KRESSER INSTITUTE FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

B12 and Folate-Deficient Anemia - Part One

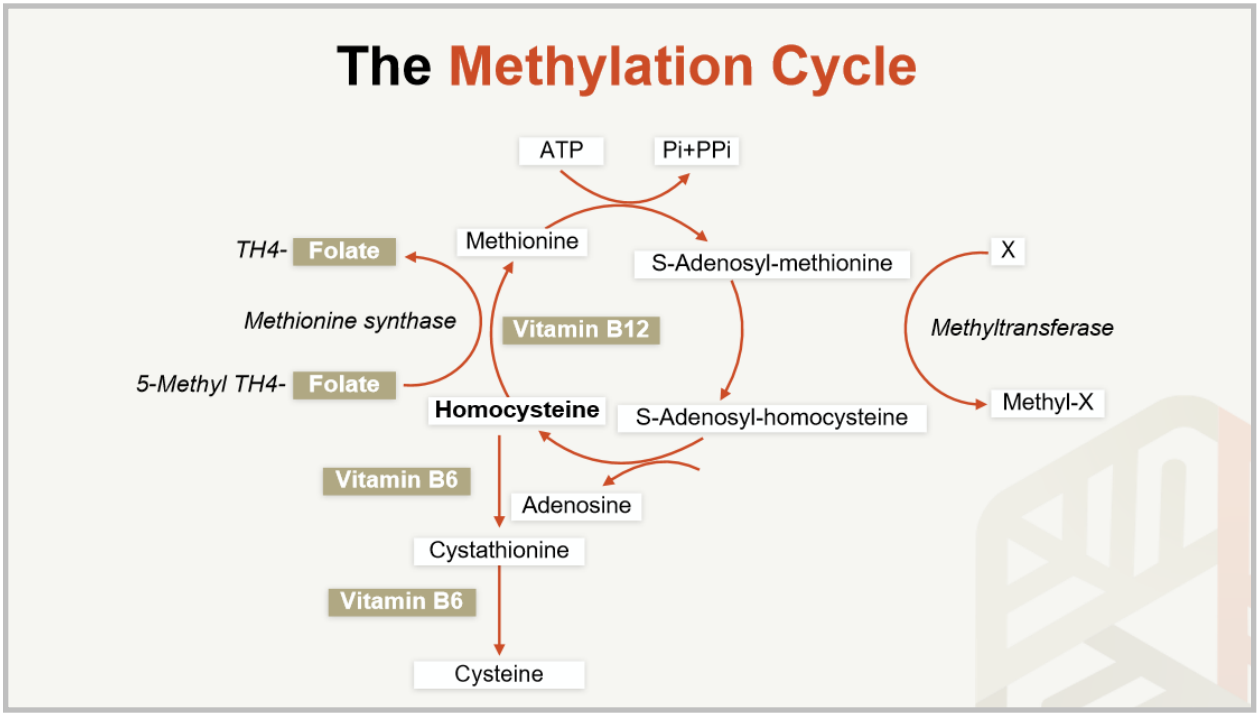
Hey, everybody. In this presentation, we're going to discuss B12- or folate-deficient anemia. B12 and folate deficiency can also cause anemia. We talked about B12 deficiency in a separate presentation. We haven't discussed folate deficiency much yet.

Folate is a water-soluble B vitamin, a necessary cofactor for synthesizing purine and thymidine nucleotides as well as converting homocysteine back into methionine in the methylation cycle, and it is a key to synthesizing new red blood cells. The most common cause of folate deficiency is nutritional, but there are genetic polymorphisms in genes that code for the MTHFR enzyme that limit the conversion of less active forms of folate to more active forms, and this can certainly predispose people to folate deficiency, and we'll talk more about that shortly.

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. For example, one study of Taiwanese children found that 31 percent of boys and 26 percent of girls had marginal folate deficiency and had poor folate status during rapid periods of growth and development. A study of pregnant women in Belgium found that 39 percent had suboptimal folate status that could put them at risk for neural tube defects, which is one of the primary issues with folate deficiency during pregnancy.

If you look at conventional sources, they will say that folate deficiency is rare, but they are using cutoffs designed to catch anemia, and they are not considering the needs of these special populations. Remember, in general, the RDA was designed to detect the level of a particular nutrient that would lead to acute deficiency syndromes. It's not the optimal level of that nutrient.



Let's talk a little bit about the genetics that can affect folate status. In the methylation cycle, homocysteine is converted back into methionine by one of two pathways. There is the dominant pathway, which is via methionine synthase conversion, and this requires a transfer of a methyl group from 5-methyltetrahydrofolate, or 5-MTHF for short. 5-MTHF is formed irreversibly by the enzyme methylenetetrahydrofolate reductase, or MTHFR, and genetic polymorphisms in MTHFR can reduce the formation of 5-MTHF and thus impair the conversion of homocysteine back into methionine, resulting in elevated homocysteine levels.

The most common MTHFR polymorphisms are C677T and A1298C. The frequency of homozygosity of C677T is highly variable according to ethnicity and geography. The highest frequency, which is over 20 percent, is reported in U.S. Hispanics, Columbians, and Amerindians in Brazil. The frequency among Caucasian populations in Europe, North America, and Australia is between 8 and 20 percent, and the lowest frequency, which is below 2 percent, is found in black populations. The frequency of homozygosity for A1298C in white populations in North America and Europe is reported to be between 7 and 12 percent. Lower frequencies are reported in Hispanics, around 4 to 5 percent, and in Asian populations, around 1 to 4 percent.

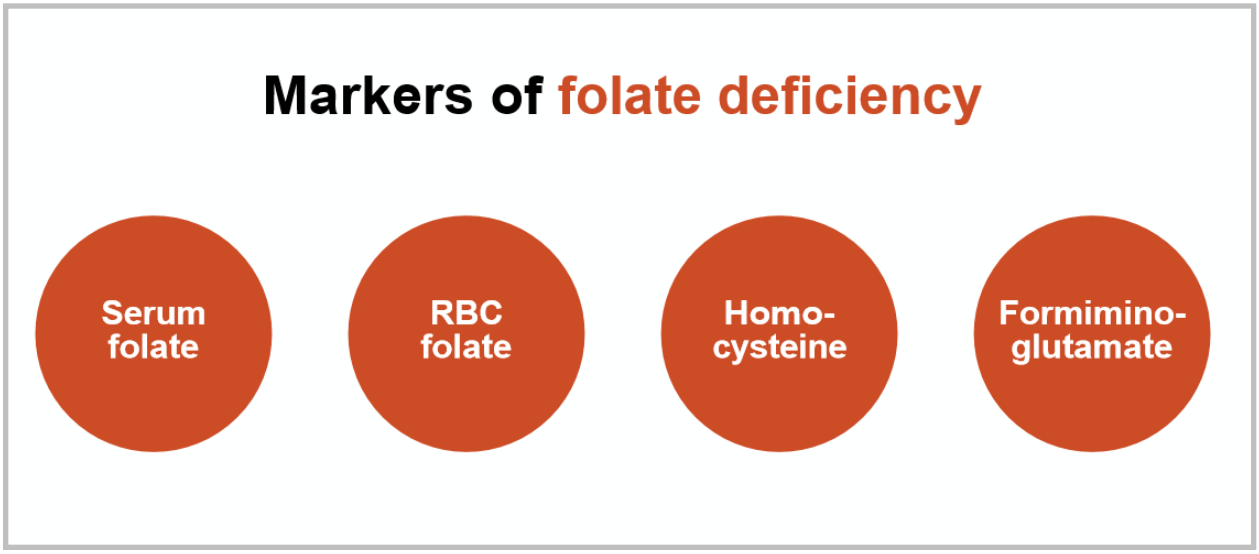
MTHFR homozygotes **have** 70–75% loss of enzyme activity.

People who are homozygous for MTHFR C677T have a 70 to 75 percent reduced activity of that enzyme, while heterozygotes, which are much more common, lose between 33 and 35 percent of enzyme activity. People who are homozygous for A1298C have a 39 percent reduction in enzyme activity, and heterozygotes for A1298C have a 17 percent reduction in enzyme activity.

Compound heterozygotes, so people who are heterozygous for C677T and then also for A1298C, may lose up to 50 percent of enzyme activity.

A recent meta-analysis reported a 16 percent decrease in erythrocyte folate levels for people who are homozygous for MTHFR C677T when compared to their wild type counterparts and an 8 percent decrease for those who are heterozygous for C677T. We see some reduction in folate levels, but not as significant as you might assume from some of the internet resources about MTHFR.

Also note that there are many other genes that affect methylation. It's extremely complex. It's an ongoing area of research. I'm going to cover it in more detail in a future advanced course, but in this presentation, we're just focusing on assessing folate deficiency and folate-deficient anemia.



Markers for assessing folate deficiency include serum folate, red blood cell folate, homocysteine, and formiminoglutamic acid, or FIGLU.

Let's start with serum folate. The lower end of the reference range is the threshold below which megaloblastic anemia begins to appear, and that is 6 mcg/L. However, homocysteine and FIGLU have been shown to increase folate levels between 6 to 8 mcg/L, and this is indicative of folate deficiency and impaired function. Serum folate is the best serum marker for assessing recent nutritional intake and will drop before red blood cell folate drops. The optimal range given this is above 8 mcg/L, but as usual, this marker should be interpreted in the context of other markers such as FIGLU and homocysteine.

Red blood cell folate concentration reflects folate body stores and the folate turnover during the last three to four months, and it is largely unaffected by diet. Red blood cell folate isn't standardized. There is a lot of potential for error. For example, red blood cell folate can be falsely low in B12 deficiency. This is a phenomenon known as folate trapping, where folate molecules remain trapped in circulation because methylfolate cannot be demethylated and polyglutamated to form its active intracellular counterpart because of the B12 deficiency. For this reason, RBC folate shouldn't be used to screen for folate deficiency. The potential value of RBC folate is that it

more accurately reflects tissue stores than serum folate, and that unlike serum folate, it is not influenced by recent folate intake. For RBC folate, I don't have a functional range. You would just use the laboratory reference range.

Homocysteine
is a sensitive—but not specific—
marker of folate deficiency.

As I mentioned in the B12 deficiency presentation, homocysteine is a very sensitive marker for both B12 and folate deficiency. The lower end of the lab range is 15, but we discussed a study that found that a homocysteine level of lower than 7.5 correlates with the lowest level of chromosomal damage in lymphocytes and an optimal level of DNA repair. I've set the lower end of the homocysteine functional range at 7 to be conservative. Note again that homocysteine can't be used alone to detect folate deficiency because B12 deficiency can also cause elevated homocysteine. When you see high homocysteine, you have to look at other markers such as serum or red blood cell folate, formiminoglutamic acid, and then urinary or serum methylmalonic acid and serum B12 to determine whether it is high because of B12 deficiency, folate deficiency, or both.

FIGLU **can be used to differentiate**
between B12 and folate deficiency
when homocysteine is elevated.

Formiminoglutamic acid, or FIGLU, as it is known, is a urine organic acid. It can be used as a marker of folate deficiency and as a means of differentiating between high homocysteine caused by B12 deficiency or high homocysteine caused by folate deficiency. The amino acid histidine is metabolized to glutamic acid in humans, and FIGLU is an intermediary in that reaction. Folate is the coenzyme that is used in that reaction, so if FIGLU builds up in the urine, it is a sign of active folate deficiency. Since FIGLU is an indicator of functional folate status, it may be the most sensitive marker of all the ones that we have for detecting folate deficiency, and it is included on the Genova urine organic acids comprehensive panel.

We talked about the urine organics dysbiosis profile back in the gut section, but one of the reasons I order a comprehensive profile is it has a bunch of other markers such as FIGLU and MMA that can be very helpful. I'll cover the interpretation of that full panel in a future advanced course, but if you only ordered it for FIGLU and MMA, I still think it would be worth it above and beyond the dysbiosis panel.