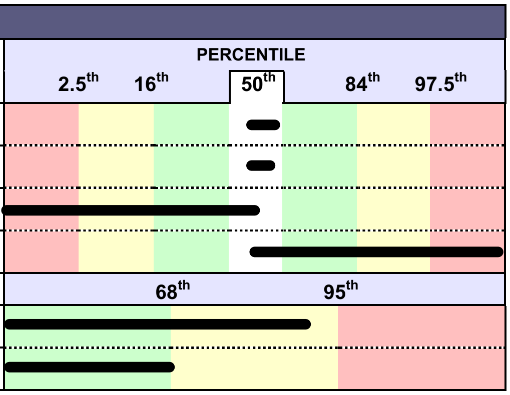
LAB #: Sample Report
PATIENT: Sample Patient
ID: Sample ID
SEX: Male
DOB: 01/01/1988 AGE: 33

CLIENT #: 12345
DOCTOR: Sample Doctor, MD
Doctor's Data, Inc.
3755 Illinois Ave.
St. Charles, IL 60174 U.S.A.

Methylation Profile; plasma

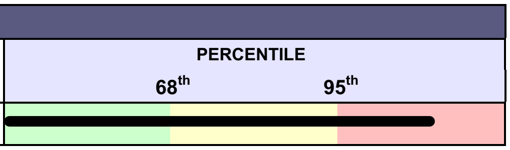
PRIMARY & INTERMEDIATE METABOLITES

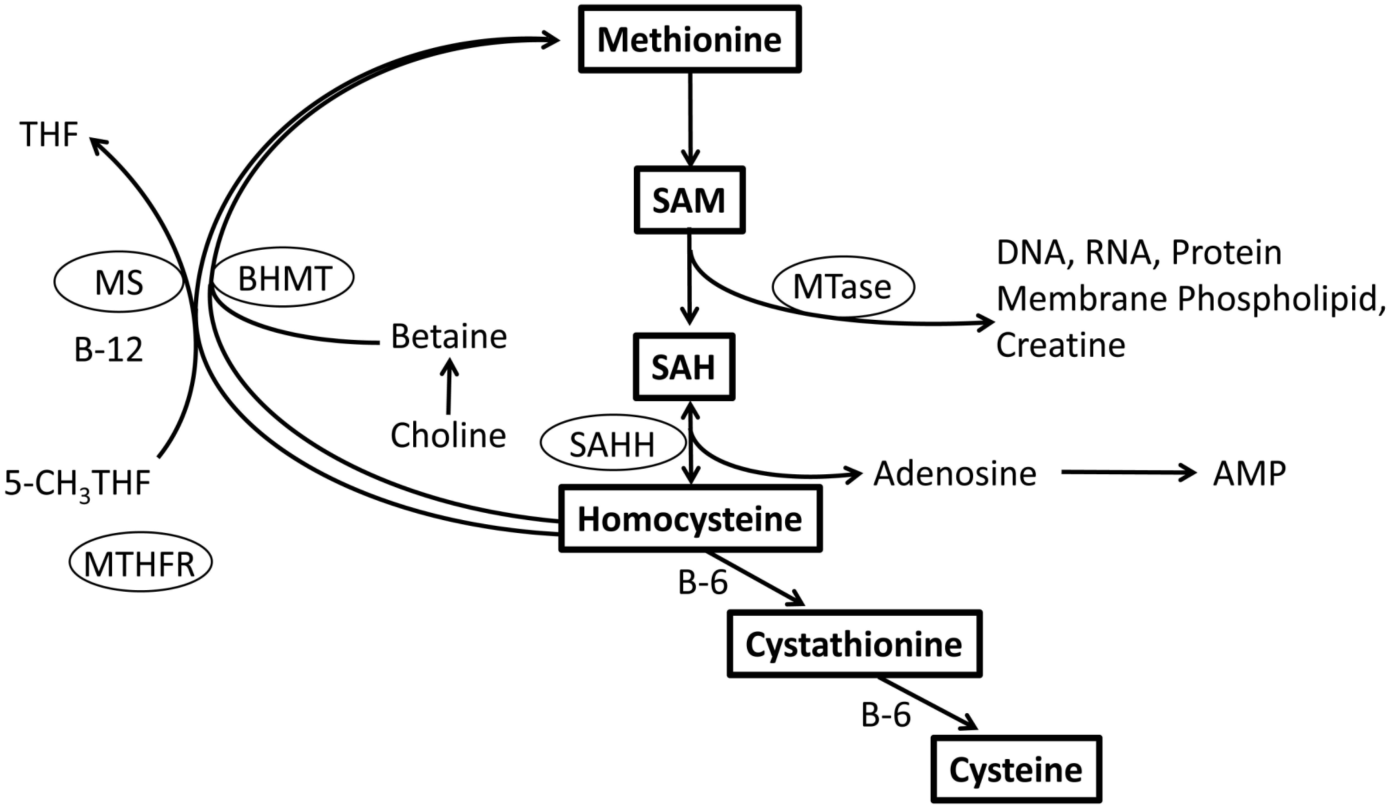
	RESULT	UNIT	REFERENCE INTERVAL
Methionine	**2.5**	**µmol/dL**	1.6- 3.6
Cysteine	**29**	**µmol/dL**	20- 38
S-adenosylmethionine (SAM)	**63**	**nmol/L**	86- 145
S-adenosylhomocysteine (SAH)	**29.3**	**nmol/L**	10- 22
Homocysteine	**10.4**	**µmol/L**	< 11
Cystathionine	**0.03**	**µmol/dL**	< 0.05



METHYLATION INDEX

	RESULT	REFERENCE INTERVAL
SAM : SAH	**2.2**	> 4





SPECIMEN DATA

Comments:

Date Collected: 01/18/2022
Date Received: 01/20/2022 <dl: less than detection limit
Date Reported: 01/26/2022
Method: LCMS

v02.11

Introduction

This test assesses metabolism of the essential amino acid methionine (Met). Methionine is paramount in two metabolic processes; (1) transmethylation that is critical for the methylation of hundreds of important molecules such as DNA, RNA, proteins, neurotransmitters and membrane phosphatidylcholine, and (2) transsulfuration that leads to the biosynthesis of cysteine and hence glutathione , both of which have many important protective / detoxification functions. Aberrant Met metabolism can be caused by nutritional deficiencies, exposures to environmental toxicants and/or genetic polymorphisms and can have significant adverse health consequences. Identification of such abnormalities can guide appropriate nutritional intervention towards normalization of methionine metabolism and decreased risk and incidence of adverse health effects.

The amino acids and intermediary amino acid metabolites were measured by liquid chromatography - mass spectrometry. Reference values are age and sex specific. If patient values deviate from normal, comprehensive descriptive paragraphs will be presented as part of the test report.

S-adenosylhomocysteine high

S-adenosylhomocysteine (SAH), a downstream metabolite in methionine metabolism, is higher than expected. SAH is a potent inhibitor of cellular methylation due to product inhibition of methyl transferase enzymes. Therefore efficient removal of SAH is critical to prevent inhibition of methylation and associated consequences. Potential consequences of compromised methylation include aberrant neurotransmitter metabolism, abnormal gene expression and silencing, cancer, cardiovascular disease and vascular occlusion, congenital heart disease/birth defects, neurodegenerative disease, poor response to environmental toxins (e.g. endogenous detoxification of arsenic), and increased risk for Down Syndrome and perhaps autism spectrum disorder. Plasma homocysteine (HCys) and SAH are positively associated with occlusive artery and cardiovascular disease and HCys is considered to be an independent risk factor for cardiovascular disease. SAH is the immediate precursor of HCys and, although present in blood at less than 1/500th the concentration of HCys, SAH may be a better indicator of vascular disease than HCys. Plasma HCys and SAH are also positively associated with genome-wide DNA hypomethylation that are common features of autoimmune disease.

SAH is formed after transfer of a methyl group from S-adenosylmethionine (SAM) to an acceptor molecule via methyltransferase (MT). SAH binds to MT with greater affinity than SAM thus efficient removal of SAH is critical to avert product inhibition of MT activity (methylation). SAH is metabolized in a reversible manor by the enzyme SAH hydrolase (SAHH) to HCys and adenosine. The reversible activity of SAHH only proceeds in the direction of HCys if there is efficient removal of HCys and adenosine. Otherwise SAH is resynthesized from HCys by SAHH. Homocysteine is normally methylated to regenerate methionine by the folate/B-12-dependent methionine synthase reaction and the betaine-homocysteine methyltransferase reaction (liver and kidneys). Alternatively HCys can be permanently removed from the methionine transmethylation cycle by conversion to cysteine via two irreversible B-6 dependent reactions (transsulfuration). Adenosine is normally phosphorylated to form adenosine nucleotides by adenosine kinase or catabolyzed to inosine by adenosine deaminase. Circumvention of the accumulation of SAH and associated inhibition of methylation can be readily accomplished in most cases by appropriate supplementation with folate (or folinic acid), B-12 (or methyl B-12), B-6 (or P-5P) and betaine.

References

1. Yi P, Melnyk S, Pogribna M et al. Increase in plasma homocysteine associated with parallel increase

in plasma S-andenosylhomocysteine and lymphocyte DNA hypomethylation. JBC 2000;275:29318-23.

2. James SJ, Cutler P, Melnyk S at al. Metabolic biomarkers of oxidative stress and impaired methylation capacity in children with autism. Am J Clin Nutr 2004;80:1611-7.

3. James SJ, Melnyk S, Pogribna M et al. Elevation in S-adenosylhomocysteine and DNA hypomethylation: potential epigenetic mechanism for homocysteine-related pathology. J Nutr 2002;132:2361S-66S.

4. Richardson B. DNA Methylation and autoimmune disease. Clin Immunol 2003;109:72-9.

5. Wagner C and Koury M. S-adenosylhomocysteine- a better indicator of vascular disease than homcysteine(c) Am J Clin Nutr 2007;86:1581-5.

6. Kerins D, Koury M, Capdevila A et al. Plasma S-adenosylhomocysteine is a more sensitive indicator of cardiovascular disease than homocysteine. Am J Clin Nutr 2001;74:723-9.

7. Manilow M, Bostom A, Kraus R. Homocysteine, diet, and cardiovascular disease. Circulation 1999;99:178-82.

S-adenosylmethionine low

S-adenosylmethionine (SAM), the first direct metabolite of normal methionine metabolism, is lower than expected. Up to half of daily methionine uptake is enzymatically converted in the liver to SAM by methionine-adenosyl transferase in the presence of ATP and magnesium. Therefore SAM may be low due to (1) low availability of methionine (check plasma methionine) (2) magnesium deficiency (check whole blood or red blood cell magnesium levels), (3) inhibition of methionine synthase activity, or (4) genetic or chemical inhibition of methionine adenosyltransferase activity. In the latter case, severe depletion of SAM can be associated with DNA hypomethylation and demyelination in the central nervous system. When dietary methionine and choline are insufficient, the folate-dependent pathway for regeneration of methionine from homocysteine is upregulated increasing the cellular requirement for folate. A potential consequence of the diversion of folate 1-carbon methyl groups towards regeneration of methionine (and SAM) may be functional depletion of folate methyl groups for DNA metabolism and integrity with potential for genetically significant consequences (e.g . genomic DNA hypomethylation). It is uncertain whether physiological decreases in SAM alone induced by nutritional deficiencies are causally related to cellular hypomethylation (J Biol Chem 2000;275:29318-23).

SAM is the principal biological methyl donor and participates in three important pathways in the liver; (1) polyamine synthesis (cell growth), (2) transmethylation, and (3) transsulfurration. Normally most of SAM is used in transmethylation reactions as a donor of its methyl group to a diverse group of hundreds of important molecules via the catalytic activity of methyl transferases. Molecules that require methylation for normal biological activity include, but are not limited to, DNA, RNA, proteins, choline, membrane phosphatidylcholine, creatine (liver), neurotransmitters and neurotransmitter receptors. Potential consequences of low SAM and compromised methylation include aberrant neurotransmitter metabolism, abnormal gene expression and silencing, immune dysregulation (autoimmunity), cancer, cardiovascular disease and vascular occlusion, congenital heart disease/birth defects, neurodegenerative disease, poor response to environmental toxins (e.g. endogenous detoxification of arsenic), and increased risk for Down

Syndrome and perhaps autism spectrum disorder. While low SAM can be associated with under methylation, it has been suggeted that the most sensitive indicator of poor methylation is the relative plasma concentrations of SAM to S-adenysylhomocysteine (methylation index). If SAM and methionine are low but the reported methylation index is normal, the condition may be remedied with appropriate intake/supplementation with methionine, folate, B-12, B-6, betaine and magnesium. Cheeses, fish, poultry, meats and some nuts (e.g. Brazil nuts, almonds and cashews) are good dietary sources of Met. Supplementation with Met should be accompanied by magnesium, B-6, folate, betaine and B-12.

References

1. James SJ, Melnyk S, Pogribna M et al. Elevation in S-adenosylhomocysteine and DNA hypomethylation: potential epigenetic mechanism for homocysteine-related pathology. J Nutr 2002;132:2361S-66S.

2. Yi P, Melnyk S, Pogribna M et al. Increase in plasma homocysteine associated with parallel increase in plasma S-andenosylhomocysteine and lymphocyte DNA hypomethylation. JBC 2000;275:29318-23.

3. James SJ, Melnyk S, Jernigan S et al. Abnormal transmethylation/transsulfuration metabolism and DNA hypomethylation among parents of children with autism. J Autism Dev Disord 2008;38:1966-75.

4. Lu SC. Regulation of glutathione synthesis. Mol Aspects Med 2009;30:42-59.

Methylation Index Low

The methylation index, a sensitive indicator of cellular methylation capacity, is lower than expected. The methionine index represents the ratio of S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH). A low value for the methylation index indicates limited capacity for methylation.

SAM is the principal biological methyl donor and normally most of SAM is used in transmethylation reactions to provide methyl groups to a diverse group of hundreds of important molecules including DNA, RNA, proteins, choline, membrane phosphatidylcholine, creatine (liver), neurotransmitters and neurotransmitter receptors. SAH is a potent inhibitor of methyltransferase enzymes (MTs), hence methylation. Potential consequences of compromised methylation include aberrant neurotransmitter metabolism, abnormal gene expression and silencing, cancer, cardiovascular disease and vascular occlusion, congenital heart disease/birth defects, neurodegenerative disease, autoimmune disease, poor response to environmental toxins (e.g. endogenous detoxification of arsenic), and increased risk for Down Syndrome and perhaps autism spectrum disorder. In a study of neurotypical (n=33) and autistic (n=20) children (ASD), plasma methionine, SAM and the methylation index (SAM to SAH ratio) were lower in the ASD group while SAH was significantly higher. An intervention trial was conducted with a subgroup of the ASD children (n=8) and it was demonstrated that supplementation with folinic acid, betaine and methyl-B-12 normalized the aforementioned indices of aberrant methionine metabolism and Methylation capacity.

SAM and SAH are substrates and products, respectively, of MTs and accumulation of SAH inhibits methyltransferase enzymes by product inhibition: SAH binds with high affinity to the active sites of MTs. Low SAM might be associated with inadequate methylation but, elevated levels of SAH, especially concomitant with low SAM has been shown to inhibit methylation of DNA in animal models. A low ratio of SAM to SAH, due to elevated SAH, was exhibited in patients with occlusive artery disease and elevated HCys. Similarly, elevated SAH in the presence of marginally decreased SAM was associated with hypomethylation of DNA and protein in patients with renal failure and elevated plasma levels of HCys.

In cells SAH accumulates when there is inefficient clearance of HCys. SAH is metabolized in a reversible manor by the enzyme SAH hydrolase (SAHH) to HCys and adenosine. The reversible activity of SAHH only proceeds in the direction of HCys if there is efficient removal of HCys and adenosine. Otherwise SAH is resynthesized from HCys by SAHH. Homocysteine is normally methylated to regenerate methionine in all cells by the folate/B-12-dependent methionine synthase reaction and the betaine-homocysteine methyltransferase reaction (liver and kidneys). Alternatively homocysteine can be permanently removed from the methionine transmethylation cycle by conversion to cysteine via two irreversible B-6 dependent reactions (transsulfuration). Circumvention of accumulation of SAH and associated inhibition of methylation can be readily accomplished in most cases by appropriate supplementation with folate (or folinic acid), B-12 (or methyl B-12), B-6 (or P-5P) and betaine.

References

1. Yi P, Melnyk S, Pogribna M et al. Increase in plasma homocysteine associated with parallel increase in plasma S-andenosylhomocysteine and lymphocyte DNA hypomethylation. JBC 2000;275:29318-23.

2. James SJ, Cutler P, Melnyk S at al. Metabolic biomarkers of oxidative stress and impaired methylation capacity in children with autism. Am J Clin Nutr 2004;80:1611-7.

3. James SJ, Melnyk S, Pogribna M et al. Elevation in S-adenosylhomocysteine and DNA hypomethylation: potential epigenetic mechanism for homocysteine-related pathology. J Nutr 2002;132:2361S-66S.

4. Richardson B. DNA Methylation and autoimmune disease. Clin Immunol 2003;109:72-9.

5. Loeher F, Tschopl M, Angst C et al. Disturbed ratio of erythrocytes and plasma S-adenosylmethionine/S-adenosylhomocysteine in peripheral arterial occlusive disease. Atherosclerosis 2001;154:147-54.

6. Perna A, Castaldo P, DeSanto N et al. Plasma proteins containing damaged L-aspartyl residues are increased in uremia: implications for mechanisms. Kidney Int 2001;59:2299-2308.