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Narrative Review

THE ROLE OF FOLATE, VITAMIN B12 AND B6 IN HYPERHOMOCYSTEINEMIA AS THE RISK FACTOR OF CARDIOVASCULAR DISEASE: NARRATIVE REVIEW

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Page : 387-398

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ABSTRAK

Penyakit Kardiovaskular (CVD), terdiri dari penyakit jantung dan pembuluh darah, diyakini menyumbang sepertiga dari seluruh kematian di seluruh dunia, dan kejadiannya terus meningkat. Penyakit ini memiliki banyak faktor yang berkontribusi, sehingga sulit untuk menentukan faktor tunggal spesifik. Salah satu faktor yang telah dikenal perannya sejak tahun 1990an adalah homosistein yang menyebabkan terjadinya penyakit pembuluh darah aterosklerotik dan keadaan hiperkoagulabilitas. Meskipun terdapat hubungan yang jelas, evaluasi dan pengobatannya masih kontroversial karena penelitian menunjukkan hasil yang bertentangan mengenai efeknya dalam menurunkan risiko CVD. Vitamin B adalah sekelompok senyawa organik yang penting untuk fungsi fisiologis tetapi tidak disintesis oleh tubuh dan harus diserap dari makanan. Dalam metabolisme homosistein, vitamin B6, B9, dan B12 beperan penting. Kekurangan vitamin ini yang terlibat dalam daur ulang homosistein secara efektif dalam siklus metionin, khususnya folat, B12, dan B6 dianggap sebagai penyebab hiperhomosisteinemia. Secara kompleks vitamin B memiliki hubungan dalam jalur homositein dan CVD.

ABSTRACT

Cardiovascular disease (CVD), encompassing ailments affecting the heart and vascular system, is estimated to contribute to one-third of global mortality, and its prevalence is continuously rising. The etiology of this condition is multifactorial, making it challenging to identify a singular causative factor. Homocysteine, a factor identified in the 1990s, is known to contribute to the development of atherosclerotic vascular disease and hypercoagulability. Although there is a definite connection, the assessment and management of this condition are still a subject of debate due to inconsistent research findings on its impact in lowering the risk of cardiovascular disease. B vitamins are a collection of chemical compounds that play a crucial role in physiological function. However, the body does not produce them naturally and they need to be obtained from dietary intake. Vitamins B6, B9, and B12 are crucial in the metabolism of homocysteine. The cause of hyperhomocysteinemia is believed to be a deficiency of certain vitamins, particularly folate, B12, and B6, which are important for effectively recycling homocysteine in the methionine cycle. Vitamin B is intricately linked to both the homocysteine and cardiovascular disease (CVD) pathways.

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INTRODUCTION

Approximately 90 years ago, Vincent du Vigneaud, who later received the 1955 Nobel Prize in chemistry, released the initial laboratory production of the sulfur-containing amino acid, homocysteine. In the following decades, homocysteine would gain recognition as a significant intermediary in the metabolism of methionine and folate[1]. In the 1960s, pathologist Kilmer McCully put out the homocysteine theory of atherosclerosis. This idea was based on McCully's findings of

thromboembolic illness in young children who had homocystinuria, an inherited metabolic abnormality that leads to significant elevations of homocysteine levels in the blood and urine[1].

Cardiovascular Disease (CVD) encompasses conditions affecting the heart and blood arteries. Cardiovascular disease is estimated to contribute to around 33% of global mortality, and its incidence continues to rise. CVD is a complex ailment influenced by multiple contributing factors, making it challenging to pinpoint a singular causative element[2]. The primary essential aspect is the effect of homocysteine. Homocysteine has been recognized as a risk factor for atherosclerotic vascular disease and hypercoagulability since the 1990s[3]. There is evidence and reports that elucidate the involvement of specific B vitamins in ameliorating hyperhomocysteinemia. Additionally, some research established a correlation between deficiencies in various B vitamins and an elevated risk of heightened homocysteine levels. Hence, this literature review aims to investigate the significance of Vitamin B (specifically B6, B9, and B12) in hyperhomocysteinemia, a known risk factor for CVD.

MATERIALS AND METHODS

The methodology for this review is a narrative review. The Pubmed, Elsevier, and Google Scholar databases are the sources of the articles cited as references. The filter tool is used to restrict the last ten years of references and it supports both English and Indonesian. "Vitamin B, Homocysteine, Cardiovascular Disease" are the keywords that were used. Boolean operators are employed in a search strategy for pre-searching. The terms "Vitamin B6; Pyridoxine; Vitamin B9; Folate; Folic acid; Vitamin B12; Cyanochobalamin" were added to the original term "Vitamin B." In the meantime, "Hyperhomocysteinemia" is added to the expand the finding of “homocysteine”.

Articles in the form of reviews, randomized control trials, non-randomized controlled trials, cross sectional, cohort and case control are included in the references. Duplicated articles and full text that cannot be obtained are not included in the references of this narrative review.

RESULTS

Search results using predetermined keywords in the PubMed, Google Scholar and Elsevier databases resulted in 351 articles. After identifying duplicate articles, 348 articles were obtained. The remaining articles were screened for full text and 38 articles were obtained for review.

DISCUSSION

Vitamin B6, B9, and B12. Vitamins are a set of chemical molecules that are necessary for regular physiological function. However, the body does not produce them naturally, thus they must be obtained in modest quantities from the die[4]. B vitamins are often generated by plants, primarily in their chloroplasts, mitochondria, and cytoplasm[5]. The eight B vitamins, including thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), vitamin B6, folate (B9), and vitamin B12, are classified as water-soluble vitamins. B vitamins work as coenzymes in the majority of enzymatic reactions that facilitate all aspects of cellular physiological activity. The vitamin's biologically active form acts as a coenzyme by binding to the protein "apoenzyme" to generate a "holoenzyme". This process enhances the enzyme's ability to catalyze a wider range of processes. In general, the actions of B vitamins can be split into their roles in catabolic metabolism, which generates energy, and anabolic metabolism, which involves the creation and alteration of bioactive molecules[4].

Vitamin B6 is an essential chemical that plays a crucial role in maintaining the health and optimal functioning of the human body.

The composition comprises a cluster of six chemical compounds that are soluble in water. The vitamins in question are pyridoxal (PL), pyridoxamine (PM), pyridoxine (PN), and 5'-phosphate. Pyridoxal phosphate (PLP), in its active form, acts as a cofactor for around 160 biochemical activities in the body. The term "PLP" is commonly used as a synonym for "vitamin B6". It is present in both eukaryotic and prokaryotic organisms. The World Health Organization (WHO) suggests that individuals should consume a daily amount of vitamin B6 ranging from 1.3 to 1.7 milligrams[6]. Vitamin B6 produces the hormone serotonin from the amino acid tryptophan in the brain and acts as a neurotransmitter[7].

Vitamin B9, also known as folate, consists of a chemical structure that includes a pteridine ring, p-aminobenzoic acid, and one or more gamma-linked glutamate residues. Folate family members serve as acceptors or receptors of one-carbon units and operate as coenzymes in pyrimidine and purine synthesis, as well as in different methylation processes. Folate intake recommendations have been provided in multiple nations. The recommended dietary allowance (RDA) for individuals aged 18 years and older is 240 µg/day, which is the quantity that can satisfy the needs of most people in the population. The RDA for pregnant women is 240 µg/day, while for breastfeeding women it is 100 µg/day. This results in a total daily intake of 480 µg/day for pregnant women and 340 µg/day for breastfeeding women[8].

Vitamin B12 (cobalamin), which was initially identified by Folkers and Smith in 1948, is widely accepted as an enzyme cofactor that facilitates many biological processes such as isomerization, methyl transfer, and dehalogenation. Authentic forms of vitamin B12 consist of Adenosylcobalamin, which features a 50-deoxyadenosyl group that is covalently linked to the cobalt ion, and Methylcobalamin, which possesses a methyl group in the higher axial position. The oxidation state of the core cobalt cation in all stable forms of vitamin B12 is +3[9]. It is taken in together with intrinsic factor, which is produced by gastric parietal cells, in the final part of the small intestine after being removed by gastric acid. It serves as a cofactor in three primary reactions: the transformation of methylmalonic acid into succinyl coenzyme A, the conversion of homocysteine into methionine, and the conversion of 5-methyltetrahydrofolate into tetrahydrofolate[10]. Antioxidants play a protective role in the pathophysiology of numerous diseases and can reduce blood pressure. A higher consumption of antioxidant vitamins was associated with a lower waist circumference and LDL/HDL ratio[11].

Homocysteine and Hyperhomocysteinemia. Homocysteine (Hcy) is a non-dietary amino acid that can be transformed into cysteine or regenerated into methionine, an essential amino acid, with the assistance of specific B vitamins [12]. Homocysteine is an amino acid that has a sulfhydryl group and is generated from methionine. It is similar to cysteine but is not involved in protein synthesis. The concentration of homocysteine is controlled by two primary pathways: remethylation, which converts it back to methionine, or transsulfuration, which converts it to cysteine while also producing hydrogen sulfide (HS). Elevated homocysteine levels can be attributed to a range of variables, such as genetic predisposition, dietary choices, lifestyle habits, and certain drugs[13].

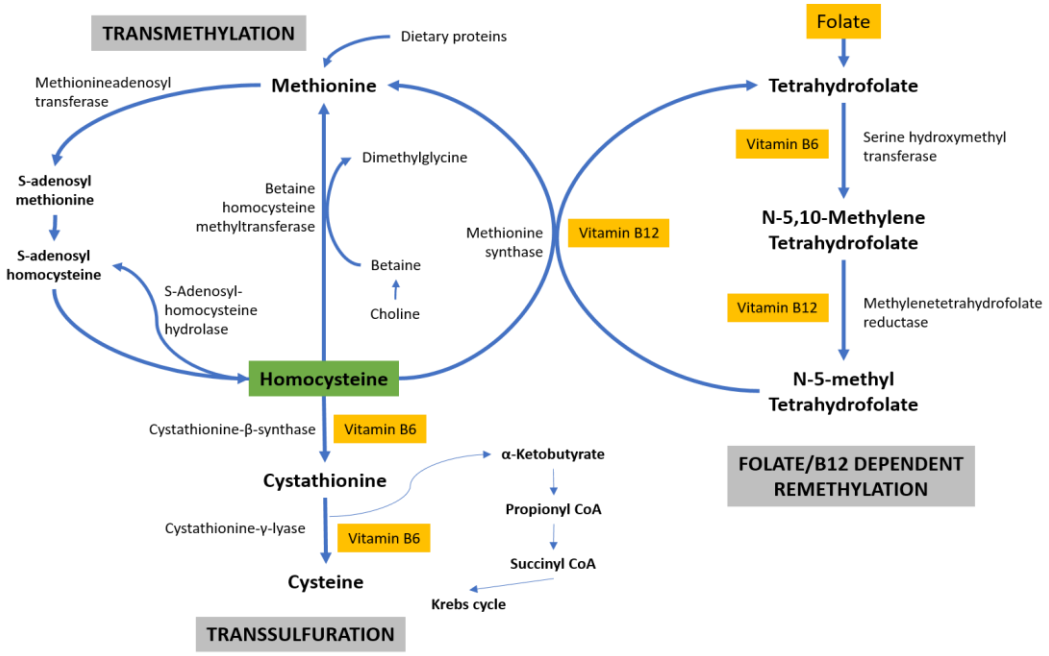

Figure 1. Scheme of homocysteine metabolism and its relationship with folate, B6 and B12.[15,16]

The measurement of homocysteine is conducted using a blood test. Prior fasting is unnecessary for blood samples. Levels below 15 µmol/L are considered within the normal range. Concentrations ranging from 15 to 30 µmol/L are classified as slightly elevated, concentrations between 30 and 60 µmol/L are classified as moderately high, and concentrations greater than 60 µmol/L are classified as very high. High levels of homocysteine are prevalent, with roughly 5% to 7% of the overall population seeing a mild elevation in homocysteine levels. Individuals afflicted with uncommon homocystinuria typically have levels over 100 µmol/L[14]. Hiperhomosisteinemia is a condition characterized by the presence of more than 15 micromol/L of homocysteine in the blood[12].

Hcy serves as a point where three primary pathways branch off in its metabolic pathway (see figure 1). These pathways, mostly found in the liver, include: (i) the conversion of Hcy back into SAH through the reverse activity of SAH hydrolase; (ii) the process of remethylation to form methionine, which relies on folate and dependent/independent with vitamin B12; and (iii) the transformation of Hcy into cystathionine through transsulfuration. Approximately half of Homocysteine (Hcy) is converted into Methionine (Met) by the process of remethylation. There are two distinct pathways for the remethylation of homocysteine (Hcy) back to methionine (Met) in order to complete the methyl cycle. The initial response is contingent upon the existence of B vitamins and folate. Folate, in the form of the coenzyme N-5-methyl tetrahydrofolate (THF), can transfer a methyl group to Hcy through a mechanism facilitated by the vitamin B12-dependent enzyme methionine synthase (MS)[15,16].

The status of folate and vitamin B12 has a significant impact on the equilibrium of homocysteine (Hcy) within cells and its subsequent levels in the bloodstream. It is important to mention that having an adequate amount of N-5-methyl THF for the process of folate-dependent Hcy remethylation is a crucial component of the "one carbon" metabolism. The enzyme N-5,10-methylene THF reductase (MTHFR) facilitates the production of N-5-methyl THF from N-5,10-methylene THF through a chemical reaction[17]. This process necessitates the presence of NADPH, which is controlled by S-adenosyl methionine (SAM)

and S-adenosyl-homocysteine hydrolase (SAH) as negative and positive regulators, respectively (see Figure 1)[16]. Vitamin B12 plays a crucial part in the remethylation process of Hcy to Met by acting as a co-factor in the enzyme Methionine synthase (MS).

The other mechanism for Hcy remethylation is independent of "one-carbon" metabolism. The process involves the utilization of betaine as a provider of methyl groups, which is produced from choline by the action of betaine-homocysteine S-methyltransferase (BHMT). The process of remethylating homocysteine (Hcy) by BHMT is mostly carried out in the liver, kidney, and lens. On the other hand, the folate/vitamin B12-dependent pathway for remethylation is present in all tissues[16,17].

The last Hcy elimination pathway involves transsulfuration, leading to the production of cysteine (Cys). The initial process involves the condensation of homocysteine (Hcy) and serine (Ser), leading to the formation of cystathionine. Subsequently, cystathionine is hydrolyzed to produce cysteine (Cys) and α-ketobutyrate. Both processes are facilitated by the B6-dependent enzymes cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE). α-Ketobutyrate is generated through the process of oxidative decarboxylation, resulting in the formation of propionyl-CoA. This propionyl-CoA is then transformed into succinyl-CoA, which serves as one of the intermediary compounds in the Krebs cycle. The transsulfuration pathway facilitates the breakdown of methionine (Met) and the transfer of sulfur atoms from methionine to serine (Ser), resulting in the production of cysteine (Cys). Cysteine serves as a precursor for the creation of proteins, coenzyme A, sulfate, and glutathione[16].

Vitamin B Deficiency and Hyperhomocysteinemia. To fully understand the mechanism of action of B vitamins, it is necessary to take into account the significant mechanistic hypotheses that have greatly influenced human research in this field. The homocysteine theory, which focuses on the involvement of specific B Vitamins (B6, B9, and B12), originated from the observation that increased levels of the potentially harmful amino acid homocysteine in fasting plasma were a separate indicator of cardiovascular disease. The primary cause is believed to be a lack of numerous crucial vitamins, such as folate, B12, and B6, which are essential for the efficient recycling of homocysteine in the methionine cycle[4].

The export of Hcy from cells into the bloodstream helps to keep its levels low inside the cells. In the absence of kidney impairment, the amount of Hcy in the bloodstream is believed to indicate the equilibrium of Hcy metabolism inside the cells. Hyperhomocysteinemia is a result of disruptions in the metabolism of Hcy, leading to its buildup in cells and eventual release into the bloodstream. The condition can be caused by genetic anomalies in enzymes involved in Hcy metabolism or, more typically, by nutritional inadequacies of vitamins essential for Hcy processing (such as folic acid, B12, B6), insufficient consumption of methionine, or other causes. The degree of hyperhomocysteinemia will vary based on its metabolic etiology. Consuming significant quantities of protein-rich diets might elevate plasma Hcy levels by 10–15% within a period of 6–8 hours[18].

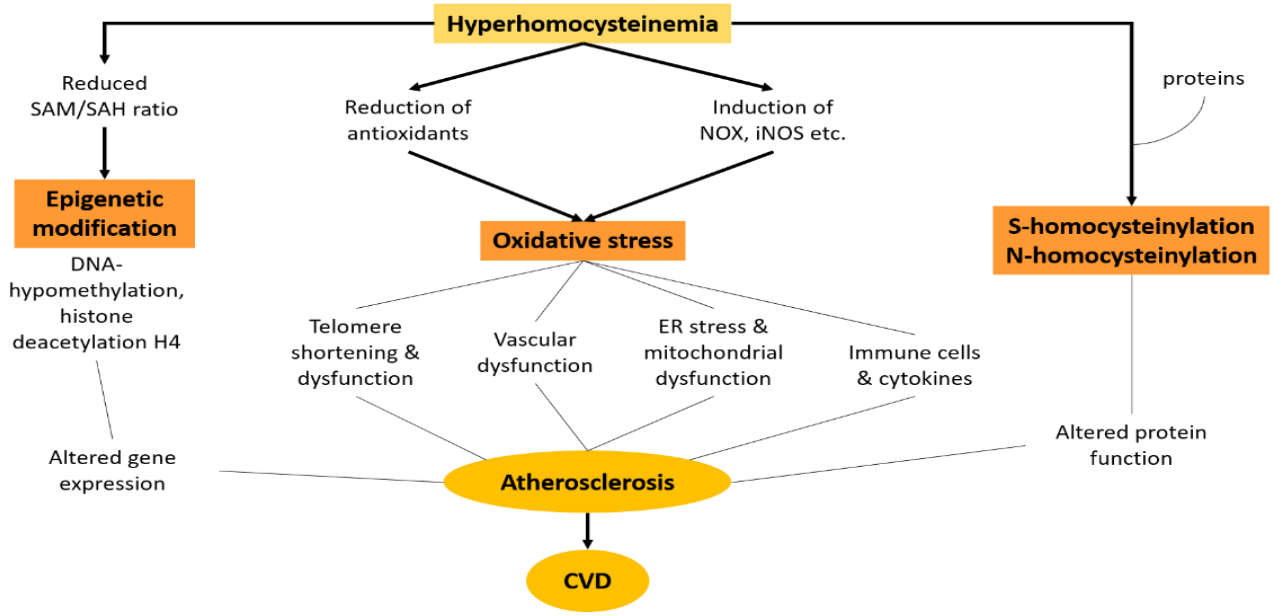

Figure 2. Pathomechanism of hyperhomocysteinemia. The role of oxidative stress, epigenetic modifications, changes in protein function, causing atherosclerosis and cardiovascular disease. *SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; NOX, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase; iNOS, inducible nitric oxide synthase; ER, endoplasmatic reticulum*[13]

In a case described by Kapur et al. in India, a patient with secondary cerebral vein thrombosis was discovered to have an uncommon presentation that was linked to Vitamin B12 insufficiency (serum cobalamin level of 68 pg/ml) and hyperhomocysteinemia (serum homocysteine level of 36 µmol/l)[19]. Tanaka et al. documented a case of a patient with an IVC thrombus who had Vitamin B12 deficiency (227 pg/mL), folic acid deficiency (2.4 ng/mL), and hyperhomocysteinemia (total homocysteine 83.1 µmol/L)[20]. Ammouri et al. documented cases of secondary acute venous thrombosis in four individuals resulting from hyperhomocysteinemia. This condition was characterized by elevated levels of homocysteine, which were impacted by a reduction in vitamin B12 levels. The drop in vitamin B12 was found to be connected with pernicious anemia[21]. Ulrich et al. documented a case of chronic combined degeneration and peripheral polyneuropathy linked to hyperhomocysteinemia (with a total homocysteine level of 48.5 µmol/L) and vitamin B12 deficiency (with a total cobalamin level of 133 ng/L)[22,23].

Hyperhomocysteinemia can also occur as a result of inadequate intake of folate, vitamin B6, and vitamin B12, leading to nutritional deficiencies[24]. The concentrations of folate, vitamin B12, and to a lesser extent, vitamin B6 in the blood have an inverse relationship with total homocysteine levels. Consequently, individuals with nutritional deficiencies leading to low levels of these substances in the blood are at a higher risk of developing hyperhomocysteinemia[25]. Elevated levels of plasma homocysteine might result from the effects of certain medications and disorders that disrupt the metabolism of folate, vitamins B6, and B12. Consequently, aberrant amounts of homocysteine could potentially serve as a diagnostic tool for identifying these conditions[26].

B12 plays a crucial role as a cofactor for two enzymes in humans: MS and methylmalonyl CoA mutase. Methionine synthase (MS) is located in the cytoplasm and facilitates the remethylation process of Hcy to produce methionine. On the other hand, methylmalonyl CoA mutase is found in the mitochondria and is responsible for converting

methylmalonyl coenzyme A (CoA) into succinyl CoA. B12 deficiency results in reduced action of both enzymes, leading to the buildup of Hcy and methylmalonic acid (MMA) and higher quantities in the plasma[13].

Folate that is 5-methylenetetrahydrofolate (5-MTHF) is the most common type in human blood, making up 82-23% of all folate. Helps to make methionine and tetrahydrofolate (THF) by giving Hcy methyl groups for remethylation. The enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) changes 5,10-methylenetetrahydrofolate (5,10-MTHF) into 5-MTHF. Because of this, it is very important that 5-MTHF is available. This enzyme's activity goes down when the MTHFR C677T polymorphism is present, which makes 5-MTHF more available. When folate levels are low, MTHF levels are low as well. New research shows that riboflavin, which comes in the form of flavin adenine dinucleotide (FAD), works with MTHFR and may be a key link between the MTHFR C677T Polymorphism and CVD[27,28].

If there is an adequate supply of methionine, homocysteine (Hcy) is removed through a transsulfuration pathway that relies on vitamin B6. Pyridoxal 5′-phosphate (PLP) is the primary biologically active form of this compound. Vitamin B6 is present in a diverse range of foods such as beef, fish, and chicken, which makes incidences of deficiency infrequent[29]. Furthermore, the intestinal bacteria produce vitamin B6, the majority of which is digested by bacteria that do not synthesize vitamin B6.

Hiperhomocystenemia and CVD. Increased levels of homocysteine have been linked to an elevated risk of cardiovascular disease (as seen in Figure 2), cerebrovascular disease, and thromboembolism. The relationship between homocysteine and cerebrovascular disease is evident, but the assessment and treatment of this correlation are still a matter of debate due to inconsistent research findings on its effectiveness in reducing the risk of cardiovascular and cerebrovascular disease. Lowering homocysteine levels has been proven to decrease cardiovascular risk in people with homocystinuria, a rare genetic illness characterized by atherosclerotic disease onset at an early age[12].

Arteriosclerosis is a condition characterized by persistent inflammation and damage to the inner layer of arteries, causing an increased ability for plasma to pass through, the accumulation of plasma lipids in plaque, and the development of fibrosis and calcification inside the plaque[26,30]. Pang et al. conducted research experiments that indicated that homocysteine has a function in the development of atherosclerosis. This is marked by an elevation in the control of inflammatory indicators such as C-reactive protein (CRP), IL-1β, IL-6, N-methyl-Daspartate receptor (NMDAr), and reactive oxygen species (ROS) in vascular smooth muscle cells (VSMC) in response to higher levels of homocysteine. This demonstrates its involvement in the development of atherosclerosis[31].

Homocysteine has the potential to induce damage to endothelial cells via multiple intracellular mechanisms. Examples of these effects include the initiation of inflammation and cell death, ameliorated generation of nitric oxide, buildup of reactive oxygen species and oxidative stress, and decreased methylation of cells. The interplay of these processes results in complex interactions, which subsequently trigger a cascade of responses within both localized and systemic atherosclerotic lesions[32]. Hcy can promote endothelial cell aging by upregulating plasminogen activator inhibitor-1 (PAI-1)[33], and telomere shortening and dysfunction may also be a cause of HCy-induced endothelial cell senescence (figure 2)[28]. Endothelial cell senescence promotes inflammation and damage to the endothelium utilizing the senescence-associated secretory

phenotype (SASP). Endothelial cell injury caused by Hcy might initiate damage to the endometrium. Several studies have demonstrated that Hcy can induce different types of endothelial cell death, including apoptosis, pyroptosis, and ferroptosis[32,34].

Hcy not only causes harmful effects connected to oxidative stress, but also influences the expression of several genes by altering DNA methylation. Deficiency of vitamin B9 and B12 or genetic variations can disrupt the action of methionine synthase and/or MTHFR, leading to the buildup of SAH and a drop in intracellular SAM levels[35]. This leads to a decreased SAM/SAH ratio and induces extensive hypomethylation (figure 2). The process of DNA hypomethylation has extensive implications as it alters the expression of numerous genes[35,36]. As an illustration, the enhanced production of telomerase and p21 due to Hcy-induced hypomethylation leads to faster telomere shortening and senescence in endothelial cells. Platelet-derived growth factor (PDGF) induces an increase in proliferation and migration in vascular smooth muscle cells, resulting in the creation of neointima. SAM may mitigate the development of neointima by decreasing endoplasmic reticulum stress and inflammation. The process of adding a methyl group to cytosine bases in eukaryotic DNA, carried out by DNA methyl transferase (DNMT), leads to the creation of a nucleotide called 5-methylcytosine. This nucleotide is typically found next to guanine nucleotides, forming what is known as CpG islands. The presence of methylated cytosines hinders the ability of transcription factors to interact with several DNA promoters, mostly due to their high concentration in CpG islands. The outcome of gene expression might be either repressed or upregulated, depending on the specific transcription factor involved. Additional consequences of DNA methylation include the deacetylation of histone H4 and modifications in histone H3 methylation, resulting in modifications to chromatin structure. To summarize, ample data is indicating that Hcy alters gene expression in the vasculature through DNA, RNA, and histone methylation[28].

A 2014 cohort study found that plasma homocysteine levels were a separate predictor of cardiovascular disease (CVD) events. Furthermore, it was elucidated that elevated Hcy levels are associated with the occurrence and degree of coronary artery disease. Nevertheless, there are still varying outcomes concerning the advantageous impacts of Hcy-lowering therapy using vitamins B6, B12, and folate[30]. In the same year, a cross-sectional investigation showed that elevated serum homocysteine levels in senior male patients with essential hypertension were a robust indicator of carotid resistive index (R), which serves as a measure of cerebral peripheral artery resistance[37].

Elevated levels of homocysteine have been correlated with increased diastolic and systolic blood pressure. When the concentration of homocysteine increases by 5 mol/L, there is a corresponding increase of 0.5 mmHg in diastolic blood pressure and 0.7 mmHg in systolic blood pressure in men. For women, there is a more pronounced association between homocysteine levels and blood pressure. Specifically, there is a rise of 0.7 mmHg in diastolic blood pressure and 1.2 mmHg in systolic blood pressure[26]. Administration of homocysteine has been shown to cause direct endothelial cell injury in vitro and in animals[26]. Hyperhomocysteinemia harms the production and function of substances that dilate blood vessels in the vascular wall. This, in turn, leads to the suppression of replication of endothelial cells, along with intensive proliferation and migration of myocytes, and defective production of components in the extracellular matrix. In addition, there is also a rise in the alteration of LDL and HDL particles,

inflammation, coagulation problems, and fibrinolysis. This leads to a reduction in flexibility due to its impact on the restructuring of blood vessel walls, leading to impaired systolic and diastolic performance[38]. Increasing the levels of LDL and reducing the levels of HDL can promote atherosclerosis, which can lead to CVD[39].

Atrial fibrillation (AF) is the prevailing and enduring irregularity of the heart's rhythm in Western countries, and it is anticipated that a substantial number of individuals will experience AF in the forthcoming years. In the ARIC and MESA cohorts, which are population-based and forward-looking, there was a slight correlation between elevated homocysteine levels and a higher likelihood of developing AF. However, the MTHFR C677T mutation did not show any association with the risk of AF. This suggests that homocysteine may serve as a new indicator for AF risk, rather than being a direct cause of the condition[40].

The 2023 guidelines published by the American Heart Association (AHA)/American Stroke Association (ASA) suggest updating the 2021 Guidelines to incorporate the use of homocysteine-lowering therapy with low-dose folic acid, or preferably with L-methylfolate and B12 in the form of methylcobalamin, for both primary and secondary prevention of ischemic stroke[41].

A Mendelian randomized trial conducted in 2021 analyzed the probable causative relationship between total homocysteine, B vitamins, and several cardiovascular illnesses, as well as the heightened risk of stroke, subarachnoid hemorrhage, and ischemic stroke. Moreover, elevated levels of folate and vitamin B6 were linked to a decreased likelihood of experiencing a stroke, particularly an ischemic stroke. Elevated folate levels were shown to be linked to a reduced risk of coronary artery disease, whereas increased levels of vitamin B6 were positively correlated with the risk of peripheral arterial disease. There is insufficient evidence to establish a correlation between vitamin B12 levels and the cardiovascular illnesses that were examined[15].

Homocysteine disrupts multiple processes and mechanisms associated with the development of atherosclerosis and cardiovascular disease. Nevertheless, the significance of this process in CVD is still not well comprehended. The issue persists due to the predominant reliance on in vitro experiments for obtaining the related conclusions. Cell culture studies frequently employ Hcy values that deviate from the physiological range observed in humans. Thus, additional in vivo investigations are required to better examine the precise effects of Hcy on CVD.

CONCLUSION AND RECOMMENDATION

Homocysteine is a significant risk factor in the development of atherosclerosis and cardiovascular disease (CVD). B vitamins, specifically B9, B12, and B6, play a crucial role in metabolism. Any deficits or disruptions in these components can impact the levels of homocysteine in the bloodstream. While the impact of vitamin B on hyperhomocysteinemia is well-established, there remains controversy on its efficacy and safety in using vitamin B for primary and secondary preventative therapy for cardiovascular disease. Therefore, further investigation involving human subjects is required to get further insights.

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