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Hyperhomocysteinemia and Cardiovascular Disorders: Is There a Correlation?

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Abstract: Homocysteine, a sulphur containing amino acid is an intermediate product in the metabolism of L-methionine. The increased serum level of homocysteine is termed as hyperhomocysteinemia, which is implicated in neurological disorders, hepatic injury and renal dysfunction. In addition, hyperhomocysteinemia is considered to be an independent risk factor for various cardiovascular disorders such as atherosclerosis, hypertension, coronary artery diseases, arrhythmias and heart failure. The present review focuses on a brief discussion about homocysteine and its pathogenic role in cardiovascular disorders.

Key words: Methionine, hyperhomocysteinemia, risk factors, cardiovascular disorders

INTRODUCTION

Homocysteine is a highly reactive sulphur-containing amino acid derived from methionine, an essential amino acid, which is the sole source of homocysteine (Mangoni and Jackson, 2002). Human plasma contains both reduced and oxidized forms of homocysteine (Durand *et al*., 2001). The highly reactive thiol group of homocysteine may allow it to form a disulphide bond with other homocysteine molecules to produce homocystine or with thiol groups of plasma proteins, such as albumin (Durand *et al*., 2001; Aguilar *et al*., 2004). The oxidized homocysteine comprises up to 99% and reduced homocysteine represents no more than 1% in plasma as reduced homocysteine is rapidly oxidized at physiological pH. The sum of all forms of homocysteine is referred as total homocysteine (Aguilar *et al*., 2004). Hyperhomocysteinemia has been associated in the pathogenesis of various disorders including cardiovascular disorders. The present review delineates the correlation between hyperhomocysteinemia and cardiovascular disorders.

SYNTHESIS AND METABOLISM OF HOMOCYSTEINE

The synthesis of homocysteine from methionine occurs through transmethylation pathway (Fig. 1). The transmethylation pathway, also known as the demethylation pathway, involves the conversion of methionine to homocysteine through a series of demethylation reactions (Prasad, 1999). The process is initiated through the activation of methionine by adenosine triphosphate (ATP) in the presence of methionine adenosyl-transferase that produces S-adenosylmethionine (SAM), which is further demethylated to S-adenosylhomocysteine (SAH) by methyltransferase (House *et al*., 1999; Aguilar *et al*., 2004). Moreover, demethylation of SAM can occur by alternative path involving methylation of glycine to methyl glycine through glycine N-methyltransferase (Durand *et al*., 2001). Finally SAH is hydrolyzed into homocysteine and adenosine, which is the sole pathway for homocysteine synthesis in the body (Selhub, 1999).

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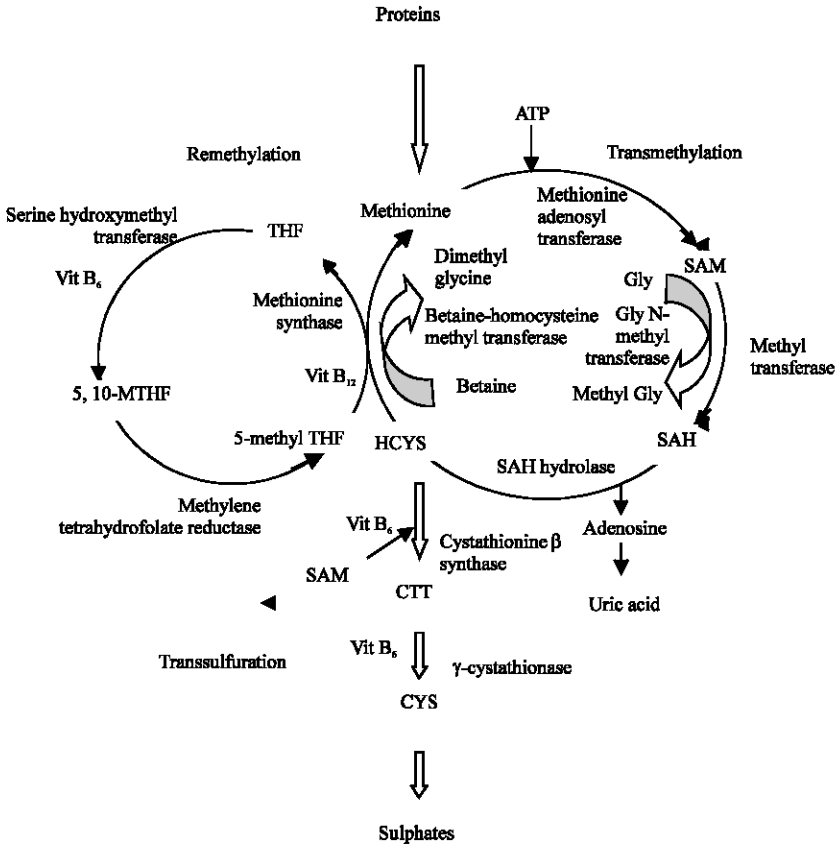

Fig. 1: Synthesis and metabolism of homocysteine. ATP-adenosine triphosphate, SAM-S-adenosyl methionine, gly-glycine, SAH-S-adenosyl homocysteine, HCYS-homocysteine, 5 methyl THF-5 methyl tetrahydrofolate, 5, 10 MTHF-5, 10 methylene tetrahydrofolate, CTT-cystathionine, CYS-cysteine

The metabolism of homocysteine involves remethylation or transsulfuration pathway (Fig. 1). The remethylation pathway involves the conversion of homocysteine back into methionine through a series of remethylation reactions (Fonseca *et al*., 1999). The remethylation of homocysteine to methionine occurs by two pathways. The first and most common, is remethylation through methionine synthase, which converts 5-methyltetrahydrofolate (5-methyl THF a derivative of folic acid) into tetrahydrofolate (THF), where 5-methyl THF acts as methyl donor and methylcobalamin, an active derivative of Vitamin B_{12} is cofactor (Durand *et al*., 2001). THF is converted into 5, 10-Methylene THF through the action of serine hydroxymethyltransferase in the presence of pyridoxal 5-phosphate, a derivative of Vitamin B_6. The 5, 10-methylene THF is converted finally to 5-methyl THF by methylene tetrahydrofolate reductase (MTHFR) (Antonio *et al*., 1997). The second and less common, pathway is the remethylation through betaine-homocysteine methyltransferase (BHMT), which functions independently of Vitamin B_{12} and folate but uses betaine as a methyl donor (Antonio *et al*., 1997; Durand *et al*., 2001). The transsulfuration pathway involves the irreversible conversion of homocysteine to cysteine (Ueland *et al*., 1993; Durand *et al*., 2001). The reaction involves cystathionine β-synthase (CBS), an enzyme dependent on pyridoxal-5-phosphate and condenses homocysteine with serine to form cystathionine (CTT), which is further converted in to cysteine

Table 1: Causes of hyperhomocysteinemia

Enzyme deficiencies
Cystathionine β-synthase
Methionine synthase
Methylenetetrahydrofolate reductase
Vitamin deficiencies
Folate
Vitamin B_6
Vitamin B_{12}
Increased methionine consumption
Demographic characteristics
Increasing age
Male sex
Postmenopausal status
Chronic medical disorders
Decreased renal function
Diabetes mellitus
Hypothyroidism
Renal transplantation
Malignant neoplasms
Drugs
Anticonvulsant agents (phenytoin, carbamazepine)
Folate antagonists (methotrexate)
Cholesterol lowering agents (cholestyramine, colestipol, nicotinic acid)
Thiazide diuretics
Cyclosporine
Metformin
Levodopa

through pyridoxal-5-phosphate-dependent-γ-cystathionase (Selhub, 1999). The cysteine thus formed is converted into sulfates, which are excreted in urine (Durand *et al*., 2001).

ETIOLOGY OF HYPERHOMOCYSTEINEMIA

Hyperhomocysteinemia is a pathological condition characterized by an increase in serum homocysteine level above the normal range of 5-15 μmol L^{-1}. Depending upon homocysteine concentration, hyperhomocysteinemia is classified as mild (15-25 μmol L^{-1}), intermediate (25-50 μmol L^{-1}) and severe (50-500 μmol L^{-1}) (Jacobsen, 1998). Hyperhomocysteinemia is caused either by genetic defects in the enzymes involved in homocysteine metabolism or by nutritional deficiency in vitamin cofactors (Jacobsen, 1998). Inherited deficiencies of enzymes in homocysteine-methionine pathway such as MTHFR and CBS produce severe hyperhomocysteinemia (Eikelboom *et al*., 1999; Virdis *et al*., 2002). The various factors leading to hyperhomocysteinemia are summarized in Table 1.

HYPERHOMOCYSTEINEMIA AND CARDIOVASCULAR COMPLICATIONS

Hyperhomocysteinemia has been associated in pathogenesis of stroke (Anan *et al*., 2006), movement disorders like huntington's chorea, parkinsonism, primary dystonia (Zocolella *et al*., 2006), depression (Sachdev *et al*., 2005), retinal vein occlusion (Chua *et al*., 2005), hepatic injury (Ferre *et al*., 2002; Woo *et al*., 2006), renal dysfunction (Ninomiya *et al*., 2004) and erectile dysfunction (Demir *et al*., 2006). Moreover, hyperhomocysteinemia has been considered to be an independent risk factor for cardiovascular disorders such as atherosclerosis (Boers, 2000), hypertension (Garfunkel *et al*., 2003), coronary artery disease (Sadeghian *et al*., 2006), arrhythmias (Rosenberger *et al*., 2006) and heart failure (Gibelin *et al*., 2006) (Fig. 2).

The highly reactive thiol group of homocysteine is readily oxidized to form Reactive Oxygen Species (ROS), which account for endothelial cytotoxicity of homocysteine (Loscalzo, 1996). Homocysteine-induced oxidative stress decreases the bioavailability of Nitric Oxide (NO) through its

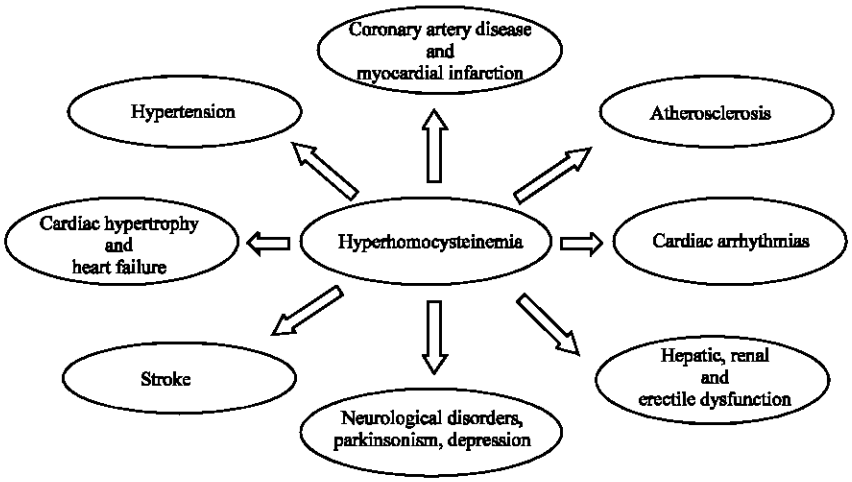

Fig. 2: Hyperhomocysteinemia and associated risk factors

oxidative inactivation. Further, peroxynitrite ($ONOO^-$), a strong oxidant generated by hyperhomocysteinemia oxidizes nucleic acids, proteins and lipids to cause cell death (Cai and Harrison, 2000). Moreover, $ONOO^-$ degrades tetrahydrobiopterin (BH_4), a cofactor necessary for activation of endothelial nitric oxide synthase (eNOS), thus leading to uncoupling of eNOS and reduced formation of NO (Milstien and Katusic, 1999). The increased intracellular homocysteine level leads to reduced activity of thioredoxin and peroxiredoxin and consequently increases the activity of NADPH oxidase, which further increases the oxidative stress (Tyagi *et al*., 2005). Furthermore, hyperhomocysteinemia impairs endothelial cell growth at G_1/S transition of cell cycle by inhibiting the expression of cyclin A, which is an important regulator of cell-cycle progression (Wang *et al*., 2002). High levels of homocysteine are noted to activate transcription factors like nuclear factor kappa-β (NFkB), which further induces the expression of various chemokines, cytokines and leukocyte adhesion molecules such as monocyte chemoattractant protein-1 (MCP-1) and interleukins, which contribute to inflammation and atherogenesis (Collins and Cybulsky, 2001). Endothelial damage by homocysteine converts normal anti-thrombotic property of endothelium to pro-thrombotic phenotype by enhancing pro-coagulant activity of factor V and XII, tissue factor and von Willebrand factor and inhibiting the expression of anti-thrombin (Welch and Loscalzo, 1998). Homocysteine added to cultured human vascular smooth muscle cells has been noted to induce expression of *c-myb* and *c-fos* genes and consequently produce proliferation of vascular smooth muscle cells (Dalton *et al*., 1997; Tang *et al*., 1998). In recent years, hyperhomocysteinemia is suggested to be a major risk factor in the progression of heart failure in clinical condition (Vasan *et al*., 2003; Naruszewicz *et al*., 2006). The cardiac hypertrophy is an initially adaptive response, but chronic hypertrophic signals involve various maladaptive pathways such as poly (ADP-ribose) polymerase (PARP), Rho-kinase, caspase-3 and tumour necrosis factor-α (TNF-α), which all together leads to cardiac dysfunction and decompensated heart failure (Balakumar and Singh, 2005-2007; Balakumar and Singh, 2006a-d; Balakumar *et al*., 2007a, b). Both preclinical and clinical studies suggest a positive relation between hyperhomocysteinemia and cardiac hypertrophy (Blacher *et al*., 1999; Joseph *et al*., 2003). The hyperhomocysteinemia has been shown to be an independent causative factor for cardiac stress and dysfunction in Spontaneously Hypertensive Rats (SHR) and normotensive rats (Joseph *et al*., 2002, 2003). In rats, the supplementation of diet with 9 g kg^{-1} of homocysteine for 10 weeks produces hyperhomocysteinemia and subsequently cause ventricular dysfunction identified by significant

increase in collagen content and the echocardiographic changes such as increase in the posterior wall and inter-ventricular septum thickness. Further, an upward shift in pressure-volume relationship in left ventricle suggests reduced cardiac compliance (Joseph *et al*., 2003). However, a recent and more chronic study of 20 weeks in hyperhomocysteinemic SHR revealed the systolic dysfunction as indicated by the significant fall in LVDP and +dP/dt (Devi *et al*., 2006). This model principally involves the oxidative stress and the inflammatory mediators in the development of heart failure (Joseph *et al*., 2003).

CONCLUSION

In conclusion, recent studies reveal that hyperhomocysteinemia is an independent factor for cardiovascular complications. Further studies are warranted to elucidate the signaling mechanisms and to design therapies for hyperhomocysteinemia-induced cardiovascular complications.

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