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Overview of homocysteine and its role in disease processes

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Abstract

Homocysteine is a sulfur-containing amino acid formed from the essential amino acid methionine. This metabolism cycle requires vitamin-derived cofactors, pyridoxine for transsulfuration and both folate and cobalamin [1]. In a normal diet there is conservation of the carbon skeleton, and about 50% of the homocysteine formed is remethylated to methionine via steps that require folic acid and vitamin B12. A deficiency of any of these three vitamins leads to modest homocysteine elevation. Why does hyperhomocysteinemia play a vital role in medical practice? It is established that homocysteine elevation is associated with different complications, mainly increased cardiovascular risk [2]. Hyperhomocysteinemia and homocystinuria is connected with occlusive artery disease, especially in the brain, the heart, and the kidney, in addition to venous thrombosis. However the increased level of homocysteine has also an impact on other systems and is connected with osteoporosis, depression, Alzheimer's disease, pregnancy problems, and others. Elevated homocysteine levels occur in both the adult and child population [3].

This review article will focus on the role of homocysteine in the nervous and cardiovascular systems, while also highlighting some controversial theories and the need for further research.

Keywords: Homocysteine; cardiovascular diseases; homocysteine metabolism; hyperhomocysteinemia; neurodegeneration, cognitive diseases

Introduction

Since its discovery in 1932, homocysteine has been the subject of considerable debate and speculation. The medical interest in this amino acid started in 1969 when a report highlighted that elevated urinary concentrations of homocystinuria in children with inborn errors of homocysteine metabolism were associated with vascular damage [20].

Its chemical properties revealed a similarity to cysteine, which is why it was named homocysteine. Homocysteine has the molecular formula C4H9N0S and is classified chemically as a thiol-containing amino acid due to the presence of a sulfur atom in its structure. It features a primary amine group (-NH2), a carboxyl group (-COOH), and a sulfhydryl group (-SH), contributing to its characteristics as a reactive thiol compound. The three-dimensional structure of homocysteine, like other amino acids, determines its solubility and reactivity, with the sulfur atom imparting unique properties that participate in redox reactions and disulfide bond formation. Homocysteine is an intermediate product in the normal biosynthesis of the amino acids methionine and cysteine [4]. It is present in plasma in four different forms: around 1% circulates as free thiol, 70–80% remains disulphide-bound to plasma albumin and approximately 20–30% of homocysteine molecules self-react to form dimers or conjugate with other thiols. Homocysteine plays a central role in the methylation cycle, being methylated to form methionine, which then participates in S-adenosylation to produce S-adenosylmethionine (SAM) [5]. SAM serves as the primary methyl donor in all cellular methylation reactions. The conversion of methionine with ATP results in the formation of SAM, where the methyl group attached to the sulfur atom of SAM can be transferred to other molecules, facilitating methylation. This process consumes energy and is thus irreversible. Demethylation of SAM yields S-adenosylhomocysteine (SAH), a thioether structurally similar to methionine. The ratio of SAM to SAH reflects the methylation potential within the cell. Hydrolysis of SAH produces homocysteine and adenosine [6].

Homocysteine has four biological functions such as being a precursor for cystathionine, cysteine and further metabolites, as a means for methionine conservation, as a methyl receptor in the betaine– an obligatory step in choline catabolism and as a substrate that is essential for the recycling of tissue folates [1].

Basis of hyperhomocysteinemia

Hyperhomocysteinemia is a medical condition characterized by elevated homocysteine levels in the blood, specifically above 15 μmol/L [7]. In healthy individuals, the total plasma homocysteine concentration typically ranges from 5.0 to 15.0 μmol/L. Levels ranging from 16 to 30 μmol/L are classified as moderate hyperhomocysteinemia, 31 to 100 μmol/L as intermediate, and values exceeding 100 μmol/L are categorized as severe hyperhomocysteinemia [8]. There are two primary forms of hyperhomocysteinemia: the first, which is rare but more severe, results from significant genetic mutations affecting enzymes involved in homocysteine metabolism. Genetic causes of hyperhomocysteinemia can be divided into defects in the transsulfuration pathway or defects in the remethylation pathway. Classical, severe hyperhomocysteinemia, also known as congenital homocystinuria, is caused by mutations in the CBS gene, leading to a defect in the transsulfuration pathway. Homozygous deficiency of cystathionine beta-synthase (CBS) results in a significant accumulation of homocysteine, with fasting total homocysteine levels increasing up to 40-fold [6],[9]. Other causes of hyperhomocysteinemia may stem from impairments in the remethylation pathway, which is responsible for converting homocysteine back to methionine. Of these, the most common is the C677T polymorphism in the *MTHFR* gene. C677T polymorphism leads to hyperhomocysteinemia with increased cardiovascular risk and low bone mineral density but without neurological deficit [9]. But the more common forms of hyperhomocysteinemia are related to secondary, environmental factors [4], [6]. Hyperhomocysteinemia can be increased by nutritional deficiencies of folate, vitamin B_6, and vitamin B_{12} [6]. Several diseases such as renal and thyroid dysfunction, cancer, psoriasis, and diabetes as well as various drugs, alcohol, tobacco, coffee, older age and menopause, are considered to be associated with moderately elevated homocysteine concentrations [6]. The kidneys are pivotal in the excretion of homocysteine, facilitating the filtration of this thiol amino acid from the plasma. Renal clearance mechanisms contribute to maintaining normative plasma homocysteine concentrations. Dysregulation of these processes can result in hyperhomocysteinemia, which is associated with various pathological conditions. Therefore, total homocysteine levels are typically significantly elevated in patients with chronic renal disease compared to the moderate increases often observed in patients with atherothrombotic vascular disease. This elevated homocysteine concentration is likely a contributing factor to the high prevalence of vascular complications seen in individuals with chronic renal failure [6].

Clinical manifestations of hyperhomocysteinemia

Severe hyperhomocysteinemia-associated disorders can manifest as neurodevelopmental delays or behavioral disturbances in pediatric populations, whereas in adults, these conditions may present with thrombotic vascular events accompanied by hematologic, neuropsychiatric, ocular, or renal pathologies. Elevated plasma homocysteine levels may also be observed in females with high-risk pregnancies or infertility. The diagnosis of classic homocystinuria (HCU) is considered in individuals exhibiting phenotypic features such as a Marfanoid habitus, lens dislocation (ectopia lentis), severe non-familial myopia, skeletal deformities, thrombotic events involving arterial or venous vessels, intellectual disability, and psychiatric manifestations. Comorbid conditions include renal impairment and infertility.

In pediatric and young adult cohorts, exclusion of hyperhomocysteinemia is imperative in individuals presenting with a Marfanoid phenotype or compatible dysmorphic features, particularly if accompanied by intellectual impairments. In young adults, screening for hyperhomocysteinemia is warranted in cases with a history of thromboembolic disease—especially in patients younger than 55 years without identifiable secondary causes—as well as in individuals experiencing recurrent or atypical thromboses, peripheral embolisms, early-onset coronary artery disease, or pulmonary hypertension secondary to chronic venous thromboembolism [18].

Homocysteine and cardiovascular disease

However there is one main connection of hyperhomocysteinemia. Mild hyperhomocysteinemia has been well established as an independent predictor of cardiovascular disease. A meta-analysis of studies published before 2002 found that a 3-μmol/L increase in fasting plasma homocysteine correlates with an 11% rise in the incidence of ischemic heart disease and a 19% increase in stroke risk. Recent studies continue to confirm that homocysteine is a strong, independent marker for cardiovascular risk. Consequently, the homocysteine hypothesis suggests that mild to moderate hyperhomocysteinemia may be a causal factor, or at least a significant risk factor, in the development of cardiovascular disease [10].

Homocysteine may contribute to cardiovascular pathology through various mechanisms, including its detrimental effects on vascular endothelium and smooth muscle cells, which lead to alterations in arterial structure and function. These effects include increased proliferation of vascular smooth muscle cells, endothelial dysfunction, oxidative damage, heightened collagen synthesis, and deterioration of arterial wall elasticity [6], [11]. Specifically, homocysteine can promote the proliferation and migration of vascular smooth muscle cells, resulting in neointimal hyperplasia and vessel narrowing, thereby exacerbating atherosclerotic plaque formation.

Studies examining homocysteine's influence on C-reactive protein (CRP) expression in vascular smooth muscle cells (VSMCs) have shown that homocysteine significantly upregulates CRP mRNA and protein levels both in vitro and in vivo [12]. Additionally, homocysteine increases the expression of the NR1 subunit of the N-methyl-D-aspartate receptor (NMDAr), while the NMDAr antagonist MK-801 reduces homocysteine-induced CRP expression in VSMCs. These findings suggest that homocysteine can initiate an inflammatory response in vascular smooth muscle cells by stimulating CRP production via the NMDAr-ROS-ERK1/2/p38-NF-κB signaling pathway. These mechanisms provide new insights into the role of homocysteine in the pathogenesis of atherosclerosis [6].

Further research is needed to fully elucidate the mechanisms by which hyperhomocysteinemia contributes to aortic stiffness. The prevailing hypotheses propose that homocysteine may influence arterial wall remodeling and damage, thereby promoting vascular stiffening and other structural changes that predispose individuals to cardiovascular events [6].

Such changes can contribute to severe damage and lead to coronary artery disease, a condition characterized by the reduction of blood flow to the heart due to atherosclerotic plaque buildup in coronary arteries. Studies have shown that individuals with hyperhomocysteinemia may have an augmented risk of myocardial infarction (heart attack). High homocysteine concentrations are associated with an increased risk of both ischemic and hemorrhagic strokes. Elevated homocysteine can contribute to cerebrovascular disease by damaging the integrity of the vascular walls and promoting thrombus formation. Another example can occur as a PAD, a condition involving narrowing of the peripheral arteries, particularly in the legs, which can lead to claudication and increased cardiovascular morbidity.

Hyperhomocysteinemia has also been linked to an increased risk of venous thrombosis [4]. Elevated homocysteine levels tend to promote platelet adhesion to endothelial cells and have been associated

with higher concentrations of prothrombotic factors, such as β-thromboglobulin, tissue plasminogen activator, and factor VIIc [6]. These changes contribute to the promotion of thrombus formation. Additionally, the increased arterial stiffness observed in hyperhomocysteinemia may be related to homocysteine-induced LDL atherogenesis, including the formation of small, dense LDL particles and their oxidative modification [11].
However, routine screening in asymptomatic individuals remains controversial and is not uniformly practiced. Management strategies often emphasize dietary modifications to ensure adequate intake of B vitamins; supplementation may be indicated in cases of deficiency, although its efficacy in primary or secondary CVD prevention is debated.

Homocysteine is implicated in various cardiovascular diseases through mechanisms that encompass endothelial dysfunction, inflammation, and atherogenesis. While the exact nature of causation is still under investigation, hyperhomocysteinemia is widely recognized as a significant risk factor for multiple cardiovascular conditions and plays the role in the development of cardiovascular disease summarizing both central and peripheral effects of homocysteine. Understanding its role may inform prevention and treatment strategies aimed at reducing cardiovascular morbidity and mortality. Further elucidation of this relationship through ongoing research will continue to shape clinical practice related to cardiovascular health.

The homocysteine and the nervous system

The correlation between hyperhomocysteinemia and neurodegenerative diseases has garnered increasing attention in recent years, as research has suggested potential links between elevated homocysteine levels and various neurological conditions, including Alzheimer's disease, Parkinson's disease, and vascular dementia.

Elevated homocysteine levels can exert neurotoxic effects through several mechanisms. Hyperhomocysteinemia is associated with increased oxidative stress and inflammation in neural tissues. Moreover, it seems quite interesting that homocysteine leads to an induction of m-RNA and protein expression of a specific protein, C-reactive protein (CRP), augmenting the NR1 subunit of NMDA receptor expression, homocysteine can promote a pro-inflammatory response in vascular smooth muscle cells of small brain arteries, by stimulating CRP production, usually enhanced by a combined NMDA-ROS-erk1/2/p38-nfKBeta signal pathway. Not only, this way homocysteine might be a promoter of atherosclerosis system, but also, small arteries can promote neurodegeneration, diminishing other capabilities of autoregulation, due to their role in autoregulation, leading to an alteration of the blood-brain barrier. This way, homocysteine might potentiate its direct neurotoxic effects [20].

Homocysteine can induce the formation of reactive oxygen species and promote endothelial dysfunction, contributing to neuronal damage and apoptosis but also as being a cysteine precursor, its elevation can disrupt the balance of other amino acids, thereby affecting neurotransmitter synthesis (e.g., cysteine impacts glutathione levels, an important antioxidant). Moreover, hyperhomocysteinemia accelerates dopaminergic cell death, probably due to the fact that hyperhomocysteinemia could cause a severe reduction in dopamine turnover in the striatum. It has been suggested that there is an ARG-rich domain, which is located in the middle portion of the third loop of the D2 receptor, which has high affinity for homocysteine. Homocysteine seems to have an allosteric antagonist activity of D2 receptors [20].

Numerous epidemiological studies have reported an association between elevated homocysteine levels and an increased risk for Alzheimer's disease. In this disease, there is emerging evidence suggesting that elevated homocysteine may influence amyloid-beta deposition and tau phosphorylation, both of which are critical pathologies in Alzheimer's disease. Homocysteine may promote the aggregation of amyloid plaques, thereby exacerbating the neurodegenerative process. Also patients with C677T polymorphism in the MTHFR gene have a higher incidence of Alzheimer's disease and epilepsy.

There is also evidence linking hyperhomocysteinemia to Parkinson's disease. Studies suggest that elevated levels may correlate with increased risk and severity of motor symptoms, although the underlying mechanisms remain to be fully elucidated. Since hyperhomocysteinemia is associated with vascular injuries and disturbances, it is logical that an increase in homocysteine levels correlates with a higher incidence of vascular dementia, often characterized by cognitive decline due to cerebrovascular pathology. Research is ongoing to assess whether interventions targeting homocysteine can translate into meaningful clinical improvements in cognitive function, neuroprotection, or disease progression in patients with neurodegenerative conditions.

Nevertheless epidemiological and experimental evidence indicated that hyperhomocysteinemia is associated with neurodegeneration, homocysteine neurotoxic effects have been so far investigated mostly by employing homocysteine concentrations (≥100 μM) much higher than homocysteine mean plasma levels (20 μM) observed in patients with neurodegenerative disorders. While evaluating the effects of a prolonged exposure to ~20 μM homocysteine in neuronal-like differentiated SH-SY5Y cells, we observed a 35 % loss of cell viability and a four-fold increase in reactive oxygen species levels in cells incubated with homocysteine for five days

compared with controls. Moreover, homocysteine increased by 30 % and around two-fold, respectively, the Comet-positive cell number and DNA damage indexes (tail length, T-DNA, olive tail moment) compared with controls [13].

In conclusion a considerable body of evidence supports a correlation between hyperhomocysteinemia and neurodegenerative diseases, establishing causality necessitates further investigation. Studies must explore the biological mechanisms involved, as well as assess the potential for therapeutic interventions aimed at lowering homocysteine levels to enhance cognitive health and mitigate the progression of neurodegenerative disorders. Recognizing hyperhomocysteinemia as a potential risk factor may influence clinical practice and public health strategies aimed at reducing neurological morbidity.

The homocysteine controversy

Mild to moderate hyperhomocysteinemia has been identified as a strong predictor of cardiovascular disease, independent from classical atherothrombotic risk factors. However, there are few controversial hypotheses, which originate from several aspects. One of the theories is that this impact depends on the severity of hyperhomocysteinemia. First, while observational studies have consistently shown an association between elevated homocysteine levels and increased cardiovascular risk, randomized controlled trials aimed at lowering homocysteine through supplementation with B vitamins (such as folic acid, B6, and B12) have not consistently demonstrated a corresponding reduction in cardiovascular events. This has raised questions about whether homocysteine is a causal factor in cardiovascular disease or merely a marker of other underlying conditions, such as poor diet or genetic predispositions.

There is a hypothesis suggesting that B-vitamin therapy exerts dual effects on atherosclerosis: while it may be beneficial by reducing homocysteine levels, its effects could depend on the stage of the disease. Specifically, in primary prevention—where no atherosclerotic lesions are present—lowering homocysteine might still confer protective benefits. Conversely, in individuals with established atherosclerotic lesions, typically the elderly, B vitamins might have neutral or even adverse effects, potentially negating any benefits from homocysteine reduction. Whether these disease-stage-dependent effects truly exist, and whether B vitamins may inadvertently promote inflammation and proliferation within atherosclerotic plaques, has yet to be conclusively studied [10].

Multiple research efforts have demonstrated that lowering homocysteine levels through B-vitamin supplementation does not consistently translate into cardiovascular benefits. Furthermore, while B vitamins effectively reduce homocysteine, they do not improve endothelial function or reduce hypercoagulability [6].

Epidemiological studies indicate a linear association between plasma homocysteine concentrations and cardiovascular disease risk; however, it remains possible that therapeutic benefits are limited to individuals with more severe hyperhomocysteinemia. The baseline homocysteine levels in large intervention trials generally ranged from 10 to 14 μmol/L—close to average age-adjusted population values—while patients with markedly higher levels (e.g., >20 μmol/L) were underrepresented, preventing definitive conclusions for this subgroup. Over the past decade, several large-scale randomized trials utilizing B-vitamin therapy have consistently shown no benefit in reducing cardiovascular events among high-risk patients [10].

Clinical interpretation and patient management

The clinical management of hyperhomocysteinemia encompasses a systematic approach aimed at identifying etiological factors, stratifying cardiovascular risk, and instituting appropriate therapeutic interventions.

A thorough assessment for potential causes of elevated homocysteine levels is warranted. This should include evaluation for deficiency states—specifically folate (vitamin B9), cobalamin (vitamin B12), and pyridoxine (vitamin B6)—which play critical roles in homocysteine metabolism. A study of organic acids in urine to determine methylmalonic acid (MMA) levels is also advised. [18] Further investigations should also consider renal dysfunction, genetic polymorphisms (e.g., MTHFR gene mutations), and lifestyle factors, including alcohol consumption and smoking status.

Lifestyle modifications may be the first step in reducing the level of homocysteine and present a direction for further, more comprehensive investigation. Smoking is associated with endothelial dysfunction, exacerbating cardiovascular risk, consequently smoking cessation programs should be integrated into management plans. Recommendations for dietary enhancements should emphasize increased intake of folate-rich foods, including dark leafy greens, legumes, fruits, and fortified cereals, to support optimal homocysteine metabolism. Engagement in regular sports activities such as aerobic and resistance exercise can improve overall cardiovascular health, potentially influencing homocysteine levels indirectly. Weight Management is another vital aspect because obesity and metabolic syndrome are correlated with cardiovascular risk and increased level

of homocysteine. Serial monitoring of plasma homocysteine levels may be indicated to assess the effectiveness of nutritional and lifestyle interventions.

When it comes to cardiovascular risk assessment in a group of high-risk patients an evidence-based recommendation is currently impossible. Vitamin supplementation is a controversial issue. Until further research provides definitive results, the existing data support a single conclusion: high-dose B-vitamin therapy does not significantly reduce cardiovascular events in high-risk patients over a five-year period. Given this evidence, a reasonable approach may be to avoid routine screening for hyperhomocysteinemia in high-risk populations. Instead, testing should be considered only when there is suspicion of an inborn error of one-carbon metabolism based on clinical phenotype, or in cases of early-onset cardiovascular disease occurring before age 50 in the patient or their family, or when B-vitamin deficiency is suspected due to medical history or comorbidities. Routine treatment of mild hyperhomocysteinemia is not recommended; intervention should be reserved for patients with fasting homocysteine levels exceeding a certain threshold, such as 20–25 μmol/L. Upon decision to treat, do not use high-dose B-vitamin preparations routinely, but start with a multivitamin containing moderate amounts of folate, B12, and B6 and switch to high-dose B vitamins only if homocysteine remains clearly elevated. All practicing doctors need to keep an eye on the literature [10].

In conclusion, clinical management of hyperhomocysteinemia should be individualized, taking into consideration underlying etiology, metabolic status, and the presence of comorbid conditions. While there is a focus on mitigating homocysteine levels, comprehensive approaches addressing cardiovascular risk factors and lifestyle modifications are paramount in delivering optimal care and improving clinical outcomes. Regular follow-up is essential to evaluate adherence and therapeutic efficacy.

Conclusion

The precise role of homocysteine in various neurological and cardiovascular diseases remains uncertain. Although homocysteine appears to function as an independent risk factor for cerebrovascular disease, dementia, and numerous other conditions, it is also associated with atherosclerosis and cardiovascular pathology. It has been hypothesized that homocysteine plays a causative role in neurological damage due to its neurotoxic effects and its capacity to induce vascular and endothelial inflammation both directly and indirectly. However, the literature presents conflicting opinions on this matter. While the combined supplementation of folic acid, vitamin B6, and vitamin B12 has been shown to effectively lower homocysteine levels, identifying which individuals may truly benefit from this intervention and under what circumstances it will be effective remains challenging [20].

In conclusion, while elevated homocysteine levels are associated with cardiovascular risk, the lack of definitive evidence demonstrating causation and the effectiveness of lowering homocysteine to improve outcomes continues to fuel academic debate and necessitates further research [19].

Several significant implications emerge from our discussion. Firstly, there is a pressing need to deepen our understanding of the mechanisms by which homocysteine damages the vascular system and to explore alternative strategies for preventing such damage beyond high-dose B-vitamin supplementation. Additionally, it is crucial to investigate the potential adverse effects of various forms of B vitamins, particularly at high doses, through cell culture and animal studies. Furthermore, epidemiological research should be utilized to examine the hypothesis that maintaining a high B-vitamin status may genuinely prevent the initial development of atherosclerosis, especially in young populations. Conducting intervention trials in this demographic presents logistical challenges, particularly when using hard clinical endpoints. Finally, ongoing and future intervention studies should aim to address unresolved questions from previous research, such as the comparative efficacy of natural folate versus folic acid, the optimal duration of follow-up—including long-term or extended tracking of existing trials—and the effects within specific populations, such as those with severe hyperhomocysteinemia. Discarding the homocysteine hypothesis prematurely could be a costly mistake in historical terms [10]. A better understanding of hyperhomocysteinemia as a modifiable risk factor for cardiovascular and neurodegenerative diseases could pave the way for innovative prevention strategies. In summary, continued research into hyperhomocysteinemia is critical for developing a comprehensive understanding of its role in human health and disease.

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Author Contributions

Investigation, A.K. and M.B.; resources, A.K., M.F., D.M., B.J., M.M., and M.B.; writing—original draft preparation, A.K., M.F., D.M., and M.B. writing—review and editing, A.K; visualization, B.J.; supervision, M.M and A.K.

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