combine to put a hydroxyl group on phenylalanine (to form tyrosine). The reaction is assisted by phenylalanine hydroxylase stimulator, a dehydratase protein that catalyzes release of H2O and increases the kinetics. Also, the monooxygenase (hydroxylase) enzyme itself is phosphorylated in a reaction catalyzed by cyclic-AMP, and phosphorylation at least doubles the kinetics for phenylalanine to tyrosine.

The following problems are associated with rate-limited formation of tyrosine from phenylalanine, often manifested by increased urine phenylalanine level.

- Iron deficiency, anemia conditions
- Subnormal tissue oxygenation, anemia, pulmonary disorders, cardiovascular problems
- Magnesium deficiency (limits phosphorylation rate)
- Aluminum excess (interferes with phosphorylation)
- Vitamin B3 or niacin deficiency (deficient NADH, NADPH)
- Vitamin B1 or thiamin deficiency (limits hexose monophosphate shunt which forms NADPH outside of cell mitochondria)
- Mitochondrial damage (could limit pyrimidine-linked dehydrogenase formation of NADPH in mitochondria)
- Biopterin insufficiency (in vivo formation is from guanosine triphosphate)
- Adrenocortical insufficiency, Addisons disease and insulin insufficiency (may down-regulate Phe hydroxylase)
- Genetic weaknesses in phenylalanine hydroxylase, biopterin reductase, or the hydroxylase stimulator protein. Severe weakness can result in phenylketonuria, PKU.

Symptoms consistent with mild/moderate hyperphenylalaninuria include fatigue, headaches, "brain fog" or mental confusion, and possibly nausea or diarrhea. Artificial sweeteners containing phenylalanine should be avoided. Also, the diet should be limited in high-phenylalanine foods: soy protein, peanuts, lima and garbanzo beans, lentils, cheese, cashews and most fish and shellfish. Availability of biopterin as a supplement is limited. The other nutritional cofactors may be supplemented if beneficial.

Phosphoethanolamine is elevated. Metabolically, phosphoethanolamine is an intermediate of the serine-to-choline sequence. Impairment of this sequence beyond phosphoethanolamine is not documented except for presumptive evidence of impaired methylation. Triple methylation by S-adenosylmethionine (SAM) of phosphatidylethanolamine produces choline. If methionine is deficient or elevated, limited SAM or rate-limited methylation could contribute to elevated phosphoethanolamine. Conditions consistent with elevated phosphoethanolamine due to impaired methylation by SAM include: mood swings, mental depression, cognitive and

Commentary

memory impairments, cholinergic dysfunction.

Other, more commonly encountered conditions featuring elevated urine phosphoethanolamine are outlined below. Elevated phosphoserine could be consistent with these conditions.

- Dietary calcium insufficiency with renal wasting of (organic) phosphorus. Bone resorption may or may not be concurrent.
- Vitamin D deficiency, also with renal wasting of phosphorus
- Hormonal or steroidal imbalances featuring hyperphosphaturia; hyperparathyroidism
- Pseudohypophosphatasia with normal alkaline phosphatase activity but with hypophosphatemia and renal loss of organic phosphates
- Hypophosphatasia due to deficient or impaired activity of alkaline phosphatase. The condition is resistant to vitamin D supplementation. Osteomalacia (adults) and rickets (children) would be consistent. This condition is uncommon but not rare and is autosomal recessive. Zinc deficiency can impair alkaline phosphatase activity and result in mildly elevated urine phosphoethanolamine, perhaps with mild hypophosphatasia.

Cystathionine , an intermediary metabolite of the essential amino acid methionine, is elevated per the urine analysis. Cystathionine is preceded by homocysteine, and it leads to cysteine and alpha-ketobutyric acid (A-KBA, which may become alpha-amino-N-butyric acid). To become cysteine and A-KBA, cystathionine is acted on by the enzyme cystathionine gamma-lyase which requires vitamin B6 as coenzyme pyridoxal 5-phosphate (P 5-P).

Clinical manifestations of cystathioninuria are variable, and some authorities do not attribute any pathology strictly to weakness of the gamma-lyase enzyme itself. Consequences may depend upon need for and levels of the ultimate metabolites of cystathionine: cysteine, glutathione, taurine, etc. Conditions variously reported to coincide with cystathioninuria include for children: hyperactivity, repeated infections, learning disorders, mental retardation and juvenile diabetes mellitus. For adults, mental aberrations, mental retardation, urinary calculi, and acromegaly are reported. For many individuals administration of vitamin B6 during infancy or childhood has resulted in normalcy when tested some years later. Most cases of cystathioninuria resolve with administration of vitamin B6 and/or pyridoxal phosphate (Ref. Mudd and Levy, "Disorders of Transsulfuration", Stanbury et al., eds. The Metabolic Basis of Inherited Disease, pp 550-551).

The essential amino acid **leucine** is elevated. A mild or moderate isolated elevation of leucine usually reflects insufficient vitamin B6 or pyridoxal 5-phosphate. Metabolic disorders of leucine are expected to involve the similarly structured essential amino acids, isoleucine and valine, and a urine leucine level above 200 micromoles per 24 hours would be expected. The other branched-chain essential amino acids are not elevated.

Alpha-aminoadipic acid (A-AAA) is an intermediary metabolite of lysine (primarily) and of tryptophan. A-AAA is elevated in the urine and the most commonly encountered cause is vitamin B6 insufficiency or pyridoxal 5-phosphate (P 5-P)dysfunction as a coenzyme for transamination. A-AAA also is a metabolite of yeast/fungi metabolism, and anecdotal evidence supports occasional increases with intestinal dysbiosis as a source. In Reye's syndrome, alpha-aminoadipic hyperaminoaciduria occurs together with hyperlysinuria. Rare metabolic and acute alpha-aminoadipic hyperaminoaciduria is documented as due to a hereditary defect in the A-AAA transaminase enzyme and in the next enzyme in the sequence, alpha-ketoadipic acid dehydrogenase. In glutaric acidemia/aciduria there can be notable alpha-aminoadipic hyperaminoaciduria due to a hereditary weakness of glutaryl CoA dehydrogenase. Riboflavin insufficiency as FAD may provoke or worsen alpha-aminoadipic hyperaminoaciduria (and glutaric acidosis) if the dehydrogenase enzymes are weak, but riboflavin may or may not improve the kinetics of defective dehydrogenases.

Oxidative Stress Commentary

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Patient values for the Oxidative Stress Markers are within Genova Diagnostics reference ranges.