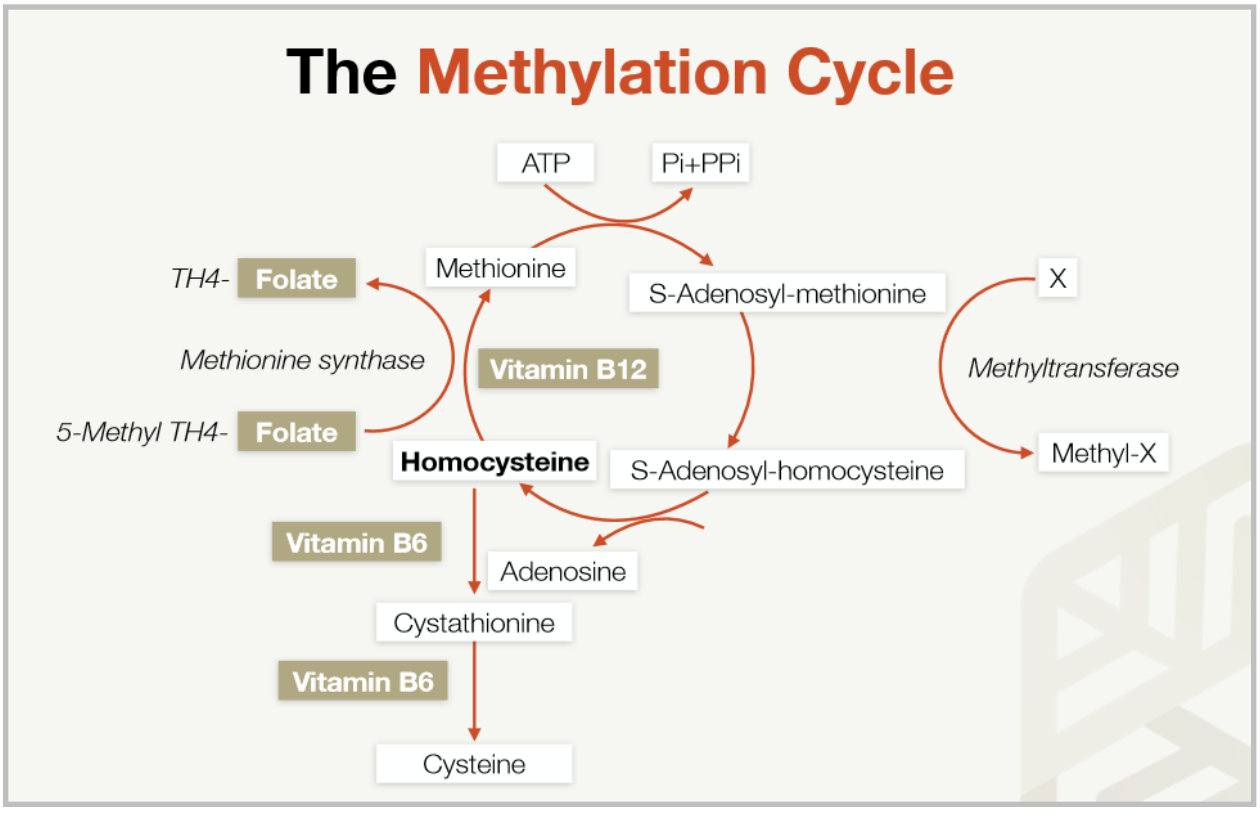
KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Impaired Methylation - Part One

Hey, everybody. In this presentation, we're going to discuss the case review blood chemistry markers for impaired methylation. This is going to be a relatively short presentation because we've already talked about these markers in other presentations: B12 in the B12 deficiency section, folate and B12 in the folate deficient anemia section, and homocysteine in the B12 and folate-deficient anemia section. Here, I'm going to cover some basics on methylation, review these markers in the context of methylation, briefly discuss follow-up testing options, and then review treatment of impaired methylation, which we already discussed in the B12- and folate-deficiency anemia presentation.

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, and the production of methyl groups results in either 5-methyltetrahydrofolate or S-adenosylmethionine, SAMe. As it is used, SAMe is converted into S-adenosylhomocysteine, which is in turn converted into homocysteine. 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.



I put a greatly simplified diagram of the methylation cycle on this slide. This is an extremely complex biochemical pathway that you can really get lost in, but I think the version I put here on this slide illustrates what you most need to understand about this pathway. The key thing to get is that if methylation is impaired, homocysteine will not be converted back into methionine and you'll see a buildup of homocysteine. As you surely know, when we discussed homocysteine earlier, elevated levels of homocysteine are associated with heart disease, Alzheimer's, and a number of other inflammatory conditions.

Methylation is extremely complex, and it confuses both clinicians and patients alike. It's easy to go down rabbit holes, and while that is interesting, it's good to have a 30,000-foot view so you know what to look for as a clinician and how to discuss it with your patients.

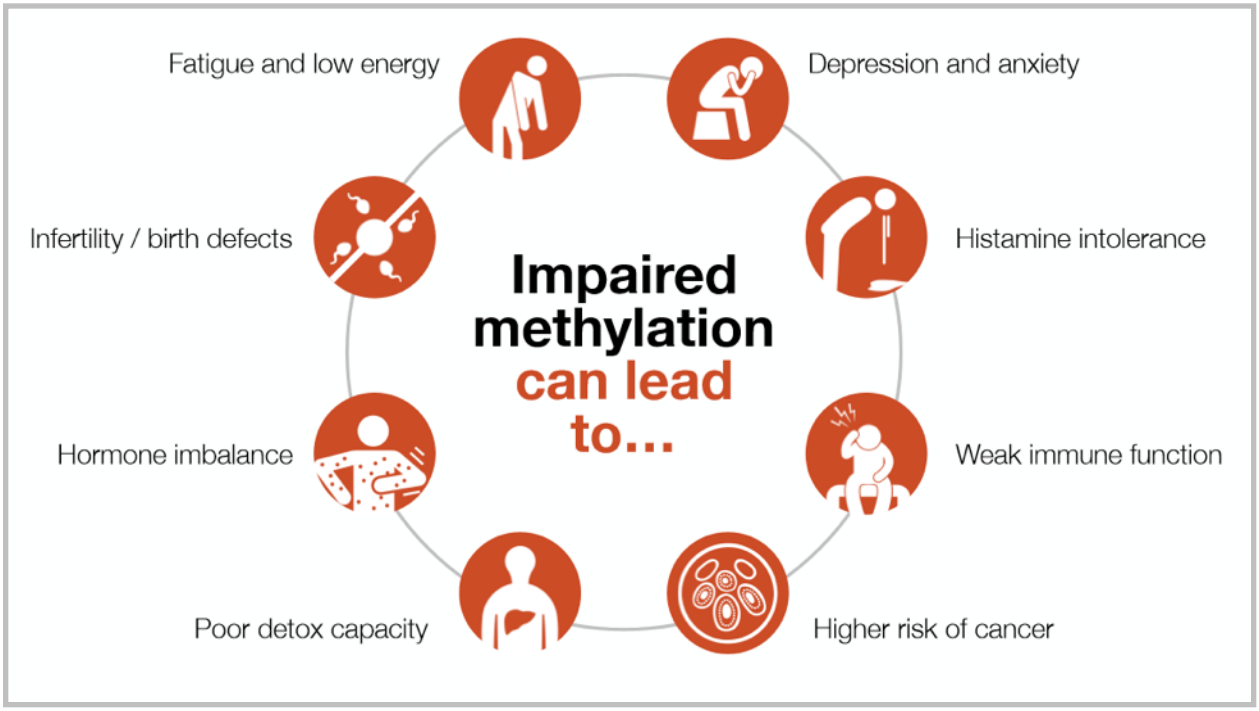
Function	Comments
Cell division, DNA, and RNA synthesis	Folate crucial for DNA and RNA synthesis
Early CNS development	Folate deficiency during pregnancy > neural tube defects
Gene expression	DNA and histone methylation regulate expression of genes
Post-transcription modification	Regulatory function 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

The table on this slide summarizes the most important functions of methylation, which are here broken down by category. This is from Dr. Kara Fitzgerald's excellent e-book on methylation that I mentioned in the B12 and folate anemia presentation, and I'll provide another link in the resources here.

The categories are: cell division, DNA and RNA synthesis (so folate in particular is crucial for DNA and RNA synthesis); early central nervous system development (which explains why folate deficiency during pregnancy can lead to neural tube defects); gene expression (perhaps the most important function of methylation is to regulate gene expression both via DNA and histone methylation); post-transcriptional modification (so methylation has a regulatory function on microRNA, mRNA translation, and protein synthesis); immune cell differentiation (methylation

affects maturation of T-cells and other immune cells, so it can have a significant impact on the immune system); neurotransmitter synthesis and metabolism (methylation via SAMe is required for production of dopamine, norepinephrine, and serotonin, so when methylation is impaired, a lot of patients will suffer from depression, anxiety, or other cognitive behavioral mood issues).

Methylation is required for histamine clearance. Histamine and methyltransferase, which require SAMe, is one of the enzymes that clears histamine along with diamine oxidase, so impaired methylation can be one of the causes of histamine intolerance or perhaps MCAD, mast cell activation disorder. Methylation is crucial for detoxification. Methylation is required for biotransformation of xenobiotics during phase 2 liver detoxification, so it is particularly important for phase 2 liver detox. It's important for hormone clearance because methylation of estrogens via COMT is required for effective estrogen clearance. Methylation plays a role in cellular energy metabolism via the production of CoQ10, carnitine, and ATP, which are important for mitochondrial energy. Methylation is important for phospholipid synthesis via the synthesis of phosphatidylcholine, and it also supports the integrity of cell membranes. Finally, deficiency of SAMe in the cerebrospinal fluid is a causative factor in demyelination, so methylation may play a role in MS and other conditions involving demyelination.



If we simplify that table even further for discussion with patients, this is what it looks like. Impaired methylation can lead to depression, anxiety, histamine intolerance, weak immune function, higher risk of cancer, poor detox capacity, hormone imbalance, infertility, birth defects, fatigue, and low energy.

As you can see, these are extremely common problems. It's true, of course, that each of these symptoms has multiple etiologies, but if you have a patient with three or four of these issues, it's likely that methylation may be playing a role.

Disorders associated with Methylation

ADD/ADHD	Bipolar disorder	Essential Hypertension
Addiction	Cancers	Fertility issues
Allergies	Chemical sensitivity	Fibromyalgia
Alzheimer's Disease	Chronic Fatigue	Insomnia
Anxiety	Cleft Palate	Multiple sclerosis
Asthma	Diabetes	Neuropathy
Atherosclerosis	Dementia	Parkinson's disease
Autism spectrum disorder	Depression	Schizophrenia
Behavioral changes	Down Syndrome	Thyroid disease

Given the many important functions of methylation, it's not difficult to understand why deficits in methylation are associated with such a wide range of conditions, and I've put just a few of these on the slide. They include ADHD, addiction, allergies, Alzheimer's disease, atherosclerosis, autism spectrum disorder, chronic fatigue, chemical sensitivity, diabetes, depression, hypertension, fibromyalgia, fertility issues, MS, Parkinson's, thyroid disease, and the list goes on and on.

Risk factors for impaired methylation can be broken down into two categories: environmental and genetic. There has been a lot of focus on MTHFR and other single nucleotide polymorphisms or SNPs and their contribution to methylation deficits, and although SNPs do play a role, environmental factors are most certainly more important. Remember, our genes haven't changed much over the past 10,000 years. Our Paleolithic ancestors and contemporary hunter-gatherers have roughly similar genes to us, but they don't suffer—or didn't suffer—from many of the conditions that were caused by impaired methylation, which suggests that the environment is the more significant factor and how the environment affects gene expression in particular.

Nutrients

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

The first environmental cause is nutrient deficiency. There are several nutrients involved in methylation pathways, and the most important, I'm sure you're already familiar with from earlier in the blood chemistry unit, are B12 and folate, but they also include others listed on this slide such as methionine, cysteine, taurine, DHA, zinc, magnesium, potassium, riboflavin, niacin, pyridoxine, betaine or trimethylglycine as it is sometimes referred to as, choline, and sulfur. Inadequate intake of any of these nutrients can impair methylation.

Let's talk a little bit about folate first. According to the NHANES data, the mean U.S. adult dietary intake of food-fortified folic acid and natural food folates ranges from 454 to 652 mcg per day, of which 190 mcg per day is estimated to come from folic acid fortification. This is from people who are eating processed and refined foods that are fortified with folate. The RDA target for folate intake is 400 mcg per day. Fortified foods would primarily include refined cereals, breads, and other processed foods, so an unfortunate consequence of Paleo and other healthy diets that avoid these foods is that some people may fall below the 400 mcg per day target for folate intake without them, if they are not eating other very folate-rich foods such as organ meats, such as liver, and adequate amounts of dark leafy greens. The U.S. dietary intake without fortified food ranges from 264 to 462 mcg, so people on the lower end of the daily intake range with fortified food

would fall below the RDA when they remove that fortified food. This is similar to the consequence of switching from iodized salt to sea salt in terms of iodine.

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

While studies suggest that most Americans do get enough folate, they are assuming intake of fortified foods, and it's possible that folate deficiency is more common in people who are eating a so-called "healthy diet," but are not eating the very nutrient-dense foods such as organ meats and other foods that are rich in folate. I've put together a list of foods that are rich in folate, and this is from the B12 and folate-deficient anemia presentation, so it may be familiar. As you can see, chicken liver—liver steals the show again—chicken liver and beef liver are the two highest sources of folate with 254 mcg and 215 mcg, respectively.