ARL Functional Pathology

Urinary Organic Acids

Clinical & Interpretive Guide

Urinary Organic Acids Clinical Guide

ASSESSING PATIENT BIOCHEMICAL & NUTRITIONAL INDIVIDUALITY

An Organic Acid profile can be utilised as an effective screening tool for areas of abnormality that may not be able to be determined from patient history alone. By using multiple metabolic markers in conjunction with one another, a sophisticated, targeted and individualised treatment plan can be more easily developed.[1]

Organic acids are a broad class of compounds used in fundamental metabolic processes of the body. Derived from dietary protein, fat and carbohydrate, they are used by the body to generate cellular energy and provide the building blocks necessary for cell function.[2] Organic acid analyses are traditionally used for the early detection/exclusion or the monitoring of inherited disorders of amino acid and organic acid metabolism.[3]

Organic acid testing provides a broad view of the body. One urine specimen can be used to evaluate gut, liver and nervous system health as well as energy metabolism and nutrient deficiencies. Understanding how these areas are functioning at any one time allows for analysis of system interaction, rather than a more reductionist approach.[1]

The Urinary Organic Acids test measures selected metabolites that serve as important diagnostic indicators of abnormal metabolism. The measurement of organic acids in urine evaluates four critical areas of metabolism:

- Gastrointestinal function
- Cellular energy & mitochondrial metabolism
- Neurotransmitter metabolism
- Amino acid/organic acid balance as influenced by vitamin/mineral cofactors

Despite the substantial information provided in the Urinary Organic Acids Profile, the interpretation is simplified by focussing on the fact that the data provides answers to four basic questions of clinical relevance:

1. Is the production of mitochondrial energy adversely affected?
2. Are functional nutritional deficiencies present?
3. Are symptoms related to excessive growth of bacteria and fungi in the gut?
4. Is there an excessive toxic load and is this adversely affecting detoxification capacity?[2]

DEFINING METABOLIC IMBALANCE

Metabolic imbalance is a common and pervasive condition that may underlie many chronic complaints, such as fatigue, gastrointestinal dysfunction, muscular/joint problems, mood disorders and headaches, which are commonly resistant to long-term treatment and sustained improvement. Evaluating multiple organ systems and biochemical pathways allows for treatment of the whole person. As with all cases, investigation of all of the potential causes of illness and disease is mandatory for effective case assessment, diagnosis, treatment regimes and management.

UNDERSTANDING METABOLIC PROCESSES

The Urinary Organic Acids test assists in understanding how nutrient metabolism is executed and determining where there may be imbalances in the metabolic cycle.

If we examine the metabolism of carbohydrate for example (see Table 1), we know that nutrient cofactors for carbohydrate metabolism are required for efficient functioning of the metabolic pathway and the subsequent production of cellular energy.

Table 1. Carbohydrate Metabolism

MEASURED COMPOUND NAME	NUTRIENT ASSOCIATIONS	METABOLIC PATHWAY
Pyruvate	Vitamins B1, B3, B5, Lipoic acid	Anaerobic energy production
Lactate	CoQ10, Vitamins B1, B3, B5, Lipoic acid	Anaerobic energy production
b-Hydroxybutyrate	Chromium, Vanadium	Glucose uptake

The B group vitamins, particularly B1 (thiamin), B3 (niacin) and B5 (pantothenic acid), provide essential cofactors for energy pathways of all body cells. As food is metabolised, specific compounds are formed at steps that require B vitamin involvement. Such steps occur in carbohydrate metabolism where pyruvate and lactate are formed. A pattern of elevated levels of these compounds may reflect enzyme failure due to a functional need for increased B vitamins, particularly thiamine and pantothenic acid.

CONSEQUENCES OF METABOLIC IMBALANCE

The following areas of metabolism may be affected by metabolic imbalance:

GASTROINTESTINAL FUNCTION

Chronic malabsorption can contribute to gastrointestinal dysfunction, nutrient insufficiencies and dysbiosis. In turn, chronic dysbiosis may result in local inflammatory reactions, increased risk of colorectal cancers, or increased intestinal permeability, with increased release of toxins and macromolecules into the body.

CELLULAR ENERGY AND MITOCHONDRIAL METABOLISM

The citric acid cycle supplies the body with its primary energy needs. Glycolysis, glycogenolysis and beta-oxidation of fats provide the precursors for this cycle. 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 premature ageing.

NEUROTRANSMITTER METABOLISM

Imbalances in serotonergic or adrenergic function are frequently associated with neuroendocrine disorders such as insomnia, depression, adrenal fatigue, eating disorders and irritable bowel syndrome (IBS). Neurotransmitter imbalances may indicate nutrient deficiencies or methylation impairments which may impact on multiple body systems.

AMINO ACID/ORGANIC ACID BALANCE

Enzyme cofactors are required in virtually every system of the body. Subsequently, deficiencies in the vitamins or minerals from which these cofactors are derived may affect a wide range of functions, including immunologic, endocrine, musculoskeletal and metabolic systems.

ANALYTES CHARACTERISTIC OF CELLULAR ENERGY AND MITOCHONDRIAL FUNCTION

The markers listed in the table below are the analytes measured as part of the Urinary Organic Acids Profile.

Gastrointestinal Function - Malabsorption and Dysbiosis Markers

MALABSORPTION MARKERS	BACTERIAL DYSBIOSIS MARKERS	YEAST/FUNGAL DYSBIOSIS MARKERS
Indoleacetic Acid (IAA)	Citramalic acid	Arabinose
Phenylacetic Acid (PAA)	Indoleacetic Acid (IAA)	Tartaric Acid
Dihydroxyphenylproprionic acid (DHPPA)	Phenylacetic Acid (PAA)	Citramalic Acid
Succinic Acid	Dihydroxyphenylproprionic acid (DHPPA)	
	Benzoic/Hippuric Acids Ratio	
	Succinic Acid	

Neurotransmitter Metabolites

MARKERS
Vanilmandelic Acid (VMA)
Homovanillic Acid (HVA)
3-methyl-4-OH-phenylglycol (MHPG)
5-OH-Indoleacetic Acid (5-HIAA)

Cellular Energy and Mitochondrial Metabolites

GLYCOLYSIS METABOLITES	CITRIC ACID CYCLE METABOLITES	KETONE & FATTY ACID METABOLITES
Lactic Acid	Citric Acid	Adipic Acid
Pyruvic Acid	Cis-Aconitic Acid	Suberic Acid
	Isocitric Acid	b-OH-b-Methylglutaric Acid (HMG)
	a-Ketoglutaric Acid (AKG)	b-OH-Butyric Acid (BHBA)
	Succinic Acid	
	Fumaric Acid	
	Malic Acid	

Organic Acids for Cofactor Need (Organic Acid/Amino Acid Balance)

B COMPLEX VITAMIN MARKERS	METHYLATION COFACTOR MARKERS	DETOXIFICATION INDICATORS	OTHER MARKERS
a-Ketoisovaleric acid (AKIV)	Methylmalonic acid	Glutaric acid	Kynurenic Acid
a-Ketoisocaproic acid (AKIC)	Formiminoglutamate (FIGlu)	Orotic acid	3-Hydroxyproprionic Acid
a-Keto-b-Methylvaleric acid (AKBM)		Pyroglutamic acid	2-Hydroxyphenylacetic Acid (2-HPAA)
			4-Hydroxyphenylpyruvic Acid (4-HPPA)
			Homogentisic Acid
			a-Ketoadipic Acid (AKAA)

INTERPRETATION OF RESULTS

For many of the organic acids that are measured, abnormally high levels in urine usually indicate low levels of a nutrient required to break down that compound. For example, Formiminoglutamic Acid (FIGlu) requires tetrahydrofolate (THF), a reduced form of folic acid, to be changed into forms that are metabolically useful. Elevated urine FIGlu indicates an insufficiency of folic acid and may occur in a number of circumstances. For example, it may be the result of dietary deficiency of folic acid or severe oxidant stress, which limits biologic reduction of folic acid to the THF form.

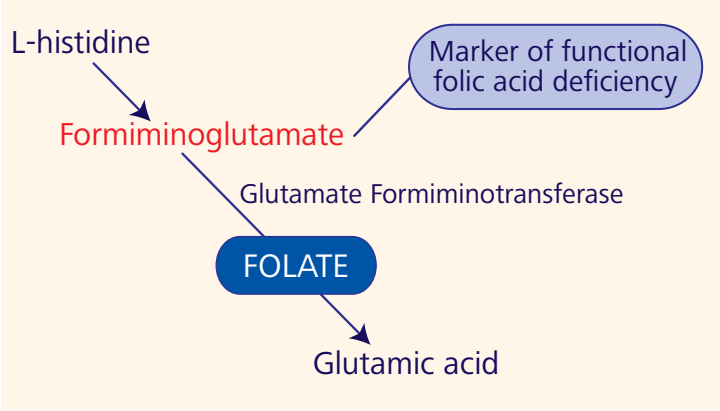

Figure 1
The amino acid L-histidine is derived from dietary protein. Folic acid works with the enzyme glutamate formiminotransferase to convert histidine to glutamic acid. High formiminoglutamate (FIGlu) indicates an insufficiency of folic acid.

A full guide to interpreting the Urinary Organic Acids report is provided overleaf.

URINARY ORGANIC ACID PROFILES

The Metabolic Analysis Profile (MAP) measures 39 organic acids, including 8 gastrointestinal metabolites, 13 cellular energy metabolites, 4 neurotransmitter metabolites and 14 amino acid metabolites. A condensed version of the MAP is the **Cellular Energy Profile (CEP)**, which measures the 13 organic acids tested in the MAP to evaluate energy and metabolism.

SUMMARY

The ability to create a personalised treatment plan based on a functional assessment of nutritional needs holds the greatest promise for improving patient outcomes.[4] Laboratory results provide guidance for an individually optimised nutritional support program.

Urinary Organic Acid analysis provides the most sensitive and specific test for mitochondrial dysfunction. The clinical relevance of this test includes, among other benefits, the ability to detect dysfunction of mitochondrial energy production as well as the presence of functional nutrient deficiencies and toxins that are adversely affecting detoxification pathways.[4]

REFERENCES

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Urinary Organic Acids Interpretive Guide

GASTROINTESTINAL FUNCTION - MALABSORPTION AND DYSBIOSIS MARKERS

MALABSORPTION & BACTERIAL DYSBIOSIS MARKERS	RESULT	POSSIBLE CAUSES	ADDITIONAL INVESTIGATIONS	TREATMENT CONSIDERATIONS
Indoleacetic Acid (IAA) Produced from bacterial degradation of unabsorbed tryptophan	High	• Malabsorption of tryptophan • Hypochlorhydria	• Investigate possible causes of malabsorption • IP • IgG Food Sensitivity • CDSA	• Mucosal support • Elimination diet • Betaine HCl • Digestive enzymes
Phenylacetic Acid (PAA) Produced from bacterial degradation of unabsorbed phenylalanine	High	• Malabsorption of phenylalanine • Hypochlorhydria and/or Clostridia overgrowth	• Investigate possible causes of malabsorption • IP • IgG Food Sensitivity • CDSA	• Mucosal support • Elimination diet • Betaine HCl • Digestive enzymes
Dihydroxyphenlyproprionic Acid (DHPPA) Produced when Clostridia acts upon unabsorbed tryptophan, tyrosine or phenylalanine	High	• Clostridium overgrowth and/ or malabsorption of tryptophan, tyrosine and/or phenlyalanine	• Investigate possible causes of malabsorption • IP • IgG Food Sensitivity • CDSA	• Antimicrobials • Probiotics • Mucosal support • Betaine HCl
Succinic Acid Produced from bacterial degradation of unabsorbed glutamine; also Citric Acid Cycle intermediate	High	• Dysbiosis • UTI • Deficiencies of Fe or B2	• Investigate possible causes of malabsorption, dysbiosis or UTI • IP • IgG Food Sensitivity • CDSA	• Mucosal support • Elimination diet • Fe and/or B2
Benzoic/Hippuric Acids Ratio Benzoate is metabolised in Phase II glycination to hippurate. Enzymes from gut bacteria may reverse this process, producing high benzoic acid	High	• Ingestion of benzoic acid prior to testing • Intestinal dysbiosis	• IP • CDSA	• Rule out high benzoate foods (e.g. plums, prunes, rhubarb, cranberries, preservative in foods) • Antimicrobials • Probiotics

YEAST/FUNGAL DYSBIOSIS MARKERS	RESULT	POSSIBLE CAUSES	ADDITIONAL INVESTIGATIONS	TREATMENT CONSIDERATIONS
Arabinose Breakdown product of hyaluronic acid; also found in certain foods	High	• Ingestion of arabinose rich foods • Joint inflammation leading to release of hyaluronic acid	• IP	• Rule out arabinose containing foods (apples, plums, cherries, grapes) • Address any joint inflammation
Tartaric Acid Breakdown product of hyaluronic acid; also found in some foods	High	• Ingestion of tartaric acid-containing foods • Joint inflammation leading to release of hyaluronic acid	• IP	• Rule out tartaric acid-containing foods (fruits, especially grapes, raisins or wine; also as “cream of tartar” in some soft drinks & baked goods) • Address any joint inflammation
Citramalic Acid Metabolite of yeast or anaerobic bacteria, including Clostridia	High	• Yeast or anaerobic bacterial overgrowth	• CDSA	• Antifungals or antimicrobials • Yeast free diet • Probiotics

NEUROTRANSMITTER METABOLITES

MARKERS	RESULT	POSSIBLE CAUSES	ADDITIONAL INVESTIGATIONS	TREATMENT CONSIDERATIONS
Vanilmandelic Acid (VMA) Noradrenalin metabolite	High	• Increased catecholamine activity/stress pattern • Possible deficient CNS dopamine receptors • Oxidant stress (if MHPG is normal or low)	• Adrenal Hormone Profile • TAS	• Adrenal support • Stress management
	Low	• Low precursors/neurotransmitters (phenylalanine, dopamine, noradrenalin) • Low cofactors (B2, B6, Mo, Cu, Fe) • Impaired methylation	• Vitamins & Minerals Analysis • HMA • Urinary Amino Acids	• L-tyrosine & B6 • B2, Mo, Cu or Fe if low • Support methylation (methionine/SAMe, B6, B12, folate, Mg)
Homovanillic Acid (HVA) Dopamine metabolite	High	• Increased catecholamine activity/stress pattern • Impaired production of noradrenalin from dopamine	• Adrenal Hormone Profile	• Adrenal support • Stress management
	Low	• Low precursors/neurotransmitters (phenylalanine, dopamine, noradrenalin) • Low cofactors (B2, B3, B6, Mg or Fe) • Impaired methylation	• Vitamins & Minerals Analysis	• L-tyrosine & B6 • B2, B3 or Fe if low • Support methylation (methionine/SAMe, B6, B12, folate, Mg)
3-methyl-4-OH-phenylglycol (MHPG) Noradrenalin metabolite	High	• Increased catecholamine activity/stress pattern • Possible deficient CNS dopamine receptors	• Adrenal Hormone Profile	• Adrenal support • Stress management
	Low	• Low precursors/neurotransmitters (phenylalanine, dopamine, noradrenalin) • Low cofactors (B2, B3, B6, Mg or Fe) • Impaired methylation (if VMA also low)	• Vitamins & Minerals Analysis	• L-tyrosine & B6 • Support methylation (methionine or SAMe, B6, B12, folate, Mg)
5-OH-Indoleacetic Acid (5-HIAA) Serotonin metabolite	High	• Increased release of serotonin from gut (possible diarrhoea-predominant IBS) •Use of SSRIs	• IgG Food Sensitivity • IP • CDSA	• Consider tryptophan-rich foods or 5-HTP & B6 (tryptophan may become deficient over time) • Rule out gut-associated food reactions (if IBS)
	Low	• Serotonin insufficiency	• Urinary Amino Acids • Vitamins & Minerals Analysis	• Tryptophan-rich foods or 5-HTP & B6 • Generally positive response seen to SSRI antidepressants

CELLULAR ENERGY AND MITOCHONDRIAL METABOLITES

GLYCOLYSIS METABOLITES	RESULT	POSSIBLE CAUSES	ADDITIONAL INVESTIGATIONS	TREATMENT CONSIDERATIONS
Lactic Acid Formed from pyruvate in anaerobic or oxygen-starved (hypoxic) conditions to allow for ongoing production of ATP	High	• Hypoxia and/or zinc deficiency • Metabolic stress (e.g. alcohol, toxic metal exposure, or anaemia) • Possibly insignificant when pyruvic acid is also high	• Iron Studies & Red Cell Zinc • Comprehensive Urine Elements Profile • FLDP	If pyruvate NOT high: • Correct hypoxia • Remove metabolic stress • Correct anaemia • Zn, CoQ10, B2, B3
	Low	Insignificant (see Pyruvic Acid)	If pyruvate also high see "Pyruvic Acid"	If pyruvate also high – see "Pyruvic Acid"
Pyruvic Acid Pyruvate feeds into the citric acid cycle & converts into acetyl CoA. Pyruvate is formed from carbohydrate via glucose or glycogen & secondarily from fats (glycerol) & glycogenic amino acids	High	• Impaired metabolism due to cofactor insufficiencies or toxic metals (As, Pb, Hg, Cd) • Muscle injury • Severe adrenal insufficiency (impaired conversion of pyruvate to alanine	• Vitamins & Minerals Analysis • Comprehensive Urine Elements Profile • Adrenal Hormone Profile	• Supplement cofactors (B1, B2, B3, B5, Mg, Lipoic acid) • Remove toxic metals • Adrenal support if required
	Low	• Deficient substrate for energy production • Impaired production from glycogen (glycogenolysis), carbohydrates (glycolysis), or proteins (gluconeogenesis)	• Urinary Amino Acids • Vitamin & Mineral Analysis • Adrenal Hormone Profile	• Gluconeogenic amino acids (e.g. L-alanine, glycine, L-serine) • B6, Mg • Correct glucose/insulin imbalances • Adrenal support if required • Consider Ca pyruvate supplementation

CELLULAR ENERGY AND MITOCHONDRIAL METABOLITES CONTINUED

CITRIC ACID CYCLE METABOLITES	RESULT	POSSIBLE CAUSES	ADDITIONAL INVESTIGATIONS	TREATMENT CONSIDERATIONS
Citric Acid or Cis-Aconitic Acid Metabolites of acetyl CoA; precursors of isocitric acid	High	• Impaired metabolism due to toxic metals (Fl, Hg, As) • Low glutathione • High amounts of dietary citric acid • Metabolic acidosis (if mildly increased cis-aconitic acid but markedly increased citric acid)	• Comprehensive Urine Elements Profile • FLDP • CDSA	• Rule out toxic metals • Glutathione
	Low	• Low or high pyruvic acid or low acetyCoA (from fatty acid oxidation)	See notes for pyruvic acid	See notes for pyruvic acid
Isocitric Acid Metabolite of cis-aconitic acid; precursor of alpha-ketoglutaric acid	High	• Impaired metabolism due to low cofactors (B3, Mg, Mn) • Aluminium toxicity	• Vitamins and Minerals Analysis • Comprehensive Urine Elements Profile • HMA	• Rule out Al toxicity • B3, Mg, Mn
	Low	• Secondary to subnormal upstream metabolites • Same causes as high cis-aconitic acid	See notes for high cis-aconitic acid	See notes for high cis-aconitic acid
Alpha-ketoglutaric Acid (AKA) Metabolite of isocitric cid, also glutamate; precursor of succinic acid	High	• Impaired metabolism due to cofactor deficiencies • Toxic metals (As, Hg, Cd, especially if pyruvate is also high) • Possible inhibition by beta-ketoglutaric acid from yeast overgrowth	• Vitamins & Minerals Analysis • Comprehensive Urine Elements Profile • HMA • CDSA	• Supplement cofactors (B1, B2, B3, B5, Mg, lipoic acid) • Remove toxic metals (As, Hg, Pb, Cd) • Address yeast overgrowth
	Low	• Secondary to subnormal upstream metabolites • Low amounts of other precursors	• Urinary Amino Acids	• Supplementation with glutamine
Succinic Acid Metabolite of alpha-ketogluturate, as well as methionine, valine & leucine; precursor of fumaric acid; also formed from bacterial action on glutamine	High	• Impaired metabolism due to low cofactors (Fe, B2) • Bacterial degradation of glutamine (e.g., dysbiosis or UTI, malabsorption &/or glutamine excess)	• Vitamins & Minerals Analysis • IP • CDSA • Urinary Amino Acids • FLDP	• Supplement Fe or B2 if low • Correct malabsorption, dysbiosis or UTI • Mucosal support
Fumaric Acid Metabolite of succinic acid, precursor of malic acid; also produced during urea cycle & formed from phenylalanine & tyrosine	High	• Impaired metabolism due to low B3 • May be secondary to high pyruvate or lactate • Yeast overgrowth	• Vitamin and Mineral Analysis • Comprehensive Urine Elements Analysis • Adrenal Hormone Profile • CDSA	• Consider B3 supplementation, unless secondary to high pyruvate or lactate • Rule out/address yeast overgrowth
Malic Acid Metabolite of fumaric acid, precursor of oxaloacetic acid; also helps NADH enter mitochondria	High	• Impaired metabolism due to low B3 • Secondary to high pyruvate • Yeast overgrowth	• Vitamins & Minerals Analysis • CDSA	• Consider B3 supplementation unless secondary to high pyruvate • Rule out/address yeast overgrowth • Sources of malic acid – used as a flavouring agent, particulary in wine. Highest levels in prunes & also found in apples, cherries, plums, apricots, peaches, cherries, rhubarb, grapes, strawberries & pears
	Very low Normal	May be secondary to low fumaric acid	• See low fumaric acid	• See low fumaric acid

CELLULAR ENERGY AND MITOCHONDRIAL METABOLITES CONTINUED

KETONE AND FATTY ACID METABOLITES	RESULT	POSSIBLE CAUSES	ADDITIONAL INVESTIGATIONS	TREATMENT CONSIDERATIONS
Adipic Acid or Suberic Acid Formed from "omega" oxidation of fats when beta-oxidation is impaired	High	• Impaired mitochondrial beta-oxidation of fats • Secondary to insufficient carnitine, B2 or acetyl CoA • Secondary to ketosis	• FLDP • Vitamins & Minerals Analysis • EFAs	• L-carnitine or acetyl-L-carnitine • B2 • Acetyl CoA precursors (cysteine, B5 Mg)
Beta-hydroxy-beta-methylglutaric Acid (HMG) Formed from acetyl CoA; precursor of cholesterol & CoQ10	High	• Citric acid cycle impairment (anaerobic glycolysis) • Carbohydrate unavailability (e.g. high protein diet, fasting, diabetes) • Inhibited utilisation of HMG (e.g. high cholesterol diet, yeast overgrowth, glucocorticoid excess statins)	• CDSA • CoQ10	Identify & correct specific underlying imbalance: • Remove yeast overgrowth • Reduce dietary cholesterol • Remove blocks in citric acid cycle
Beta-hydroxybutyric Acid (BHBA) Ketone formed from acetyl CoA	High	• Ketosis from carbohydrate unavailability (e.g fasting, diabetes strenuous exercise, ketogenic diet)	See HMG	See HMG

ORGANIC ACIDS FOR COFACTOR NEED (ORGANIC ACID/AMINO ACID BALANCE)

B COMPLEX VITAMIN MARKERS	RESULT	POSSIBLE CAUSES	ADDITIONAL INVESTIGATIONS	TREATMENT CONSIDERATIONS
a-Ketoisovaleric acid (AKIV) or a-Ketoisocaproic acid (AKIC) or a-Keto-b-Methylvaleric acid (AKBM) Metabolites of valine, leucine & isoleucine respectively	High	• Impaired metabolism due to cofactor insufficiencies or toxic metals • "Maple syrup urine disease" if markedly elevated	• Vitamins & Minerals Analysis • Comprehensive Urine Elements Profile	• Supplement cofactors: B1, B2, B3, B5, Mg, cysteine or lipoic acid • Remove toxic metals: As, Hg, Pb, Cd
	Very low Normal	• Low B6 • Low branched chain amino acids	• Vitamins & Minerals Analysis • Urinary Amino Acids	• B6 • Branched chain amino acids

ORGANIC ACIDS FOR COFACTOR NEED (ORGANIC ACID/AMINO ACID BALANCE) CONTINUED

METHYLATION COFACTOR MARKERS	RESULT	POSSIBLE CAUSES	ADDITIONAL INVESTIGATIONS	TREATMENT CONSIDERATIONS
Methylmalonic acid Metabolite of 3-HPA; precursor of succinic acid via B12	High	• Low B12 • Low glutathione (GSH is required for B12 production)	• Red blood cell B12 • FLDP	• Supplement B12 • Check pyroglutamic acid level & follow guidelines if high
Formiminoglutamate (FIGlu) Metabolite of histadine; precursor of glutamic acid via folate	High	• Impaired metabolism due to low folate or disordered folate metabolism • May be consistent with impaired methylation and/or high homocysteine • May reflect "methyl trap" due to low B12 (compromised recycling of tetrahydrofolate) • Excessive histidine supplementation	• Red blood cell folate and B12 • FLDP	• Supplement folic acid

DETOXIFICATION INDICATORS	RESULT	POSSIBLE CAUSES	ADDITIONAL INVESTIGATIONS	TREATMENT CONSIDERATIONS
Glutaric Acid Made from lysine & tryptophan via alpha-keto-adipic acid	High	• Low B2 • Inborn error of metabolism • Associated with CETP genetic polymorphism	• Red blood cell B2 • Genetic Diagnostic Testing	• Supplement B2 • Consider mitochondrial support nutrients (e.g. CoQ10)
Orotic Acid Metabolite of aspartic acid; precursor of pyrimidines	High	• Possible liver damage (alcohol), urea cycle dysfunction, ammonia excess • Impaired metabolism due to cofactor insufficiencies B3, B6, folate, Mg, glutamine, glycine, serine	• FLDP • Vitamins & Minerals Analysis • Urinary Amino Acids	• Supplement required cofactors • Liver support
Pyroglutamic Acid Intermediate in the recycling of glutathione	High	• Impaired recycling to glutathione due to cofactor insufficiencies (Mg, cysteine, glycine, glutamine) • Consistent with impaired GSH	• Vitamins & Minerals Analysis • Urinary Amino Acids	• Supplement Mg, glycine, glutamine, N-acetylcysteine (NAC)
	Low	• Low glutathione (insufficient precursors, toxicity or oxidant stress)	• FLDP • TAS	• Supplement Mg, N-acetylcysteine (NAC), glycine, glutamine • Identify & correct toxicity

ORGANIC ACIDS FOR COFACTOR NEED (ORGANIC ACID/AMINO ACID BALANCE) CONTINUED

OTHER ORGANIC ACIDS FOR COFACTOR NEED	RESULT	POSSIBLE CAUSES	ADDITIONAL INVESTIGATIONS	TREATMENT CONSIDERATIONS
Kynurenic Acid Made from tryptophan when tryptophan's metabolism to nicotinic and picolinic acids is impaired	High	• Low B6; may also indicate low vitamin B3 and/or picolinic acid	• Red blood cell B6 • Red blood cell B3	• Supplement vitamin B6 • B3 and picolinic acid
3-Hydroxypropionic Acid (3-HPA) Metabolite of propionic acid, precursor of methylmalonic acid via both biotin and Mg	High	• Low B12 (methylmalonic acid will be high) • Low biotin &/or Mg • Inborn errors of metabolism	• Red blood cell B12	• Supplement vitamin B12, biotin &/or Mg
2-Hydroxyphenylacetic Acid (2-HPAA) Metabolite of phenylaline via phenyl pyruvate	High	• Excessive phenylaline (dietary or PKU) or tyrosine • Reduced oxygenation (Fe deficiency, anaemia, pulmonary disorder) • Low tetrahydrobiopterin (BH4) - an essential cofactor for phenylaline, tyrosine, tryptophan & nitric oxide	• Urinary Amino Acids • Iron Studies	• Rule out excessive phenylaline & or tyrosine • Address oxygenation (correct anaemia, pulmonary problems, cardiac insufficiency) • Supplement vitamin C (increases BH4 levels in the body) • 5-MTHF (from folic acid) may help nitric oxide production when BH4 is low
4-Hydroxyphenylpyruvic Acid (4-HPPA) Metabolite of tyrosine, precursor of homogentisic acid)	High	• Impaired metabolism to homogenistic acid due to cofactor insufficiencies (copper, vitamin C, 0_2) • Low iron (if homogenistic acid is markedly elevated)	• Red blood cell Cu • Iron studies	• Supplement vitamin C or Cu • Improve oxygenation (correct anemia, pulmonary problems, cardiac insufficiency)
Homogentisic Acid Metabolite of 4-HPPA	High	• Impaired metabolism due to cofactor insufficiency (iron, vitamin C, 0_2) • Alkaptonuria (rare)	• Iron studies	• Supplement iron if low • Vitamin C • Improve oxygenation
Alpha-ketoadipic Acid (AKAA) Made from tryptophan & lysine via alpha-aminoadipic acid. Also a byproduct of yeast; precursor of glutaric acid	High	• May be secondary to high glutaric acid (check glutaric acid level) • Impaired metabolism due to cofactor insufficiencies • Toxic metals (As, Hg, Sb, Cd) • Secondary to yeast or fungal infection	• Vitamins & Minerals Analysis • Comprehensive Urine Elements Profile • CDSA	• Supplement cofactors (B1, B2, B3, B5, Mg, cysteine or lipoic acid) • Remove toxic metals (As, Hg, Sb, Cd) • Antifungals, anti-yeast diet • Probiotics if relevant

KEY

CDSA	Complete Digestive Stool Analysis
EFAs	Essential Fatty Acids
FLDP	Functional Liver Detoxification Profile
HMA	Hair Mineral Analysis
IP	Intestinal Permeability
TAS	Total Antioxidant Status

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NATA

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