Significance of Low Plasma Homocysteine

Richard S. Lord, Ph.D. and Kara Fitzgerald, N.D.

Metametrix Clinical Laboratory
Department of Science and Education

4855 Peachtree Industrial Blvd. 
Norcross GA 30092 USA 
www.metametrix.com
Abstract
While high plasma homocysteine is widely recognized as a cardiovascular disease risk factor, individuals with low homocysteine may also be at risk. The risk of hypohomocysteinemia derives from the fact that homocysteine is the normal intermediate for conversion of methionine into cysteine, and thus for production of glutathione, taurine and sulfate. Individuals with low homocysteine have limited capacity for response to oxidative stress and certain kinds of toxin exposure. The most common treatment for low homocysteine is administration of sulfur-containing amino acids such as methionine, N-acetylcysteine and taurine. Preformed glutathione and inorganic sulfate salts (potassium sulfate) may also be employed. Plasma methionine and urinary sulfate, pyroglutamate or alpha-hydroxybutyrate are related tests that may be performed for confirmation of significant cysteine deficit.

Introduction
Elevated homocysteine contributes to the pathophysiology of many conditions, with cardiovascular disease being the best-recognized presentation. However, elevated homocysteine is generally known to be a modifiable risk factor due to the involvement of vitamin B\textsubscript{12} and folate in the transmethylation to methionine. Correct supplementation with these vitamins can restore homocysteine to an appropriate level in most cases.

In opposition to transmethylation, homocysteine undergoes transsulfuration forming cystathionine (Figure 1). Through this pathway, homocysteine is an intermediate in the conversion of methionine to cysteine. A sensitive enzyme regulation mechanism controls whether homocysteine is predominantly transmethylated or transsulfurated. The function of this regulation is to allow rapid response to oxidative challenge by increasing the formation of glutathione, a process dependent on cysteine availability (Figure 2). Restriction of the substrate (homocysteine) can limit the formation of the product (glutathione). This means that a low homocysteine can restrict the amount of glutathione that can be produced in response to oxidative stress. Two additional detoxification factors, taurine and sulfate, are produced from cysteine (and therefore, also influenced by low homocysteine)\textsuperscript{1}.

Clinical associations
Hypohomocysteinemia shows up as a specific variable in certain presentations. It is, for instance, a key feature of the malnutrition-inflammation complex that predicts poor outcome in maintenance hemodialysis patients\textsuperscript{2}. Chronic kidney disease patients with higher homocysteine have significantly better survival. In these patients, the malnutrition-inflammation-cachexia syndrome appears to be the main cause of worsening atherosclerotic cardiovascular disease. This situation has been described as a reverse epidemiology of cardiovascular disease\textsuperscript{3}.

Hypohomocysteinemia causes reduced availability of cysteine. Cysteine restriction causes limitation in production of sulfate, taurine and glutathione\textsuperscript{16}. The limited production ability is exacerbated in conditions that cause increased demand for any of the sulfur compounds produced from homocysteine. Alcohol intake greatly increases the production of taurine\textsuperscript{17}, and many drugs and xenobiotics increase sulfate requirement for conjugation and elimination\textsuperscript{18}. One of the body’s main uses of sulfate and taurine is in Phase II liver detoxification. Taurine is involved in the formation of bile acids whereas the sulfation pathway is required for removal of steroid hormones, phenolic compounds and numerous

| Table 1. Pathologies and diseases associated with limited glutathione status. |
|-----------------------------|-----------------------------|
| **Organ pathology associated with decreased glutathione status**\textsuperscript{4} | **Specific conditions associated with reduced glutathione status** |
| Hepatic                     | Schizophrenia\textsuperscript{5} |
| Cardiovascular              | Autism\textsuperscript{6}    |
| Lungs                       | Cataracts\textsuperscript{7}  |
| Kidney                      | Accelerated aging\textsuperscript{8} |
| Genitourinary               | Hyperlipidemia\textsuperscript{9} |
| Endocrine                   | Hepatitis\textsuperscript{10,11} |
| Gastrointestinal            | AIDS\textsuperscript{12}      |
| Gallbladder                 | Adult respiratory distress syndrome\textsuperscript{13} |
| Musculoskeletal             | Diabetes\textsuperscript{9,14} |
| Neurological                | Cystic fibrosis\textsuperscript{13} |
|                             | Environmental toxicity\textsuperscript{15} |
Significance of Low Plasma Homocysteine

**Figure 1. Homocysteine transmethylation in low cysteine demand status.**
The essential amino acid methionine is converted to homocysteine for multiple metabolic purposes. The conversion involves production of S-adenosylmethionine which enters into active methyl group transfer with the formation of S-adenosylhomocysteine. When homocysteine is released by hydrolyzing the adenosyl group, it can be remethylated to form methionine. Under conditions where homocysteine conversion to methionine is the dominant flow, folate and vitamin B12 status are the critical micronutrient factors.

**Figure 2. Homocysteine transsulfuration in high cysteine demand status.**
Oxidative challenge causes reciprocal regulation in which homocysteine transmethylase (E1) is inhibited while homocysteine transulfurase (E2) is stimulated. The effect is to shift the flow of homocysteine into the formation of cysteine that can flow to glutathione and sulfate. Active methyl group formation slows as glutathione and sulfate formation increases. A by-product of this shift is increased formation of α-hydroxybutyrate. Vitamin B6 becomes the critical micronutrient governing accumulation of homocysteine. In normal vitamin B6 status, chronic oxidative challenge results in depletion of methionine and homocysteine that ultimately restricts the formation of glutathione, taurine and sulfate.
Significance of Low Plasma Homocysteine

4. The points represent homocysteine results sorted from low to high for 1400 cases reported during the interval of January through March of 2004. The red line shows the trend through the central portion of the population. Note that the number of individuals fall off steeply below the value of 4.0 nmol/ml. This point on the curve is analogous to the cutoff of 8.0 for the high limit, which is at the point where the change in population density deviates from linear physiological variation. Reference limits set at 4.0 – 8.0 nmol/ml produce the distribution of abnormalities shown in Table 2.

Table 2. Distribution of abnormalities for 1400 consecutive cases based on a reference interval of 4.0 – 8.0 nmol/ml.

<table>
<thead>
<tr>
<th>Value</th>
<th>N (out of 1400)</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4</td>
<td>191</td>
<td>13.7%</td>
</tr>
<tr>
<td>&gt; 9</td>
<td>217</td>
<td>15.5%</td>
</tr>
</tbody>
</table>

Conclusions

Low plasma homocysteine is of clinical relevance because of multiple organ and system disturbances that can result from limitation of sulfur compounds and methionine methyl donor functions. The available data suggests that a low limit of 4.0 nmol/ml reveals abnormal low results that can alert to potential need for supplemental sulfur amino acid intake.

Laboratory Data Analysis

A collection of 997 cases from the Metametrix database for the period January through March of 2004 shows the direct relationship between plasma methionine and homocysteine (Figure 3). The data demonstrates the regular fall of methionine as homocysteine levels fall. Since methionine is a principal source of methyl groups, this depletion of methionine means that limitation of biochemical processes requiring methylation adds further relevance to low homocysteine levels. Methyl donor reactions are essential for neurotransmitter synthesis, formation of cell membranes, lipid metabolism and detoxification reactions. Note that the extrapolated line goes to zero on the methionine scale when homocysteine is at ~4.0 nmol/ml, suggesting that homocysteine values below 4.0 are inconsistent with healthy physiological states by association with methionine deficiency.

Another way of assessing the point at which abnormality of test results should be set is to examine the behavior of population data for the limits of normal physiological variation. The population distribution for Metametrix homocysteine data is shown in Figure...
Significance of Low Plasma Homocysteine

References

5. Steullet P, Neijt HC, Cuenod M, De KQ. Synaptic plasticity impairment and hypofunction of NMDA receptors induced by glutathione deficit: Relevance to schizophrenia. Neuroscience 2005.