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Elevated Homocysteine

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Evidence

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Overview

Homocysteine is a non-essential amino acid and metabolite of methionine, an essential amino acid obtained in the diet. (20) Homocysteine is involved in vitamin B-dependent methylation cycles that generate and breakdown the universal methyl-group donor, S-adenosyl-methionine (SAME). Disruptions in this cycle, whether caused by reduced enzymatic expression or activity of various methylation cycle proteins including methylenetetrahydrofolate reductase (MTHFR), pyridoxal-5'-phosphate (P5P), or cystathionine B-synthase (CBS), may theoretically lead to elevated levels of homocysteine. (28)

Normal homocysteine levels can range from 5-15 $\mu\text{mol/L}$, while hyperhomocysteinemia occurs when homocysteine levels are elevated beyond 15 $\mu\text{mol/L}$. (35) Hyperhomocysteinemia can be further classified as mild (16-30 $\mu\text{mol/L}$), intermediate 100 $\mu\text{mol/L}$, or severe (>100 $\mu\text{mol/L}$). (20)

Hyperhomocysteinemia has been linked to numerous diseases, including:

- Age-related conditions, such as Alzheimer's disease, Parkinson's disease, and stroke
- Endocrine-related conditions, such as diabetes, hypothyroidism, insulin resistance, and osteoporosis
- Endothelial-related conditions, including cerebrovascular and vascular diseases
- Other conditions, such as end-stage renal disease, various cancers, schizophrenia, and complications in pregnancy ([1](#))([20](#))([28](#))

A number of factors may contribute to hyperhomocysteinemia, including:

- Genetic polymorphisms of methylation enzymes, such as MTHFR, CBS, methionine synthase, and methionine synthase reductase
- Nutrient deficiencies, such as folate, vitamin B6, vitamin B12, or betaine deficiencies
- Diet and lifestyle considerations, such as excess methionine intake, smoking, excess alcohol or caffeine intake, and sedentarism ([1](#))([33](#))

Please see the following articles for more information on the impact of [nutrition on the methylation process](#) and on [supporting patients with MTHFR polymorphisms](#).

Folic acid and vitamin B12

Folic acid and vitamin B12

0.2-0.8 mg as folic acid or 5-methylfolate (5-MTHF) per day, minimum 12 weeks for greatest benefit and maintenance for up to ~5 years, with optional 0.4-1.0 mg vitamin B12 for improved efficacy in patients with elevated homocysteine ([3](#))([5](#))([6](#))([7](#))([10](#))([12](#))([15](#))([16](#))([21](#))([23](#))([34](#))([37](#))([38](#))

- Folic acid provided primary effect on homocysteine reductions ranging between ~13-30% ([3](#))([4](#))([5](#))([6](#))([7](#))([10](#))([12](#))([15](#))([16](#))([21](#))([22](#))([23](#))([26](#))([32](#))([34](#))([40](#))
- Proportions of reductions in homocysteine were highly dependent on greater baseline homocysteine and lower baseline folate levels ([5](#))([15](#))([16](#))([29](#))([37](#))
- Higher folic acid doses ranging between 5-60 mg per day were safely used, but did not reduce homocysteine further than ingestion of 0.8 mg ([16](#))([22](#))([29](#))([32](#))([40](#))
- Most human evidence did not support greater folate bioavailability or efficacy in reducing homocysteine by 5-MTHF over folic acid, but it may provide extended retention of benefit upon discontinuation in patients with poor methylation capacity ([2](#))
- Vitamin B12 produced additional ~7% reduction in homocysteine ([4](#))([5](#))([15](#))([16](#))([21](#))

- Individual trials showed benefit of adding vitamin B6 for further reductions in homocysteine, however this was not supported in meta-analyses ([3](#)) ([5](#)) ([15](#)) ([16](#)) ([23](#)) ([34](#))
- Males may have required higher folic acid dose ranges than women ([6](#))

Omega-3 fatty acids

Omega-3 fatty acids

200-6,000 mg (~98-2,000 mg EPA/490-1,000 mg DHA) per day, for 1-12 months in patients with hyperhomocysteinemia or elevated homocysteine within normal ranges ([8](#)) ([11](#)) ([13](#)) ([17](#)) ([18](#)) ([19](#)) ([25](#)) ([30](#)) ([42](#)) ([43](#))

- Reduced homocysteine by 1.18-1.58 $\mu\text{mol/L}$ on average using wide dose ranges, as shown in meta-analyses ([8](#)) ([18](#))
- Reduced homocysteine by ~2.5-4.0 $\mu\text{mol/L}$ in patients with type II diabetes, patients on hemodialysis, or healthy adults using mid-range doses of 2,000-3,600 mg per day for 1-3 months and up to one year ([11](#)) ([17](#)) ([25](#)) ([30](#)) ([42](#)) ([43](#))
- Reduced homocysteine by ~1.6 $\mu\text{mol/L}$ over 12 months in patients younger than 65 years, previously suffering from myocardial infarction ([13](#))
- Adjunct therapy with folic acid, vitamin B6, and vitamin B12 improved efficacy ([8](#)) ([17](#))
- Adjunct aerobic exercise and cognitive stimulation may be required for benefit in some populations, including older adults with mild cognitive impairment ([19](#))

N-acetylcysteine (NAC)

N-acetylcysteine (NAC)

600 mg, 2-3 times per day, for 2-8 weeks ([14](#)) ([24](#)) ([36](#)) ([41](#))

- Reduced total homocysteine by 12-45% in healthy patients or patients at increased risk for CVD ([9](#)) ([14](#)) ([24](#)) ([36](#)) ([39](#))
- Oral formulations reduced total homocysteine in patients with end-stage renal disease by 21-25%, while intravenous formulations further reduce homocysteine during hemodialysis by ~90% ([24](#)) ([27](#)) ([31](#))
- Reduced SBP (~7.1 mmHg) and DBP (~3.3 mmHg) in hyperlipidemic men and SBP (~3.2 mmHg) in normolipidemic men; each 10% reduction in homocysteine is associated with 1.45-2.55 reduction in pulse pressure mmHg in patients undergoing hemodialysis ([14](#)) ([27](#)) ([31](#))

- Increased urinary excretion of homocysteine in its sulfonated form (36)

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