

**Results:**



Tests	Results	H/L	Reference ranges
<b>Pre-Analytical Screening</b>			
U-Creatinine	9.78		mmol/L
Specific Gravity (U-Labstix)	1.02		
pH (U-Labstix)	5		
Leucocytes (U-Labstix)	Negative		
Nitrites(U-Labstix)	Negative		
Haemoglobin (U-Labstix)	Negative		
Blood (U-Labstix)	Negative		
Protein (U-Labstix)	Negative		
Glucose (U-Labstix)	Negative		
Ascorbic Acid (U-Labstix)	Negative		
Ketones (U-Labstix)	Trace		
Urobilinogen (U-Labstix)	Trace		
Bilirubin (U-Labstix)	Trace		

<b>Urine organic acids: Glycolysis and Krebs Cycle intermediates</b>			
2-Oxoglutaric acid/2-Ketoglutaric acid	1.15		< 74.00 mmol/mol creat
Aconitic acid	<b>31.07</b>	<b>H</b>	5.20 - 16.30 mmol/mol creat
Citric acid	<b>82.43</b>	<b>L</b>	87.00 - 639.00 mmol/mol creat
D/L-2-Hydroxyglutaric acid	8.07		< 52.00 mmol/mol creat
DL-Lactic acid	2.88		< 16.40 mmol/mol creat
Fumaric acid	0.76		0.20 - 1.70 mmol/mol creat
Isocitric acid	14.19		< 119.10 mmol/mol creat
Malic acid	1.74		< 5.30 mmol/mol creat
Pyruvic acid	0.13		< 3.70 mmol/mol creat
Succinic acid	9.13		2.50 - 13.50 mmol/mol creat

<b>Urine organic acids: Fatty acid oxidation intermediates</b>			
3-Hydroxybutyric acid	<b>28.38</b>	<b>H</b>	< 6.40 mmol/mol creat
Acetoacetic acid	10.97		< 24.90 mmol/mol creat
Adipic acid	3.12		< 5.00 mmol/mol creat
Ethylmalonic acid	3.55		< 4.00 mmol/mol creat
Methylsuccinic acid	BDL		< 6.20 mmol/mol creat
Sebacic acid	0.42		< 5.00 mmol/mol creat
Suberic acid	0.96		< 1.90 mmol/mol creat

<b>Urine organic acids: Branched chain amino acid intermediates</b>			
2-Ethylhydracrylic-/2-Ethyl-3-OH-propionic acid	<b>8.48</b>	<b>H</b>	< 2.90 mmol/mol creat
2-Hydroxyisocaproic acid	0.06		< 0.39 mmol/mol creat
2-Hydroxyisovaleric acid	0.26		< 0.48 mmol/mol creat
2-Oxoisovaleric acid / 3-Methyl-2-oxobutyric acid	0.14		< 1.10 mmol/mol creat
3-Hydroxy-2-methylbutyric acid	1.93		< 6.20 mmol/mol creat
3-Hydroxyisobutyric acid	21.73		11.80 - 59.80 mmol/mol creat
3-Hydroxyisovaleric acid	8.28		< 17.20 mmol/mol creat
3-Methyl-2-oxovaleric-/2-Keto-3-methylvaleric acid	BDL		< 4.80 mmol/mol creat
3-Methylglutaconic acid	2.9		2.30 - 8.30 mmol/mol creat
3-Methylglutaric acid	<b>0.1</b>	<b>L</b>	1.00 - 6.50 mmol/mol creat
2-Ketoisocaproic acid/4-Methyl-2-oxovaleric acid	0.01		< 0.86 mmol/mol creat
Malonic acid	BDL		< 3.10 mmol/mol creat

<b>Urine organic acids: Phenylalanine and Tyrosine intermediates</b>			
Phenylpyruvic acid	BDL		< 0.76 mmol/mol creat
3-Phenyllactic acid	BDL		< 0.49 mmol/mol creat
4-Hydroxyphenyllactic acid	0.83		< 3.00 mmol/mol creat
4-Hydroxyphenylpyruvic acid	BDL		< 4.30 mmol/mol creat
Mandelic acid	0.14		< 1.70 mmol/mol creat
Homogentisic acid	0.11		< 2.80 mmol/mol creat
Succinylacetone	BDL		< 4.70 mmol/mol creat

<b>Urine organic acids: Other Amino acid intermediates</b>			
3-Hydroxyglutaric acid (Lysine Metabolism)	<b>4.17</b>	<b>H</b>	< 3.00 mmol/mol creat

Tests	Results	H/L	Reference ranges	
<b>Urine organic acids: Other Amino acid intermediates</b>				
Glutaconic acid (Lysine Metabolism)	BDL		< 3.10	mmol/mol creat
N-Acetylaspartic acid (Aspartic Metabolism)	1.25		< 7.00	mmol/mol creat
<b>Urine organic acids: Pyrimidine and Urea cycle intermediates</b>				
Orotic acid	0.5		< 1.20	mmol/mol creat
Thymine	BDL		< 0.90	mmol/mol creat
Uracil	2.21		< 22.80	mmol/mol creat
Uric acid	119.63		93.00 - 329.00	mmol/mol creat
<b>Urine organic acids: Detoxification markers</b>				
2-Hydroxybutyric acid	BDL		< 6.90	mmol/mol creat
2-Methylhippuric acid	BDL		< 13.50	mmol/mol creat
Glyceric acid	0.6		< 28.80	mmol/mol creat
Glycolic acid	8.61		< 78.10	mmol/mol creat
N-2-Methylbutyrylglycine	0.06		< 2.00	mmol/mol creat
N-Butyrylglycine	BDL		< 2.00	mmol/mol creat
N-Hexanoylglycine	BDL		< 2.00	mmol/mol creat
N-Isobutyrylglycine	0.63		< 3.80	mmol/mol creat
N-Isovalerylglycine	0.24		< 10.00	mmol/mol creat
N-Phenylpropionylglycine	BDL		< 0.60	mmol/mol creat
N-Suberylglycine	BDL		< 0.52	mmol/mol creat
N-Tiglylglycine	2.92	H	< 2.00	mmol/mol creat
N-3-Methylcrotonylglycine	BDL		< 2.00	mmol/mol creat
Oxalic acid	83.87	H	1.11 - 33.34	mmol/mol creat
Pyroglutamic acid	7.24		< 24.90	mmol/mol creat
<b>Urine organic acids: Microbiome markers</b>				
2,5-Furandicarboxylic acid	0.4		< 5.40	mmol/mol creat
2-Hydroxyphenylacetic acid	0.64	L	1.40 - 3.70	mmol/mol creat
3,4-Dihydroxyphenylpropionic acid	0.77	H	< 0.35	mmol/mol creat
3,5-Dihydroxyphenylpropionic acid (DHPPA)	BDL		< 0.38	mmol/mol creat
3-Hydroxyphenyl-3-hydroxypropionic acid (HPHPA)	4.07		< 90.00	mmol/mol creat
3-Indoleacetic acid	0.99		< 5.40	mmol/mol creat
3-Oxoglutaric acid/3-Ketoglutaric acid	BDL		< 0.11	mmol/mol creat
4-Hydroxybenzoic acid	6.8	H	< 3.60	mmol/mol creat
4-Hydroxyhippuric acid	4.63		< 30.00	mmol/mol creat
4-Hydroxyphenylacetic acid	9.38		1.40 - 14.60	mmol/mol creat
5-Hydroxymethyl-2-furoic acid (Sumiki's acid)	0.7		< 1.70	mmol/mol creat
Arabinose	5.18		< 19.40	mmol/mol creat
Benzoic acid	BDL		< 6.50	mmol/mol creat
Citramalic acid	0.56		< 4.80	mmol/mol creat
Hippuric acid	202.97		28.00 - 610.00	mmol/mol creat
Hydrocinnamic acid/3-phenylpropionic acid	BDL		< 0.219	mmol/mol creat
N-2-Furanylcarbonylglycine	BDL		< 8.40	mmol/mol creat
p-Cresol	15.22		< 118.90	mmol/mol creat
Phenylacetic acid	BDL		< 5.07	mmol/mol creat
Tartaric acid	BDL		< 64.40	mmol/mol creat
Tricarballic acid	0.97	H	< 0.44	mmol/mol creat
<b>Urine organic acids: Neurotransmitter intermediates</b>				
4-Hydroxybutyric acid (GABA metabolism)	BDL		< 3.60	mmol/mol creat
5-Hydroxyindoleacetic acid (5-HIAA)	1.22		< 5.80	mmol/mol creat
Homovanillic acid (HVA)	4.29		< 8.90	mg/mmol creat
Quinurenic acid / Kynurenic acid	BDL		< 4.10	mmol/mol creat
Quinolinic acid	0.51		< 15.10	mmol/mol creat
Vanillic acid	BDL		< 0.19	mmol/mol creat
Vanillylmandelic acid (VMA)	2.98	H	< 2.80	mmol/mol creat
HVA/VMA ratio	1.44		0.16 - 1.80	
Quinolinic acid / 5-HIAA ratio	0.41		< 2.00	

Tests	Results	H/L	Reference ranges
<b>Urine organic acids: Nutritional markers</b>			
3-Hydroxy-3-methylglutaric acid (Q10)	1.84		< 5.20 mmol/mol creat
3-Hydroxypropionic acid (Biotin)	2.43		< 11.80 mmol/mol creat
4-Pyridoxic acid (Vit B6)	BDL		< 7.50 mmol/mol creat
Ascorbic acid (Vit C)	<b>0.45</b>	<b>L</b>	4.60 - 78.00 mmol/mol creat
Glutaric acid (Riboflavin)	<b>0.54</b>	<b>L</b>	0.70 - 3.60 mmol/mol creat
Methylcitric acid (Biotin)	<b>1.17</b>	<b>L</b>	1.20 - 1.80 mmol/mol creat
Methylmalonic acid (Vit B12)	0.15		< 2.10 mmol/mol creat
Mevalonic acid (Q10)	BDL		< 0.22 mmol/mol creat
N-Acetylcysteine (Glutathione cycle)	BDL		< 0.13 mmol/mol creat
Pantothenic acid (Vit B5)	0.59		< 4.40 mmol/mol creat
Xanthurenic acid (Vit B6)	BDL		< 1.72 mmol/mol creat

### Technical

**Information:** Mahomani, Vutomi (V) Ms

#### GENERAL COMMENTS

BDL: The level of the reported metabolite is below the detection limit of the applied methodology. International reference ranges are currently applied.

South African population based reference ranges have not yet been established.

The uric acid level is determined via the chemical analyser platform with an enzyme based assay

\*Essential amino acids.

#### NUTRITIONAL MARKER COMMENTS

Low or BDL 4-pyridoxic acid, ascorbic acid, pantothenic, N-acetylcysteine may be suggestive of a deficiency/insufficiency in these micronutrient

Elevated glutaric acid, methylcitric acid, 3-hydroxy-3-methyl-glutaric acid, 3-hydroxypropionic acid, mevalonic acid, xanthurenic acid are suggestive of corresponding micronutrient marker deficiency/insufficiency. A low level is insignificant.

**Vorster, Chris (B.C.) Prof.**

#### METABOLITE SPECIFIC INTERPRETATION

Aconitic acid is a Krebs cycle intermediate that is formed from citrate by the action of the aconitase enzyme. Aconitase is likely dependent on normal iron homeostasis and is extremely sensitive to oxidative damage. During hyperammonemia aconitic acid may be excreted in high amounts along with citrate and isocitrate due to the need for a counter anion. Aconitic acid, citrate and isocitrate is also frequently increased along with other Krebs cycle intermediates in patients with coenzyme Q10 deficiency and a mitochondrial respiratory chain insufficiencies.

Physiological conditions that may induce mild to moderate ketosis include fasting (typically longer than an overnight fast), strenuous exercise and a ketogenic diet. Medical conditions include diabetic ketoacidosis, alcoholic ketoacidosis, starvation, Addison's disease and various drugs & toxins. Rare metabolic diseases that may present with ketonuria as a prominent and isolated finding include some glycogen storage diseases and succinyl-CoA:3-ketoacid CoA transferase (SCOT) deficiency. The presence of hypoglycemia in the former and persistent ketosis & metabolic acidosis in the latter are important additional observations. These disorders cannot be excluded with metabolic testing however and will require genetic confirmation.

2-Ethylhydracrylic acid (2EHA) is formed when 2-oxo-3-methylvaleric acid is metabolised via the R pathway as opposed to the usual S pathway. This may occur due to an increased or ineffective isoleucine catabolism which is known to occur during illness or ketosis and have also been observed when dysbiosis is present. Mild and non-specific increases in isoleucine and its intermediates may also be present. A highly increased 2EHA excretion is associated with a number of inherited metabolic diseases including short/branched-chain acyl-CoA dehydrogenase deficiency, beta-ketothiolase deficiency, 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency, propionic acidemia, methylmalonic acidemia, ethylmalonic encephalopathy and Barth

syndrome. In these instances, other characteristic organic acid markers are also typically present which is not the case here (PMID 15615815, 26115894).

Secondary hyperoxaluria may result due to an increased intake of oxalate or its precursors, low calcium or calcium sequestration in the gastrointestinal tract, or the loss of enteric bacteria. Spinach and rhubarb and also nuts, plums, chocolate, beetroot, strawberries and tofu are rich dietary sources. Excessive juicing of fruits and vegetables are prone to increase intake. Alternatively, excessive catabolism of exogenous or endogenous collagen produces 4-hydroxyproline and eventually oxalate. Meat and especially gelatine are important exogenous sources of collagen. Vitamin C, glycine and ethylene glycol are additional precursors and may contribute substantially in cases of excessive supplementation or intoxication. The presence of calcium in the gastrointestinal tract greatly reduces the absorption of oxalate due to the formation of insoluble complexes. When calcium intake is low or when it is sequestered in complexes with free fatty acids, as is the case in fat malabsorption, hyperoxaluria may be the result. Oxalobacter formigenes metabolises oxalate and loss of this bacterium (due to the use of antibiotics) may also increase oxalate excretion. Three inherited disorders of oxalate metabolism result in primary hyperoxaluria. Alanine-glyoxylate aminotransferase catalyses the conversion of glyoxylate to glycine. When this enzyme is deficient, primary hyperoxaluria type 1 (the most common type hyperoxaluria) result. The enzyme is dependent on pyridoxine and some of these patients respond to pyridoxine treatment. Hyperoxaluria, due to a pyridoxine deficiency, has however not been documented as a cause of hyperoxaluria.

3,4-Dihydroxyphenylpropionic acid (34DHPPA) and also 3,5-dihydroxyphenylpropionic acid (35DHPPA) results from gut microbial metabolism of polyphenolic compounds, especially caffeic acid, which are found in a variety of plant sources and coffee. Although it was initially thought that clostridial bacteria are primarily responsible for 34DHPPA production, it is now known that other bacteria can also produce it. Moreover, both 34DHPPA and 35DHPPA are now believed to have anti-inflammatory properties. Thus, while exceedingly high levels of 34DHPPA and/or 35DHPPA may be suggestive of gut dysbiosis, milder increases are likely due to an increased intake of polyphenolic compounds and may even be beneficial (PMID: 33238790, 19152477, 33470026, 31583990).

4-Hydroxybenzoic acid (4HBA) is likely derived from bacterial metabolism of tyrosine and dietary polyphenols and as such may be a marker of gut dysbiosis. After absorption it is activated in the liver by ATP dependent acid:CoA ligase and subsequently glycine conjugated by glycine N-acetyltransferase to form 4-hydroxyhippuric acid (4HHA). An increased 4HBA excretion therefore suggests an increased load or alternatively, a decreased capacity for glycine conjugation, particularly if 4HHA is inappropriately low. It has been proposed that 4HBA may disrupt the inner mitochondrial membrane and therefore 4HBA accumulation may be detrimental. It should be kept in mind however that 4HBA is also a key precursor in the coenzyme Q10 synthesis pathway.

Literature on tricarballic acid (TCA) is scarce but available evidence indicates it is produced via bacterial reduction of trans-aconitate, which is derived from a variety of food sources. TCA is an inhibitor of the Krebs cycle and of aconitase in particular. It is a chelating agent and may therefore decrease divalent cation concentrations. It is also associated with fumonisin (FB) exposure. FBs are produced in maize by the fungal pathogen, *Fusarium verticillioides*. TCA is released when FB is hydrolysed. FB is a ceramide synthase inhibitor and has been implicated in carcinogenesis, neural tube defects and stunting in adults and children.

An increased secretion of vanillylmandelic acid (VMA) is traditionally associated with neurochromaffin tumours often with a profound increase in one or both markers even though normal values do not exclude the diagnosis. Activation of the pituitary adrenocorticotrophic hormone (ACTH)-adrenal cortisol axis during physical or psychological stress is a source of moderate increases. VMA excretion may also be increased secondarily due to gut dysbiosis.

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**Disclaimer:** Comprehensive information with regards to tests, methods in use, sample requirements, analyte coverage and expected turnaround times can be viewed at <https://plim.co.za/>. It is the responsibility of the requesting clinician to order the correct tests given a particular clinical presentation. The laboratory can assist with test selection if required.

\*R = Referred