

## HOMOCYSTEINE ⇒ INFLAM-AGING

How does homocysteine fit into the picture of age-associated inflammation?

Elevated homocysteine is both a cause of, and an effect of inflammation --- a perfect example of a positive feedback loop or “vicious cycle.” There seem to be many mechanisms involved in homocysteine’s association with inflammation, but here are some choice fragments of truth:

- a. Thyroid insufficiency causes elevated homocysteine (and elevated prolactin) that decreases to normal after correction of hypothyroid. Usually the thyroid insufficiency is accompanied by a methyl donor deficiency and requires supplementation with betaine along with a natural thyroid supplement.
- b. Homocysteine blocks the metabolism of vitamin A. (This failure of vitamin A metabolism explains the connection between homocysteine and birth defects. --- Ironic, isn’t it, that there is such an irrational fear of vitamin A supplementation in pregnancy, when it is actually vitamin A deficiency, not vitamin A excess, that is associated with birth defects?)

Low vitamin A, just like low vitamin D, is associated with excessive Th1 immune activation. Excesses of the Th1 inflammatory cytokines such as TNF- $\alpha$ , IFN- $\gamma$ , IL-1 and IL-2, are associated with many autoimmune diseases, including particularly Hashimoto’s autoimmune thyroiditis and rheumatoid arthritis and Type I diabetes.

- c. The association between homocysteine and immune activation appears to involve a positive feedback loop. Elevated homocysteine activates the immune system, but uncontrolled immune system activation also increases homocysteine production.
- d. Some autoimmune conditions or pathologies involving Immuno-Neuro-Endocrine stress such as idiopathic Parkinson’s are associated with enteric-nervous system inflammation/damage. Serum homocysteine is elevated in 43% of idiopathic Parkinson subjects, and the elevated homocysteine is not entirely explained by low serum vitamin B12. But, we recall that 70-75% of the immune system is in the gut mucosa, and 60% of idiopathic Parkinson subjects are hydrogen breath test positive for small intestine bacterial overgrowth. It seems that the increased bacterial utilization of vitamin B12 (as opposed to a deficiency of B12 production) is responsible for a functional vitamin B12 deficiency and subsequent elevated homocysteine.

While excess homocysteine has been clearly identified as one of the few primary risk factors for cardiovascular disease, it is important to understand that it is not the presence of homocysteine per se that relates to cardiovascular disease, but rather the body's inability to properly metabolize homocysteine. The situation here is analogous to that of cholesterol. While elevated cholesterol levels are correlated with cardiovascular disease, it is not the presence of cholesterol itself, nor certainly the dietary intake of cholesterol that is a causative factor in cardiovascular disease.

Homocysteine is nothing more than an intermediate in the metabolism of the essential amino acid methionine. As methionine is metabolized to form the other sulfur containing amino acids, particularly cysteine, and ultimately the powerful anti-oxidant glutathione --- homocysteine is just one of the compounds that is formed along the way. Any attempt to decrease homocysteine levels by limiting methionine intake is analogous to cutting off your head to cure your headache. Homocysteine must be formed in order to properly use methionine to produce cysteine, glutathione, etc.

There are two considerations in appraising homocysteine's association with cardiovascular disease:

1. Why does excess homocysteine accumulate?

2. By what mechanism is homocysteine damaging?

1. What causes homocysteine levels to build up? The next three steps in the methionine metabolic pathway following the formation of homocysteine all require the vitamin B6 co-enzyme. The steps following that require magnesium, potassium, copper, and biotin. Insufficiency or inadequate utilization of any of these nutrients causes the buildup of homocysteine. This may be one mechanism by which the well-known damage of copper deficiency on the vascular system may be manifest. This is also one of the many ways in which magnesium is essential to cardiovascular health.

Another contribution to the buildup of homocysteine is a failure of the overflow mechanism. Homocysteine levels never accumulate under normal conditions because even if homocysteine is being formed faster than the downstream metabolic processes can handle it, it is automatically recycled back into methionine. This recycling process requires folic acid, vitamin B12, and/or the methyl donor betaine. Metabolic imbalances adversely impacting the utilization of these nutrients will also contribute to the buildup of homocysteine.

2. The next consideration regarding homocysteine is that homocysteine does not directly damage the vascular system. It is oxidized homocysteine that is toxic to the arterial endothelium. The oxidation of homocysteine is not a normal biochemical process in the body, and occurs only when there are metabolic imbalances predisposing to oxidative stress.

This idea that it is metabolic inefficiency or imbalance that leads to oxidized homocysteine and hence arterial damage is further supported by a study published in the American Journal of Clinical Nutrition. This study shows that the strongest correlation with elevated homocysteine levels is caffeine consumption. And the only metabolic stressor associated with higher levels of homocysteine than those associated with caffeine consumption are those associated with caffeine consumption plus smoking. As we know from Nutri-Spec, both caffeine and smoking exacerbate Sympathetic Imbalance, Electrolyte Stress Imbalance, and both Anaerobic and Dysaerobic Imbalances.

Also of clinical relevance is that while homocysteine is associated with, and even causative of, greater risk of cardiovascular disease, elevated homocysteine rarely acts alone. Most elevated homocysteine that leads to heart attacks or strokes is accompanied by deficient cholesterol HDL and elevated triglycerides. An elevated triglyceride to HDL ratio is a direct reflection of insulin resistance → Metabolic Syndrome. That ratio is still the #1 independent risk factor for cardiovascular disease.

Clinical Experience: A Nutri-Spec practitioner who was concerned about methionine supplementation for two of his patients with high homocysteine, high cholesterol, and cardiovascular disease, checked their homocysteine levels after several months of methionine supplementation. In both patients, homocysteine had dropped to normal. So, methionine supplementation, and certainly dietary methionine, is no problem for patients with elevated homocysteine.

What your patients with high homocysteine need above all else is the methyl donor betaine (found in your Adapto-Max (Diphasic A.M.) and in Oxy D, Complex S, and Proton Plus). Pre- and Pro-biotics to control INE stress is critical. Thyroid is sometimes essential. Other possible needs (nearly always adequately supplied by your patient's NUTRI-SPEC regimen) include vitamins B6, B12, biotin, and folic acid, and the mineral nutrients magnesium, copper, and potassium --- along with avoidance of sugar, caffeine and cessation of smoking.

#### ADDENDUM:

Question From a NUTRI-SPEC practitioner: "I am curious if there is a Metabolic Imbalance most likely to have high homocysteine?" ----- Probably

not just one NUTRI-SPEC Imbalance. Here is the way to think of it ...

- Elevated homocysteine is one of the few primary risk factors for cardiovascular disease.
- Insulin Resistance is a primary risk factor for cardiovascular disease. (Insulin resistance is the #1 cause of a high Triglyceride/HDL Ratio, the #1 risk factor for cardiovascular disease.)
- Thyroid Insufficiency is a primary risk factor for cardiovascular disease.
- And --- both Insulin Resistance and Thyroid Insufficiency are causes of elevated homocysteine.
- And --- Thyroid Insufficiency causes Insulin Resistance.

--- The interconnectedness between homocysteine, Thyroid Insufficiency, and elevated insulin are undeniable. So ...

When you look at all your male and female patients with elevated homocysteine, you are going to find an extremely high percentage are Thyroid Insufficient (or perhaps Hypothyroid/Hashimoto's). After you take out all the high homocysteine patients who clearly have Thyroid Insufficiency, what Imbalances are left? --- You will find that nearly everyone left is someone who has Insulin Resistance for some cause other than Thyroid Insufficiency. In my guesstimation, the most likely of all (--- and I cannot give you actual data backing this up) would be your Ketogenic Imbalance male patients with tubby tummies.

Another Question: “Is LOW homocysteine ever a problem, and what causes it?”

Low homocysteine is quite rare, really. One study I have seen demonstrated that only about 1 out of every 200 individuals has hypo-homocysteinemia.

If you are (foolish enough to be) reading the garbage spewing from the mouths of internet health gurus, you will find the comment that low homocysteine “means the person isn't getting enough protein ...” --- Yes, among the (very few) studies on hypo-homocysteinemia, there are several on protein malnutrition. BUT --- these studies are all looking at patients on long-term dialysis. To extrapolate from dialysis protein deficiency in severe renal disease patients to low homocysteine being caused in otherwise normal patients by not eating enough protein is purely a non sequitur --- natural cure guru mythology. Forget it.

Virtually all the studies on hypo-homocysteinemia that do not involve renal dialysis patients involve Type 1 Diabetics --- patients who are Insulin Deficient. ----- Do you see the pattern here? As described above, Insulin Resistance (high insulin) is a major cause of elevated homocysteine. Inadequately treated Type 1 Diabetes (Deficient Insulin) is the major cause of hypo-homocysteinemia.

Furthermore, when diabetics with low homocysteine are given adequate Insulin, their homocysteine rises --- and often rises to pathologically elevated levels.

