International Journal of Drug Development & Research
| April-June 2012 | Vol. 4 | Issue 2 | ISSN 0975-9344 |
Available online http://www.ijddr.in
Covered in Official Product of Elsevier, The Netherlands
SJR Impact Value 0.03 & H index 2

Review Paper
Covered in Index Copernicus with IC Value 4.68 for 2010

Hyperhomocysteinemia and Cardiovascular Disease: A Transitory Glance

Rohilla Ankur[*1], Dhama Pooja[1], Rohilla Seema[2], Dahiya Amarjeet[1], Kushnoor Ashok[1]
[1]Department of Pharmaceutical Sciences, Shri Gopi Chand Group of Institutions, Baghpat-250609, UP, India
[2]Department of Pharmaceutical Sciences, Hindu College of Pharmacy, Sonepat 131001, Haryana, India

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 (B_6), folic acid (B_9), or B_{12} 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.

*Corresponding author, Mailing address:
Ankur Rohilla
M.Pharm, Senior Lecturer,
Department of Pharmaceutical Sciences,
Shri Gopi Chand Group of Institutions,
Baghpat-250609, UP, India
E-mail: ankurrohilla1984@gmail.com

Key words:
Hyperhomocysteinemia, Homocysteine, Cardiovascular.

How to Cite this Paper:
Rohilla Ankur*, Dhama Pooja, Rohilla Seema, Dahiya Amarjeet, Kushnoor Ashok "Hyperhomocysteinemia and Cardiovascular Disease: A Transitory Glance", Int. J. Drug Dev. & Res., April-June 2012, 4(2): 70-75

Article History:----------
Date of Submission: 16-04-2012
Date of Acceptance: 11-05-2012
Conflict of Interest: NIL
Source of Support: NONE

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 B_6, 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-methylenetetrahydrofolate (MTHF) and Vitamin B_{12} 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 CARDIOVASULAR 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].

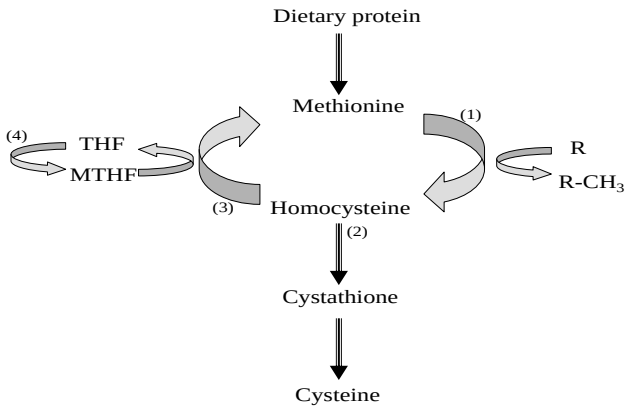

Figure 1. Diagrammatic Representation of Metabolic Pathway of HCY
(1) Trans-methylation: conversion of methionine to homocysteine. (2) Trans-sulphuration: irreversible conversion of homocysteine to cysteine via cystathione-β-synthase. (3) Re-methylation: regeneration of methionine from homocysteine mediated by methionine synthase, with 5, 10-methylenetetrahydrofolate (MTHF) and Vitamin B_{12} as essential cofactors. (4) Regeneration of methylenetetrahydrofolate (MTHF) from tetrahydrofolate (THF) catabolized by enzyme 5,10-methelene-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.

REFERENCES

1) Chambers JC, Seddon MDI, Shah S, Kooner JS. Homocysteine-a novel risk factor for vascular disease. J R Soc Med, 2001; 94: 10-13.
2) Mangoni AA, Jackson SHD. Homocysteine and cardiovascular disease: current evidence and future prospects. Am J Med, 2002; 112: 556-565.
3) Cheng S, Feng J, Wang X. Research advances in the treatment of hyperhomocysteinemia. Sheng Li Ke Xue Jin Zhan, 2011a; 42: 329-334.
4) Marosi K, Agota A, Vegh V, Joo JG, Langmar Z, Kriszbacher I, et al. The role of homocysteine and methylenetetrahydrofolate reductase, methionine synthase, methionine synthase reductase polymorphisms in the development of cardiovascular diseases and hypertension. Orv Hetil 2012; 153: 445-453.
5) den Heijer M, Koster T, Blom HJ, Bos GM, Briet E, Reitsma PH, et al. Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. N Engl J Med, 1996; 334: 759-762.
6) Ueland PM, Refsum H, Beresford SAA, Vollset SE. The controversy over homocysteine and cardiovascular risk. Am J Clin Nutr, 2000; 72: 324-332.
7) Austin R, Lentz S, Werstuck G. Role of hyperhomocysteinemia in endothelial dysfunction and atherothrombotic disease. Cell Death Differ, 2004; 11: S56-S64.
8) Tyagi N, Sedoris KC, Steed M, Ovechkin AV, Moshal KS, Tyagi SC. Mechanisms of homocysteine-induced oxidative stress. Am J Physiol Heart Circ Physiol, 2005; 289: H2649-H2656.
9) Suemastu N, Ojaimi C, Kinugawa S, Wang Z, Xu X, Koller A, et al. Hyperhomocysteinemia alters cardiac subustrate metabolism by impairing nitric oxide bioavailability through oxidative stress. Circulation, 2007; 115: 255-62.
10) Hoffman M. Hypothesis: hyperhomocysteinemia is an indicator of oxidant stress. Med Hypotheses, 2011; 77: 1088-1093.
11) Bai YP, Liu YH, Chen J, Song T, You Y, Tang ZY, et al. Rosiglitazone attenuates NF- kB dependent ICAM-1 and TNF-alpha production caused by homocysteine via inhibiting ERK1/2/p38MAPK activation. Biochem Biophys Res Commun, 2007; 360: 20-26.
12) Bostom AG, Silbershatz H, Rosenberg IH. Nonfasting plasma total homocysteine levels and all-cause and cardiovascular disease mortality in elderly Framingham men and women. Arch Intern Med, 1999; 159: 1077-1080.
13) Balakumar P, Singh AP, Ganti GS, Singh M. Hyperhomocysteinemia and cardiovascular disorders: Is there a correlation? Trends Med Res, 2007; 2: 160-6.
14) Nygard O, Vollset SE, Refsum H. Total homocysteine and cardiovascular risk profile. JAMA, 1995; 274: 1526-1533.
15) Helfenstein T, Fonseca FAH, Relvas WGM, Santos AO, Dabela ML, Matheus SCP, et al. Prevalence of myocardial infarction is related to hyperhomocysteinemia but not influenced by C677T methylenetetrahydrofolate reductase and A2756G methionine synthase polymorphisms in diabetic and non-diabetic subjects. Clin Chim Acta, 2005; 355: 165-172.
16) Herrmann M, Kindermann I, Muller S, Georg T, Kindermann M, Bohm M, et al. Relationship of plasma homocysteine with the severity of chronic heart failure. Clin Chem, 2005; 51: 1512-1515.
17) Ntaios G, Savopoulos C, Chatzopoulos S, Mikhailidis D, Hatzitolios A. Iatrogenic hyperhomocysteinemia in patients with metabolic

syndrome: a systematic review and metaanalysis. Atherosclerosis 2011; 214:11-19.

18) Prasad K. Homocysteine, a Risk Factor for Cardiovascular Disease. Int J Angiol 1999; 8: 76-86.
19) Selhub J. Homocysteine metabolism. Ann Rev Nutr, 1999; 19: 217-246.
20) Durand PM, Prost N, Loreau S, Lussier C, Blache D. Impaired homocysteine metabolism and atherothrombotic disease. Lab Invest, 2001; 81: 645-672.
21) Davies MJ. Stability and instability: two faces of coronary atherosclerosis. The Paul Dudley White Lecture 1995. Circulation, 1996; 94: 2013-2020.
22) Brattstrom L, Wilcken DEL. Homocysteine and cardiovascular disease: cause or effect? Am J Clin Nutr, 2000; 72: 315-323.
23) Mudd SH, Skovby F, Levy HL, et al. The natural history of homocystinuria due to cystathionine beta-synthase deficiency. Am J Hum Genet, 1985; 37: 1-31.
24) Langman LJ, Cole DE. Homocysteine. Crit Rev Clin Lab Sci, 1999; 36: 365-406.
25) Stabler SP, Marcell PD, Podell ER, Allen RH, Savage DG, Lindenbaum J. Elevation of total homocysteine in the serum of patients with cobalamin or folate deficiency detected by capillary gas chromatography-mass spectrometry. J Clin Invest, 1988; 81: 466-474.
26) Arnadottir M, Hultberg B, Nilsson-Ehle P, Thysell H. The effect of reduced glomerular filtration rate on plasma total homocysteine concentration. Scand J Clin Lab Invest, 1996; 56: 41-46.
27) Brattstrom L, Wilcken DE, Ohrvik J, Brudin L. Common methylenetetrahydrofolate reductase gene mutation leads to hyperhomocysteinemia but not to vascular disease: the result of a meta-analysis. Circulation, 1998; 98: 2520-2526.
28) Guthikonda S, Haynes WG. Homocysteine: role and implications in atherosclerosis. Curr Atheroscler Rep, 2006; 8: 100-106.
29) Cheng Z, Jiang X, Kruger WD, Praticò D, Gupta S, Mallilankaraman K, et al. Hyperhomocysteinemia impairs endothelium-derived hyperpolarizing factor-mediated vasorelaxation in transgenic cystathionine beta synthase-deficient mice. Blood, 2011b; 118: 1998-2006.
30) Kietadisorn R, Kietselaer BL, Schmidt HH, Moens AL. Role of tetrahydrobiopterin (BH4) in hyperhomocysteinemia-induced endothelial dysfuction: new indication for this orphan-drug?. Am J Physiol Endocrinol Metab, 2011; 300: E1176.
31) Celermajer DS, Sorensen K, Ryalls M, Robinson J, Thomas O, Leonard JV, et al. Impaired endothelial function occurs in the systemic arteries of children with homozygous homocystinuria but not in their heterozygous parents. J Am Coll Cardiol, 1993; 22: 854-858.
32) Kanani PM, Sinkey CA, Browning RL, Allaman M, Knapp HR, Haynes WG. Role of oxidant stress in endothelial dysfunction produced by experimental hyperhomocysteinemia in humans. Circulation, 1999; 100: 1161-1168.
33) Graham IM, Daly LE, Refsum HM, Robinson K, Brattstrom LE, Ueland PM, et al. Plasma homocysteine as a risk factor for vascular disease: the European Concerted Action Project. JAMA, 1997; 277: 1775-1781.
34) Sundstrom J, Sullivan L, D'Agostino RB, Jacques PF, Selhub J, Rosenberg IH, et al. Plasma homocysteine, hypertension incidence, and blood pressure tracking: the Framingham Heart Study. Hypertension, 2003; 42: 1100-1105.
35) Lim U, Cassano PA. Homocysteine and blood pressure in the Third National Health and Nutrition Examination Survey, 1988-1994. Am J Epidemiol, 2002; 156: 1105-1113.
36) van Guldener C, Nanayakkara PW, Stehouwer CD. Homocysteine and blood pressure. Curr Hypertens Rep, 2003; 5: 26-31.
37) Pierdomenico SD, Bucci A, Lapenna D, Lattanzio FM, Talone L, Cuccurullo F, et al. Circulating homocysteine levels in sustained and white coat hypertension. J Hum Hypertens, 2003; 17: 165-170.
38) Mangoni AA, Sherwood RA, Swift CG, Jackson SH. Folic acid enhances endothelial function and reduces blood pressure in smokers: a randomized controlled trial. J Intern Med, 2002; 252: 497-503.
39) Marosi K, Agota A, Végh V, Joó JG, Langmár Z, Kriszbacher I, et al. The role of homocysteine and

methylenetetrahydrofolate reductase, methionine synthase, methionine synthase reductase polymorphisms in the development of cardiovascular diseases and hypertension. Orv Hetil, 2012; 153: 445-453.

40) Sundstrom J, Vasan RS. Homocysteine and heart failure: a review of investigations from the Framingham Heart Study. Clin Chem Lab Med, 2005; 43: 987-992.
41) Vizzardi E, Bonadei I, Zanini G, Fiorina C, Raddino R, Dei Cas L. Homocysteine: a casual link with heart failure?. Minerva Med, 2009; 100: 421-427.
42) Alter P, Rupp H, Rominger MB, Figiel JH, Renz H, Klose KJ, et al. Association of hyperhomocysteinemia with left ventricular dilatation and mass in human heart. Clin Chem Lab Med, 2010; 48: 555-560.
43) Kannel WB. Incidence and epidemiology of heart failure. Heart Fail Rev, 2000; 5: 167-173.
44) Lloyd-Jones DM. The risk of congestive heart failure: sobering lessons from the Framingham Heart Study. Curr Cardiol Rep, 2001; 3: 184-190.
45) Sundstrom J, Sullivan L, Selhub J, Benjamin EJ, D'Agostino RB, Jacques PF, et al. Relations of plasma homocysteine to left ventricular structure and function: the Framingham Heart Study. Eur Heart J, 2004; 25: 523-530.
46) Agoston-Coldea L, Mocan T, Gatfosse M, Lupu S, Dumitrascu DL. Plasma homocysteine and the severity of heart failure in patients with previous myocardial infarction. Cardiol J, 2011; 18: 55-62.
47) Herrmann M, Taban-Shomal O, Hubner U, Bohm M, Herrmann W. A review of homocysteine and heart failure. Eur J Heart Fail, 2006; 8: 571-576.
48) Joseph J, Washington A, Joseph L, Koehler L, Fink LM, Hauer-Jensen M, et al. Hyperhomocysteinemia leads to adverse cardiac remodeling in hypertensive rats. Am J Physiol Heart Circ Physiol, 2002; 283: H2567-H2574.
49) Agoston-Coldea L, Mocan T, Gatfosse M, Lupu S, Dumitrascu DL. Plasma homocysteine and the severity of heart failure in patients with previous myocardial infarction. Cardiol J, 2011; 18: 55-62.
50) Givvimani S, Qipshidze N, Tyagi N, Mishra PK, Sen U, Tyagi SC.Synergism between arrhythmia and hyperhomo-cysteinemia in structural heart disease. Int J Physiol Pathophysiol Pharmacol 2011; 3: 107-119.