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Homocysteine and Cardiovascular Disease: A Narrative Review of Mechanisms, Associations, and Intervention Evidence

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Abstract

Homocysteine is a sulfur-containing intermediate in methionine metabolism whose circulating concentration reflects interactions among nutritional status, enzyme activity, kidney function, and inherited metabolic disorders. Folate and vitamin B12 participate in its remethylation to methionine, while vitamin B6 supports its conversion through the transsulfuration pathway. Elevated homocysteine concentrations have been associated with coronary and cerebrovascular disease, and experimental studies have identified potential mechanisms involving endothelial dysfunction, oxidative stress, inflammatory signaling, and impaired fibrinolysis. However, these associations and experimental observations do not establish that modest elevations directly cause clinical vascular events. Although folic acid-based supplementation lowers homocysteine concentrations, randomized trials have not consistently demonstrated corresponding reductions in cardiovascular events. Evidence of benefit is more favorable for stroke prevention in certain populations than for coronary outcomes. This narrative review examines homocysteine metabolism, proposed vascular mechanisms, observational associations, and intervention findings, emphasizing the distinction between biochemical improvement and clinical benefit. Homocysteine measurement and treatment should be interpreted according to a specific clinical indication, particularly suspected nutritional deficiency or inherited metabolic disease, rather than an elevated concentration alone.

Categories: Medical Education, Internal Medicine
Keywords: cardiovascular disease, folate, homocysteine, hyperhomocysteinemia, methionine metabolism, oxidative stress, vascular dysfunction, vitamin b12

Introduction And Background

All living organisms require sulfur for various physiological processes, and in mammals, this essential element is obtained through sulfur-containing amino acids. Homocysteine is a critical sulfur-containing amino acid generated during the metabolic processing of methionine, with average daily intake exceeding 1.8 grams. Dietary sources contribute negligible amounts of homocysteine; consequently, although dietary homocysteine intake is negligible, dietary methionine and B-vitamin status can influence circulating homocysteine concentrations [1].

In the circulatory system, homocysteine exists in multiple forms. Approximately 1% circulates as free thiol, while 70-80% forms disulfide bonds with plasma proteins, predominantly albumin. The remaining fraction combines with itself to form homocysteine dimers or with other thiols such as cysteine, creating mixed disulfides [2].

Hyperhomocysteinemia refers to an elevated circulating total homocysteine concentration. Total homocysteine includes free, disulfide-bound, and protein-bound forms. A fasting plasma concentration above 15 μmol/L is a commonly used definition, with approximately 5-15 μmol/L often cited as a reference interval. However, these values are not universal: interpretation should follow the laboratory's validated reference interval, considering the analytical platform, population, age, sex, and renal function. Biochemically, homocysteine accumulates when its remethylation to methionine or transsulfuration to cysteine is impaired. Remethylation depends on folate and vitamin B12, whereas key transsulfuration reactions require vitamin B6. Nutritional deficiencies, inherited enzyme defects, kidney dysfunction, and certain medications can therefore contribute to elevated concentrations. Hyperhomocysteinemia is a biochemical finding with multiple possible causes rather than a diagnosis identifying a single disease [3].

Total homocysteine can be measured using high-performance liquid chromatography (HPLC) or automated immunoassays, among other methods. HPLC separates analytes chromatographically, whereas immunoassays use platform-specific analytical reactions and antibody-based detection. There is no single universal HPLC cutoff distinct from a universal immunoassay cutoff; method-specific calibration and validated reference intervals should guide interpretation. Sample handling also matters because delayed separation of plasma from blood cells can produce an artificial increase in measured homocysteine [4].

Observational studies and pooled analyses have reported associations between higher circulating homocysteine concentrations and vascular outcomes, particularly ischemic heart disease and stroke. However, such associations do not establish that homocysteine is itself a causal risk factor or that lowering its concentration will prevent cardiovascular events [5,6]. Elevated plasma homocysteine concentrations may arise from inherited enzymatic deficiencies affecting cystathionine beta-synthase (CBS) or methylenetetrahydrofolate reductase (MTHFR), as well as acquired conditions including inadequate intake of folic acid, vitamin B6, and vitamin B12 [7].

Despite the unclear physiological role of homocysteine, the methyl groups released during its metabolic processing participate in numerous essential biological activities, encompassing hormone biosynthesis, protein synthesis, and DNA methylation [8]. The subsequent sections provide a detailed examination of metabolic pathways, pathogenic mechanisms, and therapeutic considerations.

Review

Literature search and narrative synthesis

This article is a narrative review. The literature was identified through searches. Additional publications were identified through PubMed and Scopus. Publications were selected for their relevance to homocysteine metabolism, laboratory measurement, cardiovascular associations, proposed mechanisms, and intervention outcomes. Evidence was synthesized qualitatively, distinguishing mechanistic investigations, observational associations, and intervention findings. No meta-analysis or quantitative pooling was performed. No formal risk-of-bias assessment using a standardized tool was performed. Consequently, this review does not provide a systematic appraisal of study quality or a formal certainty of evidence rating.

Homocysteine metabolism and its clinical relevance

Homocysteine is a sulfur-containing intermediate produced during the metabolism of methionine, an essential amino acid obtained from dietary protein. Methionine is first converted to S-adenosylmethionine, an important methyl-group donor [9]. After donating a methyl group, S-adenosylmethionine becomes S-adenosylhomocysteine, which is subsequently hydrolyzed to form homocysteine. Homocysteine therefore sits at a metabolic junction: it can be converted back to methionine or directed toward the synthesis of cysteine. These processes connect its circulating concentration with one-carbon metabolism, nutritional status, and the activity of several enzymes [10].

In the remethylation pathway, methionine synthase transfers a methyl group from 5-methyltetrahydrofolate to homocysteine, regenerating methionine. Vitamin B12 is a cofactor for methionine synthase. MTHFR contributes to this pathway by generating 5-methyltetrahydrofolate from another folate intermediate [11]. This distinction is important because vitamin B12 is a cofactor of MTHFR. An alternative route of remethylation involving betaine also operates in certain tissues. Together, these pathways help maintain methionine availability while preventing excessive accumulation of homocysteine [12].

When homocysteine enters the transsulfuration pathway, cystathionine β-synthase catalyzes its reaction with serine to form cystathionine. Subsequent reactions generate cysteine. Vitamin B6 is required for key reactions in this pathway [13]. Folate and vitamin B12 deficiency may impair remethylation, whereas defects affecting cystathionine β-synthase or vitamin B6-dependent metabolism may impair transsulfuration. Consequently, an increased plasma homocysteine concentration can arise through different biological routes; it is a finding that requires interpretation, rather than a diagnosis with a single cause [14].

Inherited disorders can produce substantial disturbances in homocysteine metabolism, but more modest elevations encountered in general clinical populations may reflect several interacting factors. Nutritional deficiency, variation in enzyme function, kidney impairment, medication exposure, and other aspects of health can affect the measured concentration. This diversity complicates the interpretation of epidemiological studies [15]. Two people with similar homocysteine concentrations may have different underlying conditions and potentially different responses to an intervention. The distinction between severe metabolic disease and modest elevations in population studies should therefore be maintained throughout this review [16].

Proposed mechanisms of vascular injury

Interest in homocysteine as a vascular risk marker was driven partly by observations in people with severe inherited disorders of its metabolism. Such observations generated the hypothesis that less marked elevations might also contribute to vascular disease [17]. Experimental research has since explored several possible mechanisms, particularly oxidative stress, endothelial dysfunction, inflammatory signaling, and altered thrombosis. These mechanisms provide biological reasons to study homocysteine, although none alone proves that a modest elevation causes a clinical cardiovascular event [18].

The vascular endothelium depends on nitric oxide to support normal vasodilation and other aspects of vascular function. Experimental studies have found that exposure to elevated homocysteine can increase

oxidative stress and reduce nitric oxide bioactivity [19,20]. Studies in cultured endothelial cells have also examined changes in reactive oxygen species and nitric oxide following homocysteine exposure [21]. These experiments strengthen the biological plausibility of an effect on vascular function, but the conditions in cells or animals may not fully represent chronic, multifactorial disease in humans [22]. In an animal model of mild hyperhomocysteinemia, investigators observed impaired endothelium-dependent vasodilation and findings consistent with an oxidative mechanism [20,23]

Other proposed mechanisms include effects on inflammatory pathways, protein modification, and coagulation. Such mechanisms may operate alongside endothelial dysfunction rather than as separate, independent processes. For example, oxidative stress could influence nitric oxide availability, which in turn could affect vascular responses. Nevertheless, evidence that a mechanism occurs under experimental conditions should be described as mechanistic evidence. It does not determine how much that mechanism contributes to myocardial infarction, stroke, or peripheral vascular disease in patients exposed to many other risk factors [23].

Experimental findings demonstrate effects within the models studied, but their contribution to clinical vascular disease remains uncertain. Cellular pathway changes should therefore be distinguished from patient-level evidence of disease causation. Interpretation requires consideration of experimental exposure, population characteristics, and other vascular risk factors [24].

Association with cardiovascular and cerebrovascular disease

Observational studies have repeatedly examined whether people with higher homocysteine concentrations experience more vascular events. A collaborative meta-analysis assessed the relationship between blood homocysteine and ischemic heart disease and stroke across multiple studies. It supports discussion of an association, but its findings should not be paraphrased as proof that homocysteine is an independent cause of disease [25,26].

Several issues complicate causal interpretation. Folate and vitamin B12 status influence homocysteine, and other characteristics associated with vascular risk may also influence its measured level. Kidney impairment is another possible contributor to an elevated concentration. Statistical adjustment can address measured differences to an extent but cannot rule out all residual confounding. Furthermore, studies can differ in participant selection, timing of blood collection, definition of an elevated result, and the outcome assessed. A relatively consistent association across studies remains scientifically relevant, while still leaving open whether homocysteine is a causal factor, a marker of another process, or both [27].

The association between homocysteine concentration and vascular disease should be interpreted separately for each clinical outcome. Observational evidence linking higher homocysteine concentrations with ischemic heart disease and stroke does not, by itself, establish an equivalent association with peripheral arterial disease. Conclusions about peripheral arterial disease require evidence from studies that specifically evaluated that outcome [25,28].

Homocysteine lowering and clinical outcomes

Folate and vitamin B12 participate in the remethylation of homocysteine to methionine, whereas vitamin B6 acts as a cofactor in the transsulfuration pathway. A meta-analysis of randomized trials demonstrated that folic acid supplementation lowers circulating homocysteine concentrations and that vitamin B12 provides an additional lowering effect [9,29,30]. However, a reduction in homocysteine concentration does not necessarily translate into fewer vascular events. Randomized trials are therefore required to evaluate clinical benefit, with myocardial infarction and stroke assessed separately as well as within clearly defined composite outcomes [31].

The Heart Outcomes Prevention Evaluation 2 (HOPE-2) trial randomized 5,522 adults aged 55 years or older with vascular disease or diabetes to folic acid, vitamin B6, and vitamin B12 or placebo for an average of five years. Although supplementation lowered homocysteine concentrations, it did not significantly reduce the primary composite outcome of cardiovascular death, myocardial infarction, or stroke. Stroke, assessed as a secondary outcome, was significantly reduced, emphasizing the importance of distinguishing individual outcomes from the composite result [30]. In the Norwegian Vitamin Trial (NORVIT), folic acid and vitamin B12 lowered mean homocysteine concentrations by 27% in patients with recent myocardial infarction but did not significantly reduce the primary composite outcome of recurrent myocardial infarction, stroke, or sudden death attributed to coronary artery disease [31,32].

Evidence concerning stroke prevention is more varied. The China Stroke Primary Prevention Trial investigated folic acid added to enalapril in adults with hypertension and found a reduction in first stroke in that study population. This result is relevant to primary prevention in the population studied; it should not be generalized without qualification to patients with established coronary disease or to every population with an elevated homocysteine concentration [32]. A meta-analysis of randomized trials reported a modest reduction in stroke with folic acid supplementation but did not find a statistically significant reduction in coronary heart disease [33].

An individual-participant meta-analysis by Clarke et al. combined eight randomized trials involving 37,485 participants. Despite an average reduction of approximately 25% in homocysteine concentrations, folic acid allocation did not significantly reduce major vascular events, major coronary events, or stroke during a median follow-up of five years [34]. In contrast, the later meta-analysis by Li et al. reported a significant reduction in stroke but no significant reduction in coronary heart disease [33,35]. The China Stroke Primary Prevention Trial also demonstrated a reduction in first stroke with enalapril plus folic acid compared with enalapril alone among Chinese adults with hypertension and no previous stroke or myocardial infarction [32]. These findings indicate that the evidence differs across clinical outcomes and study populations. Differences in the included trials, baseline folate status, background folate exposure, and primary versus secondary prevention settings may contribute to the differing estimates, but these factors should be regarded as possible explanations rather than established causes of the differences [32-34].

Taken together, randomized evidence demonstrates that folic acid-based supplementation can lower circulating homocysteine concentrations, whereas its effects on vascular events vary by outcome and population [29-34]. Biochemical improvement alone is therefore insufficient to establish cardiovascular benefit. Observational studies assess associations between homocysteine concentrations and subsequent disease, while randomized trials evaluate the effects of a specified intervention in a defined population [25,30,34]. An observational association should consequently not be interpreted as proof that vitamin-mediated lowering of homocysteine will prevent myocardial infarction or stroke.

Implications for clinical interpretation

The interpretation of an elevated homocysteine concentration depends on the clinical indication for testing. Plasma homocysteine may contribute to the investigation of suspected vitamin B12 deficiency in selected circumstances, although an elevated result is not specific and may also reflect folate deficiency [35]. Measurement of plasma total homocysteine is recommended when clinical features suggest an inherited disorder such as CBS deficiency [36-38]. These diagnostic indications are distinct from testing solely to guide cardiovascular prevention. In patients with cardiovascular risk factors, an elevated homocysteine concentration alone does not establish that vitamin supplementation will prevent myocardial infarction or stroke [30,31,34]. The intervention trials discussed in this review do not establish the clinical benefit of a strategy involving routine homocysteine screening followed by vitamin treatment in broadly defined high-risk patients; this review therefore does not recommend that strategy [31].

Gaps in the evidence

A continuing challenge is to identify whether a particular subgroup benefits from targeted intervention. Future studies could more clearly distinguish severe elevations from modest ones, record baseline folate and vitamin B12 status, account for kidney function and background folate exposure, and specify whether the aim is primary or secondary prevention [35]. Studies should report patient-important outcomes, such as first stroke or recurrent myocardial infarction, in addition to the change in homocysteine concentration. The narrative selection of literature and absence of a formal risk-of-bias assessment may introduce selection and interpretation bias. The review should not be considered an exhaustive evidence synthesis, and its conclusions should be interpreted in light of these limitations.

Further work is also needed to clarify how experimental vascular mechanisms relate to disease in humans. Laboratory findings can identify pathways worth investigating, observational research can describe patterns of risk, and randomized trials can test particular interventions in defined populations. Synthesizing these forms of evidence without treating them as interchangeable offers a more balanced account of homocysteine's clinical significance. Future research should clarify which populations, if any, benefit from targeted testing or intervention.

Limitations

This narrative review does not constitute an exhaustive systematic evidence synthesis. Literature selection may introduce selection bias, and no formal risk-of-bias assessment or quantitative pooling was performed. Included studies differ in populations, homocysteine measurement methods, thresholds, nutritional status, renal function, and clinical outcomes. Mechanistic findings, observational associations, and intervention effects address different questions and should not be treated as equivalent evidence. Older studies provide foundational context, but their applicability to contemporary clinical practice requires consideration alongside more recent evidence.

Conclusions

Homocysteine concentrations reflect nutritional status, metabolic pathways, renal function, and inherited disorders. Elevated concentrations are associated with cardiovascular and cerebrovascular outcomes, and experimental studies suggest several potential vascular mechanisms. However, these findings do not establish that modest elevations independently cause clinical events. Randomized evidence shows that vitamin supplementation lowers homocysteine, but cardiovascular benefits are inconsistent and differ by outcome and population.

Homocysteine testing and treatment should therefore be guided by a defined clinical indication, such as investigation of nutritional deficiency or inherited metabolic disease, rather than an elevated concentration alone. Laboratory results require interpretation using validated reference intervals and appropriate sample handling. Further research should establish which populations benefit from targeted intervention and assess patient-important outcomes rather than biochemical improvement alone.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Mandakini S. Kshirsagar, Sushant S. Dhanavade

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