

B12 and Folate-Deficient Anemia - Part Three

It's common in the functional and integrative medicine communities to use very high doses of methyl donors such as 5-MTHF, folinic acid, SAM-e, etc., in the treatment of folate deficiency, and until quite recently, I did this routinely as well, and I still do it at least temporarily in some cases. However, recent research has identified some potential issues with high-dose methyl donor supplementation. Dr. Kara Fitzgerald covers them in her e-book *Methylation Diet & Lifestyle*, which is a great resource. I've put a link in the resources section to it. The correct dose for methyl donor supplements is—there is really not much research on it at all, and it almost certainly varies among individuals, given all the factors that affect methylation that we've talked about. There have been side effects observed in the scientific literature with high doses, especially of 5-MTHF, and I've certainly observed this in my clinical practice as well. These include things such as anxiety, agitation, insomnia, etc.

Overmethylation may be detrimental. The scientific literature has examples of overmethylation associated with adverse effects, primarily immune dysregulation. We don't really have enough research on the long-term effects of taking super-high doses of methyl donors for many years, which makes me a little bit nervous about it. Methylation status, of course, depends on diet and lifestyle inputs, so diet and lifestyle change, in my opinion, are the safest options given everything that we've discussed.

A Cochrane systematic review published in 2014 found that food-source folate had a protective effect on cancer risk, specifically breast cancer, within the range of 153 to 400 mcg per day. This suggests that doses of folate that are found in food can have a significant impact. That said, people with underlying issues such as GI malabsorption and high toxic burden, etc., may need higher doses, at least temporarily, until those conditions are addressed.

Nutrients

Methionine

Cysteine

Taurine

DHA

Zinc

Magnesium

Potassium

Riboflavin

Niacin

Pyridoxine

Folate

Vitamin B12

Betaine (TMG)

Choline

Sulfur

There are many other nutrients that are required for optimal methylation. I've listed them here on this slide. They include methionine, cysteine, taurine, DHA, zinc, magnesium, potassium, riboflavin, niacin, pyridoxine, folate, B12, betaine (or trimethylglycine), choline, and sulfur. Of course, with a list this long, the best option is to eat a very nutrient-dense diet. I have a patient handout that you can use that lists the top food sources of all of these nutrients in the diet.

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, 1/2 cup	47
Kidney beans, canned, 1/2 cup	46
Peanuts, dry roasted, 1 ounce	41
Crab, Dungeness, 3 ounces	36
Orange, fresh, 1 small	29

Let's focus first on the dietary sources of folate and limiting them to Paleo-friendly sources plus legumes, which I think actually are Paleo, contrary to popular belief, and they are healthy when they are well tolerated and properly prepared. Of course, avoid processed and folate-fortified foods. You'll never guess what tops the list. Again, it's organ meats. Organ meats and shellfish are always the winners. Chicken liver is particularly rich in folate. It has 254 mcg per serving. Beef liver can be a significant source as well at 215. Then, the next source is boiled spinach at 131 mcg per half cup, so it's about half the amount that is found in chicken liver. In general, when you think of folate, and you talk to your patients about it, we're talking about organ meats, dark leafy greens, legumes, and avocado is actually a pretty good source.

In certain cases, it may be necessary to supplement, as I mentioned, at least temporarily until the underlying mechanisms are addressed. Typically I would start with a diet rich in folate as well as other nutrients that support methylation, retest in 60 days, and if the markers are still high, consider a trial of supplementation.



If you do supplement, it is important to avoid folic acid. This is a synthetic compound used in dietary supplements and food fortification. I've written about the differences between folate and folic acid extensively, and we'll provide a link to an article I wrote that summarizes that research. The form of folate that can enter the main folate metabolic cycle is tetrahydrofolate. Unlike these natural folates, which are metabolized to tetrahydrofolate in the mucosa of the small intestine, folic acid undergoes initial reduction and methylation in the liver, where conversion to the tetrahydrofolate form requires dihydrofolate reductase. Unfortunately, the activity of that enzyme is quite low in many humans, and combined with a high intake of folic acid, that can result in unnatural levels of unmetabolized folic acid entering the systemic circulation. We have several studies showing that excess unmetabolized folic acid is associated with several health conditions, including cancer, depressed immune function, deterioration of central nervous system function, anemia, and cognitive impairment.



The best forms to supplement with, then, are 5-MTHF, 5-methyltetrahydrofolate, or folic acid, which is 5-formyl THF. Remember, 5-MTHF is the cofactor for methionine synthase, which converts homocysteine back into methionine. I prefer starting with a lower dose of 200 to 400 mcg per day rather than the much higher doses of up to 5 or even 10 to 20 mg that some clinicians prescribe. Note that a pretty substantial number of people, in my experience, have side effects with folate. Even with the lower doses of 5-MTHF, they can experience anxiety, agitation, insomnia, and just overstimulation in general. In these cases, you can use folic acid at a dose of 800 mcg. It is better tolerated than 5-MTHF and typically still works well for normalizing folate levels. Folic acid may also selectively support cerebral folate levels in certain circumstances where autoantibodies to folate transport proteins at the blood-brain barrier are present.

Make sure to retest after 60 days to determine whether the intervention is working. You can look at serum folate levels, which are, remember, a better marker of recent intake than red blood cell folate, as well as the CBC and anemia markers and formiminoglutamic acid, or FIGLU. Once mechanisms are addressed, consider transitioning the patient to a dietary approach. If the patient can't maintain folate levels ongoing with diet, there is some uncertainty here. We have to weigh the risk of high homocysteine versus the risk of supplementing longer term with high doses of folate, which we don't really understand much about. There may not be that much of a risk, or there may be a risk. We just don't know. We do know that very high levels of homocysteine are associated with both cardiovascular disease and neurocognitive problems such as Alzheimer's and Parkinson's. It is not an easy question to answer. In those options, I would probably lean towards supplementing but using folic acid perhaps instead of methylfolate and using the lowest effective dose to get homocysteine back into the optimal range.

Okay, that's it for now. See you next time.