VITAMIN B SUPPLEMENTATION IN GERIATRIC PATIENTS: A POTENTIAL STRATEGY TO MANAGING HYPERHOMOCYSTEINEMIA IN CEREBROVASCULAR DISEASE

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ABSTRACT

Homocysteine is an amino acid synthesized in the metabolic pathway between methionine and cysteine. Its levels tend to rise with age due to physiological, lifestyle, and nutritional factors. Elevated homocysteine can induce oxidative stress, inflammation, and endothelial dysfunction, which are critical in the development of cerebrovascular diseases. These mechanisms involve increased free radicals, decreased antioxidant enzyme activity, and enhanced inflammatory responses. Specifically, elevated homocysteine heightens oxidative stress and inflammation by increasing pro-inflammatory cytokines and decreasing anti-inflammatory cytokines, leading to endothelial cell damage and apoptosis. Supplementation with vitamins B6, B9, and B12 has been shown to lower homocysteine levels and reduce the risk of ischemic stroke. However, there is currently no established guideline for the appropriate dosing of these vitamins.

Keywords: Homocysteine, Cerebrovascular, Stroke, Geriatric, Vitamin B

ABSTRAK

Homosistein adalah asam amino non-esensial yang diproduksi dalam jalur biosintesis antara metionin dan sistein. Kadarnya cenderung meningkat seiring bertambahnya usia akibat faktor fisiologis, gaya hidup, dan nutrisi. Peningkatan homosistein dapat memicu stres oksidatif, peradangan, dan disfungsi endotel, yang berperan penting pada timbulnya penyakit serebrovaskular. Mekanisme ini melibatkan adanya peningkatan radikal bebas, penurunan aktivitas enzim antioksidan, dan peningkatan respons inflamasi. Secara khusus, peningkatan homosistein meningkatkan stres oksidatif dan peradangan dengan meningkatkan sitokin pro-inflamasi dan menurunkan sitokin anti-inflamasi, yang menyebabkan kerusakan sel endotel dan apoptosis. Suplementasi dengan vitamin B6, B9, dan B12 telah terbukti menurunkan kadar homosistein dan mengurangi risiko stroke iskemik. Namun, saat ini belum ada pedoman terhadap dosis dalam penggunaan vitamin ini.

Kata Kunci: Homosistein, Serebrovaskular, Stroke, Geriatri, Vitamin B

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INTRODUCTION

Homocysteine is a non-essential amino acid formed via the biosynthesis pathway between the amino acids methionine and cysteine, characterized by a sulfhydryl group. Plasma homocysteine found in both reduced (homocysteine) and oxidized (homocystine) forms. Approximately 98-99% of homocysteine is in the oxidized form, with 80-90% bound to plasma proteins, 9% bound to cysteine and cysteinylglycine, and 1% in its free form.[1] Hyperhomocysteinemia is characterized by homocysteine levels ≥ 15 μmol/L and is classified into mild, moderate, and severe.[2] In China, a meta-analysis revealed a prevalence of 37.2%, with higher rates observed in the elderly, males, and residents of northern, inland, and rural areas.[3]

Hyperhomocysteinemia is associated with numerous diseases, especially cardiovascular and neurodegenerative conditions. High homocysteine levels can induce oxidative stress, impair endothelial function, and cause inflammation, all of which contribute to the development of atherosclerosis, coronary artery disease, and thromboembolic incidents like myocardial infarction and strokes. In the central nervous system, hyperhomocysteinemia is linked to neurodegenerative diseases like Parkinson's disease and Alzheimer's disease.[4] Treatment strategies often include dietary changes and B-vitamin supplementation to reduce homocysteine levels. These methods have demonstrated varying levels of success in lowering the risk of related diseases.[5] This review aimed to highlight the effects of homocysteine on cerebrovascular disorders, particularly in geriatric patients.

HOMOCYSTEINE METABOLISM

Homocysteine is generated by all cells and is biologically derived from methionine through multiple steps (see Figure 1). Its metabolic pathway includes several crucial enzymes, including S-adenosyl-L-methionine (SAM) synthetase/L-methionine adenosyltransferase, methyltransferase (MT), and S-adenosyl-L-homocysteine (SAH) hydrolase, which are found across different tissues.[5,6] The first step in homocysteine synthesis involves the conversion of dietary protein into methionine, followed by the transfer of an adenosine group from ATP to methionine by methionine adenosyltransferase, forming SAM. In the second step, a methyl group is transferred from SAM to recipient molecules such as DNA, RNA, proteins, and neurotransmitters, resulting in the conversion of SAM into SAH. After the methyl group transfer, SAH is subsequently

broken down by SAH-hydrolase into adenosine and L-homocysteine. [6,7]

The final step involves the metabolism of L-homocysteine through three reactions: resynthesis, remethylation, and transsulfuration. In resynthesis, homocysteine is converted back into SAH by SAH-hydrolase through a reverse catalytic reaction, with elevated SAH levels strongly inhibiting MT enzymes. During remethylation, about 50% of homocysteine is converted to methionine through two pathways.[6,7] The first pathway involves the cofactors B12 and folate, where folate is reduced to tetrahydrofolate and then metabolized to 5-Methyl-THF. Methionine synthase (MS), with vitamin B12, catalyzes the transfer of a methyl group from 5-Methyl-THF to homocysteine, converting it back to methionine, occurring in almost all tissues. The second pathway involves betaine, synthesized from choline via betaine-homocysteine methyltransferase (BHMT), primarily occurring in the liver, kidneys, and eye lens. Choline is oxidized to betaine, which donates a methyl group to homocysteine, producing methionine and dimethylglycine. In the transsulfuration reaction, homocysteine condenses with serine to produce cysteine, which is hydrolyzed into cystathionine and α-ketobutyrate. These reactions, catalyzed by cystathionine β-synthase (CBS) and cystathionine γ-lyase (CTL) and requiring vitamin B6, lead to cystathionine's use in protein synthesis and glutathione (GSH) production, with cystathionine unable to convert back into homocysteine.[6,7]

All tissues can synthesise homocysteine, but only a few organs—the liver, kidneys, small intestine, pancreas, and eye lens—can detoxify it via the transsulfuration process. While CBS enzymes are present in the brain and adipose tissues, these tissues lack CTL enzymes, which prevents them from utilizing the transsulfuration pathway. The central nervous system does not have BHMT enzymes and depends exclusively on the pathway that uses B12 and folic acid cofactors to convert homocysteine to methionine. Therefore, the central nervous system is more susceptible to hyperhomocysteinemia.[1]

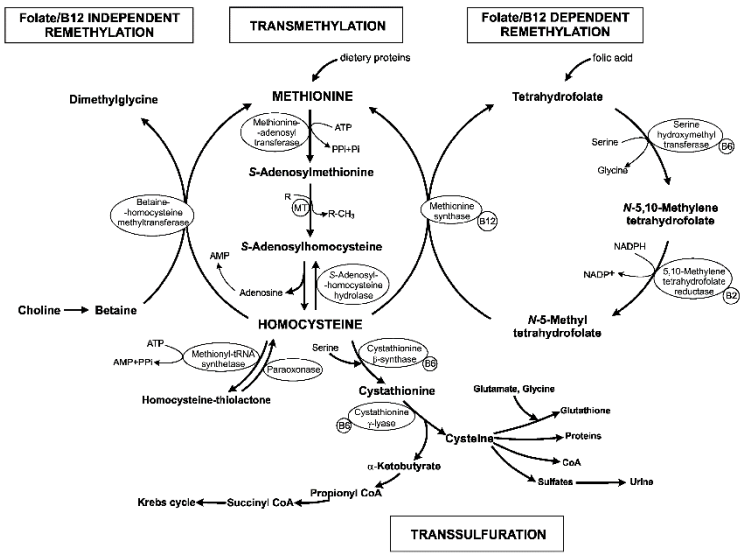

Figure 1. The schematic overview of homocysteine metabolism[7]

HYPERHOMOCYSTEINE

Hyperhomocysteinemia is defined as a condition in which homocysteine levels in the body are elevated beyond the typical range. Normal concentrations fall between 5 and 15 µmol/L, while mild elevations are classified within 15 to 30 µmol/L. Moderate elevation ranges from 30 to 100 µmol/L, and severe hyperhomocysteinemia is identified when levels exceeding 100 µmol/L.[2] Several factors influence homocysteine levels in the body, including age, genetics, lifestyle, and others. Research indicates that homocysteine levels are generally lower in women compared to men, but increase in women after menopause. Lifestyle choices, particularly in vegetarians who may lack adequate protein intake and consequently suffer from deficiencies in vitamins B6, B12, and folic acid, can impact homocysteine metabolism, leading to elevated levels.[8]

Homocysteine levels tend to be higher in the elderly due to a combination of physiological, lifestyle, and nutritional factors. is a significant contributor, as impaired renal function reduces the clearance of homocysteine from the blood, leading to its accumulation.[9] Additionally, the metabolism of homocysteine is significantly impacted by the lower levels of vitamins B6, B12, and folate that are frequently observed in elderly individuals. This deficiency is exacerbated by reduced dietary intake and absorption efficiency in older adults, leading to higher homocysteine levels.[10,11] The levels of homocysteine in the blood are further increased by lifestyle variables such as smoking and drinking alcohol, and particular senior groups are more likely to engage in these behaviors.[10] Previous

research also indicates that homocysteine levels are within normal range during ages 30-50 years but increase significantly and progressively after the age of 50.[12] Rodriguez et al. reported that individuals aged 65 years or older have an average homocysteine level of 16.5 ± 0.5 µmol/L.[13] Each 5 µmol/L increase in homocysteine level raises the risk of all-cause mortality by 33.6%.[14]

In pathological conditions, the primary cause of elevated homocysteine levels is genetic defects or mutations in the enzymes involved in homocysteine metabolism, which directly increase homocysteine levels. The most frequent cause of hyperhomocysteinemia is a deficit in Cystathionine Beta-Synthase (CBS), which inhibits the conversion of homocysteine to cystathionine by blocking the transsulfuration process.[6] Inadequate levels of cofactors necessary for homocysteine metabolism, including folic acid, vitamins B2, B6, and B12, increase the risk of hyperhomocysteinemia by 2.5-2.6 times. Additionally, various other conditions can lead to hyperhomocysteinemia, such as chronic kidney disease, anemia, hypothyroidism, neoplasm, and certain medications that affect homocysteine metabolism.[2]

The exact mechanism of hyperhomocysteinemia in chronic kidney disease (CKD) is unclear, but studies suggest that reduced kidney elimination of homocysteine—up to 70% of daily production—is a primary cause.[5] Elevated plasma homocysteine levels are linked to decreased glomerular filtration rates (GFR), with increased levels observed at a GFR of 60 ml/min and in 85-100% of end-stage renal disease (ESRD) patients.[15] Hypothyroidism and subclinical hypothyroidism are associated with higher homocysteine levels, while hyperthyroidism is linked to lower levels. Anti-thyroid medications may increase homocysteine due to reduced folate levels. In anemia, vitamin B12 and folate deficiencies can disrupt homocysteine metabolism. Additionally, homocysteine metabolism is affected in conditions like sickle-cell anemia, where dysfunctional red blood cells impair the conversion of methionine to homocysteine. [2,6]

In malignancies, studies show that mice with tumors have elevated homocysteine levels, potentially due to tumor-induced folate deficiency impairing remethylation. Certain medications can also cause hyperhomocysteinemia. Drugs such as cholestyramine, methotrexate, metformin, fibric acid derivatives, nicotinic acid, and oral contraceptives are associated with increased homocysteine levels. Cholestyramine and metformin disrupt vitamin B6 and B12 absorption, while methotrexate, fibric acid derivatives, and

nicotinic acid interfere with folate and homocysteine metabolism. The mechanism by which oral contraceptives raise homocysteine levels is not fully understood, but may involve increased production of free radicals or reduced availability of cofactors for homocysteine metabolism after three months of use.[2,9,10]

HYPERHOMOCYSTEINE AND CEREBROVASCULAR DISORDER

Hyperhomocysteinemia plays a significant role in the development of cerebrovascular disorder, although its molecular mechanisms are not yet fully understood. Homocysteine is known to be an excitatory amino acid that can be toxic to human neurons, causing disturbances in intracellular calcium balance which are implicated in the development of neurological diseases. Additionally, according to the theory of homocysteine biosynthesis, its metabolism in the brain cannot involve the transsulfuration reaction due to the absence of the CTL enzyme in the brain. Moreover, the BHMT enzyme is lacking in the central nervous system, which relies exclusively on remethylation reactions that require folic acid and vitamin B12. Hyperhomocysteinemia also contributes to endothelial dysfunction, which is closely linked to the progression of atherosclerosis.[6,16–18]

Stroke, the second leading cause of death worldwide, can be classified into ischemic stroke, resulting from a blockage in the brain's blood vessels, and hemorrhagic stroke, caused by the rupture of brain blood vessels, disrupting blood flow to the brain. Research has shown that hyperhomocysteinemia is a predictor of stroke. However, stroke is the result of complex interactions among various risk factors, making it difficult to classify hyperhomocysteinemia as a single risk factor. Persistent hyperhomocysteinemia promotes atherosclerotic plaque formation due to endothelial dysfunction through three mechanisms. First, it increases the production of free radicals; homocysteine's reactive sulfhydryl group tends to form disulfide bonds, releasing free radicals. Homocysteine also enhances the expression of Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase, which produces superoxide anion radicals, and reduces Nitric Oxide (NO) production, leading to vasoconstriction.[1] Second, hyperhomocysteinemia induces endothelial cell apoptosis. Third, homocysteine creates a prothrombotic environment by increasing platelet aggregation, vascular inflammation, and the expression of Advanced Glycation End Product (AGE) receptors, Vascular Adhesion Molecule-1 (VCAM-1), tissue factor, and matrix metalloproteinase-9 (MMP-9). The

oxidative stress triggered initiates an inflammatory cascade leading to atherosclerotic plaque formation in blood vessels.[1] Hyperhomocysteinemia results in an increase in pro-inflammatory cytokines accompanied by a decrease in anti-inflammatory cytokines, which intensifies inflammatory reactions, leading to vascular damage and further cell apoptosis.[6] Consequently, the World Health Organization (WHO) acknowledges hyperhomocysteinemia as a significant contributor to ischemic stroke and cardiovascular diseases.[19]

Elevated homocysteine is a well-established risk factor for cognitive decline and dementia, with studies showing that higher Hcy levels are associated with increased risks of AD, vascular dementia (VaD), and frontotemporal dementia (FTD).[20–22] Malaguarnera et al. discovered that homocysteine levels were significantly higher in VaD patients (26.0 ± 6.58 µmol/L) compared to the healthy control group (10.7 ± 3.0 µmol/L) and AD patients (22.3 ± 4.51 µmol/L; $p<0.001$)[23]. Alzheimer's disease, a neurodegenerative condition resulting from beta-amyloid protein deposits between nerve cells, is the most prevalent form of dementia, making up 50-80% of cases.[2] Vascular dementia, also referred to as multi-infarct dementia, is the second most prevalent form of dementia after Alzheimer's disease. It accounts for nearly half of all dementia cases and is caused by multiple small blockages in the brain's blood vessels. Research shows that patients with hyperhomocysteinemia have significantly higher blood pressure, microangiopathy, and a greater incidence of multiple infarcts.[18]

VITAMIN B6, B9, and B12

Vitamin B6

Vitamin B6, or pyridoxine, is a crucial vitamin for various physiological processes, especially in the nervous system. Its active form, pyridoxal 5'-phosphate (PLP), acts as a coenzyme in more than 150 enzymatic reactions, underscoring its importance in maintaining neurological health and function.[24,25]

Vitamin B6 plays a significant role in neurotransmitter synthesis, inhibition of glutamate production, and recovery of sensory nerves. It aids in the formation of neurotransmitters that are essential for overall nerve function and communication, such as dopamine, gamma-aminobutyric acid (GABA), and serotonin.[26] Additionally, a number of metabolic pathways, such as those involving the metabolism of amino acids, lipids, carbohydrates, and nucleic acids, are also influenced by vitamin B6.[27]

Since humans cannot synthesize Vitamin B6, it must be obtained through diet, where it is converted to its active form

by pyridoxal kinase. Vitamin B6 is abundant in meats, whole grains, vegetables, and nuts. Studies have indicated that meats such as chicken, beef, and lamb, as well as fish like snapper and tuna, are particularly rich in vitamin B6.[28] For adults, the recommended daily intake of Vitamin B6 is 1.3–1.7 mg per day.[29]

Specific to the nervous system, Vitamin B6 demonstrates neuroprotective effects. It is essential for the release of glutamate, a key neurotransmitter involved in various brain functions, underscoring its significance in maintaining neuronal health and cognitive processes.[30] In a rat model, Vitamin B6 mitigated nerve damage caused by excessive glutamate release, a factor in various neurological disorders.[31] Clinical evidence suggests a regenerative properties, as seen in patients with carpal tunnel syndrome where Vitamin B6 treatment improved sensory nerve conduction velocity and reduced symptoms.[32] Additionally, it was demonstrated in monkey experiments that neuronal death in the retina following brain ischemic damage was prevented by vitamin B6 supplementation.[33] It has also been linked with cognitive health and the prevention of neurodegenerative disorders, with studies suggesting that supplementation can improve cognitive function and support brain health in aging individuals.[25,26,30]

Vitamin B9

Folic acid, or vitamin B9, is an essential vitamin that supports numerous biological functions, including DNA methylation, which is crucial for gene regulation and protein synthesis.[34] Additionally, folic acid lowers the risk of diseases like atherosclerosis and stroke by participating in the metabolism of homocysteine, an amino acid that is connected to cardiovascular disorders when it is present in high levels.[35] It also contributes to red blood cell formation and helps prevent megaloblastic anemia, a condition marked by the production of unusually large and impaired red blood cells.[36] Vitamin B9 is found in high quantities in leafy green vegetables, legumes, seeds, and liver. Additionally, the folate content varies within different parts of meat, with higher concentrations present in fatty cuts and organ meats.[28] For adults, the advised daily intake of Vitamin B9 is 400 μg.[29]

Folic acid provides the single carbon group needed for DNA methylation, which is essential for central nervous system growth, function, and repair.[34] Research has shown that folic acid supplementation can enhance the repair mechanisms of the adult central nervous system, indicating its potential in promoting neural regeneration and

reducing the occurrence of neural tube defects and congenital abnormalities.[37]

Vitamin B12

Vitamin B12, also known as cobalamin, is a water-soluble vitamin that plays a crucial role in various biological processes, including DNA synthesis, erythropoiesis, and the maintenance of nervous system function. It is essential for neuroprotection, as it reduces neuroinflammation by neutralizing reactive species, sustaining appropriate levels of hydrogen sulfide (H_2S), mitigating the harmful effects of elevated homocysteine, and decreasing NMDA receptor-mediated excitotoxicity in central nervous system cells.[38] A deficiency in Vitamin B12 may result in various neurological symptoms, including irritability, developmental delays, and psychomotor disorders, especially in infants.[39] Plant foods do not naturally contain vitamin B12. This vitamin is mostly found in animal-derived food, including meat, fish, poultry, eggs, and dairy. Fish and marine shrimp, along with chicken and duck eggs, contain particularly high levels of vitamin B12, with the yolk of the egg having a higher concentration of B12 than the white.[28] The recommended daily allowance of Vitamin B12 for adults is 2.4 μg/day.[29]

The nervous system relies on vitamin B12 for the maintenance of myelin sheaths around nerves, which is essential for proper nerve function and signal transmission.[40] Recent research has underscored the therapeutic advantages of vitamin B12 in various conditions. For example, it has been demonstrated to promote axon growth and enhance neurological recovery following traumatic brain injury by downregulating apoptosis signaling pathways related to endoplasmic reticulum stress.[41]

VITAMIN B AND HYPERHOMOCYSTEINE

Vitamin B6, B9 (folic acid), and B12 each play a vital role in lowering homocysteine levels through their distinct but complementary mechanisms. Vitamin B6 acts as a coenzyme for cystathionine β-synthase (CBS) in the transsulfuration pathway, catalyzing the conversion of homocysteine to cystathionine, which is further metabolized into cysteine, thus reducing blood homocysteine levels.[2,30] Folic acid, converted into tetrahydrofolate (THF) and subsequently into its active form, 5-methyltetrahydrofolate (5-MTHF), transfers a methyl group to homocysteine, converting it back into methionine via the enzyme methionine synthase. This enzyme, which also requires vitamin B12 as a cofactor, facilitates this conversion.[5,42,43] Vitamin B12 is required for the processes of remethylation and transsulfuration

pathways that manage homocysteine levels. Its role as a cofactor enhances methionine synthase activity, as evidenced by increased enzyme activity in cell culture studies upon B12 supplementation.[30] Together, these vitamins ensure effective homocysteine metabolism, preventing its accumulation and contributing to overall homocysteine homeostasis.

Supplementation with vitamins B6, B9, and B12 has been demonstrated to effectively reduce homocysteine levels, which is advantageous in lowering the risk of various diseases. In a study on rats with hyperhomocysteinemic circumstances, vitamin B6 treatment significantly lowered oxidative stress and homocysteine levels.[44] A clinical study involving Chinese individuals with hyperhomocysteinemia found that a daily regimen of low-dose B vitamins (B6, B12, and folic acid) combined with betaine over a 12-week period led to a substantial reduction in plasma homocysteine levels.[45] Furthermore, In a cohort study involving elderly patients in South Africa, a six-month treatment with vitamins B6, B12, and B9 at twice the recommended daily allowance led to a significant reduction in homocysteine levels and an improvement in other cardiovascular risk factors.[46] A study by den Heijer et al. (2007) found a 46% reduction in homocysteine levels among patients with a history of pulmonary embolism or deep vein thrombosis who received vitamin B6 (50 mg), B9 (5 mg), and B12 (0.4 mg) over a period of three months.[47] Additionally, a pilot study comparing natural and synthetic vitamin B complexes found that both forms effectively increased serum levels of B vitamins and reduced homocysteine levels, underscoring the importance of these vitamins in managing oxidative stress and homocysteine metabolism.[48]

The impact of these vitamins on cognitive health has also been investigated. Evidence suggests that supplementation may lower homocysteine levels in patients with mild cognitive impairment, potentially slowing cognitive decline.[43] Since the metabolism of homocysteine depends on these B vitamins, deficiencies can result in elevated homocysteine levels, which are linked to vascular and neurodegenerative diseases.[6,15,17]

VITAMIN B AND CEREBROVASCULAR DISORDER

Increased homocysteine concentrations are a recognized risk factor for stroke, with B vitamins being essential in the breakdown of homocysteine. Supplementation with these vitamins has demonstrated a reduction in homocysteine levels, which is associated with a decreased risk of stroke.[42,49] Meta-analyses and randomized controlled trials (RCTs) have

shown that combined B vitamin intake can reduce the incidence of stroke by roughly 12-14%[50,51] Specifically, Folic acid, whether administered alone or in conjunction with low dosages of cyanocobalamin, has been linked to a notable decrease in stroke risk, particularly in regions lacking mandatory folic acid fortification.[52]

The impact of B vitamin supplementation on stroke risk is affected by various factors, such as initial folic acid levels, kidney function, and the use of antiplatelet medications.[52,53] For instance, patients with impaired kidney function who receive high doses of cyanocobalamin may experience negative effects. This indicates that using different forms of vitamin B12, like methylcobalamin or hydroxocobalamin, could be more beneficial.[53] Additionally, a meta-analysis including stroke patients demonstrated that homocysteine levels and the risk of cardiovascular and cerebrovascular events significantly decreased after B vitamin supplementation..[54] The China Stroke Primary Prevention Trial (CSPPT) and other large-scale studies have affirmed the stroke-preventive effects of folic acid, particularly among hypertensive individuals.[53,55]

The preventative impact of B vitamins on stroke risk tends to be more significant with prolonged follow-up durations and in individuals with previous histories of cardiovascular and cerebrovascular disorders. Despite these benefits, B vitamin supplementation does not significantly influence the occurrence of myocardial infarction, total mortality, or cardiovascular death.[50,51] Overall, while B vitamins, particularly B9 and vitamin B12, are essential for reducing stroke risk by lowering homocysteine levels, their effectiveness can vary based on individual health conditions and regional dietary policies.[42,52,53]

Research on the specific effectiveness of vitamin B supplementation for vascular dementia remains limited. A previous study demonstrated that folic acid and vitamin B12 supplementation lowers plasma homocysteine, inflammatory markers such IL-6, IL-8, TNF-alpha, and hs-CRP, and improve endothelial function. These improvements collectively contribute to better cognitive outcomes in patients with vascular dementia and hypertension.[56] Hyperhomocysteinemia, which is linked to cognitive decline and atrophy of the hippocampus , can result from B vitamin deficiencies.[22,57] However, the evidence regarding the long-term benefits of B vitamin supplementation for preventing or treating dementia is inconsistent. Some studies suggest that supplementation with folate and vitamin B12 can slow cognitive decline and reduce

the risk of dementia, particularly when administered early and over extended periods.[58,59] In contrast, other research indicates that while B vitamin supplementation may reduce homocysteine levels, it does not necessarily lead to significant cognitive improvements, suggesting that the relationship between B vitamins, homocysteine, and cognitive function is complex and may involve additional factors.[60]

Furthermore, whereas a higher risk of dementia is consistently associated with lower folate levels, vitamin B12 and B6 do not always show the same correlation.[58] The connection between B vitamins and cognitive health is further supported by evidence showing that individuals with Mild Cognitive Impairment (MCI) and dementia often have lower levels of these vitamins compared to non-demented elderly individuals.[22] Additionally, behavioral and psychiatric symptoms of dementia have been linked to higher homocysteine levels, suggesting a possible etiological function for homocysteine in these disorders.[59] Overall, while B vitamins and homocysteine are clearly linked to cognitive health, further research is needed to fully elucidate their roles and to develop effective prevention and treatment strategies for dementia and Alzheimer's disease.

Currently, no guidelines provide recommendations on the optimal dosage of vitamin B for the treatment of hyperhomocysteinemia to reduce stroke risk. A meta-analysis conducted by Zang et al. in 2024 indicated that supplementation with vitamin B12 at doses ≤ 0.4 mg/day, combined with vitamin B9 at ≤ 0.8 mg/day, resulted in a 35% reduction in stroke risk. When paired with folic acid, a lower dosage of vitamin B6 (≤ 10 mg/day) may help prevent strokes, although more research is needed to determine how effective vitamin B6 is in such a scenario.[61]

CONCLUSION

Hyperhomocysteinemia is a major risk factor for cerebrovascular diseases, particularly ischemic stroke, due to its effects on endothelial dysfunction, oxidative stress, and prothrombotic states. The metabolism of homocysteine requires vitamins B6, B9, and B12 as key enzymes and cofactors. Previous trials have shown that vitamin B supplementation can lower homocysteine levels and reduce stroke risk, though few studies have reported positive outcomes in patients with cognitive disorders. Future research should aim to develop comprehensive guidelines for vitamin B supplementation as a therapeutic strategy for hyperhomocysteinemia in geriatric patients.

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