KRESSER INSTITUTE FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Blood Chem Impaired Methylation Review

Methylation is a biochemical process involving the transfer of an active methyl group between molecules. Methyl groups consist of hydrogen attached to three carbon atoms.

1. Production of methyl groups results in either 5-methyltetrahydrofolate or S-adenosylmethionine, SAMe.
2. As it is used, SAMe is converted into S-adenosylhomocysteine, which is in turn converted into homocysteine.
3. Homocysteine is then recycled back into methionine via the dominant methionine synthase pathway, which requires 5-MTHF as the cofactor, or the lesser pathway, homocysteine methyltransferase in the liver and kidneys.

If methylation is impaired, homocysteine will not be converted back into methionine, and you'll see a buildup of homocysteine.

MOST IMPORTANT FUNCTIONS OF METHYLATION

Function	Comments
Cell division, DNA, and RNA synthesis	Folate crucial for DNA and RNA synthesis
Early CNS development	Folate deficiency during pregnancy > neural tube defects
Gene expression	DNA and histone methylation regulate expression of genes
Post-transcription modification	Regulatory function on microRNA translation and protein synthesis
Immune cell differentiation	Maturation of T-cells and other immune cells
Neurotransmitter synthesis and metabolism	Methylation via SAMe required for production of dopamine, norepineprhine, epinephrine & serotonin
Histamine clearance	Histamine N-methyltransferase, which requires SAMe, clears histamine
Detoxification	Methylation required for biotransformation of xenobiotics during phase II liver detoxification
Hormone clearance	Methylation of estrogens via COMT required for effective estrogen clearance
Cellular energy metabolism	Production of CoQ10, carnitine, and ATP > mitochondrial energy
Phospholipid synthesis	Synthesis of phosphatidylcholine, supports integrity of cell membranes
Myelination of peripheral nerves	Deficiency of SAMe in CSF causative in demyelination

If we simplify the above table for discussion with patients, impaired methylation can lead to:

- Depression and anxiety
- Histamine intolerance
- Weak immune function
- Higher risk of cancer
- Poor detox capacity
- Hormone imbalance
- Infertility/birth defects
- Fatigue and low energy.

Deficits in methylation are associated with a wide range of conditions.

Risk factors for impaired methylation can be broken down into two categories: environmental and genetic, with environmental being the most significant and common of the two.

The first environmental cause is nutrient deficiency.

NUTRIENTS INVOLVED IN METHYLATION PATHWAYS

Methionine	Niacin
Cysteine	Pyridoxine
Taurine	**Folate**
DHA	**Vitamin B12**
Zinc	Betaine (TMG)
Magnesium	Choline
Potassium	Sulfur
Riboflavin	

DIETARY SOURCES OF FOLATE

Food	mcg DFE per serving
Chicken liver, one	254
Beef liver, 3 ounces	215
Spinach, boiled, 1/2 cup	131
Black-eyed peas, boiled, 1/2 cup	105
Asparagus, boiled, 4 spears	89
Lettuce, romaine, shredded, 1 cup	64
Avocado, raw, sliced, 1/2 cup	59
Spinach, raw, 1 cup	58
Green peas, frozen, boiled, ½ cup	47
Kidney beans, canned, ½ cup	46
Peanuts, dry roasted, 1 ounce	41
Crab, Dungeness, 3 ounces	36
Orange, fresh, 1 small	29

B12 INTAKE RECOMMENDATIONS

- Current RDA is 2.4 mcg.
- Studies on minimizing chromosomal damage and improving DNA repair suggest taking 7 mcg.
- The average daily intake of hunter-gatherers is 17.6 mcg.

There is no tolerable upper intake level for B12, and no toxicity threshold has been found. Therefore, advising higher intakes is safer than advising lower intakes.

HIGHEST DIETARY SOURCES OF B12

Food	Amount (mcg per 100g)
Clam	99
Lamb liver	90
Beef liver	83
Duck liver	54
Oyster	35
Pork liver	26
Caviar	20
Mackerel	19
Herring	19
Mussel	12
Crab	11
Sardine	9
Salmon	6

If the patient is not eating organ meats or fish, it's possible they are not getting enough B12.

Additional risk factors for impaired methylation

1. Competition for methyl donors. One particular function of methylation may be in overdrive and sucking up available methyl donors at the expense of other functions of methylation. This could be due to:
   - Environmental toxins
   - Mast cell activation syndrome (MCAS) or histamine intolerance
   - High estrogens
   - Acute or chronic stress
   - Chronic infection or immune challenge
2. Inhibition of methylation
   - Methylation inhibitors can interfere with methylation-dependent functions in the body.
     - Elevated homocysteine levels, which are most often caused by B12 and folate deficiency, will increase S-adenosylhomocysteine and impair methylation.
     - Valproic acid is a histone deacetylase inhibitor.
     - Cholestyramine interferes with the absorption of folate, fat-soluble vitamins, and other nutrients required for methylation.
     - OCPs deplete magnesium, B6, B2, and riboflavin, and increase estrogen levels, which both impairs methylation and increases the need for methylation.

- PPIs reduce the absorption of folate and other methyl donors.
- Antibiotics deplete beneficial bacteria.
- Nitrous oxide oxidizes cobalamin

GENETICS

- Polymorphisms in methylation-related genes can lead to reduced methylation capacity.
- Methylenetetrahydrofolate reductase (MTHFR) is the best known, but many other genes affect methylation, including COMT, MTR, MTRR, and BHMT.
- Most common MTHFR polymorphisms are C677T and A1298C.
- Homozygous C677T: 70 to 75 percent loss of enzyme activity
- Heterozygotes, or people with one polymorphism in MTHFR C677T, lose 33 to 35 percent of enzyme activity.
- Homozygous A1298C has a 39 percent reduction in enzyme activity
- Heterozygotes for A1298C have a 17 percent reduction of enzyme activity.
- Compound heterozygotes who have one copy of C677T and one copy of A1298C may lose as much as 52 percent of enzyme activity.

MARKERS OF IMPAIRED METHYLATION

Marker	Value
Serum folate	Low
RBC folate	Low
Serum B12	Low
Serum MMA	High
Serum homocystine	High
Urine MMA	High
Urine FIGLU	High

The bolded markers are included in the case review panel.

- Homocysteine is also an inverse marker. When it's high, it means that more B12 and folate are required to convert homocysteine back into methionine. Thus, high homocysteine can indicate B12 and/or folate deficiency.
- MMA (Urine organic acids) is high in vitamin B12 deficiency.
- High urine FIGLU (Urine organic acids) indicates folate deficiency.

Follow-up testing for impaired methylation - functional methylation testing. Consider the methylation pathways panel from Health Diagnostics and Research Institute.

TREATMENT

- There has been a recent trend toward using high-dose methyl donors in supplement form to treat methylation-related problems.
- There is some evidence that suggests that overmethylation may be detrimental.
- Overmethylation has been associated with adverse effects, primarily immune dysregulation.
- We don't really have enough research on the effects of long-term supplementation with high-dose methyl donors.
- Methylation status depends on diet and lifestyle inputs, and I think diet and lifestyle change is the safest option.

Refer to handout on methylation nutrients and foods. All of the nutrients involved in the methylation cycle can be obtained from food in a nutrient-dense diet.

SUPPLEMENT PROTOCOL

- Avoid folic acid.
    - Folic acid undergoes initial reduction and methylation in the liver, where a conversion to the THF form requires dihydrofolate reductase. Unfortunately, a lot of human beings have a relatively low activity of dihydrofolate reductase in the liver, and combined with a high intake of folic acid from fortified foods, this may result in unnatural levels of unmetabolized folic acid entering the systemic circulation.
- The best forms to supplement with are 5-MTHF or folinic acid, 5-formyl-THF.
    - Remember, 5-MTHF is a cofactor for methionine synthase, which converts homocysteine back into methionine.
- Start with a lower dose of 200 to 400 mcg per day of 5-MTHF.
- Many individuals experience side effects even with lower doses of 5-MTHF, including anxiety, agitation, insomnia, and overstimulation. These effects may pass after a short period of time.
- However, some patients just cannot tolerate 5-MTHF. In these cases, use folinic acid at a dose of 800 mcg per day, which is much better tolerated than 5- MTHF, and typically works pretty well for normalizing folate.
- Retest after 60 days.
- Once underlying mechanisms are addressed, consider transitioning to a dietary approach.
- If the patient is unable to maintain their folate levels just with diet alone, weigh the risk of high homocysteine, which is an inflammatory protein associated with cardiovascular

disease and cognitive disorders such as Alzheimer's, versus the risk of supplementing long-term with higher doses of methyl donors, which, as you know, has been shown to have some adverse effects in certain studies.

- As far as I can tell, the best option in these cases is probably to supplement, but use the lowest effective dose, and then continue to address mechanisms that are known to impair methylation.