Nordic Laboratories

PATIENT:	**Sample Report**	TEST REF:	**###-##-#####**
TEST NUMBER:	##########	COLLECTED:	dd/mm/yyyy
PATIENT NUMBER:	##########	RECEIVED:	dd/mm/yyyy
GENDER:	Male	TESTED:	dd/mm/yyyy
AGE:	46	PRACTITIONER:	**Nordic Laboratories**
DATE OF BIRTH:	dd-mm-yyyy	ADDRESS:	

TEST NAME: Methylation Profile - Plasma

Methylation Profile; plasma

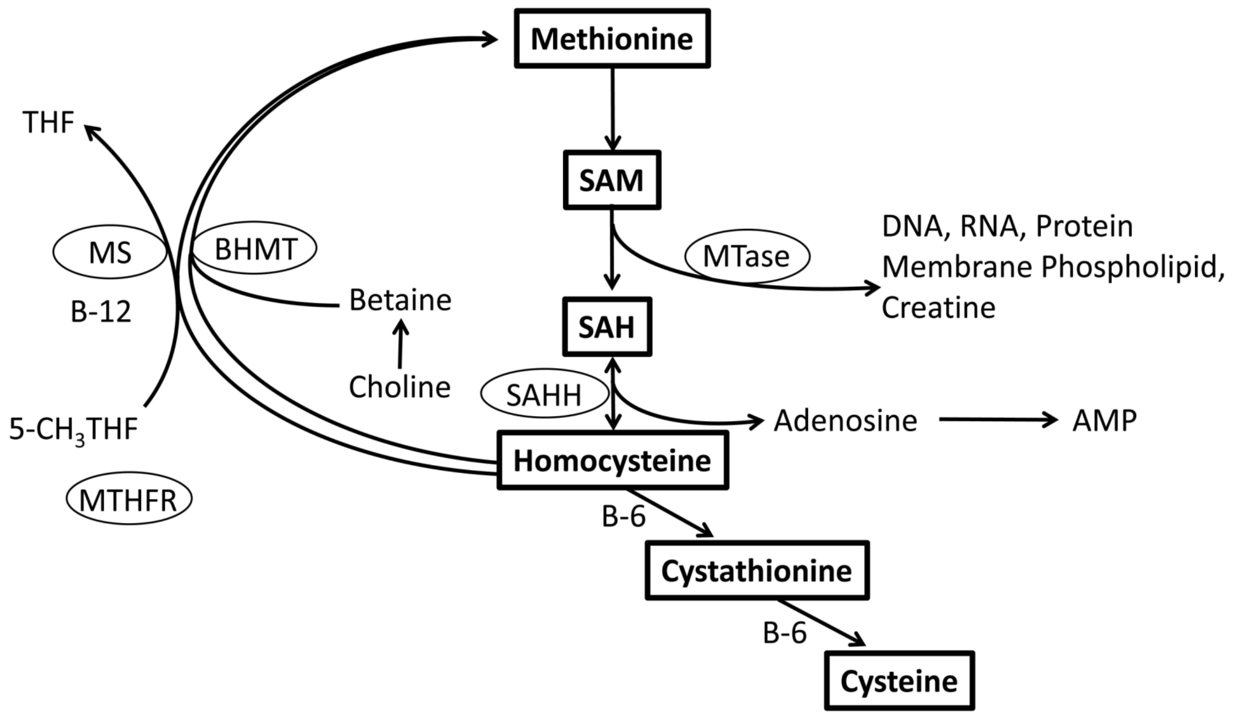
PRIMARY & INTERMEDIATE METABOLITES

	RESULT	UNIT	REFERENCE INTERVAL	PERCENTILE (2.5th, 16th, 50th, 84th, 97.5th)
Methionine	**3.3**	**µmol/dL**	1.6– 3.6	
Cysteine	**31**	**µmol/dL**	20– 38	
S-adenosylmethionine (SAM)	**85**	**nmol/L**	86– 145	
S-adenosylhomocysteine (SAH)	**15.6**	**nmol/L**	10– 22	
Adenosine	**48**	**nmol/L**	20– 80	

	RESULT	UNIT	REFERENCE INTERVAL	PERCENTILE (68th, 95th)
Homocysteine	**13.1**	**µmol/L**	< 11	
Cystathionine	**0.12**	**µmol/dL**	< 0.05	

METHYLATION INDEX

	RESULT	REFERENCE INTERVAL	PERCENTILE (68th, 95th)
SAM : SAH	**5.5**	> 4	



SPECIMEN DATA

Comments:

Date Collected: **d/mm/yyyy**
Date Received: **d/mm/yyyy**
Date Completed: **d/mm/yyyy**
Method: **LCMS**

<dl: **less than detection limit**

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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.

Homocysteine high

Homocysteine (HCys), a sulfur-containing amino acid, is higher than expected. Homocysteine is a normal and important amino acid derived exclusively from methionine metabolism but it must be processed efficiently. Plasma HCys levels may be elevated due to a variety of nutritional insufficiencies, genetic polymorphisms and lifestyle factors. Other conditions that may be associated with high HCys are advanced age (especially women), hypothyroidism, systemic lupus erythematosus, impaired kidney function, and some medications (e.g. nitric oxide exposure, theophylline, methodrexate, L-dopa, fibrates and excessive doses of nicotinic acid,). Regardless of the cause(s) elevated HCys levels are associated with a wide variety of adverse health conditions: primarily coronary, cerebral and peripheral occlusive arterial diseases and venous thromboembolism. The mechanism(s) for the association of high HCys with arterial diseases have not been elucidated. Elevated plasma HCys is also been associated ectopic lentitis, myopia, spontaneous abortion, rheumatoid arthritis, neuropsychiatric disorders, osteoporosis and other musculoskeletal disorders (HCys interferes with crosslinking of collagen). Except for rare cases of extreme genetic disorders most cases of elevated levels of HCys can be greatly ameliorated or normalized with appropriate nutritional intervention (folate, B-12, B-6, betaine) and changes in lifestyle (e.g. cessation of chronic alcohol consumption). Homocysteine is a branch point in methionine metabolism in that it can be methylated to regenerate methionine (methionine transmethylation cycle) for protein synthesis or S-adenosylmethionine synthesis, or converted to cysteine (transsulfuration). Homocysteine is normally methylated to regenerate methionine by the folate/B-12-dependent methionine synthase reaction and additionally the betaine-homocysteine methyltransferase reaction (liver and kidneys). Regeneration of methionine by methionine synthase requires the activity of methylenetetrahydrofolate reductase (MTHFR). Alternatively HCys can be permanently removed from the methionine transmethylation cycle by conversion to cysteine via two irreversible B-6 dependent reactions (transsulfuration). Appropriate metabolism of HCys by the transsulfuration pathway involves two B-6 dependent enzymes; cystathione beta-synthase (CBS) and cystathionase to produce cysteine. Numerous studies have shown inverse relations between plasma HCys and status of folic acid, B-6 and B-12. Betaine provides necessary methyl groups and is effective for lowering HCys in subjects who do not respond well to B vitamin therapy alone. Riboflavin has been shown to function as a co-factor for MTHFR with moderate efficacy in lowering elevated plasma HCys levels. In general folate-based B vitamin supplementation can be very effective in lowering plasma HCys.

A relatively common variant of MTHFR entails a cytosine (C) to thymine (T) mutation at nucleotide 677. The C to T mutation of MTHFR is associated with elevated levels of HCys but various forms of folate (e.g. folinic acid) appear to be very effective in lowering HCys even in the homozygous genotype (T/T). Hyperhomocystinuria is a very rare autosomal recessive genetic disorder (about 1 in 200,000 births) that results from defective activity of CBS; patients have severe hyperhomocysteinemia and a high incidence of vascular pathology that often results in early death from myocardial infarction, stroke or pulmonary embolism.

Plasma HCys is commonly higher in post menopausal women compared to premenopausal women and age matched men. It has been suggested that the high methylation capacity in women of child bearing years contributes to their low risk for and incidence of coronary artery disease. Plasma HCys and S-adenosylhomocysteine are positively correlated with genome-wide DNA hypomethylation and are common features of autoimmune disease. Maternal elevations in HCys are associated with increased risk for congenital heart disease.

Methionine load test: A methionine load test can be performed to further evaluate the capacity to metabolize HCys in patients with personal or family history of premature cardiovascular disease. As presented by the Nutrition Committee of American Heart Association (Circulation 1999;99:178-82), the test entails measurement of fasting plasma HCys and HCys levels 2 hours after consumption of 100 mg L-methionine/kg body weight (mixed in orange juice). "The 2- hour post-load protocol has been extensively validated and the test may reveal about 40 % of subjects with HCys-related cardiovascular disease but with normal fasted levels of HCys". In a study of 363 subjects free of clinically apparent vascular disease, women greater than 50 years of age exhibited significantly greater increases in post-load HCys than men of similar age and women less than 50 years of age. Post methionine-load HCys levels in renal transplant patients were reduced by 22% (average) with vitamin B-6 (50 mg/day), 26% with folic acid plus B-12 but, folate supplementation alone (up to 5 mg/day) was ineffective. It has been suggested that B-6, B-12 and folate supplementation should be used to lower basal and post methionine-load test elevations in plasma HCys.

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. Richardson B. DNA Methylation and autoimmune disease. Clin Immunol 2003;109:72-9.
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8. Wagner C and Koury M. S-adenosylhomocysteine- a better indicator of vascular disease than homcysteine(c) Am J Clin Nutr 2007;86:1581-5.

9. 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.

10. 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.

11. Verkleig-Hagoot AC, Verlinde M, Ursem M et al. Maternal hypercysteinaemia is a risk factor for congenital heart disease. BJOG 2006;113:1412-8.

Cystathionine high

Cystathionine is higher than expected. Cystathionine is an intermediary metabolite that is formed in the sequential enzymatic conversion of methionine to cysteine; specifically, the B-6-dependent conversions of homocysteine to cystathionine to cysteine (transsulfuration). Mildly elevated cystathionine can be an acquired nutritional condition that is readily corrected with adequate B-6/P-5-P supplementation. It can also be an inherited condition that can be resolved with supplementation of B-6/P-5-P and limitation of foods that are high in methionine. A rare (4 out of 10,000), but more severe homozygous cystathioninemia occurs; many individuals with this later condition appear to be normal and asymptomatic. However, if the decreased conversion of cystathionine to cysteine is accompanied by insufficient dietary cysteine, there could also be a cysteine deficiency. Cysteine deficiency could be associated with insufficient levels of intracellular glutathione and taurine. Associated conditions might include: magnesium deficiency, headaches, inflammation, excessive oxidative stress, environmental sensitivity, fatigue, biliary insufficiency (fat and fat soluble vitamin malabsorption), occlusive arterial disease, myopia, osteoporosis and other skeletal disorders.

References

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

2. 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.

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

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