

Patient: **SAMPLE PATIENT**

Order Number:

Completed: January 29, 2008

Age: 31

Received: January 22, 2008

Sex: F


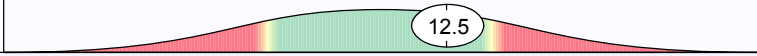
Collected: January 20, 2008

MRN:

Glycolysis Metabolites


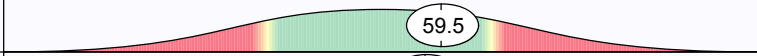
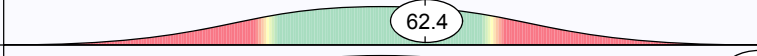


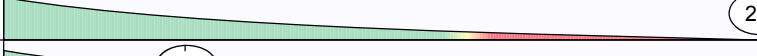
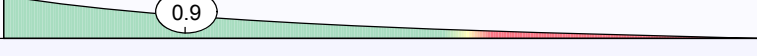
Reference Range

mmol/mol creatinine

1. Lactic Acid		6.3-36.4
2. Pyruvic Acid		1.1-15.4

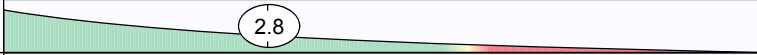
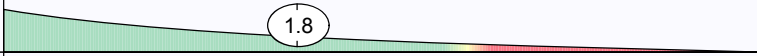
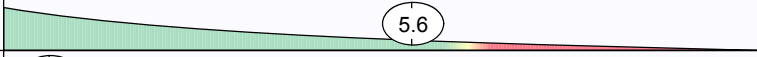
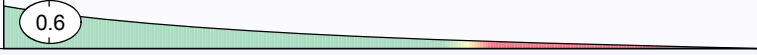
Citric Acid Cycle Metabolites

mmol/mol creatinine

3. Citric Acid		21.9-475.1
4. Cis-Aconitic Acid		1.4-76.8
5. Isocitric Acid		3.7-87.4
6. a-Ketoglutaric Acid (AKA)		0.5-16.0
7. Succinic Acid		<= 20.0
8. Fumaric Acid		<= 1.4
9. Malic Acid		<= 2.4

Ketone and Fatty Acid Metabolites

mmol/mol creatinine

10. Adipic Acid		<= 5.2
11. Suberic Acid		<= 3.0
12. b-OH-b-Methylglutaric Acid (HMG)		<= 6.7
13. b-OH-Butyric Acid (BHBA)		<= 6.4

Creatinine Concentration

mol / L

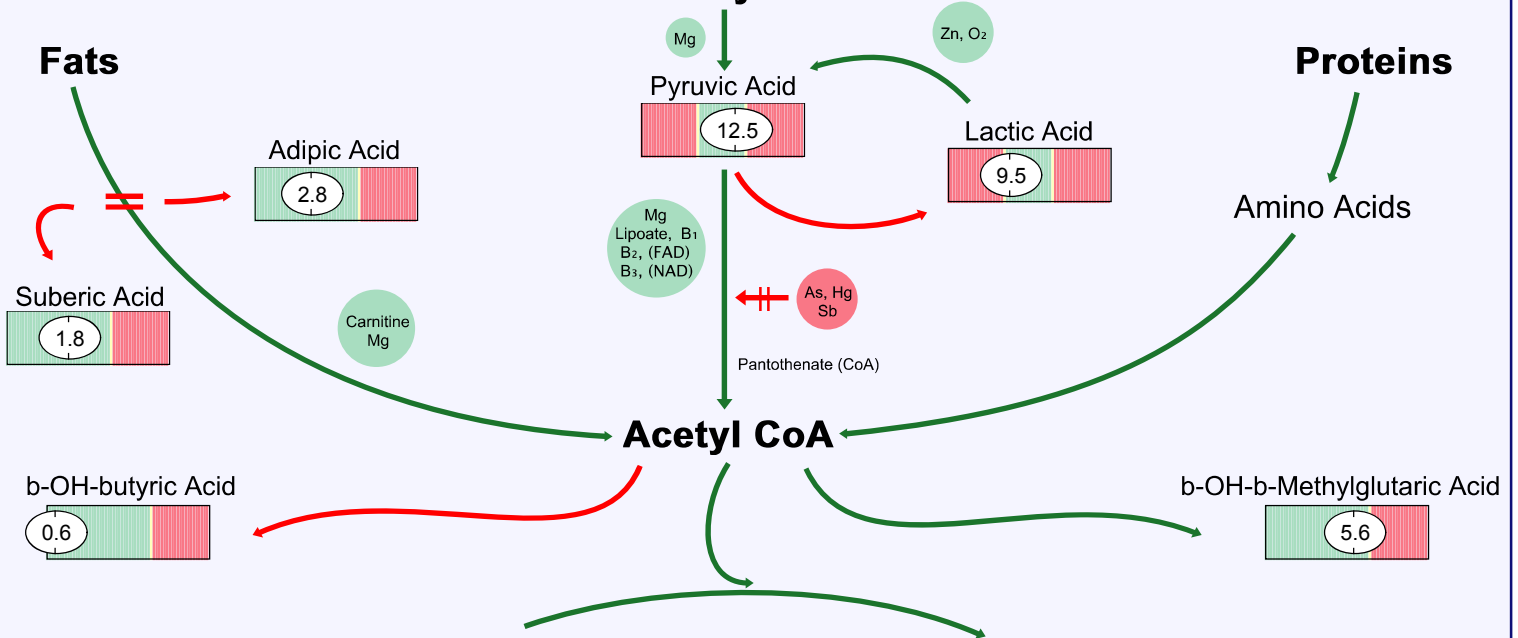
14. Creatinine Concentration		0.0031-0.0195
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Lab Comments

This test has been developed and its performance characteristics determined by GSDL, Inc. It has not been cleared or approved by the U.S. Food and Drug Administration.

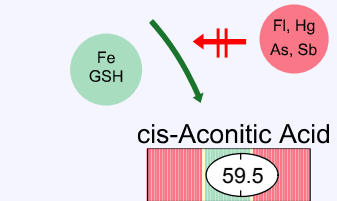
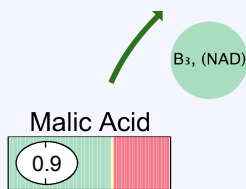
Kreb's Cycle at a Glance

Carbohydrates

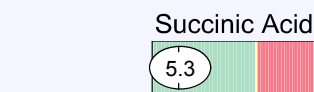
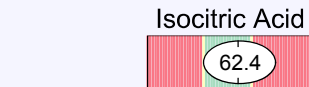
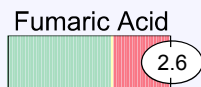


Oxaloacetic Acid

Citric Acid

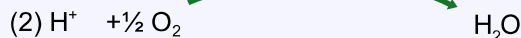


Citric Acid Cycle

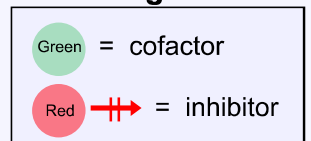


NADH / FADH₂

Electron Transport and Oxidative Phosphorylation



Legend



Commentary

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

Analyte Histogram Changes: The shape of the histograms for many of the analytes on this test have changed. The new histograms more accurately reflect the distribution of results for the reference population and for expected, normal levels. No reference range changes have been made.

ANALYTES CHARACTERISTIC OF CELLULAR ENERGY AND MITOCHONDRIAL FUNCTION

These markers are metabolites from four important biochemical pathways in the body, all of which significantly impact the production and availability of energy at the cellular level: glycolysis, the citric acid cycle (Krebs cycle) and both beta-oxidation and omega-oxidation of fatty acids. These analytes provide unique insight into macronutrient catabolism and mitochondrial function in cells. Abnormal levels may be associated with fatigue, malaise, myalgia, headache, muscle weakness, myopathy, hypotonia, or acid-base imbalance. This test is intended to be a diagnostic aid for acquired disorders in these pathways. It is not intended for diagnosis of inborn errors of organic acid metabolism, as this would require extensive molecular genetics testing. However, significantly abnormal findings could be consistent with such inborn errors.

If significant abnormalities persist after removal of toxics, supplementation of appropriate nutrients, dietary and hormonal adjustments, and correction of intestinal dysbiosis or infection, it is suggested that the patient be referred to a medical center with capabilities for diagnosis and treatment of congenital metabolic defects.

Citric Acid, or citrate, is measured to be high. Citric acid is a key component of the citric acid cycle and is formed inside the mitochondria from acetyl coenzyme A and oxaloacetic acid.

Citric acid is essential in the production of bicarbonate, a compound that helps to maintain proper pH in the body. Elevated urinary citrate may be a sign of a metabolic pH imbalance (metabolic acidosis), possibly due to damaged proximal tubular function in the kidney that results in urinary wasting of citrate. Another possible cause of elevated urine citrate is pancreatic dysfunction, as bicarbonate production would be reduced, leading to less utilization of citric acid. In this situation, cis-aconitic and isocitric acids may be also elevated.

However, if cis-aconitic or isocitric acids are low, this may be indicative of impaired enzymatic conversion within the citric acid cycle. The enzyme cis-aconitase converts citric acid into cis-aconitic acid. This enzyme requires the presence of a sulfhydryl (-SH) group from cysteine or glutathione and it is activated by ferrous iron (Fe⁺²). Deficiencies of methionine, cysteine, glutathione, or iron, would result in sub-optimal enzyme efficiency. In addition, toxic elements with high sulfur affinity, like arsenic, antimony and mercury, may impair cis-aconitase activity. Also, xenobiotic toxicity, if it depletes glutathione, or increased oxidative stress from any cause may lead to elevated citrate. Excess fluorine can combine with acetate and, as fluoroacetate, can also inhibit the cis-aconitase enzyme. Any of the above situations may result in increased urinary citrate.

Alpha-ketoglutaric Acid (alpha-ketoglutarate or AKG) is measured to be elevated. Alpha-ketoglutaric acid is formed from isocitrate or from the deamination or transamination of glutamate (a process requiring vitamin B6). Metabolism of alpha-ketoglutaric acid then leads to the formation of succinyl CoA.

Commentary

Elevated alpha-ketoglutaric acid can be due to specific weakness in the alpha-ketoglutaric acid dehydrogenase complex that converts alpha-ketoglutarate to is downstream citric acid cycle metabolite, succinic acid.

Dehydrogenase enzymes require vitamin B1 as thiamin pyrophosphate, vitamin B2 as FAD, vitamin B3 as NAD, and lipoic acid. Phosphorylation requiring magnesium is also involved, and coenzyme A is needed. Coenzyme A is formed from the nutrients pantothenic acid, cysteine, and magnesium, and requires phosphorylation and energy from CTP and ATP. Insufficiencies of these nutrients or cofactors may cause elevated alpha-ketoglutaric acid. Arsenic can also inhibit the dehydrogenase enzyme.

Elevated alpha-ketoglutaric acid also may be accompanied by elevated glyoxylate and oxalate. If there is weakness in the decarboxylation of glyoxylate and alpha-ketoglutarate, renal stone (calcium oxalate) formation is possible. This is not a common condition, and its diagnosis should be made from urine levels of oxalate and glyoxylate. In this case, supplements of vitamin B6 or pyridoxal 5-phosphate may be beneficial. (B6 aids the transformation of glyoxylate to glycine and thus decreases oxalate formation.)

Moderate increase in urinary alpha-ketoglutaric acid may occur, without clinical significance, with low-carbohydrate or high-protein diets (where metabolic need is increased).

Fumaric Acid (fumarate) is elevated. Fumarate is an intermediate in the citric acid cycle and it is also produced when argininosuccinic acid becomes arginine in the urea cycle. Both reactions occur within the mitochondrial matrix. A minor amount is contributed by oxidative catabolism of phenylalanine and tyrosine. Fumarate becomes malate (malic acid) and both may be elevated if malate dehydrogenase is weak. That enzyme requires vitamin B3 as NAD. Weakness in either pyruvate carboxylase or pyruvate dehydrogenase (usually evidenced by elevated lactic acid or high pyruvic acid) can also result in elevated fumaric acid. If malic acid is also high, investigate that as a reason for high fumarate.

INTERPRETATION AT A GLANCE

Citric Acid is elevated.

<u>Possible Conditions</u>	<u>Possible Remedies</u>	<u>Confirming Tests</u>
Impaired transformation to cis-aconitic acid		
Glutathione or cysteine insufficiency	GSH 250-1000 mg/d NAC 100-1000 mg/d	Amino acid analysis RBC GSH assay
Iron deficiency	Iron 5-20 mg/d	Serum Fe, ferritin
Oxidant stress	Antioxidant therapy	Oxidative Stress analysis
Elemental excesses: F, Hg, Sb, As	Detoxification Assess water quality elements with provocation	Hair or RBC element analyses Urine toxic
Urinary citrate wasting, acidosis		
Pancreatic bicarbonate insufficiency,	Alkalization with bicarbonate	Urine pH, blood gas/electrolyte/

Commentary

secondary to citrate loss	after meals Referral to metabolic specialist	anion gap Salivary pH Creatinine clearance Digestive stool analysis Amino acid analysis
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Alpha-ketoglutaric Acid (AKG) is elevated.

<u>Possible Conditions</u>	<u>Possible Remedies</u>	<u>Confirming Tests</u>
Weak AKG dehydrogenase activity		
Cofactor insufficiency: B ₁ , B ₂ (FAD), B ₃ (NAD), lipoic acid, Mg	Vitamin B ₁ 25-100 mg/d Vitamin B ₂ 5-50 mg/d Vitamin B ₃ 20-50 mg/d or niacinamide 20-200 mg/d lipoic acid 25-200 mg/d Mg 100-200 mg/d	Vitamin analysis RBC or Hair element analyses
Coenzyme A or cysteine insufficiency	Pantothenic acid 50-500 mg/d Cystine 100-1000 mg/d, or NAC 100-1000 mg/d Mg 100-200 mg/d	Amino acid analysis Vitamin analysis
Toxic element burden: As, Hg, Sb, Cd, Te, Bi, Co	Detoxification	Hair, RBC element analyses Urine toxic elements w/ provocation
<u>Less Common:</u>		
Metabolic acidosis	Alkalizers, electrolyte replenishment	Blood lactic, pyruvic acids, blood gases
	Referral to a specialist	electrolytes, urine pH
Disordered glucose or glycogen metabolism / glycogen storage disease	Referral to a specialist	Biochemical genetics testing
Congenital disorder of organic acid metabolism (e.g. multiple dehydrogenase dysfunction)	Referral to a specialist	Biochemical genetics testing

Fumaric Acid is elevated.

<u>Possible Conditions</u>	<u>Possible Remedies</u>	<u>Confirming Tests</u>
Use of DL-fumaric or DL-malic acid supplements	Change to L-forms	Check labels
Secondary to pyruvate or lactate excesses	See Elevated Pyruvic or Lactic Acids	See Elevated Pyruvic or Lactic Acids
Secondary to elevated malate	See Elevated Malic or	See Elevated Malic or