Hyperhomocysteinemia (Hcy) is an independent risk factor for cardiovascular diseases (CVD) and associated with primary causes of mortality and morbidity throughout the world. Association between Hcy and CVD has been a question for biologists over the last five decades. The circulating levels of Hcy can be increased by defects in enzymes involved in the metabolism of several B and therefore for homocysteine. Although researchers have yielded conflicting findings on the link between homocysteine and CVD risk, but there is convincing evidence on link between B vitamin deficiencies and increased CVD risk. This review identifies the research conducted on this subject matter and provides a framework for the factors associated with Hcy and CVD.

Abstract

Hyperhomocysteinemia: The independent risk factor of cardiovascular diseases

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Hyperhomocysteinemia (Hcy) is an independent risk factor for cardiovascular diseases (CVD) and associated with primary causes of mortality and morbidity throughout the world. Association between Hcy and CVD has been a question for biologists over the last five decades. The circulating levels of Hcy can be increased by defects in enzymes involved in the metabolism of several B and therefore for homocysteine. Although researchers have yielded conflicting findings on the link between homocysteine and CVD risk, but there is convincing evidence on link between B vitamin deficiencies and increased CVD risk. This review identifies the research conducted on this subject matter and provides a framework for the factors associated with Hcy and CVD.

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Hyperhomocysteinemia (Hcy) is an independent risk factor for cardiovascular diseases (CVD) and associated with primary causes of mortality and morbidity throughout the world. Association between Hcy and CVD has been a question for biologists over the last five decades. The circulating levels of Hcy can be increased by defects in enzymes involved in the metabolism of several B and therefore for homocysteine. Although researchers have yielded conflicting findings on the link between homocysteine and CVD risk, but there is convincing evidence on link between B vitamin deficiencies and increased CVD risk. This review identifies the research conducted on this subject matter and provides a framework for the factors associated with Hcy and CVD.

Key words: Hyperhomocysteinemia; CVD; Methionine; Homocysteine

How to Cite:
Introduction

The burden of non-communicable chronic diseases, including the CVDs, is rapidly rising around the globe, affecting all parts of world’s population [1]. Contrarily to the previous classification of chronic diseases as “diseases of affluence” they are now arising at a much faster rate in poorer countries than in developed areas of the world [2]. According to cardiovascular diseases account for around 30% of global deaths, and this figure is expected to increase further by 2030 [3]. While deaths caused due to CVD decreased by 31% between 2000 and 2010 [4], it is still projected to continue to be the world’s leading cause of death. Given substantial research in the field of its prevention and treatment, CVD infests the developed and developing regions alike. It is accounted for one in every three deaths [1], while 80% of total deaths caused by CVD have been reported to occur in resource limited countries [3]. Asian and African regions of the world are showing highest mortality and prevalence of cardiovascular diseases in the world. People with old age are the main victims of heart disease. Cardiovascular disease is one out of five major causes of “years lived with disability” (YLD) in poor countries [5]. CVD causing premature deaths thus ask for more health care budgets and reducing the GDP by 6.77% together with diabetes [6]. Almost all the parts of World’s population are facing a rise in non-communicable chronic diseases. Cardiovascular diseases are one of them which are focusing the underdeveloped population [7]. Research for prevention and treatment is still unable to control cardiovascular diseases in developed and developing countries [8]. This review summarizes the research conducted on Hcy and provides a framework for factors associated with Hcy and CVD.

Methods

Literature search strategy and selection criteria

References included in this review article were searched by using NCBI (PUBMED) and Google scholar, by the use of terms Hcy, CVD, Methionine, Homocysteine. Articles resulting from these searches were reviewed and relevant references were cited in this review article. This included articles published in English. Case reports published online were also included in this study. We selected 24 peer reviewed research articles and 35 review articles for this study.

Discussion

Risk factors for development of CVD

The detection of risk factors plays a key role in primary prevention of chronic diseases. Like other non-communicable diseases, several factors which increase the possibility of developing CVD have also been reported, including hypertension, smoking, diabetes, high serum cholesterol and obesity [9].

Overview of Homocysteine metabolism

Homocysteine (Hcy), a sulfur metabolite-containing essential amino acid, methionine, is formed regularly during methionine metabolism and its low concentrations (5-15µmol/L) are normally present in the plasma. HCY metabolism requires two separate pathways (transulfuration and remethylation), dependent upon B vitamins [10]. The pathway of transulfuration is triggered at times when methionine is present in excess amounts. During this cycle, HCY is converted to cysteine and subsequently converted to cystathione. Vitamin B6 (pyridoxine) acts as a cofactor, HCY is largely remethylated during the periods of low methionine to be converted back to methionine [11]. During metabolism of sulfur containing amino acid, homocysteine is produced as a metabolite whose normal plasma concentration is 5-15 µmol/L [12]. In the presence of in excess amount of methionine, transulfurationpathway is activated to convert homocysteine to cystathione leading to the formation of cysteine. But in the presence of low levels of methionine, re-methylation of homocysteine starts to synthesize methionine [13]. Methyl tetrahydrofolate (from Vitamin B9) and Vitamin B12 act as cofactors in this process [14]. Both of these pathways require the mediation of S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH). High levels of HCY are linked to reduced methylation potential, whereas this potential is increased by the presence of Vitamins B9 and B12 [15]. High levels of HCY have been considered a risk factor for cardiovascular disease for nearly half a century, the association between genetic disability to breakdown HCY and premature atherosclerotic disease was reported [16]. The hypothesis discussed above has been researched several times and found conflicting and inconsistent results. Recent research community has observed the linkage between CVD and abnormally high levels of HCY which suggests HCY as a new risk factor for coronary artery disease (CAD) [17]. A cohort study showed the independent association of HCY level with all-cause plus cardiovascular mortality [18]. A study found increased HCY in patients with ischemic heart disease (IHD) as compared to those of controls. It was also demonstrated that increased HCY is a factor for cardiovascular disease as well as atherosclerosis in IHD patients [19]. In 2005, Chua with his team studied the association of HCY and coronary lesion risk in Chinese population with acute myocardial infarction. They suggested the higher HCYconcentration is a major risk factor for coronary atherosclerosis [20]. Vitamin B supplementation to control the increased levels of HCY has no significant improvement in carotid intima medial thickness (CIMT) and flow mediated dilatation (FMD) but pooled effect showed little improvement in FMD and CIMT with HCY reduction [21]. A study was reported which showed double-blind placebo controlled for treating increased HCY by folic acid and it was found considerable improvement in study subjects. On the other hand no significant improvement was observed in case of atherosclerosis or carotid distensibility [22]. Another meta-analysis of 8 randomized, placebo-controlled study, folic acid showed decrease in HCY levels by 25% over the period of 5 years on average. No major impact was observed on other cardiovascular events including arterial revascularization [23].

It was found that vitamin B supplementation plays no significant role for the prevention of CVD [24]. Folic acid
is effective for CVD prevention in patients who are also affected by kidney disease [25]. In a meta-analysis studies, it was found high HCY levels as an independent predictor of mortalities including CVD mortalities [26]. The arterial inflexibility has been found to cause occurrence of first CVD in community based Framingham Heart Study [27]. High HCY levels have been observed in IHD patients in Homocystein Slovakia cross-sectional population showing the association between increased homocysteine and CVD [28]. Another study also showed the similar relationship between CVD and hyper-homocysteinemia [29]. Meta analyses of 17 studies showed the increased levels of HCY(5µmol/L) as a risk factor for CAD and increase in cholesterol level [30]. Another meta-analysis study did not agree with [31]. In this meta-analysis, no relationship was found between higher HCY and coronary artery disease. Another meta-analysis study showed decrease in homocysteine levels by 3µmol/L was shown to decrease the risk of IHD by 16% [32]. It will also decrease the risk of deep vein thrombosis and stroke by 25% and 24% respectively. Including 72 case control studies and 20 prospective studies, it was evident that decrease in HCY levels decreases the cardiovascular disease risk. In HCY collaboration study 2002, increase in HCY levels was suggested to be an independent and modest predictor of IHD and stroke. Other meta-analysis of 24 retrospective and 3 prospective studies, showed some association between increased HCY and venous thrombosis [33]. Despite of a large number of studies on causes, treatment and mechanism of increased levels of HCY, confusions and contradictions exist about the association of HCY and CVD which needs more studies [34].

Hyperhomocysteinemia and its determinants

Homocysteinuria is characterized by huge elevations in HCY levels (as high as 50 times their normal values), premature thrombosis and cardiovascular illnesses. It results from rare inborn errors in HCY metabolism, in which defects in certain enzymes crucial for HCY metabolism lead to the accumulation of HCY in blood and ultimately passage in urine occur [35]. Slight increments (15-25µmol/L) in HCY concentration may, however, be due to dietary factors associated with its metabolism [36]. Many genetic and environmental factors are now known to determine the HCY levels including lifestyles, behaviors, old age, maleness smoking, caffeine, menopause, chronic alcohol intake, deficiency of vitamins and impairment of renal function. It was indicated that independently of other lifestyle factors, age, and intake of folate and B vitamin supplements, reducing smoking and coffee intake could result in a 0.1- to 1.7-µmol/liter change in plasma total HCY level. This study also suggested that avoiding smoking, caffeine and folate and vitamin B supplementation shows decrease in plasma homocysteine levels [37].

The association between HCY concentrations, demographic and lifestyle factors as well as with B vitamin status was also investigated. Plasma tHCY was found to be higher in non-users of vitamin supplements. A survey was conducted to observe the association of HCY with lifestyle and vitamin B supplementation which showed the supplement users on much safer side [38]. In fact, increased concentrations of HCY are genetically determined. Some genotypes are known to cause rare types of conditions linked with premature atherothrombosis. Gene mutations are responsible for the loss of some enzymes including Methylenetetrahydrofolatereductase (MTHFR) and Crystathione b- synthase (CBS) linked to plasma HCY levels [29]. Certain rare genotypes have shown the association with premature atherothrombosis. The gene mutations in Methylenetetrahydrofolatereductase (MTHFR) and Crystathioneβ-synthase (CBS) have been shown to be associated with hyper-homocysteinemia [29].

Possible mechanisms involved in linking HCY with CVD

In spite of the partial recognition of HCY as a risk factor for CVD, the biological mechanisms involved in this relationship have not been completely identified. However, several mechanisms have been proposed to explain the relationship of hyperhomocysteinemia (HHCY) with the development of vascular disease. These potential mechanisms include endothelial dysfunction, production of reactive oxygen species (ROS) with consequent LDL oxidation, increased monocyte adhesion, activation of coagulation factors and inflammatory pathway and hypofibrinolysis caused by HHCY [39].

Atherosclerosis, being an inflammatory process, has been suggested to exhibit rapid progression due to the role of HCY in chronic inflammation [40]. HCY has been known to enhance the development of several pro inflammatory cytokines, which can contribute to atherogenesis by influencing vascular inflammation [41]. HCY has also been studied to impair normal cellular function, including vascular endothelial cells. This role of HCY has been supported in a study, in which it was found that increments in HCY levels can induce vascular endothelial dysfunction. HHCY has been recognized to impair endothelial vasodilation—an early step in atherosclerotic lesion development. This role of HCY in causing cellular dysfunction has been suggested (not validated) to be due to the involvement of reactive oxygen species (ROS) produced by auto oxidation of HCY. HCY has also been studied to lower nitric oxide bioavailability (the vasodilator) and decreasing the expression of antioxidant enzymes. Vascular injury due to the ability of HCY to cause endoplasmic stress is another mechanism of vascular injury [41]. Another different mechanism for linking CVD and HCY was observed. Reduced mRNA for atheroprotective lipoprotein Apo A-1 and thus reduced concentration of Apo A-1 was identified in MTHFR deficient mice. The findings of their study showed that HHHCY may contribute to CVD by decreased Apo A-1 expression, which is the main protein component of HDL [42]. As previously mentioned, HDL is known for its roles in CVD protection.
and its negative relation with HCY indicates CVD risk development. This role of HCY in reducing HDL production was also supported in which a strong negative correlation was established between plasma HCY and HDL levels[43]. HCY secondary to genetic causes as well as dietary HHcy has been found to cause significant increase in HCY-thiolactone, which is an atherogenic metabolite. These studies support that HHcy is associated with several mechanisms which promote CVD, providing a basis for establishing a direct role of HCY in raising cardiovascular disease risk [44].

Role of dietary factors
As already mentioned, HCY being an intermediate produced during methionine metabolism, is normally present in the plasma. But the concentrations are maintained by the mechanisms responsible for its conversion into either cysteine or into methionine itself. The role of B vitamins as cofactors in HCY metabolism, predispose a vitamin deficient person to HHcy and thus to CVD development. Administration of methionine and provision of vitamin (cobalamin, choline, folate and / pyridoxine) deficient diets have been used as model for inducing experimental HHcy, in addition to genetic alterations of enzymes involved in HCY metabolism. The use of these approaches indicates the important role of certain dietary factors in influencing plasma HCY levels [45]. A study reviewed by Elmadfa concluded that vegetarians, especially vegans, are at risk of developing HHcy due to low dietary intake of vitamin B12 which is found predominantly in animal foods [46]. The authors recommended the use of well-planned vegetarian diets to avoid such complications. Folate is available in variety of plant and animal foods including liver, mushrooms and green leafy vegetables (especially spinach, broccoli). The food sources of vitamin B6 include meats, whole grains, vegetables and nuts, with greater bioavailability of pyridoxine derived from animal foods. Vitamin B12 is found in foods bound to protein and thus, high protein foods including egg, fish, meat, organ meats, milk, and cheese are its richest sources [47]. As folic and vitamin B12 do not share the same food sources, therefore a careful planning is required to fulfill the requirements of these vitamins. A well-balanced diet including all food groups can be of benefit [48]. High dietary protein intakes have also been found to increase circulating HCY levels, as HCY is an amino acid metabolite. In a dietary controlled study, a high protein diet (containing 21% energy from proteins or 4.45g methionine per day) was demonstrated to increase total HCY levels throughout the day. Fasting HCY levels were not affected by one week high protein diet, indicating the effects of overnight fast on normalizing HCY levels [49].

A large body of research support the role of folate in decreasing HCY levels and folic acid supplementation has now been suggested as a safe preventive measure in high risk individuals. Dietary deficiency of vitamin B6, B9 and absorptive insufficiency of vitamin B12 are important factors responsible for HHcy. Therefore, dietary improvement by providing the food sources of B vitamins in abundance may prevent vascular disease by lowering serum HCY [40]. HCY levels can be reduced by increasing the intake of fruits and vegetables by enhancing dietary folic intake. Patients with hypercystenemia and cardiovascular disease have shown improvement with a daily dose of folic acid at a concentration of 0.65-10mg [50]. However, supplemental folate can mask the neurological symptoms of B12 deficiency if it occurs at the same time. Therefore, simultaneous supplementation of both vitamins is recommended. Administration of recommended dose (1mg/day) of vitamin B12 can cause 10-15% reduction in HCY levels. The effect of B12 supplementation has been found to increase nitric oxide concentrations and an improvement in endothelial function. Pyridoxine (vitamin B6) in a dosage of 10-250 mg/day along with folate therapy, has a greater effect on HCY lowering than folate administration alone. However, chronic administration of B6 may result in peripheral neuropathy [51]. The relationship of folate and HCY concentration in Mediterranean IHD patients was investigated, IHD patients had lower folate intakes and serum folate levels as compared to the controls. Dietary folate intake was found to have a strong influence on fasting HCY levels [49]. Combination of vitamins rather than either one alone has been found to have much pronounced effect on HCY lowering. A randomized placebo controlled intervention showed a significant improvement in HCY levels with B vitamin supplementation [21]. A meta-analysis was conducted to assess the Meta-analysis for investigating the effects of different doses of folate supplementation on HCY levels as well as the effects of combination therapy of B12 and B6 with folic acid. The authors, after analyzing 25 randomized controlled trials, concluded that daily dose of more than 0.8 mg/day of folic acid are required to achieve maximum HCY reduction. Recommended a dose of folate (0.8mg/day) for considerable reduction in high homocysteine levels [52]. Vitamin B12 was found to be associated with additional 7% reduction in HCY levels but B6 supplementation along with folate did not appear to have a significant effect [53]. Therefore, combined administration of vitamins B9 and B12 were found to have greater effect than either one alone [54]. Similar results have previously been found in comparatively smaller meta-analysis [55]. A much lower dose of folate supplementation (0.5-5mg/day) along with 0.5 mg of B12 was found to reduce HCY levels by a quarter to a third. This difference might have been due to the inclusion of older data in that meta-analysis. Vitamin B6 was not found to have a significant role in HCY lowering, as was found in 2005 meta-analysis [56]. Although the role of B vitamins in HCY lowering has been established, studies on the effects of this lowering on subsequent cardiovascular events have yielded conflicting results. In a randomized placebo controlled trial, daily folic acid dose of 800mcg for three years was found to decrease plasma t HCY levels by 26% in 819 adults with HHcy. In spite of the improvement in HCY concentration, folate supplementation was unable to slow down the development of atherosclerotic lesion or progression of arterial stiffening [22].

Heart outcomes Prevention Evaluation 2 determined the prolonged effects of Vitamin B9, B12 and B6
administration on vascular events in high risk population. the results of this large, prospective, randomized clinical trial report that although HCY levels were significantly reduced by daily supplementation of folic acid, pyridoxine and cobalam in over a period of five years but did not reduce the cardiovascular disease incidence [57]. A meta-analysis on the use of Vitamin B supplement was conducted that showed decrease in HCY and improvement in endothelial function in short term trails only [21]. Therefore, despite the well-known role of dietary factors in reducing HCY levels, their effects on lowering the CVD risk are still not validated. The studies have produced inconsistent data on the influence of HCY lowering achieved by vitamin supplementation on reducing cardiovascular disease incidence. Therefore, this subject requires further investigation [58].

Risk factor control as primary prevention of CVD
A large body of data strongly supports investments in prevention as the most sustainable solution for CVD endemic. Clear evidence supports the fact that primary prevention and individual health care interventions play an important role in reducing the disease burden. Reducing cardiovascular risk factors has been responsible for more than 50% decline in CVD mortality [59]. Several modifiable risk factors can be targeted for CVD risk prevention in high risk as well as in general population. Behavioral risk factors, including smoking, physical inactivity, alcohol abuse, and unhealthy diet, have been linked to vascular disease development and progression. Identification of these easily modifiable factors can lead to prevention of majority of fatal cardiovascular events [60]. Promotion of knowledge about the CVD risk factors as well as their control therefore, remains a strategy for rapid decline in the CVD prevalence. High plasma HCY levels have been identified to be linked to CVD and their causal relationship has been identified. Presence of some CVD risk factors can result in HHCY. Reductions in smoking and taking a healthy diet can be used as approaches for lowering HCY concentrations. In addition, certain dietary modifications can also result in improvement in HCY levels. Dietary intake or supplementation of vitamins B9, B6 and B12 can be of benefit [61].

Conclusion
In spite of a variety of knowledge on the subject, the association between HCY and CVD remains conflicting. However, the current evidence suggests a possible role of high levels of HCY in causing CVD and opens new avenues for researches in the field of nutrition, public health and medicine.

Conflict of interest
The author declares no conflict of interest.

Authors’ Contribution
Alifa Tanweer: conceive the idea and write manuscript
Abida Bano: Proof reading, article setting and submission
Warda Fatima: Data Collection and technical supervision
Hasnain Javed: Writing the article and financial support

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