Hyperhomocysteinemia and Cardiovascular Disease: A Transitory Glance

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Abstract
Hyperhomocysteinemia (Hhcy) is a medical condition characterized by abnormally large levels of homocysteine in blood. The involvement of homocysteine (Hcy) in various biochemical reactions causes deficiencies of the vitamins like pyridoxine (B6), folic acid (B9), or B12, leading to higher Hcy levels. Hhcy has been considered as an independent risk factor for various cardiovascular diseases like endothelial dysfunction, vascular inflammation, atherosclerosis, hypertension, cardiac hypertrophy and heart failure. The review article critically explains about the mechanisms involved in the Hhcy-induced development and progression of various cardiovascular disorders.

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INTRODUCTION
Hcy is a highly reactive sulphur-containing amino acid derived from methionine, an essential amino acid, which is the solitary resource of Hcy [1, 2, 3]. When excess Hcy is produced in the body and not readily converted into methionine or cysteine, it is excreted out of the tightly regulated cell environment into the blood. It is the role of the liver and kidney to remove excess Hcy from the blood. In many individuals with inborn errors of Hcy metabolism, kidney or liver disease, nutrient deficiencies, Hcy levels rise beyond normal levels lead to Hhcy [4]. Thus, Hhcy can be defined as a pathological condition characterized by an increase in plasma concentration of total Hcy [4, 5, 6]. Hhcy increases the
generation of ROS by activating NADPH oxidase, downregulates the endothelial nitric oxide synthase (eNOS) and thus reduces the bioavailability of nitric oxide (NO) [7, 8, 9, 10]. Moreover, Hhcy has been noted to increase the production of proinflammatory cytokines like tumor necrosis factor-α (TNF-α) by activating nuclear factor-kappa B (NF-κB) [11]. The elevated homocysteine concentration is an independent risk factor for various cardiovascular disorders [12, 13]. Hhcy is associated with an increased risk of cardiovascular complications such as atherosclerosis, endothelial dysfunction, hypertension, myocardial infarction and chronic heart failure (CHF) [7, 8, 13, 14, 15, 16, 17]. The review decisively explains about the correlation between excess Hcy concentration and cardiovascular disorders.

**SYNTHESIS AND METABOLISM OF HCY**

Hcy is a sulphur containing amino acid which is generated from the metabolism of methionine, the synthesis and metabolism of which involves four steps (Fig 1). The first step is transmethylation pathway which involves the conversion of methionine to homocysteine [18]. Second step is the transsulphuration pathway that involves the irreversible conversion of homocysteine to cysteine in presence of cystathione-β-synthase (CBS), a rate limiting enzyme and vitamin B6, an essential cofactor [19, 20]. The third step is the re-methylation pathway during which the regeneration of methionine from homocysteine occurs that is mediated by methionine synthase alongwith 5,10-methlenetetrahydrofolate (MTHF) and Vitamin B12 as essential cofactors. The last step is the regeneration of methylenetetrahydrofolate (MTHF) from tetrahydrofolate (THF) which is catabolized by enzyme 5,10-methelene-tetrahydrofolate reductase [10, 13].

**HHCY AND CARDIOVASCULAR DISORDERS: AN OVERVIEW**

Epidemiological evidences and observational studies data suggest an association between elevated Hcy levels and increased risk of cardiovascular complications like atherosclerosis, endothelial dysfunction, hypertension, myocardial infarction and chronic heart failure [7, 8, 13, 14, 15, 16, 17]. Atherosclerosis is characterized by a thickening of the arterial wall due to smooth muscle cell proliferation, lipid deposits and fibrosis [21, 22]. The rupture of lipid-containing atherosclerotic plaques results in thrombosis that further leads to myocardial infarction and stroke [21]. Moreover, Hhcy has been found to be associated with primary thrombotic disorder affecting arteries and veins [23]. In addition, Hhcy has been noted to be associated with a factor or factors that primarily cause venous and arterial thrombosis. It has also been reported that very high homocysteine concentrations are thrombogenic. It was evident that in patients presented with cystathionine-β-synthase (CBS) deficiency and inborn errors of homocysteine remethylation, the accumulation of the precursor of homocysteine, S-adenosylhomocysteine (SAH), occurs that ultimately leads to hypomethylation of some essential components [10, 24]. The role of SAH in Hhcy condition was evidenced by the fact that the therapy which lowers plasma homocysteine concentration also reduced SAH and restored impaired transmethylation reactions. The well reported common causes of Hhcy may be attributed to low serum or red cell folate concentrations, vitamin B-12 deficiency, decline in renal function and the TT genotype for the common C677T/MTHFR polymorphism alongwith low folate status [25, 26, 27, 28]. Further, the interrelations between endothelium-dependant vasodilatation mediated by NO release and plasma homocysteine have been established [29, 30]. It has been shown that that endothelium-dependant vasodilatation is reduced in Hhcy patients.
but not in their obligate heterozygote parents evidencing the probable role of Hhcy in the development and progression of endothelium dysfunction. Additionally, several groups established 3-fold increase in circulating homocysteine after a standard methionine load diet that reduced endothelium-dependant vasodilatation [31]. In another study, it was demonstrated that treatment with oral ascorbic acid, a potent antioxidant, prevented endothelial dysfunction associated with a 2-3-fold increase in homocysteine after a standard methionine load [22, 32]. The vascular risk associated with Hhcy has been observed to be stronger in hypertensive individuals [3-33, 34]. Hence, the attention has been focused on the direct relations of plasma homocysteine to blood pressure and hypertension because it has been suggested that the adverse risk associated with Hhcy is mediated in part by the positive association of homocysteine with hypertension [35, 36]. In the third National Health and Nutrition Examination Survey (NHANES III), it was observed that persons with higher plasma homocysteine concentrations showed a 2-3-fold increase in the prevalence of hypertension when compared to persons with normal homocysteine levels [35, 37]. Additionally, a potential role of homocysteine in the pathogenesis of hypertension was evidenced by the fact that homocysteine-lowering treatment reduced systolic and diastolic blood pressures [38]. Thus, a considerable body of evidence suggests a role for plasma homocysteine in the pathogenesis of hypertension [34, 36, 39]. Furthermore, plasma homocysteine has been suggested to be increased in CHF patients and hence, represents a newly recognized risk marker [40, 41, 42]. The data from clinical studies indicate that Hhcy is associated with an increased incidence of CHF as well as with the severity of the disease [43, 44, 45, 46]. The results from various studies show that Hhcy causes adverse cardiac remodeling characterized by interstitial and perivascular fibrosis resulting in increased myocardial stiffness [47]. It has been noted that Hhcy affects the pump function of the myocardium, the underlying mechanism of which potentially involves the direct effects of homocysteine on the myocardium as well as NO independent vascular effects [16, 47]. In addition, it has been also suggested that Hhcy derived endothelial dysfunction induced an increased expression of adhesion molecules followed by immigration and activation of inflammatory cells, secretion of chemokines, altered fibroblast and cardiomyocyte function and an increased collagen synthesis that has been ultimately lead to CHF [48, 49, 50].

Figure 1. Diagrammatic Representation of Metabolic Pathway of HCY

(1) Trans-methylation: conversion of methionine to homocysteine. (2) Trans-sulphuration: irreversible conversion of homocysteine to cysteine via cystathione-β-synthase. (3) Re-methylation: regeneration of methionine from homocysteine mediated by methionine synthase, with 5, 10-methylenetetrahydrofolate (MTHF) and Vitamin B12 as essential cofactors. (4) Regeneration of methylenetetrahydrofolate (MTHF) from tetrahydrofolate (THF) catabolized by enzyme 5,10-methyene-tetrahydrofolate reductase.
CONCLUSION

The impaired metabolism of Hcy in blood produces the Hhcy which has been regarded as an independent risk factor for many cardiovascular diseases as it exerts negative role on endothelial membrane. However, many studies have reported a significant correlation between Hhcy and cardiovascular complications but data from ongoing studies are awaited to clarify this issue further. Hence, new studies are demanded in order to provide the evidence of involvement of potent signaling markers in Hhcy-induced cardiovascular complications and new therapies to relieve this condition.

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