Malabsorption and Dysbiosis Markers

Organix
SUPPORT GUIDE

Cellular Energy and Mitochondrial Markers

Neurotransmitter Metabolites

Toxin and Detoxification Markers

Oxalate Markers

Oxidative Stress Markers

GENOVA DIAGNOSTICS®

CONTENTS

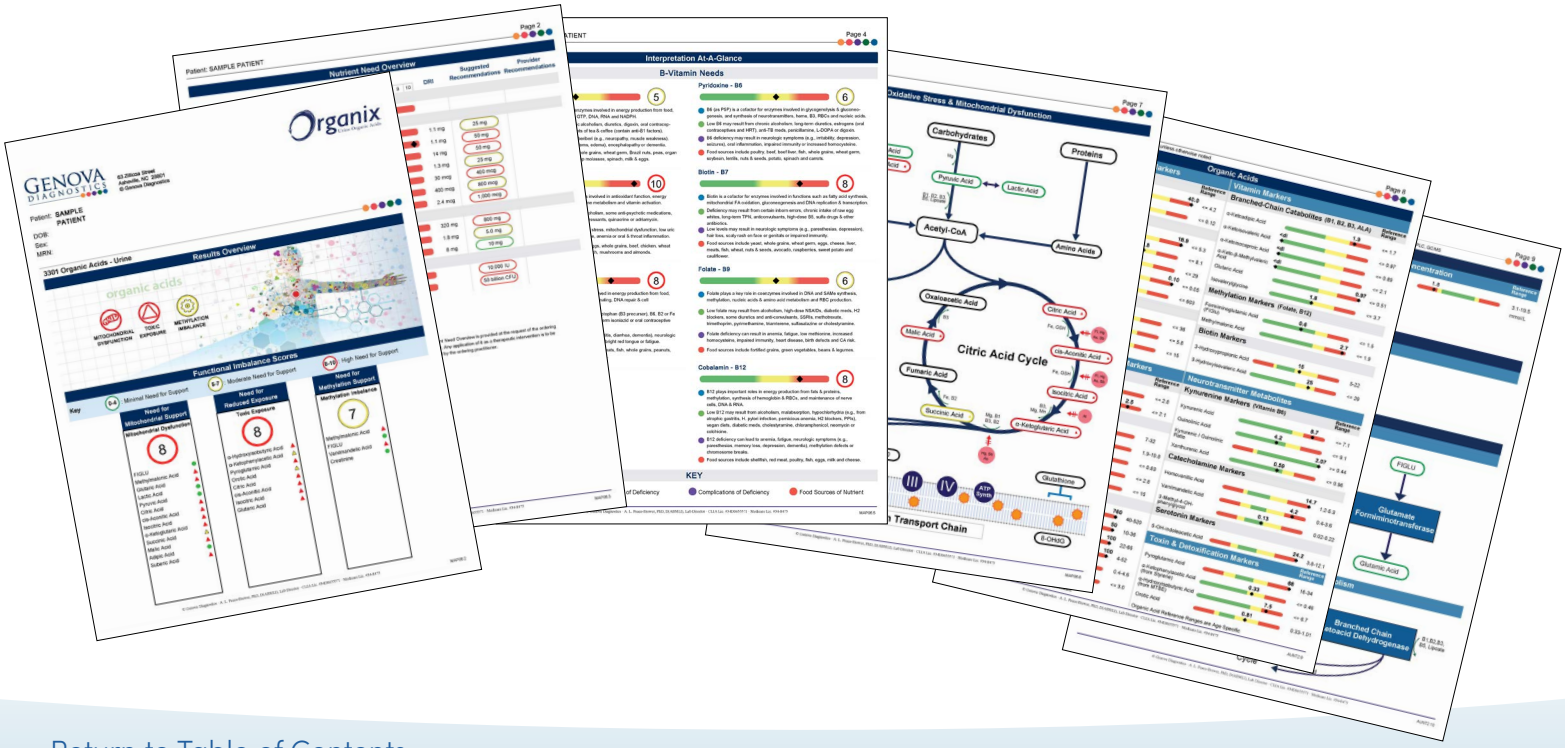
The Organix Profile is a functional nutritional assessment of urinary organic acids. Organic acids are a broad class of compounds formed during fundamental metabolic processes in the body. Metabolic reactions produce carboxylic acid compounds derived from the digestion of dietary protein, fat, and carbohydrates. The resulting organic acids are used by the body to generate cellular energy and provide many of the building blocks necessary for cell function.

What is a functional assessment?

The quantitative measurement of specific organic acids in the urine offers a functional assessment of nutrient status. Enzymes that are responsible for metabolizing organic acids are vitamin and mineral dependent. With this, elevations in organic acids can speak to a functional need for these nutrients on a cellular and biochemical level, even despite normal serum levels.[1-7] Recommendations for nutrient supplementation based on elevated organic acid results are generated using a literature-based proprietary algorithm.

The Organix Profile report categorizes results into major metabolic areas:

- Malabsorption and Dysbiosis Markers
- Cellular Energy and Mitochondrial Markers
- Vitamin Markers
- Neurotransmitter Metabolites
- Toxin and Detoxification Markers
- Oxalate Markers
- Oxidative Stress Markers



MALABSORPTION AND DYSBIOSIS MARKERS

The compounds of bacterial and yeast origin are byproducts of bacterial and fungal activity in the GI tract.[8,9] Many of these bacterial metabolites can result from the fermentation of dietary phenols and flavonoids. Therefore, in the absence of dysbiosis, high levels of these phenolic metabolites can reflect a healthy intake of antioxidant-rich foods.[10]

Malabsorption and dysbiosis markers are usually evaluated as a group for overall trends rather than individually. When multiple markers are elevated, a stool test may provide further information regarding dysbiosis or other GI dysfunction.

MALABSORPTION MARKERS

Indolacetic Acid

Indoleacetic acid (IAA), or indole-3-acetate, is produced by the bacterial fermentation of the amino acid tryptophan.[11] IAA can be formed from several common gut microbes such as Clostridia species, Escherichia coli, and Saccharomyces species.[12-14]

High Levels:

Elevated IAA in the urine suggests incomplete digestion and absorption of tryptophan in the intestine, allowing colonic bacteria to convert tryptophan to IAA. Elevations may also reflect an overgrowth of bacteria acting on tryptophan.

Clinical Associations:

IAA elevations and altered tryptophan metabolism have been associated with systemic inflammation, psychologic and cognitive function, autism, and chronic diseases such as cardiovascular disease.[15-17] Hartnup's disease, a genetically-linked dysfunction in the transport of free-form amino acids across the intestinal mucosa, can cause severe elevations of urinary IAA.[18]

Phenylacetic Acid

Phenylacetic acid (PAA) is produced by the bacterial metabolism of phenylalanine. Several bacterial strains are known to produce PAA, including Bacteroidetes and Clostridium species.[9]

High Levels:

Elevated PAA in the urine suggests incomplete digestion and absorption of phenylalanine in the intestine, allowing colonic bacteria to convert phenylalanine to PAA. Elevations may also reflect an overgrowth of bacteria, which convert phenylalanine to PAA.[9] Dietary polyphenols may also contribute to PAA elevation.[19]

Clinical Associations:

There is a clinical correlation between decreased urinary PAA and depressive symptoms.[20-22]

DYSBIOSIS MARKERS

Dihydroxyphenylpropionic Acid (DHPPA)

Dihydroxyphenylpropionic acid (DHPPA), also known as 3,4 dihydroxyphenylpropionic acid, is a byproduct of the fermentation of dietary phenols by several bacteria, including some Clostridia spp. and others. Although once thought to identify the presence of specific dysbiotic bacteria, ongoing research suggests there are several bacterial species potentially involved.

High Levels:

Elevated DHPPA levels may reflect dietary intake of polyphenols. They may also suggest dysbiosis or bacterial overgrowth, increasing dietary polyphenol conversion.

3-Hydroxyphenylacetic Acid and 4-Hydroxyphenylacetic Acid

3-Hydroxyphenylacetic acid and 4-Hydroxy-phenylacetic acid are produced by the bacterial fermentation of amino acids, much like IAA.[9,12]

High Levels:

Amino acids that are not digested and absorbed can be metabolized by bacteria in the gut to form these organic acids. Clinicians often use these markers to reflect protein malabsorption or dysbiosis. However, dietary intake of polyphenols such as wine, grapes, green tea, and grape seed extract can also contribute to increased levels.[23-26]

Clinical Associations:

These organic acid byproducts may exhibit free radical scavenging properties, which lends to further support for use of these organic acid markers as an indication of antioxidant consumption.[27-29]

Much like IAA and PAA, there is an inverse correlation between these markers and depressive symptoms.[20-22]

Benzoic Acid and Hippuric Acid

Benzoic acid and hippuric acid are formed from the bacterial metabolism of polyphenols. Urinary benzoic acid may also come from ingestion of food preservatives such as sodium benzoate. Hippuric acid is made when sodium benzoate is conjugated with glycine.[30]

High Levels:

Increased metabolism by imbalanced gut flora may increase levels. Additionally, dietary intake of polyphenols or food preservatives can also increase levels of these organic acids.

Clinical Associations:

Elevated levels of urinary hippuric acid have been associated with several clinical conditions that may be linked to dysbiosis.[31,32] For example, elevated urinary hippurate was associated with an increase in blood pressure, likely due to the direct effect of gut-microbial products on blood pressure. However, in other studies low hippuric acid excretion has also been attributed to dysbiosis, which supports its use as a biomarker for general microbial alterations.[33]

YEAST/FUNGAL DYSBIOSIS MARKERS

D-Arabinitol

D-Arabinitol is a sugar alcohol produced specifically by Candida spp.[34,35] The majority of the published literature shows a correlation between serum or urinary D-arabinitol levels and systemic invasive candidiasis in immunocompromised individuals.[35] Several articles have suggested that D-arabinitol is a useful marker for diagnosis of candidiasis in this patient population as well as potentially be a prognostic indicator in a broad range of conditions. While discrete literature evaluating the clinical application to GI candidiasis has not been conducted, D-arabinitol has been used as a functional indicator of relevant clinical Candida overgrowth owing to the existing body of literature. Given that only certain Candida species produce D-arabinitol, it may serve as an indirect assessment for subclinical candidiasis.

High Levels:

Elevated D-arabinitol may indicate Candida overgrowth. Probiotics were shown to reduce urinary D-arabinitol levels in children with autism.[36] A direct evaluation via stool testing should be considered as an appropriate follow-up to elevated D-arabinitol and a clinical suspicion of GI candidiasis.

Citramalic Acid and Tartaric Acid

Citramalic acid and tartaric acid are yeast metabolites that are also influenced by dietary intake of fruits, wine, and sugars.[37-41]

High Levels:

Though often used by clinicians to gain insight into yeast overgrowth, it should be noted that fruit intake can influence levels. High levels may simply reflect a high dietary fruit intake. A high intake of sugars feeds gastrointestinal yeast, which can promote yeast overgrowth. When these markers are elevated, and dietary influences have been ruled out, a stool test may be warranted to evaluate the presence of yeast in the GI tract.

As noted, the malabsorption and dysbiosis marker levels can also be influenced by common foods, supplements, or preservatives; correlation with the patient's dietary intake is encouraged. [25,26,37-40,42-61]

Urinary Metabolite	Common Dietary Sources
Indoleacetic acid	High tryptophan intake, green/black tea
Phenylacetic acid	Wine/grapes
Dihydroxyphenylpropionic acid	Whole grains, chocolate, coffee, green/black tea, olives/ olive oil, citrus fruits (animal studies)
3-Hydroxyphenylacetic acid & 4-Hydroxyphenlyacetic acid	Wine/grapes, cranberries, green/black tea, berries, orange juice, grape seed extract
Benzoic acid/Hippuric acid	Orange juice, elderberry, huckleberry, food preservative, berries, other flavonoids
Citramalic acid	Apples, cranberries, sugar beets
Tartaric acid	Wine/grapes, chocolate, food additive/preservative

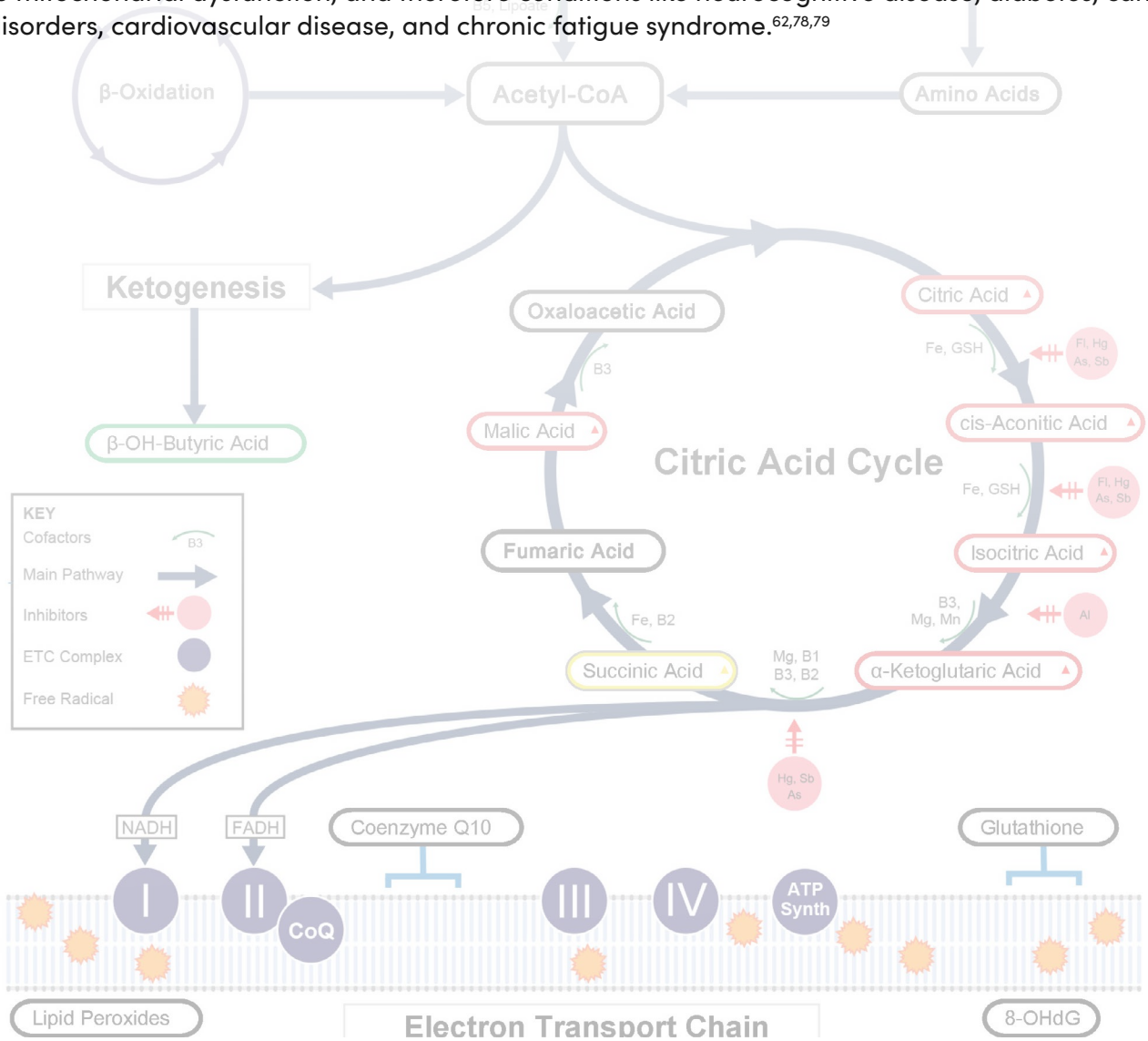
CELLULAR ENERGY AND MITOCHONDRIAL MARKERS

The cellular energy and mitochondrial metabolite markers reflect the body's ability to process dietary macronutrients to feed the Krebs cycle (Citric Acid Cycle) and subsequent energy production. Abnormalities throughout the Krebs cycle, as well as in fatty acid oxidation, glycolysis, and protein metabolism may reflect enzymatic dysfunction and functional nutrient insufficiencies.

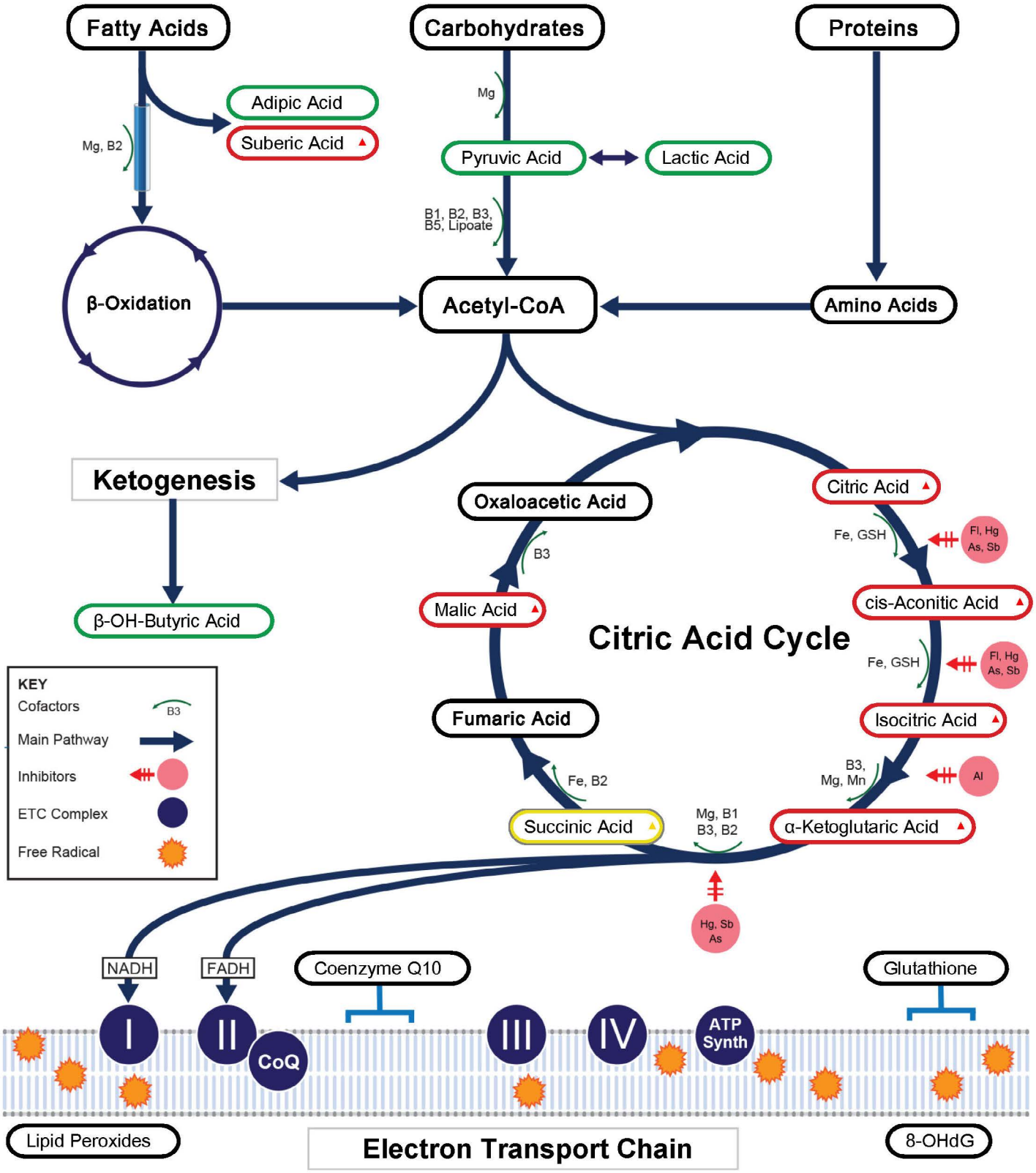
Various factors can alter mitochondrial enzymes such as nutrient and vitamin deficiency, toxins, genetic polymorphisms, and underlying disease. The enzymes catalyzing the transformation of these Krebs Cycle intermediates require a variety of nutrient cofactors, such as iron, niacin, magnesium, manganese, thiamin, riboflavin, pantothenic acid, and lipoic acid.[62-72] Toxic exposures and metals including, but not limited to, mercury, arsenic, and lead can interfere with mitochondrial function.[62,63,73]

Abnormal urinary excretion of these organic acids may provide a window into various clinical conditions, as well as potential therapeutic targets to correct mitochondrial dysfunction.[74-77]

Mitochondrial dysfunction has been associated with several diseases. The presence of enzymatic antagonists within the Krebs cycle, or lack of specific nutrient cofactors for these enzymes, may contribute to mitochondrial dysfunction, and therefore conditions like neurocognitive disease, diabetes, cancer, mood disorders, cardiovascular disease, and chronic fatigue syndrome.[62,78,79]



Oxidative Stress & Mitochondrial Dysfunction



FATTY ACID METABOLISM

Adipic Acid and Suberic Acid

Dietary fatty acids are metabolized into fuel sources using beta-oxidation. Fatty acid conversion into Acetyl-CoA requires transport across the mitochondrial membrane via the carnitine shuttle.[80] When beta-oxidation is impaired, fats are metabolized using an alternate pathway called omega-oxidation. Omega-oxidation results in elevated levels of dicarboxylic acids such as **adipic acid and suberic acid.**

Impaired beta-oxidation occurs in carnitine deficiency or enzymatic dysfunction due to lack of nutrient cofactors.[81,82] Vitamin B_2 and magnesium play a role in optimizing beta-oxidation.[83-88]

High Levels:

Elevated levels of adipic and suberic acid may reflect insufficient carnitine or lack of nutrient cofactors for proper beta-oxidation.[86,88,89]

Clinical Associations:

Increased omega-oxidation metabolites can be seen in ketosis, insulin resistance, diabetes, fasting, or low carbohydrate intake. Elevations of suberic and adipic acid can lead to further mitochondrial dysfunction by injuring the cell membrane and producing free-radical damage. [80,90,91]

CARBOHYDRATE METABOLISM

Lactic Acid and Pyruvic Acid

Lactic acid and pyruvic acid are byproducts of glycolysis. Carbohydrates, which contain glucose, are broken down through glycolysis to form pyruvate and two ATP molecules. Pyruvate can also be generated through the catabolism of various amino acids, including alanine, serine, cysteine, glycine, tryptophan and threonine.[92] Magnesium is an important cofactor for a number of glycolytic enzymes necessary to produce pyruvate.[93] Optimally, pyruvic acid is oxidized to form Acetyl-Co-A to be used aerobically via the Krebs Cycle to produce energy. In an anaerobic state, lactic acid is formed instead.

High Levels:

An elevated pyruvic acid would reflect an inability to form Acetyl-Co-A to feed the Krebs Cycle. Pyruvate uses the pyruvate dehydrogenase complex to form Acetyl-Co-A. A different enzyme, pyruvate carboxylase, is responsible for the conversion of pyruvate into oxaloacetate. Nutrient cofactors, such as vitamin-B_1, B_2, B_3, B_7, magnesium, and lipoate are needed to support the pyruvate dehydrogenase and pyruvate carboxylase enzymes.[62,64,94-97] Insufficiency in any of these nutrients can raise levels of pyruvic acid. In vitro studies have shown there are some toxins that can also affect these enzymes, such as antimony, mercury, and cadmium.[98,99] Pyruvate elevations can also be seen with a high intake of carbohydrates, as well as rare genetic forms of pyruvate dehydrogenase deficiency.[92]

Any anerobic or low oxygen state, including pulmonary disease, anemia, sleep apnea, among others can lead to elevations of lactic acid. Elevations of urinary lactic acid can also be the result of strenuous exercise, insulin resistance, dysglycemia, and alcohol dependence.[100-104] Zinc is an essential component in the enzymes which regulate glycolysis, such as lactate dehydrogenase (LDH). LDH converts lactate back to pyruvate in the liver via the Cori cycle.[92,105,106] Elevations may be seen with a functional need for zinc.

Low Levels:

Low levels of pyruvic acid might imply low carbohydrate intake, lack of magnesium cofactors for glycolytic enzymes, or lack of insulin.[93,107]

Clinical Associations:

Pyruvate metabolism abnormalities play important roles in cancer, heart failure, and neurodegeneration.[92]

α-Hydroxybutyric Acid

α-Hydroxybutyric acid (2-Hydroxybuturic acid [2-HB]) is a marker that relates to oxidative stress. 2-HB is an organic acid produced from α-ketobutyrate via the enzymes lactate dehydrogenase (LDH) or α-hydroxybutyrate dehydrogenase (HBDH). These enzymes are catalyzed by NADH. Oxidative stress creates an imbalance in NADH/NAD ratios, which leads directly to the production of 2-HB. Being that 2-HB's precursor α-ketobutyrate is a byproduct in the glutathione (GSH) synthesis pathway, an increased demand for GSH may ultimately result in increased 2-HB. Increased oxidative stress associated with insulin resistance increases the rate of hepatic glutathione synthesis. Plasma 2-HB is highly associated with insulin resistance and may be an effective biomarker for prediabetes.[108,109] A study on type 2 diabetics showed that GSH infusion restored the NADH/NAD balance and resulted in improvement of insulin sensitivity and beta cell function.[110]

High levels:

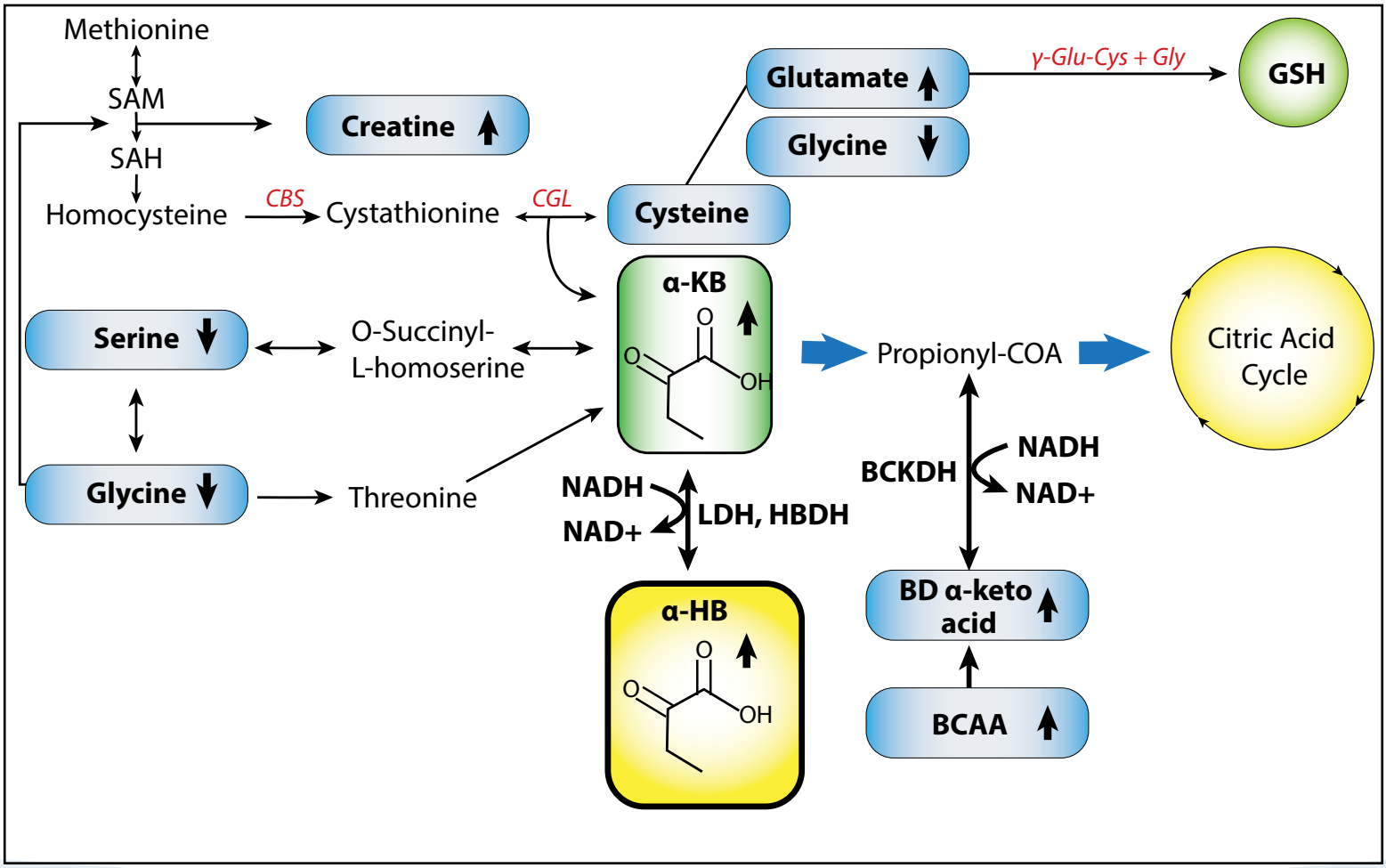
Higher circulating levels of 2-HB are associated with insulin resistance and prediabetes.[108,109]

Elevated α-hydroxybutyric acid may be seen with oxidative stress. Evaluate oxidative stress markers such as lipid peroxides and 8-hydroxydeoxyguanosine (8-OHdG) and ensure adequate antioxidant intake and glutathione status.

Hard physical exercise can result in lactic acidosis and accumulation of 2-HB.[111]

Low levels:

There are no known clinical associations with low levels of α-hydroxybutyric acid.



β-Hydroxybutyric Acid

β-Hydroxybutyrate is a ketone body. During periods of fasting, exercise, and metabolic disease, ketone bodies are generated in the liver and become an energy source instead of glucose.

High Levels:

Low carbohydrate intake and ketogenic diets may increase urinary levels of beta-hydroxybutyrate. The severity of ketosis is not accurately reflected by the degree of ketonuria. Only a small amount of the body burden of ketones is excreted in the urine; most must be oxidized in extrahepatic tissues using and depleting available oxygen.

Clinical Associations:

In the absence of dietary influence, elevations are sometimes used as an early indicator of diabetes, impaired glucose tolerance, and worsening glycemic control.[112-114]

β-Hydroxy-β-Methylglutaric Acid

β-Hydroxy-β-Methylglutaric acid (HMG) is a precursor to cholesterol and coenzyme Q10 (CoQ10) synthesis. It is a product of hydroxymethylglutaryl-coenzyme A (HMGCoA). HMGCoA- reductase is a rate limiting enzyme in cholesterol production. Medications that interfere with this enzyme may result in elevated HMG and subsequent low levels of cholesterol and CoQ10.[115] CoQ10 is important for cellular energy production in the mitochondrial respiratory chain.

High Levels:

Urinary β-hydroxy-β-methylglutaric acid is often elevated in patients taking statin medications and red yeast rice. CoQ10 supplementation has been shown to help ameliorate statin-associated myopathies.[116]

There are also inborn errors of metabolism which can elevate HMG. These affect the HMGCoA reductase enzyme with varying degrees of onset and clinical manifestations such as neurodevelopment disorders and cardiomyopathy.[117]

ENERGY METABOLISM (KREBS CYCLE, CITRIC ACID CYCLE)

Citric Acid, cis-Aconitic Acid and Isocitric Acid

A two-carbon group from Acetyl-CoA is transferred to oxaloacetate to form citric acid. Citric acid is then converted to isocitric acid through a cis-aconitic intermediate using the enzyme aconitase. Aconitase is an iron-sulfate protein that controls iron homeostasis.[118]

High Levels:

Iron deficiencies and overload at the systemic or cellular levels can negatively impact the aconitase enzyme and overall mitochondrial health and function.[119] Due diligence with iron assessment is recommended when levels of these organic acids are abnormal. Glutathione may also be an important means of modulating aconitase activity during oxidative stress.[120] Various toxins may influence mitochondrial enzymes and contribute to mitochondrial dysfunction, such as fluoride, aluminum, mercury, arsenic, and tin.[121-124]

Low Levels:

Low levels of these analytes may reflect insufficient precursors, or suboptimal glycolysis or fatty acid oxidation.

α-Ketoglutaric Acid

Isocitric acid is converted to α-ketoglutaric acid using the enzyme isocitrate dehydrogenase. α-ketoglutarate is a rate-determining intermediate in the Krebs Cycle[125] and provides an important source of glutamine and glutamate that stimulates protein synthesis and bone tissue formation, inhibits protein degradation in muscle, and constitutes an important metabolic fuel for cells of the gastrointestinal tract.[125] α-ketoglutaric acid is then converted to Succinyl CoA using the enzyme α-ketoglutarate dehydrogenase. This enzyme complex is very similar to the pyruvate dehydrogenase complex with similar nutrient cofactor needs.

High Levels:

Elevations can be seen with nutrient cofactor deficiencies needed for the enzymatic conversion of α-ketoglutarate such as vitamin B_3, zinc, magnesium, and manganese. Higher levels are seen in mitochondrial oxidative phosphorylation disorders and mitochondrial dysfunction.[126] Genetic abnormalities with the enzyme itself can also limit conversion of α-ketoglutarate, causing elevations.[127]

Low Levels:

Low levels of α-ketoglutarate may reflect lack of precursors higher up from enzymatic dysfunction due to lack of nutritional cofactors, genetic defects, or toxin exposures.

Succinic Acid

Succinyl CoA becomes succinic acid using succinyl CoA synthetase. This reaction produces NADH which directly provides electrons for the electron transport chain or respiratory chain.[127]

Succinic acid requires the enzyme succinate dehydrogenase to become fumarate. This enzyme is iron-based and requires vitamin B_2 to support flavin adenine dinucleotide (FAD) as a redox coenzyme.[128] Succinate dehydrogenase plays a critical role in mitochondrial metabolism. Impairment of this enzyme's activity has been linked to a variety of diseases such as cancer and neurodegenerative diseases.[129]

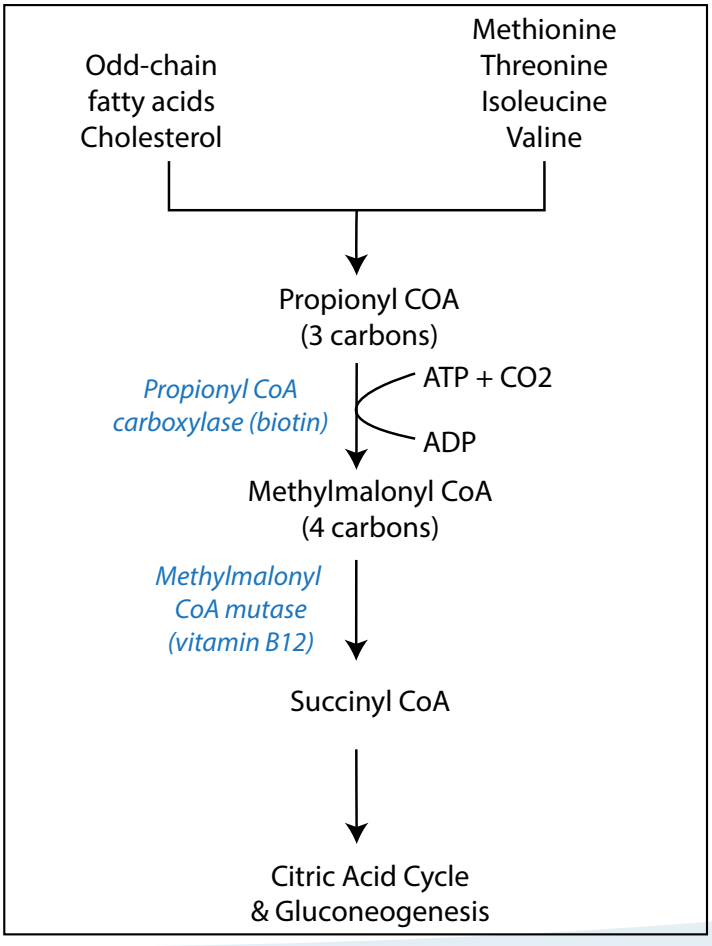
High Levels:

Elevated levels of mitochondrial succinate are seen in nutritional cofactor insufficiencies of succinate dehydrogenase or primary enzymatic defects. Succinate can also be formed peripherally by microbes in the GI tract. The major producers of succinate in the gut are bacteria belonging to the Bacteroidetes phylum. However, it is typically detected at low rates in the gut lumen because it is rapidly converted to propionate, a major short chain fatty acid.[130]

Several studies indicate that elevations in both succinate and fumarate play a role in oncogenesis by causing DNA damage and hypermethylation.[131]

Low Levels:

Low levels of succinic acid can be seen with poor dietary intake or absorption of branched-chain amino acids. Branched-chain amino acids are catabolized to acetyl-CoA or succinyl-CoA to feed the Krebs cycle. Additionally, vitamin B_{12} deficiency can induce a defect in the conversion of methylmalonyl-CoA to succinyl-CoA at the distal end of the valine and isoleucine pathways which can then decrease succinyl-CoA.[132]



Malic Acid

Fumaric acid uses the fumarase enzyme to become **malic acid**. Malate dehydrogenase catalyzes the conversion of malic acid into oxaloacetate. Two forms of this enzyme exist in eukaryotes. One operates within the mitochondria to contribute to the Krebs Cycle; the other is in the cytosol where it participates in the malate/aspartate shuttle.[133] Riboflavin is an important cofactor for this enzyme and overall mitochondrial energy production and cellular function.[134]

At the end of each Krebs cycle, the four-carbon oxaloacetate has been regenerated, and the cycle continues.

High Levels:

High levels of malic acid can be seen if its dehydrogenation to oxaloacetic acid is reduced from lack of vitamin B_3 as NAD. Malic acid also has many food sources, such as vegetables, as well as fruits like apples and pears. It is also an additive and preservative in beverages, throat lozenges, and syrups.[135]

VITAMIN MARKERS

There are groups of organic acids commonly used to assess the status of specific B-vitamins. By measuring organic acids that are known to rely on specific nutrients for enzymatic metabolism, clinicians can gain insight into functional vitamin needs.

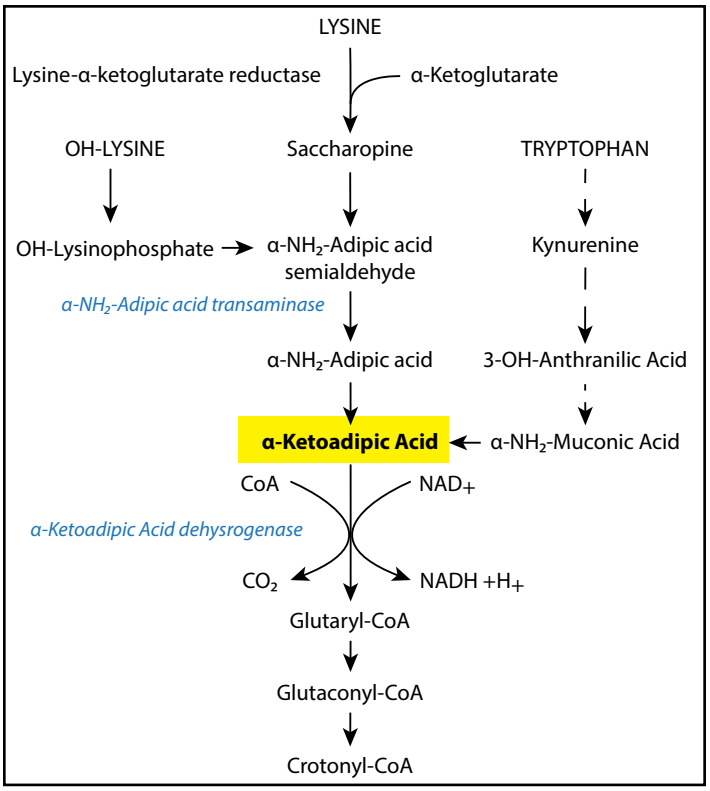
BRANCHED-CHAIN CATABOLITES

α-Ketoadipic Acid

α-Ketoadipic acid (AKAA; 2-Oxoadipic acid, 2-Ketoadipic acid) is an organic acid formed from α-aminoadipic acid (which originates with lysine) and also from α-aminomuconic acid (derived from tryptophan).[136] AKAA metabolizes to form glutaryl-CoA via oxidative decarboxylation. The cofactors needed in this step are Coenzyme A, NAD, thiamine pyrophosphate (vitamin B_1), lipoic acid, and vitamin B_2.[189]

High Levels:

Elevations in urinary AKAA may reflect enzymatic dysfunction due to nutritional cofactor needs.[72] Mitochondrial oxidative phosphorylation disorders are also associated with higher levels of AKAA.[126]



α-Ketoisovaleric Acid, α-Ketoisocaproic Acid, and α-Keto-β-Methylvaleric Acid

Of the essential amino acids, there are three branched-chain amino acids (leucine, isoleucine, and valine). Unlike most amino acids, the initial step of branched-chain amino acid (BCAA) metabolism does not take place in the liver. They increase rapidly in systemic circulation after protein intake and are readily available for use. Skeletal muscle is where most of the initial catabolism of BCAA takes place using branched-chain aminotransferase enzymes to form α-ketoacids, which are then released from muscles back into the blood to be further metabolized, mainly in the liver.[137] BCAA act as substrates for protein synthesis, energy production, neurotransmitter production, glucose metabolism, immune response, and many other beneficial metabolic processes.[137]

- **α-Ketoisovaleric Acid (AKIV)** is produced from the essential amino acid valine. It then metabolizes to become succinyl Co-A. AKIV is glucogenic.
- **α-Ketoisocaproic Acid (AKIC)** is produced from leucine and further metabolizes to form acetyl-CoA and acetoacetate. AKIC is ketogenic.
- **α-Keto-β-Methylvaleric Acid (AKBM)** comes from isoleucine, and further metabolizes to form acetyl-CoA and succinyl-CoA. AKBM is therefore both glycogenic and ketogenic.

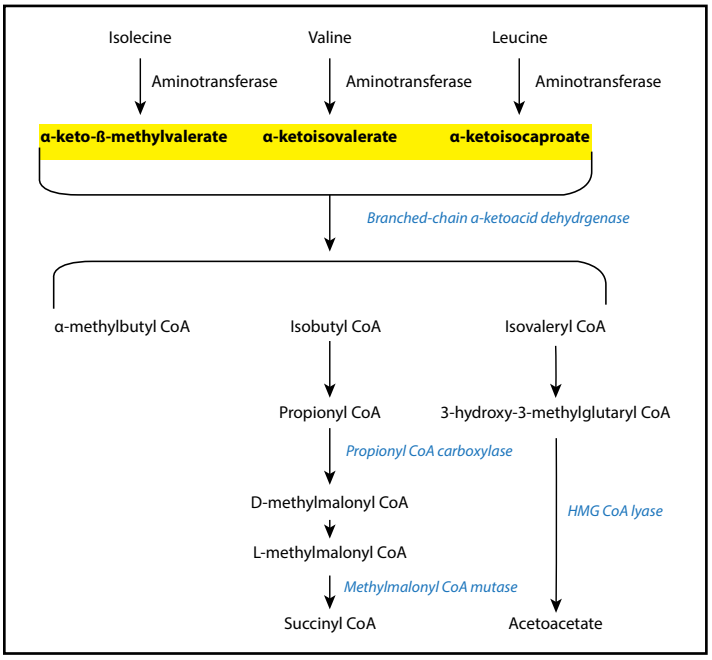
These α-ketoacids then require an enzyme complex called branched-chain α-keto acid dehydrogenase (BCKD) for further metabolism.[138] This enzyme complex requires multiple vitamin cofactors, such as vitamin B_1, B_2, B_3, B_5, and lipoic acid.[72,139-141]

High Levels:

Urinary elevations of these ketoacids can be the result of functional need for the vitamin cofactors to support BCKD.[72,141]

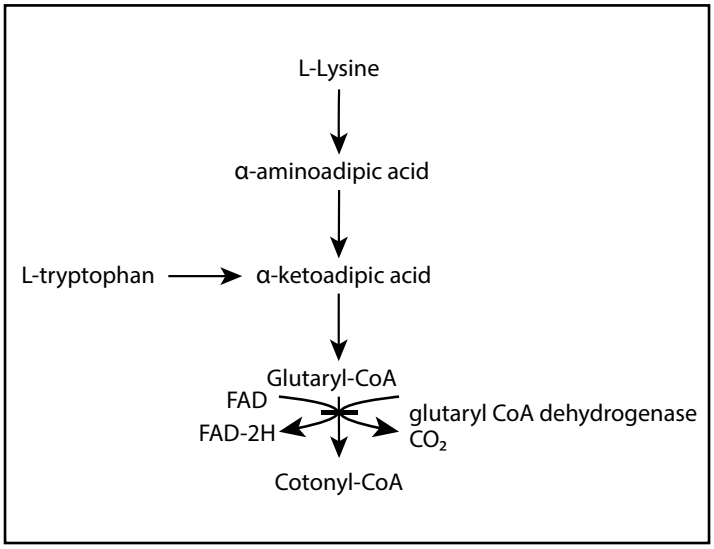
A genetic defect of the α-keto acid dehydrogenase enzyme complex is responsible for maple syrup urine disease, which results in very elevated levels of AKIC, AKIV, AKMB.[137]

Elevated plasma levels of branched-chain amino acids have been associated with insulin resistance as a result of decreased catabolism for energy production. This metabolic disturbance may be compounded by further nutrient deficiencies limiting the activity of the BCKD enzyme.[142,143]



Glutaric Acid

Glutaric acid is formed from the essential amino acids lysine and tryptophan through the intermediaries of α-ketoadipic acid and glutaryl-CoA. Glutaryl-CoA is further metabolized to glutaconyl- and crotonyl-CoA by an enzyme called glutaryl-CoA dehydrogenase. This enzyme requires riboflavin (vitamin B_2) as a cofactor.



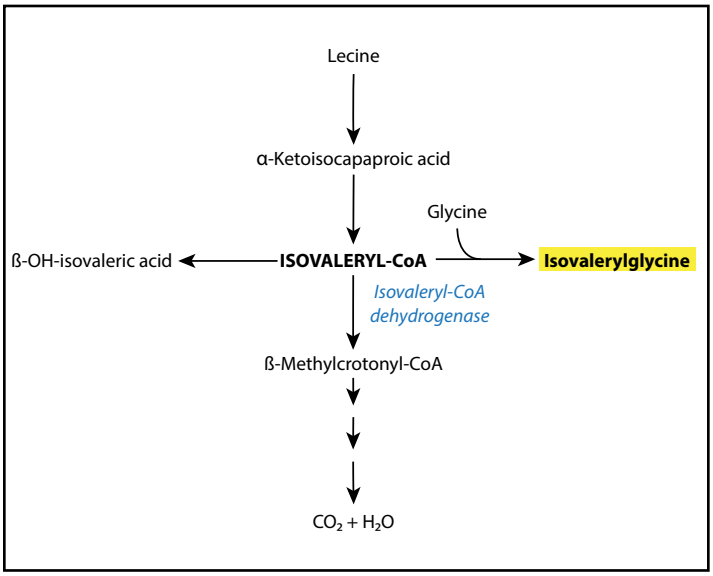
High Levels:

Elevations of urinary glutaric acid may reflect enzymatic insufficiency requiring vitamin B_2 or mitochondrial electron transport dysfunction.

Deficiencies of the enzyme glutaryl-CoA dehydrogenase, and multiple acyl-CoA dehydrogenase deficiency (MADD), are well-studied inborn errors of metabolism which result in significant glutaric aciduria. However, milder forms of this rare mitochondrial disorder exist and can result in adult-onset presentations. Late-onset forms can present as atypical beta-oxidation disorders with exercise intolerance, muscle weakness, and CNS dysfunction.[144,145] In these cases, riboflavin, carnitine, and CoQ10 have been used therapeutically.[145-147]

Isovalerylglycine

Isovalerylglycine is produced from leucine catabolism. It is further metabolized via isovaleryl-CoA dehydrogenase. This enzyme requires vitamin B_2 as a cofactor.[148,149]



High Levels:

Acyl-CoA dehydrogenase enzymes are not only involved in branched-chain amino acid metabolism, but also beta-oxidation of fatty acids.[89] Enzymatic dysfunction and elevations in isovalerylglycine are seen when there is a functional nutrient cofactor need and in certain inborn errors of metabolism. However, elevations of isovalerylglycine are also seen in problematic mitochondrial fatty acid beta-oxidation.[150,151]

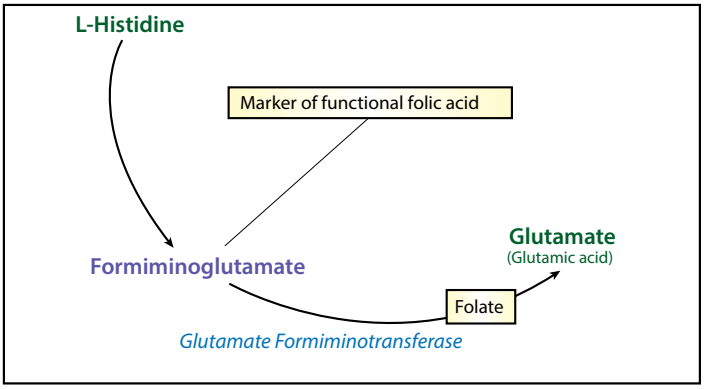
Carnitine, glycine, vitamin B_2, and antioxidants have been used therapeutically to treat abnormal levels of isovalerylglycine.[152-154]

There is an association between elevated isovalerylglycine and anorexia nervosa. The mechanism is believed to be due to poor thyroid conversion of vitamin B_2 into active FAD, which normalized in some patients after a refeeding program.[155]

METHYLATION MARKERS

Formiminoglutamic Acid

Formiminoglutamic Acid (FIGlu) is an intermediary organic acid in the conversion of the amino acid histidine to glutamic acid. This enzymatic conversion requires tetrahydrofolic acid.[156]



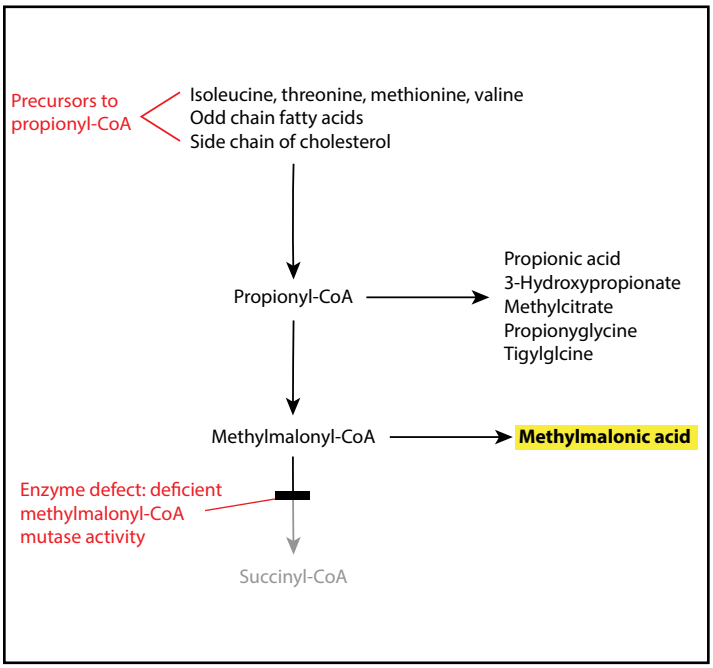
High Levels:

FIGlu elevations in urine have been used as a marker for folate deficiency dating back to the 1950's.[2,157] In addition to folate deficiency, elevated urinary FIGlu may also reflect vitamin B_{12} status since folate recycling requires vitamin B_{12} as a cofactor and both are critical steps in the methylation cycle.[158]

There are multiple clinical associations with elevated urinary FIGlu, including acute and chronic alcohol use, pregnancy, and oral contraceptive use.[159-162]

Methylmalonic Acid

Methylmalonic acid (MMA) is formed from propionyl-CoA via methylmalonyl-CoA. Major dietary sources of propionyl-CoA include valine, isoleucine, methionine, threonine, and odd chain fatty acids.[163] Methylmalonyl-CoA is converted to succinyl-CoA to feed the Krebs cycle via the enzyme methylmalonyl-CoA mutase. This enzyme is very vitamin B_{12} dependent. In B_{12} deficiency, methylmalonyl-CoA is hydrolyzed to methylmalonic acid.[164]



High Levels:

The most common cause of MMA in the urine is vitamin B_{12} deficiency. However, a rare deficiency of the methylmalonyl-CoA mutase enzyme is another. Any underlying condition which results in vitamin B_{12} deficiency should be considered, such as reduced intestinal absorption, chronic alcoholism, or strict vegan diets.[164]

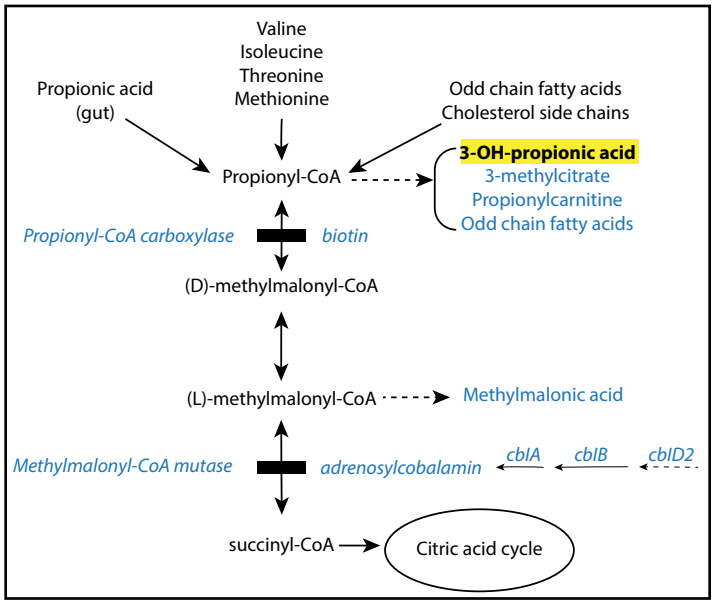
Methylmalonic acid, as a functional biomarker, is considered a more sensitive index of B_{12} status when compared to serum B_{12}.[165-170] Urinary MMA correlates with serum MMA, making the simple urine test a useful screening tool for B_{12}deficiency in at-risk populations, such as the elderly or patients with GI dysfunction.[167,171]

Vitamin B_{12}therapy lowers MMA. Monitoring this metabolite may help prevent the consequences of B_{12}deficiency, such as cognitive decline and neuropathy.[169,172,173]

BIOTIN MARKERS

3-Hydroxypropionic Acid

3-Hydroxypropionic acid (3-HPA) is a major urinary metabolite of propionic acid. Propionic acid is derived from dietary branched-chain amino acids, odd-chain fatty acids, and can be produced in the gut by bacterial fermentation of fiber. The biotin-dependent enzyme propionyl CoA carboxylase is responsible for metabolizing propionic acid to methylmalonyl CoA, which is subsequently isomerized to succinyl CoA. Decreased activity of this enzyme shunts propionyl CoA into alternative pathways which form 3-HPA.



High Levels:

As noted, biotin is a cofactor in the propionyl-CoA-carboxylase enzyme.[174] Reduced activity of this enzyme due to functional biotin deficiency can cause elevations of the urinary organic acid 3-hydroxypropionic acid. However, in isolation, it may not be as sensitive a marker as 3-hydroxyisovaleric acid to diagnose marginal biotin deficiency.[175]

There are inborn errors of metabolism associated with this organic acid. When the propionyl-CoA-carboxylase enzyme is deficient, the result is propionic acidemia and elevated urinary 3-hydroxypropionic acid. Some isolated case reports reveal the possibility of a later onset in this enzyme deficiency.[176]

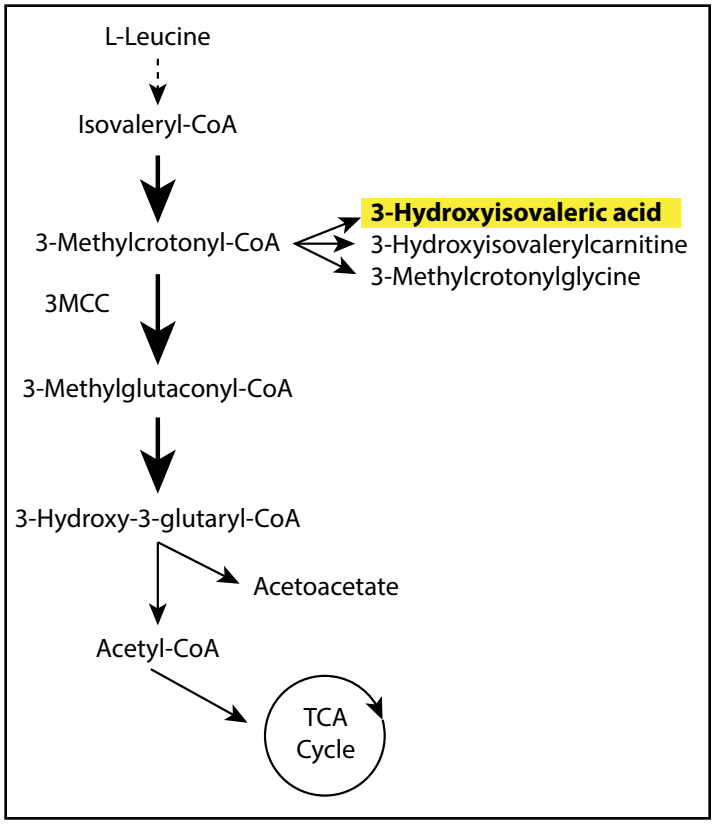
Because of the relationship between propionyl-CoA and methylmalonyl CoA, 3-HPA elevations have also been observed in inborn errors causing methylmalonic acidemia.[177]

Low Levels:

Low levels of urinary 3-hydroxypropionic acid may be seen with decreased amino acid and fatty acid precursors from maldigestion, malabsorption or impaired fatty acid oxidation. Because the propionic acid precursor is also made in the GI tract, decreased fiber intake or antibiotic use can result in lower urinary 3-hydroxypropionic acid as well.[178] In fact, low protein diets and antibiotics are used acutely to treat inborn errors of metabolism which cause propionic acidemia.[179]

3-Hydroxyisovaleric Acid

3-Hydroxyisovaleric acid (3-HIA) is formed from the metabolism of the branched-chain amino acid leucine. Methylcrotonyl-CoA carboxylase catalyzes an essential step in this pathway and is biotin dependent. Reduced activity of this enzyme leads to an alternate pathway of metabolism resulting in 3-hydroxyisovaleric acid.



High Levels:

The urinary excretion of 3-HIA has been shown to be an early and sensitive indicator for marginal biotin deficiency.[175]

Elevated levels of 3-HIA in pregnant women reflect reduced or marginal biotin status.[180] Smoking and anticonvulsant medication can also increase this metabolite as a reflection of accelerated biotin metabolism and therefore marginal deficiency.[181,182]

NEUROTRANSMITTER METABOLITES

These organic acid compounds are down-stream metabolites of neurotransmitter synthesis and degradation.[73] Many of the neurotransmitter metabolites in urine primarily reflect peripheral metabolism, as in the enteric nervous system. Elevations in these organic acids can represent altered neurotransmitter metabolism. This can be due to enzymatic nutrient cofactor needs, or genetic predispositions. Toxins, chronic illness, and stress can also influence results.[183,184]

KYNURENINE MARKERS

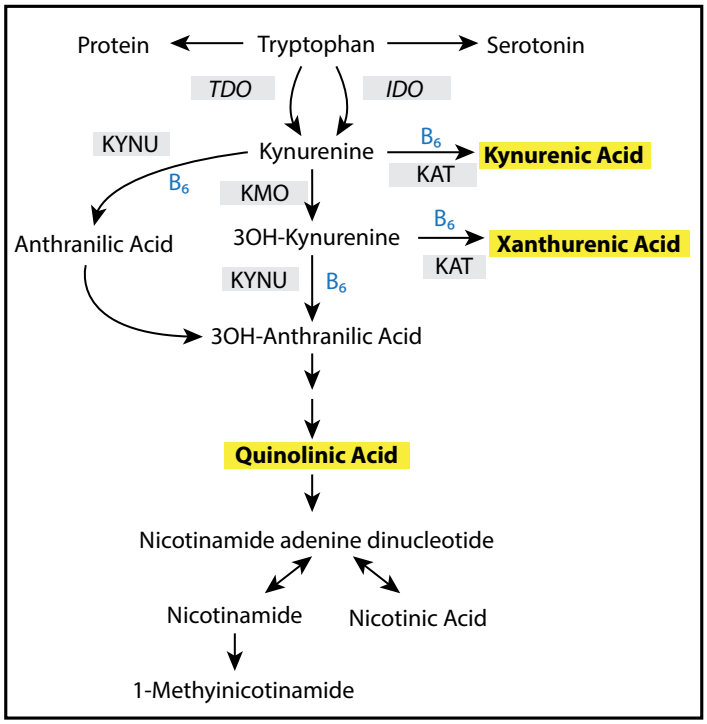
Kynurenic Acid and Quinolinic Acid

Kynurenic acid and Quinolinic acid are tryptophan metabolites formed through the kynurenine pathway. Tryptophan is the amino acid precursor to serotonin; its major route for catabolism is the kynurenine pathway. Important products of the kynurenine pathway include xanthurenic acid and kynurenic acid, which can further metabolize into quinolinic acid.

The historical importance of this pathway has mainly been as a source of the coenzyme NAD+, which is important for all redox reactions in the mitochondria. However, it is now understood that kynurenic and quinolinic acid have physiologic implications. This alternate pathway is upregulated in response to inflammation and stress, which can lead to deficient serotonin production.[185]

Kynurenic acid has shown some neuroprotective properties in the brain, since it can stimulate NMDA receptors. However, its importance on the periphery is still not fully elucidated. Some studies outline anti-inflammatory, analgesic, antiatherogenic, antioxidative, and hepatoprotective properties to peripheral kynurenic acid.[186-188] The correlation to levels of urinary excretion needs further study.

Quinolinic acid, in and of itself, can be inflammatory and neurotoxic.



High Levels:

The kynurenine pathway is particularly sensitive to vitamin B_6 deficiency, which can elevate urinary kynurenic acid (and xanthurenic acid).[189-191] Vitamin B_2 is also an important vitamin cofactor in the enzymatic conversion reactions within the pathway.[192] Because a major-end product of this pathway is also NAD+, elevations in kynurenic and quinolinic acid may also reflect vitamin B_3 need.

Oral contraceptives and estrogen therapy have been implicated in increasing quinolinic acid excretion both from altered tryptophan metabolism directly, as well as vitamin B_6 insufficiency.[193]

Many of the intermediates and products in the kynurenine pathway are implicated in numerous neurological and psychiatric diseases, such as depression. Alterations in this pathway also have some connection to the development of insulin resistance, diabetes, tumor growth and proliferation, and inflammatory myopathies.[194-198]

Kynurenic/Quinolinic Acid Ratio

Because of the specific inflammatory component of quinolinic acid, as well as the potentially protective role of kynurenic acid peripherally (as outlined above), laboratories measure the ratio of kynurenic acid to quinolinic acid. This ratio can act as a measure of disturbed kynurenine pathway metabolism. It suggests that tryptophan is catabolized via the kynurenine pathway, rather than the serotonin pathway. There is literature regarding a low kynurenic/quinolinic ratio association with neurotoxicity and major depressive disorder.[199,200]

Xanthurenic Acid

Xanthurenic acid is produced as part of the kynurenine pathway of tryptophan catabolism, along with kynurenic and quinolinic acid, as previously outlined.

High Levels:

Because this pathway is heavily dependent on vitamin B_6, elevations of xanthurenic acid can reflect a functional need for vitamin B_6.[201] Kynurenine pathway metabolites may also become elevated when there are needs for vitamin B_6.[202,203]

Elevations in urinary xanthurenic acid are seen with increased intake of tryptophan, and in high estrogen states. Pregnancy and oral contraceptive use is associated with elevated levels of urinary xanthurenic acid where a functional nutrient need for B-vitamins is pronounced.[5,204]

Abnormalities in the kynurenine pathway have been associated with many clinical conditions including immune suppression, cancer, and inflammatory conditions.[201]

Administration of vitamin B_6 can decrease xanthurenic acid excretion.[205,206]

CATECHOLAMINE MARKERS

Homovanillic Acid

Homovanillic acid (HVA), or 3-Methoxy-4-Hydroxyphenylacetic acid, is a metabolite of dopamine. Although dopamine is an important brain neurotransmitter, a substantial amount of dopamine is produced in the GI tract.[207]

In neurotransmitter production, dopamine is formed from phenylalanine and tyrosine using several enzymes which require nutrient cofactors such as iron, tetrahydrobiopterin, and pyridoxal phosphate.[208] Dopamine then becomes norepinephrine using the enzyme dopamine beta-hydroxylase, which requires copper and ascorbic acid for optimal activity.[209]

Dopamine can be metabolized to homovanillic acid using both monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT).[207] MAO requires a vitamin B_2 (FAD) cofactor, while the COMT enzyme requires SAM, magnesium, and vitamin B_6.[210,211]

High Levels:

Elevations of homovanillic acid can be seen with lack of vitamin cofactors for enzymes within the metabolism of dopamine or the production of norepinephrine. Quercetin supplementation can elevate plasma HVA and perhaps urinary excretion.[212] Dietary flavanols, such as tomatoes, onions, and tea are also known to elevate urinary HVA.[213]

Like VMA, urinary HVA is elevated in conditions such as neuroblastoma and neural crest tumors.[214,215] And, since dopamine regulates emotional and motivational behavior, changes in dopamine levels, and subsequent HVA levels, have been studied in the overall stress response, PTSD, mood disorders, and autism.[216-221]

Low Levels:

Low levels of urinary HVA imply deficient production of dopamine due to decreased amino acid precursors or lack of vitamin cofactors throughout the production cycle. It may also reflect impaired methylation of dopamine to HVA. Low dopamine turnover and low HVA levels are seen in some mood disorders and as an effect of various antidepressants.[222,223]

Vanilmandelic Acid

Vanilmandelic acid (VMA) is formed in the liver by the oxidation of 3-methoxy-4-hydroxyphenylglycol.[224] As a downstream metabolite of tyrosine-derived catecholamines, levels of VMA can reflect the overall synthesis and metabolism of catecholamines.[225] Whether norepinephrine or epinephrine are metabolized into VMA or 3-methoxy-4-OH-phenylglycol (MHPG) depends on the presence and specificity of various available aldehyde reductase and dehydrogenase enzymes.[226]

High Levels:

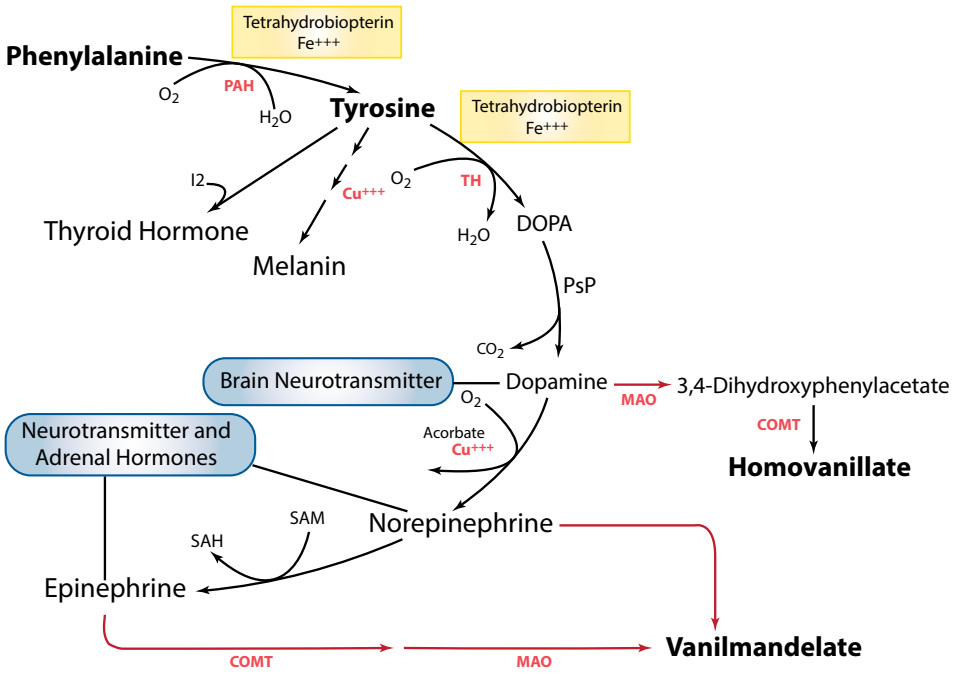
Centrally-acting medications, such as antidepressants and stimulants used for ADHD can elevate overall catecholamines and therefore urinary metabolites.[227,228] Urinary levels have been shown to correlate with generalized anxiety disorder.[229] VMA is sometimes used in the work up of pheochromocytoma, neural crest tumors, renovascular hypertension, and neuroblastoma in the right clinical context.[230-233] Elevations in catecholamine urinary metabolites have been shown to correlate with the physiologic stress response, exercise, and PTSD.[234-237]

Low Levels:

Low levels of catecholamine metabolites can reflect insufficient amino acid precursors for neurotransmitter production, nutrient cofactor insufficiencies for enzymatic conversion, and genetic abnormalities in enzyme function. Methylation is required for neurotransmitter creation and metabolism. Thus, methylation defects or lack of methylation cofactors may contribute to abnormal levels. Copper is an important cofactor for dopamine beta-hydroxylase, which forms norepinephrine from dopamine. In copper deficiency, norepinephrine formation can be impaired and potentially lower VMA levels.

Manganese released into the synaptic cleft may influence synaptic neurotransmission. Dietary manganese deficiency, which may enhance susceptibility to epileptic functions, appears to affect manganese homeostasis in the brain, probably followed by alteration of neural activity.[238]

There are studies which evaluate the neurotoxicity of manganese. Elevated levels of VMA and HVA have been seen in manganese toxicity from occupational exposure which induces a CNS condition similar to Parkinson's disease.[239,240]



3-Methyl-4-Hydroxy-Phenylglycol

3-Methyl-4-OH-Phenylglycol (MHPG) is a byproduct of the central nervous system's norepinephrine metabolism. MHPG metabolizes to vanilmandelic acid (VMA) in the liver using the enzymes alcohol dehydrogenase and aldehyde dehydrogenase. Urinary MHPG was originally thought to represent CNS sympathetic output, but is now known to be principally derived from peripheral neuronal NE metabolism.[241]

MHPG has been widely studied as a marker to predict response to medications used in mood disorders or as a biomarker to monitor pharmacotherapies.[242-245]

High Levels:

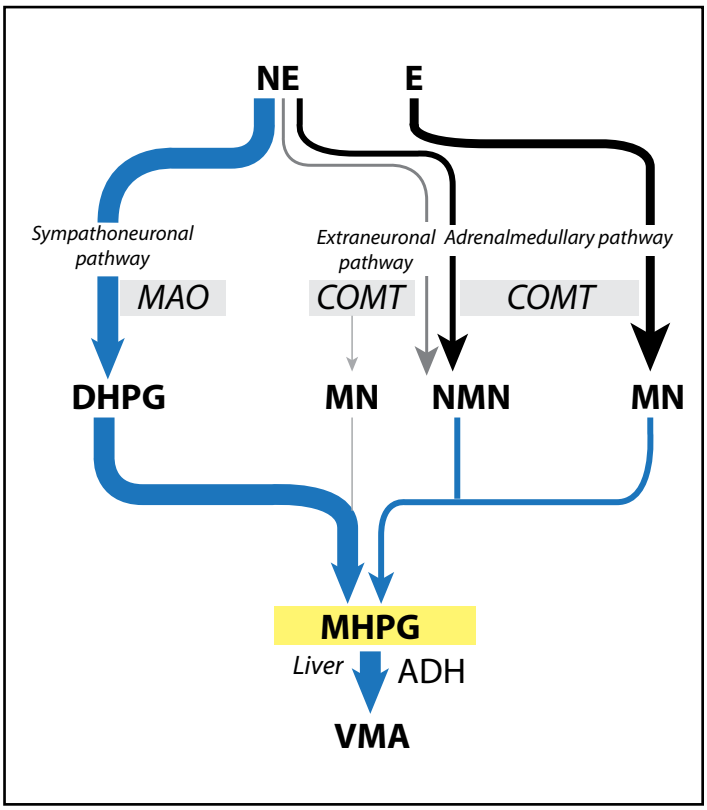
The role of hepatic alcohol and aldehyde dehydrogenase explains the clinical observations that ethanol consumption decreases the excretion of VMA, while increasing MHPG.[246,247]

Because norepinephrine is involved in the pathophysiology of hot flashes in postmenopausal women, MHPG levels have been studied in this patient population.[248,249] Interestingly, folic acid was found to interact with receptors causing subjective improvement in symptoms.[250]

Sleep deprivation can act as a stimulus to the peripheral sympathetic nervous system, which can influence central nervous noradrenergic neurotransmitter levels and elevate MHPG.[251] As a central nervous system metabolite, levels can correlate with central catecholaminergic disturbances, as in anxiety and seizures.[252,253] Elevated MHPG levels have also been associated with the stress response.[254]

Pheochromocytomas are rare, mostly benign tumors of the adrenal medulla which can secrete catecholamines causing a wide array of sympathetic symptoms. These tumors contain MAO and COMT. They can therefore produce MHPG. However, because peripheral sympathetic nerves can also contribute to high MHPG, using MHPG for diagnosis of pheochromocytoma limited. VMA is also not very sensitive for diagnosis of pheochromocytoma because it can be made in the liver from MHPG.

Although neither organic acid is diagnostic of pheochromocytoma, it is possible to see elevations of these analytes in the disease.[255]



Low Levels:

Since catecholamines are made from dopamine, low levels of the MHPG metabolite can result from low levels of dopamine, dopamine amino acid precursors, nutrient enzymatic cofactor deficiencies in dopamine metabolism, and overall methylation defects.

Low levels of MHPG have been correlated to mood and behavioral disorders, anorexia, and ADHD.[256-258]

SEROTONIN MARKERS

5-Hydroxyindolacetic Acid

5-Hydroxyindolacetic acid (5-HIAA) is a downstream metabolite of serotonin, which is formed from the essential amino acid tryptophan. Most blood serotonin and urinary 5-HIAA comes from serotonin formation outside of the CNS, primarily the liver and enterochromaffin cells in the gastrointestinal tract. Serotonin is further metabolized by monoamine oxidase to become 5-HIAA.[259]

High Levels:

Elevations, as well as low levels of urinary 5-HIAA, can reflect underlying intestinal microbial balance.[260] Serotonin produced by intestinal enterochromaffin cells is necessary for GI motility.[261] Because of this, antidepressants such as tricyclics and serotonin selective reuptake inhibitors have been used in treating IBS.[262] Enterochromaffin cells and their serotonin signaling are influenced by overall inflammatory responses to bacteria in the GI tract.

Diets rich in tryptophan and serotonin have been shown to increase urinary 5-HIAA. Bananas, plantains, kiwi, pineapple, nuts, and tomatoes, among other foods, can cause elevations of this urinary metabolite.[259]

The excretion of 5-HIAA seems to vary among individuals who supplement with 5-hydroxytryptophan (5HTP).[259]

Carcinoid tumors are well-differentiated neuroendocrine tumors derived from the enterochromaffin cells in the GI tract and lung. These tumors secrete vasoactive peptides, especially serotonin which causes flushing and diarrhea. Urinary 5-HIAA levels are elevated in patients with carcinoid syndromes.[263]

It should be noted that certain medications may cause false abnormalities in urinary 5-HIAA, and/or interfere with electrochemical detection on chromatography. These include guaifenesin, aspirin, and acetaminophen.[259,264-267] Many medications can alter serotonin levels and therefore impact urinary 5-HIAA levels. Due diligence is recommended to investigate medications as a possible etiology of abnormal levels.[259,267,268]

Abnormalities, both high and low, in urinary 5-HIAA can be caused by methylation defects, as well as vitamin and mineral nutrient cofactor deficiencies.

Low Levels:

Decreased 5-HIAA levels can reflect low tryptophan intake, or malabsorption/maldigestion of tryptophan. Medications, like MAO inhibitors, decrease serotonin turnover and decrease 5-HIAA.[269] Low levels of urinary 5-HIAA have been observed in cardiovascular disease, metabolic syndrome, IBS patients, and those with mood disorders and migraines.[270-272]

TOXIN AND DETOXIFICATION MARKERS

These urinary markers can reflect exposure to environmental toxins, or up-regulation of detoxification pathways in response to exposures. When these markers are elevated, the recommendation is to identify, minimize, and remove exposures. Clinicians may consider the use of antioxidants and nutritional support of detoxification pathways. For further information on environmental toxins, the following websites may be helpful:

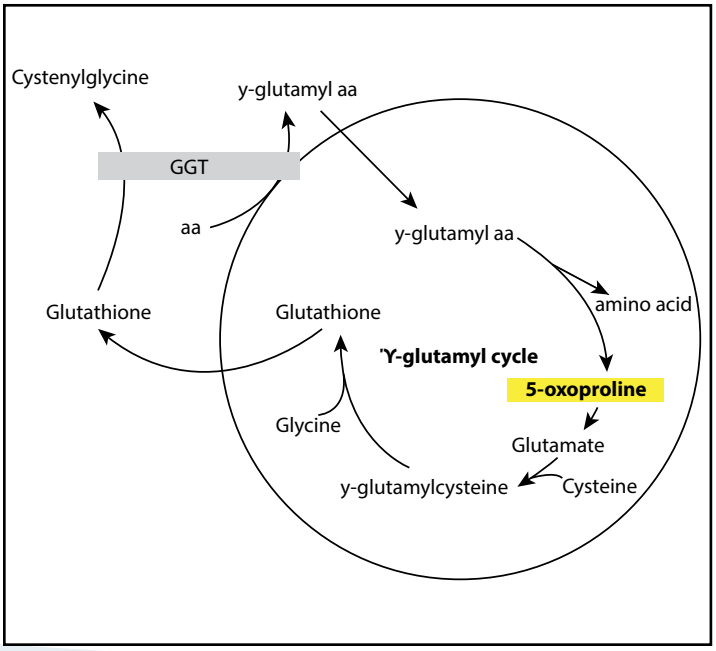
Environmental Working Group: https://www.ewg.org/
Agency for Toxic Substances and Disease Registry: https://www.atsdr.cdc.gov/

Pyroglutamic Acid

Pyroglutamic acid (5-Oxoproline) is produced and utilized in the gamma-glutamyl cycle. This cycle is needed to assist in the production and recycling of glutathione (GSH), a powerful antioxidant.

Glutathione is a tripeptide, consisting of glutamate, cysteine, and glycine. Using the gamma-glutamyl cycle, GSH is divided into cysteinyl glycine and a gamma-glutamyl molecule which attaches to another amino acid for transport across a membrane or into a cell. Gamma-glutamyl transferase then splits off that attached amino acid, and the glutamate becomes pyroglutamic acid (5-oxoproline). Cysteinyl glycine is also broken down and transported into the cell as cysteine and glycine.

The entire GSH molecule needs to be reformed intracellularly from pyroglutamic acid by recombining cysteine, glycine, and glutamic acid using GSH synthetase.[273,274] This enzymatic reformation requires cofactors such as ATP and magnesium.[275]



High Levels:

Elevations in pyroglutamic acid can reflect lack of precursors (glycine, cysteine, glutamine) or nutrient cofactors for GSH recycling (magnesium). Most specifically, pyroglutamic acid has been proposed as a measure of glycine availability.[276,277]

Oxidative stress, in general, can upregulate the detoxification pathways and result in elevated pyroglutamic aciduria.[278,279] Significant toxic exposures, such as medication toxicities, can deplete ATP, interrupting GSH recycling and causing elevations in pyroglutamic acid. In rare cases, this can result in metabolic acidosis.[280-282]

Deficiency in glutathione synthetase has also been described in literature as presenting with pyroglutamic aciduria.[283]

Low Levels:

Because pyroglutamic acid formation is dependent on glutathione entering the gamma-glutamyl cycle, an insufficient amount of GSH or its precursors and necessary cofactors can result in low pyroglutamic acid.

α-Ketophenylacetic acid (from Styrene)

α-Ketophenylacetic acid, also known as phenylglyoxylic acid (PGA), is a urinary metabolite of styrene, toluene, xylenes, and ethylbenzene. It acts as a urinary marker of recent exposure via inhalation, contact, oral, and others.[284] The biologic half-life of styrene in humans is fairly short and corresponds with the disappearance of PGA from the urine.[285,286]

Styrene is widely used for synthesis of polymers such as plastics, rubbers, and surface coating. It is also used in the pharmaceutical industry. Styrene is commonly applied in the manufacturing of paints, pigments, and glues. Co-exposure to other solvents, like toluene and ethyl acetate is common in workplaces where styrene is a concern.[287] Since toluene and xylene are components of unleaded gasoline, workers at gas stations are at potential risk of exposure, as well as the general population.[288]

Styrene exposure may interfere with peripheral metabolism of thyroid hormones by inhibiting conversion of T4 to T3.[289] It may also affect DNA repair capacity and damage.[290] There are also clinical associations with insulin resistance, oxidative stress, and inflammation.[291]

α-Hydroxyisobutyric Acid (from MTBE)

α-Hydroxyisobutyric acid is a major urinary metabolite of the industrial solvent methyl tert-butyl ether (MTBE). MTBE was a gasoline additive discontinued in the early 2000's used to reduce automobile emissions. Due to significant leakage from underground storage tanks, ongoing exposure to MTBE exists in soil and ground water. There is also data available on levels of MTBE in ambient air.[292] Urinary α-hydroxyisobutryic acid is a marker of recent MTBE exposure.[293,294]

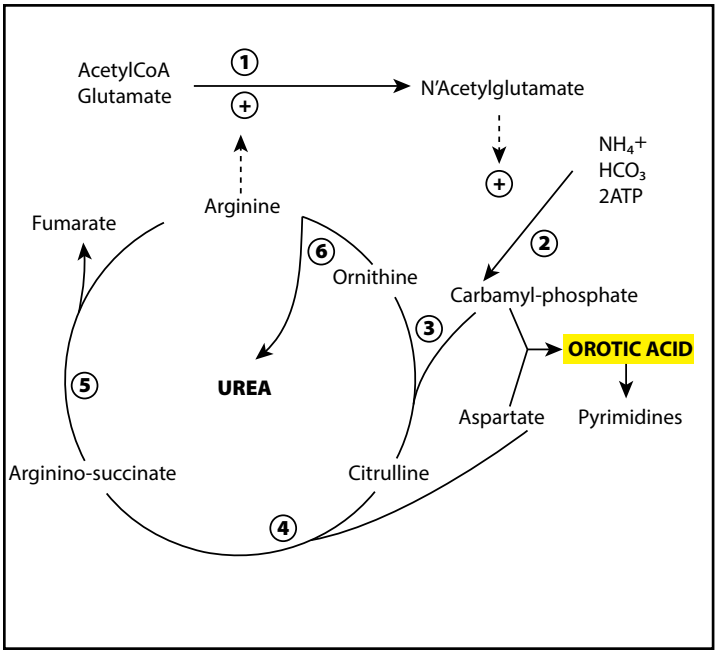
Although, MTBE was initially designated as "non-carcinogenic", recent studies suggest some interesting clinical associations. Exposure to MTBE has been linked to type 2 diabetes as a result of disrupted zinc homeostasis and glucose tolerance.[295] There are also clinical associations with autism, DNA oxidative damage, and methylation defects.[296-299] Studies on cancer, reproductive abnormalities, nonalcoholic fatty liver, and neurotoxicity have been either negative or inconclusive thus far.[300-302]

Orotic Acid

Orotic acid is an organic acid which serves as an intermediate in nucleotide synthesis and is linked to arginine metabolism as a urea cycle marker for nitrogen balance.[303]

It is formed from aspartic acid and carbamoyl phosphate.[304] Carbamoyl phosphate plays an important role in the body because it brings nitrogen into the urea cycle for detoxification and disposal. Carbamoyl phosphate enters the urea cycle to react with ornithine to form citrulline. When ammonia levels significantly increase or the liver's capacity for detoxifying ammonia into urea decreases, carbamoyl phosphate leaves the mitochondria and instead enters the pyrimidine pathway. This stimulates orotic acid biosynthesis and subsequent urinary excretion.[305]

Orotic acid can also be found in the diet. The richest dietary sources include cow's milk and dairy products. Most urinary orotic acid is synthesized in the body as an intermediate in nucleotide synthesis.[306] Although it is also linked with abnormalities in arginine metabolism as a urea cycle marker for nitrogen balance, orotic acid plays no direct role in the urea cycle, yet is increased in urea cycle disorders.[303] Hyperammonemia is characteristic of all urea cycle disorders; orotic acid is only elevated in a few.[303]



High Levels:

Elevations of orotic acid are seen in with hereditary deficiencies of urea-cycle enzymes, ammonia overload as seen in high protein diets, and abnormalities in arginine metabolism.[303,305]

Any hepatotoxin or underlying liver condition can affect ammonia metabolism and increase orotic acid. There are studies that show elevations in orotic acid after drinking alcohol, which then declined with abstinence.[307]

Orotic acid excretion is increased by allopurinol and 6-azauridine seemingly related to action of these drugs on pyrimidine synthesis.[308]

There are animal studies which show a link between orotic aciduria and hypertension. Orotic acid can induce endothelial dysfunction by contributing to vascular and systemic insulin resistance which impacts nitric oxide production, leading to hypertension.[309] Random case studies also show an association between megaloblastic anemia and orotic aciduria as a result of hereditary defects in pyrimidine synthesis.[310]

Low Levels:

There is no clinical significance to low levels of urinary orotic acid.

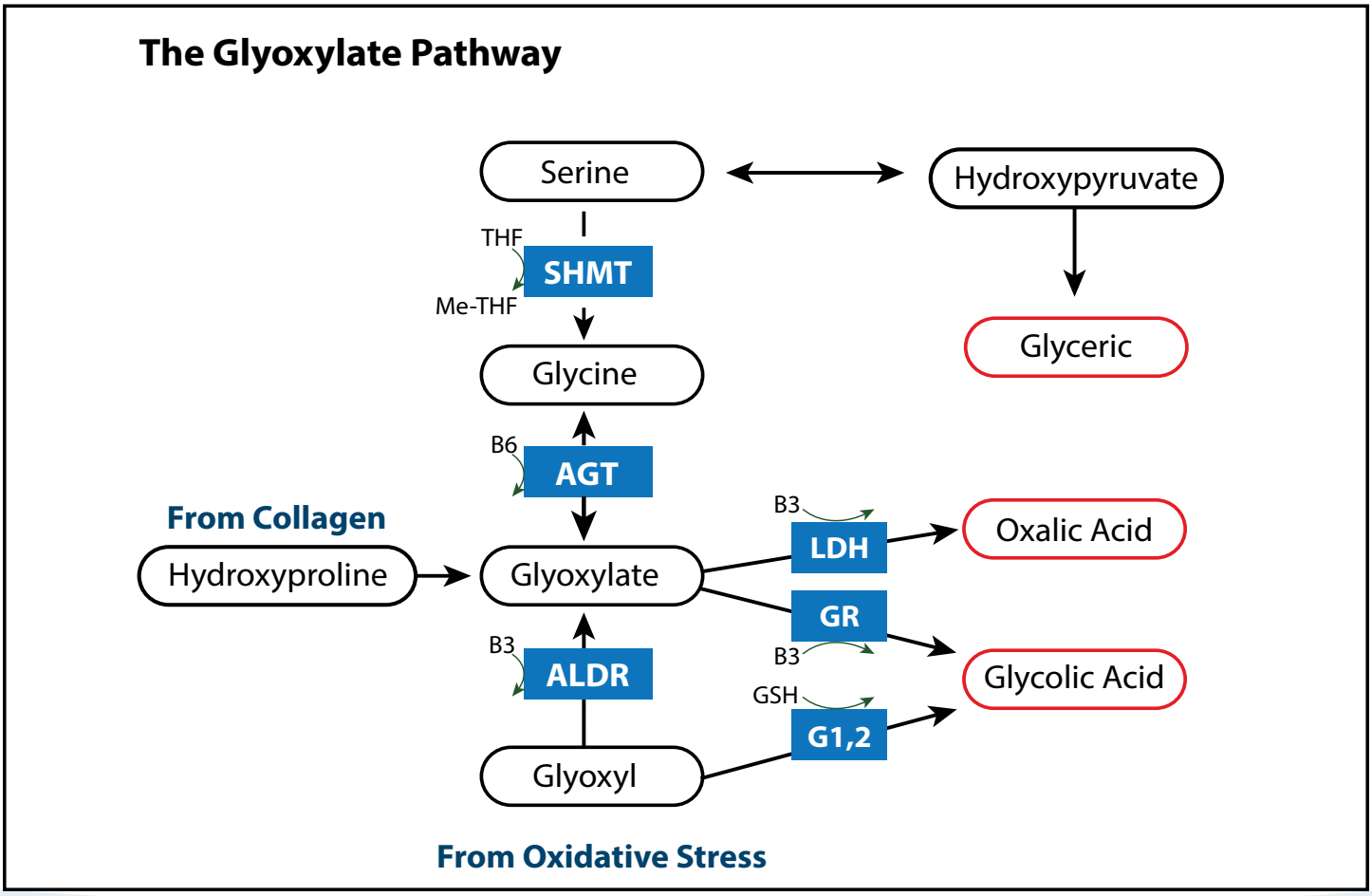
OXALATE MARKERS

The oxalate markers are a collection of 3 organic acids that are metabolic end-products of the glyoxylate pathway (see diagram). They consist of glyceric acid, glycolic acid, and oxalic acid. As a collection of biomarkers, the oxalate markers may provide insight into abnormal metabolism in the glyoxylate pathway which ultimately could result in higher levels of oxalic acid.

The oxalates may have specific clinical relevance to patients suffering from recurrent kidney stones, as high levels of oxalic acid are a strong risk factor in kidney stone development.[311] Also, there is evidence to support the notion that increased levels of oxidative stress and/or metabolic dysfunction may ultimately contribute to dysfunctional oxalate metabolism leading to higher excretion of oxalic acid.[312]

Higher systemic levels of oxalic acid are found in inborn errors of disease which contribute to a condition known as oxalosis where calcium-oxalate crystals can be deposited in systemic tissues.[313] This most commonly occurs in the kidney, however there is evidence of deposition in other tissues to a lesser degree. The accumulation of calcium oxalate deposits in the absence of hereditary disease is termed "dystrophic oxalosis" and is not well studied in the literature. However, calcium oxalate deposits have been reported in atherosclerotic plaques, lymph nodes, myocardium, ocular tissues, as well as various endocrine organs in a small number of studies.[312]

As will be discussed, there are many factors than can influence the glyoxylate pathway, ultimately predisposing individuals to higher oxalic acid levels. It is known that this puts a person at risk for urolithiasis, however what is not known is the degree to which oxalic acid levels may contribute to dystrophic oxalosis. To date, there is no evidence to support any connection between the fungal mycobiome and disordered oxalate metabolism. Therefore, utilization of these markers to suggest fungal overgrowth should be discouraged.



Glyceric Acid

Glyceric acid is an organic acid that stems from the catabolism of the amino acid serine.[314] Severe elevations in glyceric acid are an indication of a rare inborn error of metabolism known as glyceric aciduria. One form of glyceric aciduria is the result of a defect in the enzyme glycerate kinase which removes glyceric acid from the system.[313] While many case studies have linked this disorder with severe developmental abnormalities,[315] there is some debate as to whether glycerate kinase deficiency is the cause or rather a confounding variable.[316]

Another glyceric aciduria is referred to as primary hyperoxaluria type 2 (PH2). This rare genetic condition results in excessive production of oxalates in the system in the form of oxalic acid. Over time, systemic deposition of oxalates in body tissues can occur which is a process known as oxalosis. This disease is characterized by urolithiasis, nephrocalcinosis, and deposition of oxalates in other body tissues.[313]

High Levels

Aside from these rare inborn errors of metabolism, elevated levels of glyceric acid have been demonstrated in a few metabolomic studies. One study demonstrated that glyceric acid was among 3 metabolites that correlated in patients with rheumatoid arthritis.[317] Furthermore, correlation between glyceric acid was amongst a small handful of metabolites that were able to effectively identify patients with schizophrenia and bipolar as compared to controls.[318] These profiles suggest that more subtle metabolic abnormalities may result in elevated urinary glyceric acid excretion.

It is known that a deficiency in the enzyme glyoxylate reductase leads to excessive levels of glyceric acid resulting in primary hyperoxaluria type 2 and oxalosis.[319] This enzyme requires vitamin B_3 in the form of NAD as a cofactor. Whether subclinical elevations in glyceric acid could be an indication of a functional need for vitamin B_3 has not been studied in the literature. Interestingly, niacin has been shown to be effective in clinical trials with patients suffering from schizophrenia. Glycerate kinase requires magnesium as a cofactor to convert glyceric acid. Therefore, magnesium deficiency may play a role in glyceric acid levels.

Lastly, glyceric acid is formed during metabolism of fructose and serine (previously mentioned). The contribution of fructose intake to total urinary glyceric acid excretion has not been fully elucidated. A careful dietary recall should be considered with increased glyceric acid in the absence of suspected metabolic defects.

Low Levels

The clinical relevance of low urinary glyceric acid has not been studied in the peer-reviewed literature. However, knowing that glyceric acid accumulation is the result of breakdown of both serine and fructose, it is possible that low glyceric acid may be caused by low amino acid status and/or low fructose intake.

Glycolic Acid

Glycolic acid is another byproduct of the oxalate pathway and comes from the conversion of glyoxylic acid. Urinary levels of glycolic acid have most commonly been studied in the rare inborn error of metabolism primary hyperoxaluria type 1 (PH1). PH1 is caused by a deficiency of alanine:glyoxylate aminotransferase (AGT) which converts glyoxylic acid into glycine.[320] When this pathway is blocked, due to inborn error, glyoxylic acid ultimately leads to higher production of glycolic acid and oxalic acid.[321]

Clinically, PH1 results in a similar clinical presentation as PH2 with increased oxalic acid excretion and calcium oxalate deposition (oxalosis). This can ultimately progress to renal calcinosis and kidney failure.[322]

Aside from inborn error, a large portion of glycolic acid is derived from metabolism of glycine and hydroxyproline. It has been projected that between 20% and 50% of urinary glycolate comes from hydroxyproline in the form of collagen turnover in the body.[323] Supplementation or recent intake of collagen or collagen-rich foods may influence levels of glycolic acid in the urine.

Another important source of glycolic acid is the molecule glyoxal.[312] Glyoxal is derived, in part, from oxidative stress in the forms of lipid peroxidation and protein glycation.[324] The majority of this glyoxal is converted into glycolic acid utilizing glutathione as a cofactor.[325]

High Levels

Extremely high levels of urinary glycolic acid are suspicious of a metabolic defect in the glyoxylate pathway such as in PH1. However, this rare inborn error is commonly diagnosed early in life. To note, Genova's urinary organic acid testing is not designed for the diagnosis of metabolic inborn errors. However, the enzyme defect responsible for PH1 (AGT) is dependent on vitamin B_6 as a cofactor.[326] The extent to which urinary glycolic acid could be a functional indicator of vitamin B_6 insufficiency has not been studied, however patients with PH1 have shown improvement with B_6 intervention.[327]

Aside from inborn error, higher levels of glycolic acid may be indicative of increased oxidative stress.[312] This is because oxidative stress causes higher levels of glyoxal which is ultimately converted into glycolic acid for excretion utilizing glutathione as a cofactor.[325] Lower levels of glutathione may promote more conversion of glyoxal to oxalic acid (see below).

Lastly, a large proportion of glycolic acid comes from collagen in the form of hydroxyproline.[323] Consumptions of foods high in collagen should be considered with unexplained elevations in glycolic acid. The extent to which accelerated turnover of collagen, such as in catabolic conditions, contributed to urinary glycolic acid has not been studied in the literature.

Low Levels

The clinical relevance of low levels of urinary glycolic acid has not been fully explored. Low levels of glycolic acid precursors could potentially explain low levels of this end-product. This could be found in lower overall oxidative stress burden or low collagen turnover. Glycine is also a precursor to the glyoxylase system and could theoretically result in low downstream metabolites, such as glycolic acid.

Oxalic Acid

Oxalic acid is the metabolic end-product of the glyoxylase pathway and is derived from the oxidation of glyoxylate.[321] In the cell, the majority of glyoxylate is converted into glycine or glycolic acid. However, in some instances there may be greater oxidation of glyoxylate to oxalic acid. This leads to increased urinary excretion of oxalic acid. As 80% of kidney stones are calcium-oxalate stones, an increase in oxalic acid is strongly correlated to frequency of urolithiasis.[328]

As mentioned previously, there are inborn errors of metabolism that cause elevated oxalic acid such as primary hyperoxaluria. The dramatically elevated levels of oxalic acid in these conditions lead to renal calculi formation and systemic oxalosis. However, there are other clinical circumstances that can predispose an individual to have higher urinary oxalic acid levels, including recent dietary intake of oxalate-rich roods.

The relationship between diet and urinary oxalic acid levels is complex and dependent on many variables. While the majority of oxalic acid originates from endogenous production, it is estimated that 40% of urinary oxalic acid is derived from the diet, however these levels are largely dependent on the microbiome and intake of dietary calcium.[329] Specifically, the gut bacteria Oxalobacter formigenes degrades dietary oxalates and there is a direct correlation between concentrations of this bacteria and lower oxalate levels. The absence of Oxalobacter formigenes is also correlated to increased oxalate stone formation.

Food sources that lead to higher oxalic acid excretion include spinach, rhubarb, beets, nuts, chocolate, tea, wheat bran, and strawberries.[311] However, it is well-documented cooking oxalate-rich foods dramatically reduces the oxalate concentration. Furthermore, often these foods are also high in calcium which inhibits oxalate absorption at the intestinal lining.[311]

Aside from dietary intake, oxalic acid concentrations will vary based on a number of factors. As previously mentioned, oxidative stress may play a large role in the formation of oxalic acid. This is because glutathione is responsible for the neutralization of glyoxal created by free radical damage.[325] With lower glutathione levels, glyoxal is more likely to shunt toward glyoxylate and ultimately could become oxalic acid.[325]

High Levels

Elevated urinary oxalic acid can be a result of several factors. First, dietary intake of oxalate-rich foods must be considered, especially in the context of dysbiosis and microbiome deficiency. A GI Effects stool test may be warranted to evaluate the concentration of Oxalobacter formigenes alongside other microbiota capable of degrading dietary oxalates. Calcium intake should be assessed as moderate calcium intake has been shown to decrease oxalate absorption and stone formation.

Hydroxyproline, a component of collagen, is a potential precursor to glyoxylate (discussed above). Higher consumption of collagen-rich foods and supplements may contribute to elevations in urinary oxalic acid.[323] It is also estimated that 5-20% of urinary oxalic acid excretion stems from collagen turnover in the body.[323]

Ascorbic acid intake has been evaluated as a contributor toward oxalate levels because ascorbic acid is metabolized into oxalic acid. While individuals who are predisposed toward stone formation appear to have increased urinary oxalic acid excretion after ascorbic acid loads,[330] in general the research has shown that vitamin C intake is not associated with urinary oxalic acid or kidney stone risk.[331,332]

Oxidative stress is another factor potentially driving the formation of oxalic acid (as discussed previously). Clinically, evaluating glutathione and lipid peroxide levels may be helpful to determine the need to support with antioxidants. Not only may antioxidants, such as glutathione, assist in neutralizing the oxalate precursor glyoxal, but they may also assist in prevention of calcium oxalate deposition to urothelium and subsequent renal damage.[333,334] Also, metabolic syndrome may also preclude risk toward increased formation and excretion of oxalic acid whereas weight, BMI, and insulin resistance have all demonstrated positive correlations with urinary oxalic acid.[328] Whether these associations are due to oxidative stress disturbances is yet to be determined.
Lastly, micronutrient insufficiencies may also play

a role in oxalic acid levels. Glyoxylate is mostly converted to glycine through the enzyme AGT, which utilizes vitamin B_6 as a cofactor (discussed above). Vitamin B_6 therapy has been used in the setting of primary hyperoxaluria with varying degrees of success. Also, intake of vitamin B_6 has been shown to decrease risk of kidney stones in some, but not all, investigations.[331]

Urinary creatinine

Urinary creatinine is commonly used as a laboratory standardization when evaluating urinary analytes.[335-337] Creatinine excretion is influenced by muscle mass and body habitus since creatinine formation occurs in muscle. Dietary intake of proteins containing arginine and glycine (precursors of creatine) and creatine supplementation can elevate levels.[338] Hydration status may also play a role in urinary creatinine levels.

8-Hydroxy-2'-deoxyguanosine (8-OHdG)

8-Hydroxy-2'-deoxyguanosine (8-OHdG) is a byproduct of oxidative damage to guanine bases in DNA.[339] It is used as a biomarker for oxidative stress and carcinogenesis. It has been studied to estimate DNA damage after exposure to carcinogens including tobacco smoke, asbestos fibers, heavy metals, and polycyclic aromatic hydrocarbons.[340] 8-OHdG levels are positively associated with markers of inflammation and evening cortisol, indicating that increased physiological or psychosocial stress is associated with increased oxidative damage.[341,342]

High levels

Elevated 8-OHdG indicates oxidative damage to DNA. Diseases including cardiovascular disease, COPD, cancer, thyroid disease, and diabetes have been associated with excessive concentrations of 8-OHdG.[339,343-350] Minimizing exposure to xenobiotics and cigarette smoke, stress management, and increasing antioxidant intake may prevent further oxidative damage.[341,342,351] Increased physical activity is associated with a reduction in urinary 8-OHdG levels.[352] Green tea catechins decreased 8-OHdG concentrations in patients with Alzheimer's disease.[353]

REFERENCES

1. Kałużna-Czaplińska J. Noninvasive urinary organic acids test to assess biochemical and nutritional individuality in autistic children. Clin Biochem. 2011;44(8-9):686-691.

2. Broquist HP, Luhby AL. Detection and isolation of formiminoglutamic acid from urine in folic acid deficiency in humans. Proceedings of the Society for Exp Biol Med Soc. 1959;100(2):349-354.

3. Sun A-l, Ni Y-h, Li X-b, et al. Urinary methylmalonic acid as an indicator of early vitamin B12 deficiency and its role in polyneuropathy in type 2 diabetes. J Diabet Res. 2014;2014.

4. Kwok T, Cheng G, Lai W, Poon P, Woo J, Pang C. Use of fasting urinary methylmalonic acid to screen for metabolic vitamin B12 deficiency in older persons. Nutrition. 2004;20(9):764-768.

5. Brown R, Thornton MJ, Price J. The effect of vitamin supplementation on the urinary excretion of tryptophan metabolites by pregnant women. J Clin Invest. 1961;40(4):617-623.

6. Lehotay DC, Clarke JT, Renaldo P. Organic acidurias and related abnormalities. Crit Rev Clin Lab Sci. 1995;32(4):377-429.

7. Mock DM. Biotin: From Nutrition to Therapeutics. J Nutr. 2017;147(8):1487-1492.

8. Hryhorczuk LM, Novak EA, Gershon S. Gut flora and urinary phenylacetic acid. Science. 1984;226(4677):996.

9. Mora Brugues J, Gonzalez Sastre F. Influence of intestinal flora on the elimination of phenylacetic acid in urine. Clin Chem. 1986;32(1 Pt 1):223.

10. Del Rio D, Stalmach A, Calani L, Crozier A. Bioavailability of Coffee Chlorogenic Acids and Green Tea Flavan-3-ols. Nutrients. 2010;2(8):820.

11. Blaut M, Clavel T. Metabolic Diversity of the Intestinal Microbiota: Implications for Health and Disease. J Nutr. 2007;137(3):751S-755S.

12. Russell WR, Duncan SH, Scobbie L, et al. Major phenylpropanoid-derived metabolites in the human gut can arise from microbial fermentation of protein. Mol Nutr Food Res. 2013;57(3):523-535.

13. Rao RP, Hunter A, Kashpur O, Normanly J. Aberrant synthesis of indole-3-acetic acid in Saccharomyces cerevisiae triggers morphogenic transition, a virulence trait of pathogenic fungi. Genetics. 2010;185(1):211-220.

14. Evenepoel P, Meijers BKI, Bammens BRM, Verbeke K. Uremic toxins originating from colonic microbial metabolism. Kidney Int.76:S12-S19.

15. Karu N, McKercher C, Nichols DS, et al. Tryptophan metabolism, its relation to inflammation and stress markers and association with psychological and cognitive functioning: Tasmanian Chronic Kidney Disease pilot study. BMC Nephrol. 2016;17(1):171.

16. Sallée M, Dou L, Cerini C, Poitevin S, Brunet P, Burtey S. The Aryl Hydrocarbon Receptor-Activating Effect of Uremic Toxins from Tryptophan Metabolism: A New Concept to Understand Cardiovascular Complications of Chronic Kidney Disease. Toxins. 2014;6(3):934-949.

17. Gevi F, Zolla L, Gabriele S, Persico AM. Urinary metabolomics of young Italian autistic children supports abnormal tryptophan and purine metabolism. Mol Autism. 2016;7:47.

18. Wong PW, Lambert AM, Pillai PM, Jones PM. Observations on nicotinic acid therapy in Hartnup disease. Arch Dis Child. 1967;42(226):642-646.

19. Feliciano RP, Boeres A, Massacessi L, et al. Identification and quantification of novel cranberry-derived plasma and urinary (poly)phenols. Arch Biochem Biophys. 2016;599:31-41.

20. Sabelli H, Fawcett J, Gusovsky F, Edwards J, Jeffriess H, Javaid J. Phenylacetic acid as an indicator in bipolar affective disorders. J Clin Psychopharmacol. 1983;3(4):268-270.

21. Sabelli HC, Fawcett J, Gusovsky F, et al. Clinical studies on the phenylethylamine hypothesis of affective disorder: urine and blood phenylacetic acid and phenylalanine dietary supplements. J Clin Psych. 1986;47(2):66-70.

22. Sabelli HC, Javaid JI, Fawcett J, Kravitz HM, Wynn P. Urinary phenylacetic acid in panic disorder with and without depression. Acta Psych Scand. 1990;82(1):14-16.

23. Henning SM, Wang P, Abgaryan N, et al. Phenolic acid concentrations in plasma and urine from men consuming green or black tea and potential chemopreventive properties for colon cancer. Mol Nutr Food Res. 2013;57(3):483-493.

24. Jacobs DM, Fuhrmann JC, van Dorsten FA, et al. Impact of Short-Term Intake of Red Wine and Grape Polyphenol Extract on the Human Metabolome. J Agric Food Chem. 2012;60(12):3078-3085.

25. Zamora-Ros R, Achaintre D, Rothwell JA, et al. Urinary excretions of 34 dietary polyphenols and their associations with lifestyle factors in the EPIC cohort study. Sci Rep. 2016;6:26905-26905.

26. Ward NC, Croft KD, Puddey IB, Hodgson JM. Supplementation with grape seed polyphenols results in increased urinary excretion of 3-hydroxyphenylpropionic Acid, an important metabolite of proanthocyanidins in humans. J Agric Food Chem. 2004;52(17):5545-5549.

27. Amic A, Markovic Z, Markovic JMD, Jeremic S, Lucic B, Amic D. Free radical scavenging and COX-2 inhibition by simple colon metabolites of polyphenols: A theoretical approach. Computat Biol Chem. 2016;65:45-53.

28. Manach C, Williamson G, Morand C, Scalbert A, Remesy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. Am J Clin Nutr. 2005;81(1 Suppl):230s-242s.

29. Selma MV, Espin JC, Tomas-Barberan FA. Interaction between phenolics and gut microbiota: role in human health. J Agric Food Chem. 2009;57(15):6485-6501.

30. Badenhorst CP, Erasmus E, van der Sluis R, Nortje C, van Dijk AA. A new perspective on the importance of glycine conjugation in the metabolism of aromatic acids. Drug Metab Rev. 2014;46(3):343-361.

31. Lees HJ, Swann JR, Wilson ID, Nicholson JK, Holmes E. Hippurate: the natural history of a mammalian-microbial cometabolite. J Proteome Res. 2013;12(4):1527-1546.

32. Loo RL, Zou X, Appel LJ, Nicholson JK, Holmes E. Characterization of metabolic responses to healthy diets and association with blood pressure: application to the Optimal Macronutrient Intake Trial for Heart Health (OmniHeart), a randomized controlled study. Am J Clin Nutr. 2018;107(3):323-334.

33. Williams HR, Cox IJ, Walker DG, et al. Differences in gut microbial metabolism are responsible for reduced hippurate synthesis in Crohn's disease. BMC Gastroenterol. 2010;10:108.

34. Christensson B, Sigmundsdottir G, Larsson L. D-arabinitol--a marker for invasive candidiasis. Med Mycol. 1999;37(6):391-396.

35. Yeo SF, Wong B. Current status of nonculture methods for diagnosis of invasive fungal infections. Clin Microbiol Rev. 2002;15(3):465-484.

36. Kałużna-Czaplińska J, Błaszczyk S. The level of arabinitol in autistic children after probiotic therapy. Nutrition. 2012;28(2):124-126.

37. Sugimoto N, Forsline P, Beaudry R. Volatile profiles of members of the USDA Geneva Malus Core Collection: utility in evaluation of a hypothesized biosynthetic pathway for esters derived from 2-methylbutanoate and 2-methylbutan-1-ol. J Agric Food Chem. 2015;63(7):2106-2116.

38. Hulme AC. The isolation of l-citramalic acid from the peel of the apple fruit. Biochim Biophys Acta. 1954;14(1):36-43.

39. Liu H, Garrett TJ, Su Z, Khoo C, Gu L. UHPLC-Q-Orbitrap-HRMS-based global metabolomics reveal metabolome modifications in plasma of young women after cranberry juice consumption, J Nutr Biochem. 2017;45:67-76.

40. Khorassani R, Hettwer U, Ratzinger A, Steingrobe B, Karlovsky P, Claassen N. Citramalic acid and salicylic acid in sugar beet root exudates solubilize soil phosphorus. BMC Plant Biol. 2011;11:121.

41. Marconi O, Floridi S, Montanari L. Organic acids profile in tomato juice by HPLC with UV detection. J Food Qual. 2007;30(2):253-266.

42. van der Hooft JJ, de Vos RC, Mihaleva V, et al. Structural elucidation and quantification of phenolic conjugates present in human urine after tea intake. Analyt Chem. 2012;84(16):7263-7271.

43. Jacobs DM, Fuhrmann JC, van Dorsten FA, et al. Impact of short-term intake of red wine and grape polyphenol extract on the human metabolome. J Agric Food Chem. 2012;60(12):3078-3085.

44. Hanske L, Loh G, Sczesny S, Blaut M, Braune A. The bioavailability of apigenin-7-glucoside is influenced by human intestinal microbiota in rats. J Nutr. 2009;139(6):1095-1102.

45. Gonthier M-P, Verny M-A, Besson C, Rémésy C, Scalbert A. Chlorogenic Acid Bioavailability Largely Depends on Its Metabolism by the Gut Microflora in Rats. J Nutr. 2003;133(6):1853-1859.

46. Rios LY, Gonthier M-P, Rémésy C, et al. Chocolate intake increases urinary excretion of polyphenol-derived phenolic acids in healthy human subjects. Am J Clin Nutr. 2003;77(4):912-918.

47. Booth AN, Jones FT. Metabolic fate of hesperidin, eriodictyol, homoeriodictyol, and diosmin. J Biol Chem. 1958;230(2):661-668.

48. Henning SM, Wang P, Abgaryan N, et al. Phenolic acid concentrations in plasma and urine from men consuming green or black tea and potential chemopreventive properties for colon cancer. Mol Nutr Food Res. 2013;57(3):483-493.

49. Feliciano RP, Boeres A, Massacessi L, et al. Identification and quantification of novel cranberry-derived plasma and urinary (poly)phenols. Arch Biochem Biophys. 2016;599:31-41.

50. Gill CI, McDougall GJ, Glidewell S, et al. Profiling of phenols in human fecal water after raspberry supplementation. J Agric Food Chem. 2010;58(19):10389-10395.

51. Koli R, Erlund I, Jula A, Marniemi J, Mattila P, Alfthan G. Bioavailability of various polyphenols from a diet containing moderate amounts of berries. J Agric Food Chem. 2010;58(7):3927-3932.

52. Roowi S, Mullen W, Edwards CA, Crozier A. Yoghurt impacts on the excretion of phenolic acids derived from colonic breakdown of orange juice flavanones in humans. Mol Nutr Food Res. 2009;53 Suppl 1:S68-75.

53. Pereira-Caro G, Ludwig IA, Polyviou T, et al. Identification of Plasma and Urinary Metabolites and Catabolites Derived from Orange Juice (Poly)phenols: Analysis by High-Performance Liquid Chromatography-High-Resolution Mass Spectrometry. J Agric Food Chem. 2016;64(28):5724-5735.

54. de Ferrars RM, Cassidy A, Curtis P, Kay CD. Phenolic metabolites of anthocyanins following a dietary intervention study in post-menopausal women. Mol Nutr Food Res. 2014;58(3):490-502.

55. Heinrich J, Valentova K, Vacek J, et al. Metabolic profiling of phenolic acids and oxidative stress markers after consumption of Lonicera caerulea L. fruit. J Agric Food Chem. 2013;61(19):4526-4532.

56. Leth T, Christensen T, Larsen IK. Estimated intake of benzoic and sorbic acids in Denmark. Food Add Contam Part A, Chem, Analys, Control, Exp Risk Assess. 2010;27(6):783-792.

57. Williamson G, Clifford MN. Colonic metabolites of berry polyphenols: the missing link to biological activity? Brit J Nutr. 2010;104 Suppl 3:S48-66.

58. Loke WM, Jenner AM, Proudfoot JM, et al. A metabolite profiling approach to identify biomarkers of flavonoid intake in humans. J Nutr. 2009;139(12):2309-2314.

59. Krog-Mikkelsen I, Hels O, Tetens I, Holst JJ, Andersen JR, Bukhave K. The effects of L-arabinose on intestinal sucrase activity: dose-response studies in vitro and in humans. Am J Clin Nutr. 2011;94(2):472-478.

60. Regueiro J, Vallverdú-Queralt A, Simal-Gándara J, Estruch R, Lamuela-Raventós RM. Urinary tartaric acid as a potential biomarker for the dietary assessment of moderate wine consumption: a randomised controlled trial. Brit J Nutr. 2014;111(9):1680-1685.

61. Lawson AM, Chalmers RA, Watts RW. Urinary organic acids in man. I. Normal patterns. Clin Chem. 1976;22(8):1283-1287.

62. Pieczenik SR, Neustadt J. Mitochondrial dysfunction and molecular pathways of disease. Exp Mol Pathol. 2007;83(1):84-92.

63. Caito SW, Aschner M. Mitochondrial Redox Dysfunction and Environmental Exposures. Antiox Redox Signal. 2015;23(6):578-595.

64. Depeint F, Bruce WR, Shangari N, Mehta R, O'Brien PJ. Mitochondrial function and toxicity: role of the B vitamin family on mitochondrial energy metabolism. Chemico-biol Interact. 2006;163(1-2):94-112.

65. Wojtczak L, Slyshenkov VS. Protection by pantothenic acid against apoptosis and cell damage by oxygen free radicals--the role of glutathione. BioFactors. 2003;17(1-4):61-73.

66. Tsoukalas D, Alegakis A, Fragkiadaki P, et al. Application of metabolomics: Focus on the quantification of organic acids in healthy adults. Int J Mol Med. 2017;40(1):112-120.

67. Astarita G, Langridge J. An emerging role for metabolomics in nutrition science. J Nutrigenet Nutrigenom. 2013;6(4-5):181-200.

68. Anderson NM, Mucka P, Kern JG, Feng H. The emerging role and targetability of the TCA cycle in cancer metabolism. Protein Cell. 2017.

69. Cardaci S, Ciriolo MR. TCA Cycle Defects and Cancer: When Metabolism Tunes Redox State. Int J Cell Biol. 2012;2012:161837.

70. Rojczyk-Golebiewska E, Kucharzewski M. Influence of chosen metals on the citric acid cycle. Pol Merkur Lekarski. 2013;34(201):175-178.

71. Strydom CRC. The effect of selected metals on the central metabolic pathways in biology: A review. Water SA. 2006.

72. Solmonson A, DeBerardinis RJ. Lipoic acid metabolism and mitochondrial redox regulation. J Biol Chem. 2018;293(20):7522-7530.

73. Tsoukalas D, Alegakis A, Fragkiadaki P, et al. Application of metabolomics: Focus on the quantification of organic acids in healthy adults. Int J Mol Med. 2017;40(1):112-120.

74. Nicolson GL. Mitochondrial dysfunction and chronic disease: treatment with natural supplements. Alt Therap Health Med. 2014;20 Suppl 1:18-25.

75. Parikh S, Goldstein A, Koenig MK, et al. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. Genet Med. 2015;17(9):689-701.

76. Wajner M, Goodman SI. Disruption of mitochondrial homeostasis in organic acidurias: insights from human and animal studies. J Bioenerget Biomembr. 2011;43(1):31-38.

77. Nicolson GL. Mitochondrial Dysfunction and Chronic Disease: Treatment With Natural Supplements. Integr Med. 2014;13(4):35-43.

78. Dimmock DP, Lawlor MW. Presentation and Diagnostic Evaluation of Mitochondrial Disease. Pediatr Clin North Am. 2017;64(1):161-171.

79. Haas RH, Parikh S, Falk MJ, et al. The In-Depth Evaluation of Suspected Mitochondrial Disease: The Mitochondrial Medicine Society's Committee on Diagnosis. Mol Gen Metab. 2008;94(1):16-37.

80. Sharma S, Black SM. Carnitine homeostasis, mitochondrial function, and cardiovascular disease. Drug Discovery Today Dis Mech. 2009;6(1-4):e31-e39.

81. Kałużna-Czaplińska J, Socha E, Rynkowski J. B vitamin supplementation reduces excretion of urinary dicarboxylic acids in autistic children. Nutr Res. 2011;31(7):497-502.

82. Altura BM, Gebrewold A, Altura BT, Brautbar N. Magnesium depletion impairs myocardial carbohydrate and lipid metabolism and cardiac bioenergetics and raises myocardial calcium content in-vivo: relationship to etiology of cardiac diseases. Biochem Mol Biol Int. 1996;40(6):1183-1190.

83. Kaluzna-Czaplinska J, Socha E, Rynkowski J. B vitamin supplementation reduces excretion of urinary dicarboxylic acids in autistic children. Nutr Res. 2011;31(7):497-502.

84. Nagao M, Tanaka K. FAD-dependent regulation of transcription, translation, post-translational processing, and post-processing stability of various mitochondrial acyl-CoA dehydrogenases and of electron transfer flavoprotein and the site of holoenzyme formation. J Biol Chem. 1992;267(25):17925-17932.

85. Olsen Rikke K, Koňaříková E, Giancaspero Teresa A, et al. Riboflavin-Responsive and -Non-responsive Mutations in FAD Synthase Cause Multiple Acyl-CoA Dehydrogenase and Combined Respiratory-Chain Deficiency. Am J Human Genet. 2016;98(6):1130-1145.

86. Green A, Marshall T, Bennett M, Gray R, Pollitt R. Riboflavin-responsive ethylmalonic—adipic aciduria. J Inherit Metab Dis. 1985;8(2):67-70.

87. Liang W-C, Tsai K-B, Lai C-L, Chen L-H, Jong Y-J. Riboflavin-responsive glutaric aciduria type II with recurrent pancreatitis. Ped Neurol. 2004;31(3):218-221.

88. De Visser M, Scholte H, Schutgens R, et al. Riboflavin-responsive lipid-storage myopathy and glutaric aciduria type II of early adult onset. Neurology. 1986;36(3):367-367.

89. Gregersen N. Riboflavin-responsive defects of beta-oxidation. J Inherit Metab Dis. 1985;8 Suppl 1:65-69.

90. Villarreal-Pérez JZ, Villarreal-Martínez JZ, Lavalle-González FJ, et al. Plasma and urine metabolic profiles are reflective of altered beta-oxidation in non-diabetic obese subjects and patients with type 2 diabetes mellitus. Diabetol Metabol Syndr. 2014;6:129.

91. Chang B, Nishikawa M, Nishiguchi S, Inoue M. L-carnitine inhibits hepatocarcinogenesis via protection of mitochondria. Int J Cancer. 2005;113(5):719-729.

92. Gray LR, Tompkins SC, Taylor EB. Regulation of pyruvate metabolism and human disease. Cell Mol Life Sci. 2014;71(14):2577-2604.

93. Garfinkel L, Garfinkel D. Magnesium regulation of the glycolytic pathway and the enzymes involved. Magnesium. 1985;4(2-3):60-72.

94. Mayes PA, Bender DA. Glycolysis and the oxidation of pyruvate. Harper's illustrated biochemistry' pp. 2003:136-144.

95. Stacpoole PW. The pyruvate dehydrogenase complex as a therapeutic target for age-related diseases. Aging Cell. 2012;11(3):371-377.

96. Ravindran S, Radke GA, Guest JR, Roche TE. Lipoyl domain-based mechanism for the integrated feedback control of the pyruvate dehydrogenase complex by enhancement of pyruvate dehydrogenase kinase activity. J Biol Chem. 1996;271(2):653-662.

97. Shipman K. Clinical biochemistry: Metabolic and clinical aspects (3rd edn). In: SAGE Publications Sage UK 2015.

98. Tirmenstein MA, Mathias PI, Snawder JE, Wey HE, Toraason M. Antimony-induced alterations in thiol homeostasis and adenine nucleotide status in cultured cardiac myocytes. Toxicology. 1997;119(3):203-211.

99. Chapatwala KD, Rajanna B, Desaiah D. Cadmium induced changes in gluconeogenic enzymes in rat kidney and liver. Drug Chem Toxicol. 1980;3(4):407-420.

100. Schlecht I, Gronwald W, Behrens G, et al. Visceral adipose tissue but not subcutaneous adipose tissue is associated with urine and serum metabolites. PloS one. 2017;12(4):e0175133.

101. Friedrich N, Skaaby T, Pietzner M, et al. Identification of urine metabolites associated with 5-year changes in biomarkers of glucose homoeostasis. Diab Metab. 2017.

102. Mostafa H, Amin AM, Teh CH, Murugaiyah V, Arif NH, Ibrahim B. Metabolic phenotyping of urine for discriminating alcohol-dependent from social drinkers and alcohol-naive subjects. Drug Alcohol Dep. 2016;169:80-84.

103. Hira HS, Shukla A, Kaur A, Kapoor S. Serum uric acid and lactate levels among patients with obstructive sleep apnea syndrome: which is a better marker of hypoxemia? Ann Saudi Med. 2012;32(1):37-42.

104. Nikolaidis S, Kosmidis I, Sougioultzis M, Kabasakalis A, Mougios V. Diurnal variation and reliability of the urine lactate concentration after maximal exercise. Chronobiol Int. 2018;35(1):24-34.

105. TAMAKI N, IKEDA T, FUNATSUKA A. Zinc as activating cation for muscle glycolysis. J Nutr Sci Vitaminol. 1983;29(6):655-662.

106. IKEDA T, KIMURA K, MORIOKA S, TAMAKI N. Inhibitory effects of Zn2+ on muscle glycolysis and their reversal by histidine. J Nutr Science Vitaminol. 1980;26(4):357-366.

107. Kaplan RS, Mayor JA, Blackwell R, Maughon RH, Wilson GL. The effect of insulin supplementation on diabetes-induced alterations in the extractable levels of functional mitochondrial anion transport proteins. Arch Biochem Biophys. 1991;287(2):305-311.

108. Dorcely B, Katz K, Jagannathan R, et al. Novel biomarkers for prediabetes, diabetes, and associated complications. Diabetes Metab Syndr Obes. 2017;10:345-361.

109. Gall WE, Beebe K, Lawton KA, et al. alpha-hydroxybutyrate is an early biomarker of insulin resistance and glucose intolerance in a nondiabetic population. PloS one. 2010;5(5):e10883.

110. Paolisso G, Giugliano D, Pizza G, et al. Glutathione infusion potentiates glucose-induced insulin secretion in aged patients with impaired glucose tolerance. Diab Care. 1992;15(1):1-7.

111. Landaas S, Pettersen JE. Clinical conditions associated with urinary excretion of 2-hydroxybutyric acid. Scand J Clin Lab Invest. 1975;35(3):259-266.

112. Trico D, Prinsen H, Giannini C, et al. Elevated alpha-Hydroxybutyrate and Branched-Chain Amino Acid Levels Predict Deterioration of Glycemic Control in Adolescents. J Clin Endocrinol Metab. 2017;102(7):2473-2481.

113. Mahendran Y, Vangipurapu J, Cederberg H, et al. Association of ketone body levels with hyperglycemia and type 2 diabetes in 9,398 Finnish men. Diabetes. 2013;62(10):3618-3626.

114. Cobb J, Eckhart A, Perichon R, et al. A novel test for IGT utilizing metabolite markers of glucose tolerance. J Diab Sci Technol. 2015;9(1):69-76.

115. Rundek T, Naini A, Sacco R, Coates K, DiMauro S. Atorvastatin Decreases the Coenzyme Q10 Level in the Blood of Patients at Risk for Cardiovascular Disease and Stroke. Arch Neurol. 2004;61(6):889-892.

116. Qu H, Guo M, Chai H, Wang Wt, Gao Zy, Shi Dz. Effects of Coenzyme Q10 on Statin-Induced Myopathy: An Updated Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc. 2018;7(19):e009835.

117. Wortmann SB, Kluijtmans LA, Engelke UFH, Wevers RA, Morava E. The 3-methylglutaconic acidurias: what's new? J Inherit Metab Dis. 2012;35(1):13-22.

118. Bullock GC, Delehanty LL, Talbot A-L, et al. Iron control of erythroid development by a novel aconitase-associated regulatory pathway. Blood. 2010;116(1):97-108.

119. Paul BT, Manz DH, Torti FM, Torti SV. Mitochondria and Iron: current questions. Expert Rev Hematol. 2017;10(1):65-79.

120. Han D, Canali R, Garcia J, Aguilera R, Gallaher TK, Cadenas E. Sites and Mechanisms of Aconitase Inactivation by Peroxynitrite: Modulation by Citrate and Glutathione. Biochemistry. 2005;44(36):11986-11996.

121. Pace C, Dagda R, Angermann J. Antioxidants protect against arsenic induced mitochondrial cardio-toxicity. Toxics. 2017;5(4):38.

122. Zatta P, Lain E, Cagnolini C. Effects of aluminum on activity of Krebs cycle enzymes and glutamate dehydrogenase in rat brain homogenate. Eur J Biochem. 2000;267(10):3049-3055.

123. Carocci A, Rovito N, Sinicropi MS, Genchi G. Mercury toxicity and neurodegenerative effects. In: Rev Environ Contam Toxicol. Springer; 2014:1-18.

124. Houston MC. The role of mercury and cadmium heavy metals in vascular disease, hypertension, coronary heart disease, and myocardial infarction. Altern Ther Health Med. 2007;13(2):S128-S133.

125. Wu N, Yang M, Gaur U, Xu H, Yao Y, Li D. Alpha-Ketoglutarate: Physiological Functions and Applications. Biomol Ther (Seoul). 2016;24(1):1-8.

126. Dougherty FE. Metabolic testing in mitochondrial disease. Paper presented at: Seminars in neurology2001.

127. Tretter L, Adam-Vizi V. Alpha-ketoglutarate dehydrogenase: a target and generator of oxidative stress. Philos Trans R Soc Lond B Biol Sci. 2005;360(1464):2335-2345.

128. Rutter J, Winge DR, Schiffman JD. Succinate dehydrogenase - Assembly, regulation and role in human disease. Mitochondrion. 2010;10(4):393-401.

129. Van Vranken JG, Na U, Winge DR, Rutter J. Protein-mediated assembly of succinate dehydrogenase and its cofactors. Crit Rev Biochem Mol Biol. 2015;50(2):168-180.

130. Connors J, Dawe N, Van Limbergen J. The Role of Succinate in the Regulation of Intestinal Inflammation. Nutrients. 2018;11(1):25.

131. Wentzel JF, Lewies A, Bronkhorst AJ, Van Dyk E, Du Plessis LH, Pretorius PJ. Exposure to high levels of fumarate and succinate leads to apoptotic cytotoxicity and altered global DNA methylation profiles in vitro. Biochimie. 2017;135:28-34.

132. Harris RA, Joshi M, Jeoung NH, Obayashi M. Overview of the Molecular and Biochemical Basis of Branched-Chain Amino Acid Catabolism. J Nutr. 2005;135(6):1527S-1530S.

133. Minarik P, Tomaskova N, Kollarova M, Antalik M. Malate dehydrogenases-structure and function. Gen Physiol Biophys. 2002;21(3):257-266.

134. Depeint F, Bruce WR, Shangari N, Mehta R, O'Brien PJ. Mitochondrial function and toxicity: role of the B vitamin family on mitochondrial energy metabolism. Chemico-biol Interact. 2006;163(1-2):94-112.

135. Kim D CJ, Cheng T, Gindulyte A, He J, He S, Li Q, Shoemaker BA, Thiessen PA, Yu B, Zaslvasky L, et. al. PubChem 2019 update: improved access to chemical data. Nucleic Acids. 2019.

136. Wilson R, Wilson C, Gates S, Higgins J. α-Ketoadipic aciduria: A description of a new metabolic error in lysine-tryptophan degradation. Ped Res. 1975;9(6):522-526.

137. Holeček M. Branched-chain amino acids in health and disease: metabolism, alterations in blood plasma, and as supplements. Nutr Metab. 2018;15(1):33.

138. Holecek M. Branched-chain amino acids in health and disease: metabolism, alterations in blood plasma, and as supplements. Nutr Metab (Lond). 2018;15:33.

139. Shibata K, Nakata C, Fukuwatari T. High-performance liquid chromatographic method for profiling 2-oxo acids in urine and its application in evaluating vitamin status in rats. Biosci Biotechnol Biochem. 2016;80(2):304-312.

140. Danner DJ, Davidson ED, Elsas LJ. Thiamine increases the specific activity of human liver branched chain α-ketoacid dehydrogenase. Nature. 1975;254(5500):529-530.

141. Shibata K, Sakamoto M. Urinary branched-chain 2-oxo acids as a biomarker for function of B-group vitamins in humans. J Nutr Sci Vitaminol. 2016;62(4):220-228.

142. Adams SH. Emerging Perspectives on Essential Amino Acid Metabolism in Obesity and the Insulin-Resistant State. Adv Nutr. 2011;2(6):445-456.

143. Shibata K, Nakata C, Fukuwatari T. High-performance liquid chromatographic method for profiling 2-oxo acids in urine and its application in evaluating vitamin status in rats. Biosci Biotechnol Biochem. 2016;80(2):304-312.

144. Beresford MW, Pourfarzam M, Turnbull DM, Davidson JE. So doctor, what exactly is wrong with my muscles? Glutaric aciduria type II presenting in a teenager. Neuromuscul Dis. 2006;16(4):269-273.

145. Behin A, Acquaviva-Bourdain C, Souvannanorath S, et al. Multiple acyl-CoA dehydrogenase deficiency (MADD) as a cause of late-onset treatable metabolic disease. Rev Neurol. 2016;172(3):231-241.

146. Chalmers RA, Bain MD, Zschocke J. Riboflavin-responsive glutaryl CoA dehydrogenase deficiency. Mol Genet Metab. 2006;88(1):29-37.

147. Chokchaiwong S, Kuo Y-T, Lin S-H, et al. Coenzyme Q10 serves to couple mitochondrial oxidative phosphorylation and fatty acid β-oxidation, and attenuates NLRP3 inflammasome activation. Free Rad Res. 2018;52(11-12):1445-1455.

148. Finocchiaro G, Ito M, Tanaka K. Purification and properties of short chain acyl-CoA, medium chain acyl-CoA, and isovaleryl-CoA dehydrogenases from human liver. J Biol Chem. 1987;262(17):7982-7989.

149. Bei F, Sun JH, Yu YG, et al. Two novel isovaleryl-CoA dehydrogenase gene mutations in a Chinese infant. Gene. 2013;524(2):396-400.

150. Merritt JL, 2nd, Norris M, Kanungo S. Fatty acid oxidation disorders. Ann Transl Med. 2018;6(24):473-473.

151. Sahai I, Garganta CL, Bailey J, et al. Newborn Screening for Glutaric Aciduria-II: The New England Experience. JIMD reports. 2014;13:1-14.

152. Manoli I, Venditti CP. Disorders of branched chain amino acid metabolism. Transl Sci Rare Dis. 2016;1(2):91-110.

153. Chinen Y, Nakamura S, Tamashiro K, et al. Isovaleric acidemia: Therapeutic response to supplementation with glycine, l-carnitine, or both in combination and a 10-year follow-up case study. Mol Genet Metab Rep. 2017;11:2-5.

154. Shigematsu Y, Sudo M, Momoi T, Inoue Y, Suzuki Y, Kameyama J. Changing plasma and urinary organic acid levels in a patient with isovaleric acidemia during an attack. Ped Res. 1982;16(9):771-775.

155. Capo-chichi CD, Guéant J-L, Lefebvre E, et al. Riboflavin and riboflavin-derived cofactors in adolescent girls with anorexia nervosa. Am J Clin Nutr. 1999;69(4):672-678.

156. Cooperman JM, Lopez R. The role of histidine in the anemia of folate deficiency. Exp Biol Med. 2002;227(11):998-1000.

157. Rabinowitz JC, Tabor H. The urinary excretion of formic acid and formiminoglutamic acid in folic acid deficiency. J Biol Chem. 1958;233(1):252-255.

158. FIsH MB, POLLYCOVE M, FEICHTMEIR TV. Differentiation between Vitamin B12—deficient and Folic Acid—deficient Megaloblastic Anemias with C14—Histidine. Blood. 1963;21(4):447-461.

159. Shojania AM. Oral contraceptives: effect of folate and vitamin B12 metabolism. Can Med Assoc J. 1982;126(3):244-247.

160. Sullivan LW, Herbert V. Suppression of hematopoiesis by ethanol. J Clin Invest. 1964;43(11):2048-2062.

161. Metz J, Stevens K, Brandt V. Urinary formiminoglutamic acid in the megaloblastic anaemias associated with pregnancy and malnutrition. BMJ. 1962;2(5317):1440.

162. Rosenauerová-ostrá A, Hilgertová J, Šonka J. Urinary formiminoglutamate in man normal values related to sex and age. Effects of low calorie intake and alcohol consumption. Clin Chim Acta. 1976;73(1):39-43.

163. Wongkittichote P, Mew NA, Chapman KA. Propionyl-CoA carboxylase–a review. Mol Genet Metab. 2017;122(4):145-152.

164. Fowler B, Leonard J, Baumgartner M. Causes of and diagnostic approach to methylmalonic acidurias. J Inherit Metabol Dis. 2008;31(3):350-360.

165. Harrington DJ. Laboratory assessment of vitamin B12 status. J Clin Pathol. 2017;70(2):168-173.

166. Herrmann W, Obeid R, Schorr H, Geisel J. Functional vitamin B12 deficiency and determination of holotranscobalamin in populations at risk. Clin Chem Lab Med. 2003;41(11):1478-1488.

167. Ward MG, Kariyawasam VC, Mogan SB, et al. Prevalence and Risk Factors for Functional Vitamin B12 Deficiency in Patients with Crohn's Disease. Inflamm Bowel Dis. 2015;21(12):2839-2847.

168. Hin H, Clarke R, Sherliker P, et al. Clinical relevance of low serum vitamin B12 concentrations in older people: the Banbury B12 study. Age Ageing. 2006;35(4):416-422.

169. Tangney CC, Tang Y, Evans DA, Morris MC. Biochemical indicators of vitamin B12 and folate insufficiency and cognitive decline. Neurology. 2009;72(4):361-367.

170. Klee GG. Cobalamin and folate evaluation: measurement of methylmalonic acid and homocysteine vs vitamin B12 and folate. Clin Chem. 2000;46(8):1277-1283.

171. Kwok T, Cheng G, Lai WK, Poon P, Woo J, Pang CP. Use of fasting urinary methylmalonic acid to screen for metabolic vitamin B12 deficiency in older persons. Nutrition. 2004;20(9):764-768.

172. Favrat B, Vaucher P, Herzig L, et al. Oral vitamin B12 for patients suspected of subtle cobalamin deficiency: a multicentre pragmatic randomised controlled trial. BMC Fam Pract. 2011;12:2-2.

173. Sun AL, Ni YH, Li XB, et al. Urinary methylmalonic acid as an indicator of early vitamin B12 deficiency and its role in polyneuropathy in type 2 diabetes. J Diab Res. 2014;2014:921616.

174. Tong L. Structure and function of biotin-dependent carboxylases. Cell Mol Life Sci. 2013;70(5):863-891.

175. Mock NI, Malik MI, Stumbo PJ, Bishop WP, Mock DM. Increased urinary excretion of 3-hydroxyisovaleric acid and decreased urinary excretion of biotin are sensitive early indicators of decreased biotin status in experimental biotin deficiency. Am J Clin Nutr. 1997;65(4):951-958.

176. Surtees RAH, Matthews EE, Leonard JV. Neurologic outcome of propionic acidemia. Ped Neurol. 1992;8(5):333-337.

177. Baumgartner MR, Hörster F, Dionisi-Vici C, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. Orph J Rare Dis. 2014;9(1):130.

178. Xiong X, Liu D, Wang Y, Zeng T, Peng Y. Urinary 3-(3-hydroxyphenyl)-3-hydroxypropionic acid, 3-hydroxyphenylacetic acid, and 3-hydroxyhippuric acid are elevated in children with autism spectrum disorders. BioMed Res Int. 2016;2016.

179. Chapman KA, Gropman A, MacLeod E, et al. Acute management of propionic acidemia. Mol Genet Metab. 2012;105(1):16-25.

180. Mock DM, Quirk JG, Mock NI. Marginal biotin deficiency during normal pregnancy. Am J Clin Nutr. 2002;75(2):295-299.

181. Sealey WM, Teague AM, Stratton SL, Mock DM. Smoking accelerates biotin catabolism in women. Am J Clin Nutr. 2004;80(4):932-935.

182. Mock DM, Dyken ME. Biotin catabolism is accelerated in adults receiving long-term therapy with anticonvulsants. Neurology. 1997;49(5):1444-1447.

183. Wu H, Jiang K, Gu G, Wu Y, Yu S. [The relationship of occupational stress and the level of some hormone metabolites in urine]. Chin J Indust Hygiene Occup Dis. 2014;32(2):83-86.

184. Tsoukalas D, Alegakis A, Fragkiadaki P, et al. Application of metabolomics: Focus on the quantification of organic acids in healthy adults. Int J Mol Med. 2017;40(1):112-120.

185. Jeon SW, Kim YK. Inflammation-induced depression: Its pathophysiology and therapeutic implications. J Neuroimmunol. 2017;313:92-98.

186. Cosi C, Mannaioni G, Cozzi A, et al. G-protein coupled receptor 35 (GPR35) activation and inflammatory pain: Studies on the antinociceptive effects of kynurenic acid and zaprinast. Neuropharmacol. 2011;60(7-8):1227-1231.

187. Pawlak K, Mysliwiec M, Pawlak D. Kynurenine pathway - a new link between endothelial dysfunction and carotid atherosclerosis in chronic kidney disease patients. Adv Med Sci. 2010;55(2):196-203.

188. Lugo-Huitron R, Blanco-Ayala T, Ugalde-Muniz P, et al. On the antioxidant properties of kynurenic acid: free radical scavenging activity and inhibition of oxidative stress. Neurotoxicol Teratol. 2011;33(5):538-547.

189. Bender DA, Njagi EN, Danielian PS. Tryptophan metabolism in vitamin B6-deficient mice. Br J Nutr. 1990;63(1):27-36.

190. Rios-Avila L, Coats B, Chi Y-Y, et al. Metabolite Profile Analysis Reveals Association of Vitamin B-6 with Metabolites Related to One-Carbon Metabolism and Tryptophan Catabolism but Not with Biomarkers of Inflammation in Oral Contraceptive Users and Reveals the Effects of Oral Contraceptives on These Processes. J Nutr. 2015;145(1):87-95.

191. Brown RR, Yess N, Price JM, Linkswiler H, Swan P, Hankes LV. Vitamin B6 Depletion in Man: Urinary Excretion of Quinolinic Acid and Niacin Metabolites. J Nutr. 1965;87(4):419-423.

192. Theofylaktopoulou D, Ulvik A, Midttun Ø, et al. Vitamins B 2 and B 6 as determinants of kynurenines and related markers of interferon-γ-mediated immune activation in the community-based Hordaland Health Study. Br J Nutr. 2014;112(7):1065-1072.

193. Rose D, Toseland P. Urinary excretion of quinolinic acid and other tryptophan metabolites after deoxypyridoxine or oral contraceptive administration. Metabolism. 1973;22(2):165-171.

194. Davis I, Liu A. What is the tryptophan kynurenine pathway and why is it important to neurotherapeutics? Exp Rev Neurotherap. 2015;15(7):719-721.

195. Schwarcz R, Bruno JP, Muchowski PJ, Wu HQ. Kynurenines in the mammalian brain: when physiology meets pathology. Nat Rev Neurosci. 2012;13(7):465-477.

196. Zheng P, Chen JJ, Huang T, et al. A novel urinary metabolite signature for diagnosing major depressive disorder. J Proteome Res. 2013;12(12):5904-5911.

197. Oxenkrug G. Serotonin-kynurenine hypothesis of depression: historical overview and recent developments. Curr Drug Targets. 2013;14(5):514-521.

198. Rider LG, Schiffenbauer AS, Zito M, et al. Neopterin and quinolinic acid are surrogate measures of disease activity in the juvenile idiopathic inflammatory myopathies. Clin Chem. 2002;48(10):1681-1688.

199. Kandemir H, Taneli F. The possible role of the kynurenine pathway and the Cytokine levels in the adolescents with major depression. Klin Psikofarmakol Bult. 2019;29:271-273.

200. Myint AM. Kynurenines: from the perspective of major psychiatric disorders. FEBS J. 2012;279(8):1375-1385.

201. Ciorba MA. Kynurenine pathway metabolites: relevant to vitamin B-6 deficiency and beyond. Am J Clin Nutr. 2013;98(4):863-864.

202. Payne IR, Walsh EM, Whittenburg EJR. Relationship of dietary tryptophan and niacin to tryptophan metabolism in schizophrenics and nonschizophrenics. Am J Clin Nutr. 1974;27(6):565-571.

203. LINKSWILER H. Biochemical and Physiological Changes in Vitamin B6 Deficiency. Am J Clin Nutr. 1967;20(6):547-557.

204. Luhby AL, Brin M, Gordon M, Davis P, Murphy M, Spiegel H. Vitamin B6 metabolism in users of oral contraceptive agents. I. Abnormal urinary xanthurenic acid excretion and its correction by pyridoxine. Am J Clin Nutr. 1971;24(6):684-693.

205. Chiang EP, Selhub J, Bagley PJ, Dallal G, Roubenoff R. Pyridoxine supplementation corrects vitamin B6 deficiency but does not improve inflammation in patients with rheumatoid arthritis. Arthr Res Ther. 2005;7(6):R1404-1411.

206. Yess N, Price JM, Brown RR, Swan PB, Linkswiler H. Vitamin B6 Depletion in Man: Urinary Excretion of Tryptophan Metabolites. J Nutr. 1964;84(3):229-236.

207. Eisenhofer G, Aneman A, Friberg P, et al. Substantial production of dopamine in the human gastrointestinal tract. J Clin Endocrinol Metab. 1997;82(11):3864-3871.

208. Schneider G, Kack H, Lindqvist Y. The manifold of vitamin B6 dependent enzymes. Structure. 2000;8(1):R1-6.

209. Ash DE, Papadopoulos NJ, Colombo G, Villafranca J. Kinetic and spectroscopic studies of the interaction of copper with dopamine beta-hydroxylase. J Biol Chem. 1984;259(6):3395-3398.

210. Ma Z, Liu H, Wu B. Structure-based drug design of catechol-O-methyltransferase inhibitors for CNS disorders. Br J Clin Pharmacol. 2014;77(3):410-420.

211. Gaweska H, Fitzpatrick PF. Structures and Mechanism of the Monoamine Oxidase Family. Biomol Concepts. 2011;2(5):365-377.

212. Weldin J, Jack R, Dugaw K, Kapur RP. Quercetin, an over-the-counter supplement, causes neuroblastoma-like elevation of plasma homovanillic acid. PedDev Pathol. 2003;6(6):547-551.

213. Combet E, Lean ME, Boyle JG, Crozier A, Davidson DF. Dietary flavonols contribute to false-positive elevation of homovanillic acid, a marker of catecholamine-secreting tumors. Int J ClinChem. 2011;412(1-2):165-169.

214. Nishi M, Miyake H, Takeda T, Takasugi N, Hanai J, Kawai T. Urinary vanillylmandelic acid and homovanillic acid levels in randomly-sampled urine for the mass screening of neuroblastoma. Jap J Clin Oncol. 1990;20(3):268-270.

215. Barco S, Gennai I, Reggiardo G, et al. Urinary homovanillic and vanillylmandelic acid in the diagnosis of neuroblastoma: report from the Italian Cooperative Group for Neuroblastoma. Clin Biochem. 2014;47(9):848-852.

216. Baik J-H. Dopamine Signaling in reward-related behaviors. Front Neural Circ. 2013;7(152).

217. Kaluzna-Czaplinska J, Socha E, Rynkowski J. Determination of homovanillic acid and vanillylmandelic acid in urine of autistic children by gas chromatography/mass spectrometry. Int Med J Exp Clin Res. 2010;16(9):Cr445-450.

218. De Bellis MD, Lefter L, Trickett PK, Putnam FW. Urinary catecholamine excretion in sexually abused girls. J Am Acad Child Adoles Psych. 1994;33(3):320-327.

219. Barthelemy C, Bruneau N, Cottet-Eymard J, et al. Urinary free and conjugated catecholamines and metabolites in autistic children. J Autism Develop Dis. 1988;18(4):583-591.

220. Frankenhaeuser M, Lundberg U, Von Wright MR, Von Wright J, Sedvall G. Urinary monoamine metabolites as indices of mental stress in healthy males and females. Pharmacol Biochem Behav. 1986;24(6):1521-1525.

221. Lykouras L, Markianos M, Hatzimanolis J, Malliaras D, Stefanis C. Association of biogenic amine metabolites with symptomatology in delusional (psychotic) and nondelusional depressed patients. Progr Neuro-Psychopharmacol Biol Psych. 1995;19(5):877-887.

222. Agren H. Life at risk: markers of suicidality in depression. Psychiatr Dev. 1983;1(1):87-103.

223. Linnoila M, Karoum F, Potter WZ. Effects of Antidepressant Treatments on Dopamine Turnover in Depressed Patients. Arch Gen Psychiatr. 1983;40(9):1015-1017.

224. Eisenhofer G, Kopin IJ, Goldstein DS. Catecholamine Metabolism: A Contemporary View with Implications for Physiology and Medicine. Pharmacol Rev. 2004;56(3):331.

225. Kopin IJ. Evolving views of the metabolic fate of norepinephrine. Endocrinol Exp. 1982;16(3-4):291-300.

226. Maas J. MHPC: Basic Mech Psychopathol. Academic Press; 2012.

227. Grouzmann E, Lamine F. Determination of catecholamines in plasma and urine. Best Pract Res Clin Endocrinol Metab. 2013;27(5):713-723.

228. Alam N, Wasi N, Naeem S, et al. Methylphenidate increases the urinary excretion of vanillylmandelic acid in rats that is attenuated by buspirone co-administration. Pak J Pharm Sci. 2019;32(2 (Supplementary)):895-898.

229. Garvey MJ, Noyes R, Jr., Woodman C, Laukes C. The association of urinary 5-hydroxyindoleacetic acid and vanillylmandelic acid in patients with generalized anxiety. Neuropsychobiology. 1995;31(1):6-9.

230. Williams CM, Greer M. Homovanillic Acid and Vanilmandelic Acid in Diagnosis of Neuroblastoma. JAMA. 1963;183(10):836-840.

231. Sunderman FW, Jr. Measurements of Vanilmandelic Acid for the Diagnosis of Pheochromocytoma and Neuroblastoma. Am J Clin Pathol. 1964;42(5):481-497.

232. Gregianin L, McGill A, Pinheiro C, Brunetto A. Vanilmandelic acid and homovanillic acid levels in patients with neural crest tumor: 24-Hour urine collection versus random sample. Ped Hematol Oncol. 2009;14:259-265.

233. Januszewicz W, Wocial B. Urinary excretion of catecholamines and their metabolites in patients with renovascular hypertension. Jap Heart J. 1978;19(4):468-478.

234. Helin P, Kuoppasalmi K, Laakso J, Harkonen M. Human urinary biogenic amines and some physiological responses during situation stress. Int J Psychophysiol. 1988;6(2):125-132.

235. Brantley PJ, Dietz LS, McKnight GT, Jones GN, Tulley R. Convergence between the Daily Stress Inventory and endocrine measures of stress. J Consult Clin Psychol. 1988;56(4):549-551.

236. Dikanovic M, Kadojic D, Demarin V, et al. The effect of stress hormones on cerebral hemodynamics in patients with chronic posttraumatic stress disorder. Acta Clin Croat. 2009;48(4):405-411.

237. Pequignot JM, Peyrin L, Mayet MH, Flandrois R. Metabolic adrenergic changes during submaximal exercise and in the recovery period in man. J Appl Physiol. 1979;47(4):701-705.

238. Takeda A. Manganese action in brain function. Brain Research Reviews. 2003;41(1):79-87.

239. Ai LB, Chua LH, New AL, et al. Urinary homovanillic acid (HVA) and vanillymandelic acid (VMA) in workers exposed to manganese dust. Biol Trace Elem Res. 1998;64(1-3):89-99.

240. Chen P, Chakraborty S, Mukhopadhyay S, et al. Manganese homeostasis in the nervous system. J Neurochem. 2015;134(4):601-610.

241. Robertson D, Low PA, Polinsky RJ. Primer on the Autonomic Nervous System. Academic Press; 2011.

242. Montoya A, Escobar R, Garcia-Polavieja MJ, et al. Changes of urine dihydroxyphenylglycol to norepinephrine ratio in children with attention-deficit hyperactivity disorder (ADHD) treated with atomoxetine. J Child Neurol. 2011;26(1):31-36.

243. Hopkins SC, Sunkaraneni S, Skende E, et al. Pharmacokinetics and Exposure-Response Relationships of Dasotraline in the Treatment of Attention-Deficit/Hyperactivity Disorder in Adults. Clin Drug Invest. 2016;36(2):137-146.

244. Garvey M, Hollon SD, DeRubeis RJ, Evans MD, Tuason V. Does 24-h urinary MHPG predict treatment response to antidepressants? I. A review. J Affect Dis. 1990;20(3):173-179.

245. Perry G, Fitzsimmons B, Shapiro L, Irwin P. Clinical study of mianserin, imipramine and placebo in depression: blood level and MHPG correlations. Br J Clin Pharmacol. 1978;5(S1):35S-41S.

246. Eisenhofer G, Kopin IJ, Goldstein DS. Catecholamine metabolism: a contemporary view with implications for physiology and medicine. Pharmacol Rev. 2004;56(3):331-349.

247. Mårdh G, Luehr CA, Vallee BL. Human class I alcohol dehydrogenases catalyze the oxidation of glycols in the metabolism of norepinephrine. Proc Nat Acad Sci USA. 1985;82(15):4979-4982.

248. Freedman RR. Biochemical, metabolic, and vascular mechanisms in menopausal hot flashes. Fertility Sterility. 1998;70(2):332-337.

249. Freedman RR. Pathophysiology and treatment of menopausal hot flashes. Paper presented at: Seminars in reproductive medicine2005.

250. Gaweesh SS, Abdel-Gawad MMM, Nagaty AM, Ewies AAA. Folic acid supplementation may cure hot flushes in postmenopausal women: a prospective cohort study. Gynecol Endocrinol. 2010;26(9):658-662.

251. Müller HU, Riemann D, Berger M, Müller W. The influence of total sleep deprivation on urinary excretion of catecholamine metabolites in major depression. Acta Psych Scand. 1993;88(1):16-20.

252. Baliga L, Rao A, Raja A, Rao SN. A study of urinary excretion of biogenic amine metabolites in epilepsy. Acta Neurol Scand. 1983;68(6):413-416.

253. Garvey MJ, Tollefson GD, Orsulak PJ. Elevations of urinary MHPG in depressed patients with panic attacks. Psychiatry Res. 1987;20(3):183-187.

254. Frankenhaeuser M, Lundberg U, Rauste von Wright M, von Wright J, Sedvall G. Urinary monoamine metabolites as indices of mental stress in healthy males and females. Pharmacol Biochem Behav. 1986;24(6):1521-1525.

255. Lehnert H. Pheochromocytoma: Pathophysiology and Clinical Management. Vol 31: Karger Medical and Scientific Publishers; 2004.

256. Seiden LS, Miller FE, Heffner TG. Neurotransmitters in Attention Deficit Disorder. Attention Deficit Disord Pod: Attention Deficit Disord Pod. 2013:223.

257. Schildkraut JJ, Orsulak PJ, Schatzberg AF, et al. Toward a biochemical classification of depressive disorders. I. Differences in urinary excretion of MHPG and other catecholamine metabolites in clinically defined subtypes of depressions. Arch Gen Psychiatry. 1978;35(12):1427-1433.

258. Gerner RH, Gwirtsman HE. Abnormalities of dexamethasone suppression test and urinary MHPG in anorexia nervosa. Am J Psych. 1981.

259. Corcuff J-B, Chardon L, El Hajji Ridah I, Brossaud J. Urinary sampling for 5HIAA and metanephrines determination: revisiting the recommendations. Endocr Connect. 2017;6(6):R87-R98.

260. Motomura Y, Ghia JE, Wang H, et al. Enterochromaffin cell and 5-hydroxytryptamine responses to the same infectious agent differ in Th1 and Th2 dominant environments. Gut. 2008;57(4):475-481.

261. Hasler WL. Serotonin and the GI tract. Curr Gastroenterol Rep. 2009;11(5):383-391.

262. Sikander A, Rana SV, Prasad KK. Role of serotonin in gastrointestinal motility and irritable bowel syndrome. Clin Chim Acta. 2009;403(1-2):47-55.

263. Zuetenhorst JM, Korse CM, Bonfrer JM, Peter E, Lamers CB, Taal BG. Daily cyclic changes in the urinary excretion of 5-hydroxyindoleacetic acid in patients with carcinoid tumors. Clin Chem. 2004;50(9):1634-1639.

264. Pedersen AT, Batsakis JG, Vanselow NA, McLean JA. False-Positive Tests for Urinary 5-Hydroxyindoleacetic Acid: Error in Laboratory Determinations Caused by Glyceryl Guaiacolate. JAMA. 1970;211(7):1184-1186.

265. Davidson FD. Paracetamol-associated interference in an HPLC-ECD assay for urinary free metadrenalines and catecholamines. Ann Clin Biochem. 2004;41(Pt 4):316-320.

266. Daya S, Anoopkumar-Dukie S. Acetaminophen inhibits liver trytophan-2,3-dioxygenase activity with a concomitant rise in brain serotonin levels and a reduction in urinary 5-hydroxyindole acetic acid. Life Sci. 2000;67(3):235-240.

267. Coward S, Boa FG, Sherwood RA. Sulfasalazine interference with HPLC assay of 5-hydroxyindole-3-acetic acid. Clin Chem. 1995;41(5):765-766.

268. Bhagat CI, Dick M. Naproxen interferes positively with 5-hydroxyindoleacetate assay. Clin Chem. 1982;28(5):1240.

269. Dunlop SP, Coleman NS, Blackshaw E, et al. Abnormalities of 5-hydroxytryptamine metabolism in irritable bowel syndrome. Clin Gastroenterol Hepatol. 2005;3(4):349-357.

270. Moskwa A, Chojnacki J, Wiśiewska-Jarosińska M, et al. [Serum serotonin concentration and urine 5-hydroxyindole acetic acid excretion in patients with irritable bowel syndrome]. Pol Merkur Lekarski. 2007;22(131):366-368.

271. Bousser MG, Elghozi JL, Laude D, Soisson T. Urinary 5-HIAA in migraine: Evidence of lowered excretion in young adult females. Cephalalgia. 1986;6(4):205-209.

272. Afarideh M, Behdadnia A, Noshad S, et al. Association of peripheral 5-hydroxyindole-3-acetic acid, a serotonin derivative, with metabolic syndrome and low-grade inflammation. Endocr Pract. 2015;21(7):711-718.

273. Emmett M. Acetaminophen toxicity and 5-oxoproline (pyroglutamic acid): a tale of two cycles, one an ATP-depleting futile cycle and the other a useful cycle. Clin J Am Soc Nephrol. 2014;9(1):191-200.

274. Lu SC. Glutathione synthesis. Biochim Biophys Acta. 2013;1830(5):3143-3153.

275. Dinescu A, Cundari TR, Bhansali VS, Luo JL, Anderson ME. Function of conserved residues of human glutathione synthetase: implications for the ATP-grasp enzymes. J Biol Chem. 2004;279(21):22412-22421.

276. Metges CC, Yu YM, Cai W, et al. Oxoproline kinetics and oxoproline urinary excretion during glycine- or sulfur amino acid-free diets in humans. Am J Physiol Endocrinol Metab. 2000;278(5):E868-876.

277. Persaud C, Forrester T, Jackson AA. Urinary excretion of 5-L-oxoproline (pyroglutamic acid) is increased during recovery from severe childhood malnutrition and responds to supplemental glycine. J Nutr. 1996;126(11):2823-2830.

278. Lord RS. Long-term patterns of urinary pyroglutamic acid in healthy humans. Physiol Rep. 2016;4(4):e12706.

279. Naudi A, Jove M, Ayala V, et al. Cellular dysfunction in diabetes as maladaptive response to mitochondrial oxidative stress. Exp Diab Res. 2012;2012.

280. Emmett M. Acetaminophen toxicity and 5-oxoproline (pyroglutamic acid): a tale of two cycles, one an ATP-depleting futile cycle and the other a useful cycle. Clin J Am Soc Nephrol. 2014;9(1):191-200.

281. Brooker G, Jeffery J, Nataraj T, Sair M, Ayling R. High anion gap metabolic acidosis secondary to pyroglutamic aciduria (5-oxoprolinuria): association with prescription drugs and malnutrition. Ann Clin Biochem. 2007;44(4):406-409.

282. Luyasu S, Wamelink MMC, Galanti L, Dive A. Pyroglutamic acid-induced metabolic acidosis: a case report. Acta Clin Belg. 2014;69(3):221-223.

283. Creer MH, Lau BW, Jones JD, Chan KM. Pyroglutamic acidemia in an adult patient. Clin Chem. 2019;35(4):684-686.

284. Creta M, Moldovan H, Poels K, et al. Integrated evaluation of solvent exposure in an occupational setting: air, dermal and bio-monitoring. Toxicol Lett. 2018;298:150-157.

285. Ikeda M, Imamura T, Hayashi M, Tabuchi T, Hara I. Evaluation of hippuric, phenylglyoxylic and mandelic acids in urine as indices of styrene exposure. Int Arch Arbeitsmed. 1974;32(1-2):93-101.

286. Wigaeus E, Lof A, Nordqvist MB. Uptake, distribution, metabolism, and elimination of styrene in man. A comparison between single exposure and co-exposure with acetone. Br J Indust Med. 1984;41(4):539-546.

287. Eitaki Y, Kawai T, Kishi R, Sakurai H, Ikeda M. Stability in urine of authentic phenylglyoxylic and mandelic acids as urinary markers of occupational exposure to styrene. J Occup Health. 2008:0804030004-0804030004.

288. Szűcs S, Toth L, Legoza J, Sarvary A, Adany R. Simultaneous determination of styrene, toluene, and xylene metabolites in urine by gas chromatography/mass spectrometry. Arch Toxicol. 2002;76(10):560-569.

289. Santini F, Mantovani A, Cristaudo A, et al. Thyroid function and exposure to styrene. Thyroid. 2008;18(10):1065-1069.

290. Wongvijitsuk S, Navasumrit P, Vattanasit U, Parnlob V, Ruchirawat M. Low level occupational exposure to styrene: Its effects on DNA damage and DNA repair. Int J Hygiene Environ Health. 2011;214(2):127-137.

291. Won YL, Ko Y, Heo K-H, Ko KS, Lee M-Y, Kim K-W. The effects of long-term, low-level exposure to monocyclic aromatic hydrocarbons on worker's insulin resistance. Safety and health at work. 2011;2(4):365-374.

292. Organization WH. Methyl tertiary-butyl ether (MTBE) in drinkingwater, background document for development of WHO Guidelines for Drinking-Water Quality. World Health Organization, Geneva(WHO/SDE/WSH/0508/122). 2005.

293. Amberg A, Rosner E, Dekant W. Toxicokinetics of methyl tert-butyl ether and its metabolites in humans after oral exposure. Toxicol Sci. 2001;61(1):62-67.

294. Amberg A, Rosner E, Dekant W. Toxicokinetics of methyl tert-butyl ether and its metabolites in humans after oral exposure. Toxicol Sci. 2001;61(1):62-67.

295. Saeedi A, Fardid R, Khoshnoud MJ, Kazemi E, Omidi M, Mohammadi-Bardbori A. Disturbance of zinc and glucose homeostasis by methyl tert-butyl ether (MTBE); evidence for type 2 diabetes. Xenobiotica. 2017;47(6):547-552.

296. Andreoli R, Spatari G, Pigini D, et al. Urinary biomarkers of exposure and of oxidative damage in children exposed to low airborne concentrations of benzene. Environ Res. 2015;142:264-272.

297. Kalkbrenner AE, Windham GC, Zheng C, et al. Air Toxics in Relation to Autism Diagnosis, Phenotype, and Severity in a U.S. Family-Based Study. Environ Health Perspect. 2018;126(3):037004-037004.

298. Salimi A, Vaghar-Moussavi M, Seydi E, Pourahmad J. Toxicity of methyl tertiary-butyl ether on human blood lymphocytes. Environ Sci Pollut Res. 2016;23(9):8556-8564.

299. Rota F, Conti A, Campo L, et al. Epigenetic and Transcriptional Modifications in Repetitive Elements in Petrol Station Workers Exposed to Benzene and MTBE. Int J Environ Res Pub Health. 2018;15(4):735.

300. O'Callaghan JP, Daughtrey WC, Clark CR, Schreiner CA, White R. Health assessment of gasoline and fuel oxygenate vapors: neurotoxicity evaluation. Reg Toxicol Pharmacol. 2014;70(2 Suppl):S35-42.

301. Gray TM, Steup D, Roberts LG, et al. Health assessment of gasoline and fuel oxygenate vapors: reproductive toxicity assessment. Reg Toxicol Pharmacol. 2014;70(2 Suppl):S48-57.

302. Yang J, Wei Q, Peng X, Peng X, Yuan J, Hu D. Relationship between methyl tertiary butyl ether exposure and non-alcoholic fatty liver disease: a cross-sectional study among petrol station attendants in southern China. Int J Environ Res Pub Health. 2016;13(10):946.

303. Brosnan ME, Brosnan JT. Orotic Acid Excretion and Arginine Metabolism. J Nutr. 2007;137(6):1656S-1661S.

304. Nyc JF, Mitchell HK. Synthesis of Orotic Acid from Aspartic Acid. J Am Chem Soc. 1947;69(6):1382-1384.

305. Visek WJ. Nitrogen-stimulated orotic acid synthesis and nucleotide imbalance. Cancer Res. 1992;52(7 Suppl):2082s-2084s.

306. Löffler M, Carrey EA, Zameitat E. Orotate (orotic acid): An essential and versatile molecule. Nucleosid Nucleotid Nucl Acids. 2016;35(10-12):566-577.

307. Visek WJ, Shoemaker JD. Orotic acid, arginine, and hepatotoxicity. J Am Coll Nutr. 1986;5(2):153-166.

308. Salerno C, Crifo C. Diagnostic value of urinary orotic acid levels: applicable separation methods. J Chromatog B, Analyt Technol Biomed Life Sci. 2002;781(1-2):57-71.

309. Choi Y-J, Yoon Y, Lee K-Y, et al. Orotic Acid Induces Hypertension Associated with Impaired Endothelial Nitric Oxide Synthesis. Toxicol Sci. 2015;144(2):307-317.

310. Haggard ME, Lockhart LH. Megaloblastic anemia and orotic aciduria. A hereditary disorder of pyrimidine metabolism responsive to uridine. Am J Dis Child (1960). 1967;113(6):733-740.

311. Massey LK, Roman-Smith H, Sutton RA. Effect of dietary oxalate and calcium on urinary oxalate and risk of formation of calcium oxalate kidney stones. J Am Dietet Assoc. 1993;93(8):901-906.

312. Lange JN, Wood KD, Knight J, Assimos DG, Holmes RP. Glyoxal formation and its role in endogenous oxalate synthesis. Adv Urol. 2012;2012:819202.

313. Rashed MS, Aboul-Enein HY, AlAmoudi M, et al. Chiral liquid chromatography tandem mass spectrometry in the determination of the configuration of glyceric acid in urine of patients with D-glyceric and L-glyceric acidurias. Biomed Chromatog. 2002;16(3):191-198.

314. Van Schaftingen E. D-glycerate kinase deficiency as a cause of D-glyceric aciduria. FEBS Lett. 1989;243(2):127-131.

315. Wadman S, Duran M, Ketting D, et al. D-Glyceric acidemia in a patient with chronic metabolic acedosis. Clin Chim Acta. 1976;71(3):477-484.

316. Kalim A, Fitzsimons P, Till C, et al. Further evidence that d-glycerate kinase (GK) deficiency is a benign disorder. Brain Develop. 2017;39(6):536-538.

317. Madsen RK, Lundstedt T, Gabrielsson J, et al. Diagnostic properties of metabolic perturbations in rheumatoid arthritis. Arthr Res Therap. 2011;13(1):R19.

318. Yang J, Chen T, Sun L, et al. Potential metabolite markers of schizophrenia. Mol Psych. 2013;18(1):67-78.

319. Kemper MJ, Conrad S, Müller-Wiefel DE. Primary hyperoxaluria type 2. Eur J Ped. 1997;156(7):509-512.

320. Danpure CJ, Jennings PR. Peroxisomal alanine:glyoxylate aminotransferase deficiency in primary hyperoxaluria type I. FEBS Lett. 1986;201(1):20-24.

321. Dietzen DJ, Wilhite TR, Kenagy DN, Milliner DS, Smith CH, Landt M. Extraction of glyceric and glycolic acids from urine with tetrahydrofuran: utility in detection of primary hyperoxaluria. Clin Chem. 1997;43(8 Pt 1):1315-1320.

322. Barratt TM, Kasidas GP, Murdoch I, Rose GA. Urinary oxalate and glycolate excretion and plasma oxalate concentration. Arch Dis Childhood. 1991;66(4):501-503.

323. Knight J, Jiang J, Assimos DG, Holmes RP. Hydroxyproline ingestion and urinary oxalate and glycolate excretion. Kidney Int. 2006;70(11):1929-1934.

324. Rabbani N, Thornalley PJ. Dicarbonyls (glyoxal, methylglyoxal, and 3-deoxyglucosone). Uremic Toxins. 2012:177-192.

325. Knight J, Wood KD, Lange JN, Assimos DG, Holmes RP. Oxalate Formation From Glyoxal in Erythrocytes. Urology. 2016;88:226.e211-225.

326. Dindo M, Oppici E, Dell'Orco D, Montone R, Cellini B. Correlation between the molecular effects of mutations at the dimer interface of alanine-glyoxylate aminotransferase leading to primary hyperoxaluria type I and the cellular response to vitamin B(6). J Inherit Metab Dis. 2018;41(2):263-275.

327. Leumann E, Hoppe B, Neuhaus T. Management of primary hyperoxaluria: efficacy of oral citrate administration. Ped Nephrol. 1993;7(2):207-211.

328. Taylor EN, Curhan GC. Determinants of 24-hour urinary oxalate excretion. Clin J Am Soc Nephrol. 2008;3(5):1453-1460.

329. Trinchieri A. Diet and renal stone formation. Minerva medica. 2013;104(1):41-54.

330. Traxer O, Huet B, Poindexter J, Pak CY, Pearle MS. Effect of ascorbic acid consumption on urinary stone risk factors. J Urol. 2003;170(2 Pt 1):397-401.

331. Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Intake of vitamins B6 and C and the risk of kidney stones in women. J Am Soc Nephrol. 1999;10(4):840-845.

332. Tsao CS, Salimi SL. Effect of large intake of ascorbic acid on urinary and plasma oxalic acid levels. Int J Vitamin Nutr Res. 1984;54(2-3):245-249.

333. Selvam R. Calcium oxalate stone disease: role of lipid peroxidation and antioxidants. Urol Res. 2002;30(1):35-47.

334. Khan SR. Hyperoxaluria-induced oxidative stress and antioxidants for renal protection. Urol Res. 2005;33(5):349-357.

335. Armstrong MD, Shaw K, Wall P. The phenolic acids of human urine. J Biol Chem. 1956;218:293.

336. Cocker J, Mason HJ, Warren ND, Cotton RJ. Creatinine adjustment of biological monitoring results. Occup Med. 2011;61(5):349-353.

337. GARDE AH, HANSEN ÅM, KRISTIANSEN J, KNUDSEN LE. Comparison of Uncertainties Related to Standardization of Urine Samples with Volume and Creatinine Concentration. Ann Occup Hygiene. 2004;48(2):171-179.

338. Baxmann AC, Ahmed MS, Marques NC, et al. Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C. Clin J Am Soc Nephrol. 2008;3(2):348-354.

339. Graille M, Wild P, Sauvain JJ, Hemmendinger M, Guseva Canu I, Hopf NB. Urinary 8-OHdG as a Biomarker for Oxidative Stress: A Systematic Literature Review and Meta-Analysis. Int J Mol Sci. 2020;21(11).

340. Valavanidis A, Vlachogianni T, Fiotakis C. 8-hydroxy-2' -deoxyguanosine (8-OHdG): A critical biomarker of oxidative stress and carcinogenesis. J Environ Sci Health Part C. 2009;27(2):120-139.

341. Black CN, Bot M, Révész D, Scheffer PG, Penninx B. The association between three major physiological stress systems and oxidative DNA and lipid damage. Psychoneuroendocrinology. 2017;80:56-66.

342. Irie M, Tamae K, Iwamoto-Tanaka N, Kasai H. Occupational and lifestyle factors and urinary 8-hydroxydeoxyguanosine. Cancer Sci. 2005;96(9):600-606.

343. Wu LL, Chiou CC, Chang PY, Wu JT. Urinary 8-OHdG: a marker of oxidative stress to DNA and a risk factor for cancer, atherosclerosis and diabetics. Int J Clin Chem. 2004;339(1-2):1-9.

344. Di Minno A, Turnu L, Porro B, et al. 8-Hydroxy-2-deoxyguanosine levels and heart failure: A systematic review and meta-analysis of the literature. Nutr, Metab, Cardiovasc Diseases. 2017;27(3):201-208.

345. Guo C, Li X, Wang R, et al. Association between Oxidative DNA Damage and Risk of Colorectal Cancer: Sensitive Determination of Urinary 8-Hydroxy-2'-deoxyguanosine by UPLC-MS/MS Analysis. Sci Rep. 2016;6:32581.

346. Qing X, Shi D, Lv X, Wang B, Chen S, Shao Z. Prognostic significance of 8-hydroxy-2'-deoxyguanosine in solid tumors: a meta-analysis. BMC Cancer. 2019;19(1):997.

347. Urbaniak SK, Boguszewska K, Szewczuk M, Kaźmierczak-Barańska J, Karwowski BT. 8-Oxo-7,8-Dihydro-2'-Deoxyguanosine (8-oxodG) and 8-Hydroxy-2'-Deoxyguanosine (8-OHdG) as a Potential Biomarker for Gestational Diabetes Mellitus (GDM) Development. Molecules. 2020;25(1).

348. Masugata H, Senda S, Murao K, et al. Association between urinary 8-hydroxydeoxyguanosine, an indicator of oxidative stress, and the cardio-ankle vascular index in hypertensive patients. J Atheroscl Thromb. 2012;19(8):747-755.

349. Ece H, Mehmet E, Cigir BA, et al. Serum 8-OHdG and HIF-1α levels: do they affect the development of malignancy in patients with hypoactive thyroid nodules? Contemp Oncol. 2013;17(1):51-57.

350. Halczuk KM, Boguszewska K, Urbaniak SK, Szewczuk M, Karwowski BT. 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) and 8-hydroxy-2'-deoxyguanosine (8-OHdG) as a Cause of Autoimmune Thyroid Diseases (AITD) During Pregnancy?Yale J Biol Med. 2020;93(4):501-515.

351. Kawasaki Y, Li YS, Ootsuyama Y, Nagata K, Yamato H, Kawai K. Effects of smoking cessation on biological monitoring markers in urine. Genes Environ. 2020;42:26.

352. Hara M, Nishida Y, Shimanoe C, et al. Intensity-specific effect of physical activity on urinary levels of 8-hydroxydeoxyguanosine in middle-aged Japanese. Cancer Sci. 2016;107(11):1653-1659.

353. Arab H, Mahjoub S, Hajian-Tilaki K, Moghadasi M. The effect of green tea consumption on oxidative stress markers and cognitive function in patients with Alzheimer's disease: A prospective intervention study. Caspian J Intern Med. 2016;7(3):188-194.

800.522.4762 ● www.gdx.net