

Blood Chem B12 and Folate-Deficiency Anemia and Anemia of Chronic Disease Review

FOLATE

- A water-soluble B vitamin and a necessary cofactor in the methylation cycle.
- It is a key to synthesizing new red blood cells.
- Most common cause of folate deficiency is nutritional.
 - Also, MTHFR genetic polymorphisms
 - MTHFR homozygotes have 70 to 75 percent loss of enzyme activity but with a nutrient rich diet and no other significant mutations, there can be enough enzymatic activity to avoid deficiency without supplementing.
 - Compound heterozygotes, heterozygous for C677T and for A1298C, may lose up to 50 percent of enzyme activity.
- GI malabsorption and inflammation, infections such as H. pylori, hypochlorhydria, alcoholism, and certain drugs such as metformin when used long term can also cause folate deficiency.
- Populations that are at risk for folate deficiency include children; people who don't eat folate-rich foods, which include organ meats such as liver, dark leafy greens, and some legumes; people with GI disorders and infections; alcoholics; diabetics taking metformin; and pregnant and lactating women who have an increased demand for folate.

MARKERS OF FOLATE DEFICIENCY

- Serum folate is the best serum marker for assessing recent nutritional intake of folate. Optimal range is above 8 mcg/L.
- RBC folate reflects body stores during last three to four months, not diet.
- Homocysteine is sensitive, but high level can indicate B12 and/or folate deficiency.
- Formiminoglutamate (FIGLU) can be used to differentiate between B12 and folate deficiency when homocysteine is elevated. High urine FIGLU indicates folate deficiency.

Treatment of B12 or folate-deficient anemia starts with addressing underlying causes.

You can refer back to the B12 deficiency presentation/review for more information on diagnosis and the treatment of B12 deficiency.

CONCERN WITH HIGH DOSES OF METHYL DONORS

- Such as 5-MTHF, folinic acid, SAM-e, etc., in the treatment of folate deficiency,
- Overmethylation may be detrimental.
- Side effects observed in the scientific literature with high doses, especially of 5-MTHF include things such as anxiety, agitation, and insomnia.
- Overmethylation is also associated with primarily immune dysregulation.
- We don't have enough research on the long-term effects of taking high doses of methyl donors for many years, so diet and lifestyle change, in my opinion, are the safest options.

OTHER NUTRIENTS THAT ARE REQUIRED FOR OPTIMAL METHYLATION

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, 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

In certain cases, it may be necessary to supplement at least temporarily until the underlying mechanisms are addressed. 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, avoid folic acid.

Folic acid is a synthetic compound used in dietary supplements and food fortification. The form of folate that can enter the main folate metabolic cycle is tetrahydrofolate.

Folic acid undergoes initial reduction and methylation in the liver where conversion to the tetrahydrofolate form requires dihydrofolate reductase. Activity of that enzyme is quite low in many humans. This can result in unnatural levels of unmetabolized folic acid entering the systemic circulation.

Several studies have showed 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 of folate to supplement with are:

- 5-MTHF, 5-methyltetrahydrofolate, or folinic 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..
- Note that a pretty substantial number of people in my experience have side effects with folate including anxiety, agitation, insomnia, and just overstimulation in general.

- In these cases, you can use folinic acid at a dose of 800 mcg. It is better tolerated than 5-MTHF and typically still works well for normalizing folate levels.
- Retest after 60 days. Consider testing serum folate level, which is a better marker of recent intake than red blood cell folate, as well as the CBC, anemia markers, and formiminoglutamic acid, or FIGLU.
- Once underlying issues are addressed, transition the patient to a dietary approach.
- If the patient can't maintain folate levels ongoing with diet, you 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.
- 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.
- I would probably lean towards supplementing but using folinic acid perhaps instead of methylfolate and using the lowest effective dose to get homocysteine back into the optimal range.

ANEMIA OF CHRONIC DISEASE (ACD)

- Also referred to as anemia of chronic inflammation.
- It can be caused by something as simple as a viral infection, a UTI, H. pylori infection, or an autoimmune disease.
- Anemia of chronic inflammation is an adaptive or protective mechanism to limit the amount of iron a person absorbs when pathogens are present.
- All living things, including bacteria and cancer cells, depend on iron to sustain life.
- The body can regulate how much iron it absorbs and absorb only what is needed to make red blood cells but not enough to nourish pathogens or feed cancer cells.
 - In this situation, hemoglobin levels will often decrease slightly, typically to the range of 9.5 to 10.5 g/dL, and stabilize at that level until the underlying condition is cured.
- Ferritin can be used to distinguish between iron-deficiency anemia and anemia of chronic disease in about two-thirds of patients, but it is not reliable in the other third.
- Hemoglobin is often low in both anemias but typically not below 9.5 g/dL in ACD.

	Serum iron	Serum ferritin	Iron saturation	TIBC/ UIBC	Soluble transferrin receptor	Reticulocyte hemoglobin content	Hemoglobin	MCV	RDW	White blood cell
Anemia of Chronic Disease (ACD)	Low	High	Low	Low	Normal	Normal	Low, but rarely <9.5 g/dL	Normal to slightly low	Normal	High, low, or normal
Iron Deficiency Anemia (IDA)	Low	Low	Low	High	High	Low	Low; may be <9.5 g/dL	Low	High	Normal

POPULATIONS AT RISK FOR ACD

Population	Risk factors
Elderly	H. pylori, other chronic inflammatory conditions common with aging
People with chronic infections	H. pylori, tick-borne illness, reactivated viral infections, GI pathogens
People with autoimmune disease	Rheumatoid arthritis, IBD, Hashimoto's, etc.
People with other chronic, inflammatory conditions	Osteoarthritis, interstitial cystitis, etc.

ACD is the most common cause of anemia in the elderly.

- If you see markers of anemia such as low serum iron or iron saturation, check TIBC and ferritin.
 - If TIBC is low and ferritin is high, it is likely that it is ACD, especially if RDW is normal, MCV is normal or low normal, and white blood cells are high or low.
 - If there is any question, run soluble transferrin receptor and reticulocyte hemoglobin content. If those are normal, it is virtually certain you're looking at ACD.
- Address any underlying causes you've identified that can result in ACD.
- If the patient has ACD and iron deficiency concurrently, do what you can to resolve the ACD first, particularly if there is a pathogen present, because if you feed that pathogen iron, it could get worse.
- If you are absolutely certain there is no pathogen and it is just inflammation that is present, try to get the inflammation under control before supplementing with iron, or just focus on more iron-rich foods.
- If ACD doesn't resolve after addressing the underlying causes you identify, or if there are signs of more serious disease present, refer to a hematologist, a gastroenterologist, or a nephrologist.