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Combinational Effect of Angiotensin Receptor Blocker and Folic Acid Therapy on Uric Acid and Creatinine Level in Hyperhomocysteinemia Associated Hypertension

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Abstract

Homocysteine [HSCH2CH2CH(NH2)COOH] (Hcy), is a sulfur-containing amino acid of 135.18 Da of molecular weight, generated during conversion of methionine to cysteine. If there is a higher accumulation of Hcy in the blood, i.e. usually above 15 μmol/L, it leads to a condition referred to as hyperhomocysteinemia. A meta-analysis of observational study suggested an elevated concentration of Hcy in blood, which is termed as the risk factors leading to ischemic heart disease (IHD) and stroke. Further experimental studies stated that Hcy can lead to an increase in the proliferation of vascular smooth muscle cells and functional impairment of endothelial cells. The analyses confirmed some of the predictors for Hcy presence, such as serum uric acid (UA), systolic blood pressure, and hematocrit. However, angiotensin-converting enzyme inhibitors Angiotensin-converting enzyme (ACE) inhibitors and angiotensin converting enzyme inhibitors (ARBs) (except losartan) alone are inadequate for controlling UA and creatinine level, although the addition of folic acid may be beneficial in hypertensive patients who are known to have a high prevalence of elevated Hcy. We hypothesized that combination therapy with an ARB (olmesartan) and folic acid is a

promising treatment for lowering the UA and creatinine level in hyperhomocysteinemia associated hypertension.

Keywords: Homocysteine, hyperhomocysteinemia, hypertension, creatinine, angiotensin receptor blocker, folic acid

Highlights

1. Higher accumulation of Homocysteine in the blood leads to a hyperhomocysteinemia.
2. Folic acid is a good candidate as a supplement for treating the hyperhomocysteinemia associated hypertension.
3. Folic acid does not affect the function of normal cell.

Introduction

Hcy was identified in 1932 by Butz and du Vigneaud at the University of Illinois as an amino acid of biological importance [1]. Mudd *et. al.* in 1964 for the first time identified the enzyme defects in cystathionine β synthase causing homocystinuria [2]. A study in 1969 stated the role played by a high level of Hcy in causing atherosclerosis through deposition of fibrin, oxidant stress, the release of cytokine, inflammation and other related mechanisms [3-5].

Synthesis of Homocysteine

In the synthesis of Hcy, methionine (has a methyl group attached with a sulfur atom) is converted to S−Adenosyl Methionine (SAMe), in the presence of methionine adenosyltransferase (MAT) and ATP with the addition of adenosine to the sulfur which activates the methyl group [6]. Removing the methyl group from SAMe leads to the formation of SAH (S−Adenosyl Hcy). Further, in the presence of a hydrolase enzyme, SAh is converted to Hcy by adenosine removal [7] (Figure 1).

Metabolism of Homocysteine

Metabolism of Hcy is carried out in three different ways:

1) In liver cells, the transsulfuration pathway is catalyzed by Vitamin B6, which leads to the conversion of Hcy (around 60%) to cysteine (Cys). Cys can be used as building blocks for many proteins that can be used in the formation of glutathione (GSH), which is an anti-oxidant or oxidized to form the taurine (an amino acid) [8, 9].

2) Hcy can also be reconverted to Met through the addition of a methyl group. The methyl group can be added in the presence of methionine synthase enzyme and vit. B12, where methylated folic acid (Methyltetrahydrofolate, MTHF) acts as the methyl group donor [10-13].

3) In another liver pathway, choline is converted to betaine (TMG), which acts as the methyl group donor [14, 15]

The prevalence of hyperhomocysteinemia in India varies from 52%-84% which is caused due to elevated levels of Hyc [16, 17].In the case of fasting, the total plasma concentration of Hcy seemed to be low, i.e. 5-15 μmol/L using HPLC techniques, in case of healthy humans. Application of immunoassay techniques for the determination of levels of Hcy yielded 5-12 μmol/L concentration [18]. A concentration level higher than 100 μmol/L leads to severe severe hyperhomocysteinemia, whereas 16-30 μmol/L of Hcy leads to moderate condition and a value between 31-100 μmol/L leads to the intermediate condition [19-21].

Elevated Hcy levels are connected with various pathologies both in adults and children. Causes of high Hcy concentration include genetic mutations in 5, 10-methylenetetrahydrofolate reductase (MTHFR) and enzyme deficiencies of methionine synthase (MS) and cystathionine β-synthase (CβS) (21-23).

Homocysteine Associated cardiovascular problem

All forms of hypertension related to high systolic and diastolic pressure as well as high pulse pressure, have been treated as recognizable and independent risk factors for determination of cardiovascular morbidity and mortality. For reducing such risk factors, anti-hypertensive treatment needs to be adopted that uses anti-hypersensitive agents, alone or in combination [22]. Furthermore, Hyc as an independent risk factor leading to cardiovascular modalities, due to the increase in the oxidative stress [23-25].

Some of the population-based studies have stated a direct interlinking between the levels of Hcy with blood pressure, especially systolic. A previous study stated that the increase in plasma Hcy concentration by 5 μmol/L leads to an increase in the blood pressure by 0.7/0.5 mmHg and 1.2/0.7 mmHg, in men and women, respectively. A meta-analysis study in an observational study suggested that an elevated level of total blood Hyc concentrations are associated with the risk of IHD and stroke [26-28]. With every 3 μmol/L elevation in the level of Hcy, the risk of IHD increased by around 11% and that of stroke increased by around 19% [29].

Arteriolar constriction

The structure, as well as functionality of arteries, are affected by high levels of Hcy. As mentioned earlier, the proliferation of vascular smooth muscle cell and impairment of endothelial function can be an after-effect of increased Hcy concentration [30, 31], thus leading to increased arteriolar constriction as well as peripheral resistance. It may also lead to an increase in the blood pressure by elevating the total peripheral resistance, especially by small resistant arterioles and arteries [32-34].

Insulin Resistance:

The increased resistance of insulin (hyperinsulinemia) associated with clinical manifestation of hyperhomocysteinemia elevated blood pressure. The condition of hyperinsulinemia may lead to an increase in the level of Hcy as well as elevate blood pressure through various mechanisms. On the contrary, factors like dietary habits also contribute to insulin resistance [35-37]. In summary, metabolic disturbances and long-term hyperhomocysteinemia together with vascular remodeling suggested that enhanced oxidative stress, endothelium dysfunction, and decreased PPARγ expression in the vessel wall could be underlying mechanisms for hyperhomocysteinemia associated hypertension [38].

Hyperuricemia and creatinine

Hyperuricemia leads to urate crystal deposition in between the joints, thus becoming a prime risk factor in the development of gout [39]. In addition to this, it also leads to other clinical diseases, such as cardiovascular and cerebrovascular conditions. Elevated concentration of UA is linked to increased rates of cardiovascular (CV) morbidity and mortality, stroke, chronic kidney disease, metabolic syndrome, and hypertension in the general population [40-49]. Multivariate analysis study was conducted to detect that systolic blood pressure, UA, and hematocrit are the predictors for increased Hcy concentration, [50-52]. Moreover, the various study explores significant correlations between Hcy, uric acid, and creatinine [53, 54].

Arrhythmias

Slightly enhance the micromolar concentration of Hcy between 50-500 micromole/Liter in the blood leads to inhibition of cardiac Na^+ and K^+ channels and transient outward current which prolongs the action potential and change in electrophysiologic properties of the heart [55-57].

Effect of ACE inhibitors and ARBs in hyperhomocysteinemia associated hypertension

The vasodilatory property of RAAS inhibitor candidates, like ACE inhibitors and ARBs and have found to reduce the risk of CV disease via oxidative stress management [58]. However, ACEIs drugs like enalapril have been found to be non-effective in controlling the blood pressure in the presence of Hcy ≥15 μmol/L [59-61]. On the other hand, a randomized study on ACE inhibitor like captopril has statistically insignificant effects on tHcy after 4 weeks or creatinine [62] while Enalapril may also increase in plasma tHcy among the hypertensive patients[63]. Moreover, the treatment group receiving enalapril significantly increase the serum uric acid concentration and [64] which is an independent risk factor for oxidative stress, stroke/ transient ischemic attack at the value ≥ 6.35 mg/dl[65]. However, ACEIs inhibit the synthesis of biologically active peptide Angiotensin II by blocking the ACE but the synthesis of AngII resumed due to activation of a non-ACE pathway that will be mediated in the presence of chymase, kallikrein, cathepsin G, and elastase-2 enzyme[66]. Hence, the oxidative stress is enhanced by activation of the AT1 receptor [67-69].

A recent animal study shows that mild to moderate increase in Hcy concentration leads to increase expression and binding and of AT1 Receptor that mediated vascular injury [70, 71]. A previous study showed no significant change in the levels of plasma Hcy in hypertensive patients administered with Olmesartan [72-74]. However, when these patients were treated with either candesartan or amlodipine, at least $2\,\mu mol\,l^{-1}$ increase in Hcy concentration was observed in the study patients [75-77]. Moreover, ARBs increase the level of serum creatinine and uric acid (except Losartan) because losartan inhibits URAT1, a major transporter in the kidney for uric acid reabsorption while other ARBs does not do it at therapeutic concentration [78-84].

Folic acid

Folate is an essential element required in synthesis of pyrimidine, purine (precursors of DNA and RNA, respectively) and amino acid metabolism including Hcy. Deficiency of folate results in increasing the risk of getting hyperhomocysteinemia [85, 86].

However, ACE inhibitors and ARBs (except losartan) alone are inadequate for controlling UA and creatinine level, although the addition of folic acid may be beneficial, in hypertensive patients who are known to have a high prevalence of elevated homocysteine (Hcy)[87-90]. Conventional hyper uric acid therapies aim at either reducing UA production using xanthine oxidase (XO) inhibitors, such as allopurinol, or increasing renal UA excretion with drugs, such as benzene bromide malone and probenecid. However, these agents can effectively lower the serum UA levels but they do have a number of side effects, including allergic reactions, liver damage, kidney damage, bone marrow suppression and gastrointestinal symptoms [91-93]. Thus, we need safe and effective therapeutic approaches. Hence fore, Folic acid is several folds more potent as an inhibitor of Xanthine oxidase than the know inhibitor allopurinol, which results decrease the level of uric acid [94, 95].

Conclusion:

In the clinical setting, RAAS inhibitor is the first choice of drug for the treatment of hypertension by medical practitioners but the determination of homocysteine level is not very frequent for diagnosis of hypertension in adults and geriatric patients that may arise certain blood pressure related consequences. So, folic acid could be a good candidate as a supplement for treating the hyperhomocysteinemia associated hypertension. Moreover, folic acid does not affect the function of normal cell i.e could be used as nutrients and growth supplement for damage cell due to oxidative stress.

Most of the previous studies also demonstrated that use of folic acid (0.4 mg/day) supplementation failed to lower blood Hcy, uric acid and creatinine level, while high dose 1000 mg does not significantly lower the uric acid concentration. Contradictions in the study outcomes might be due to small sample size and differences in population characteristics, for example, patients treated with or without folate supplementation.

Thus, as a future perspective, we need to establish an adequate dose of folic acid as a supplement with ARB like Olmesartan for the treatment of hyperhomocysteinemia associated hypertension.

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Conflict of interest

Authors declare no conflict of interest

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Figure Ligands:

1. Synthesis and metabolism of Homocysteine

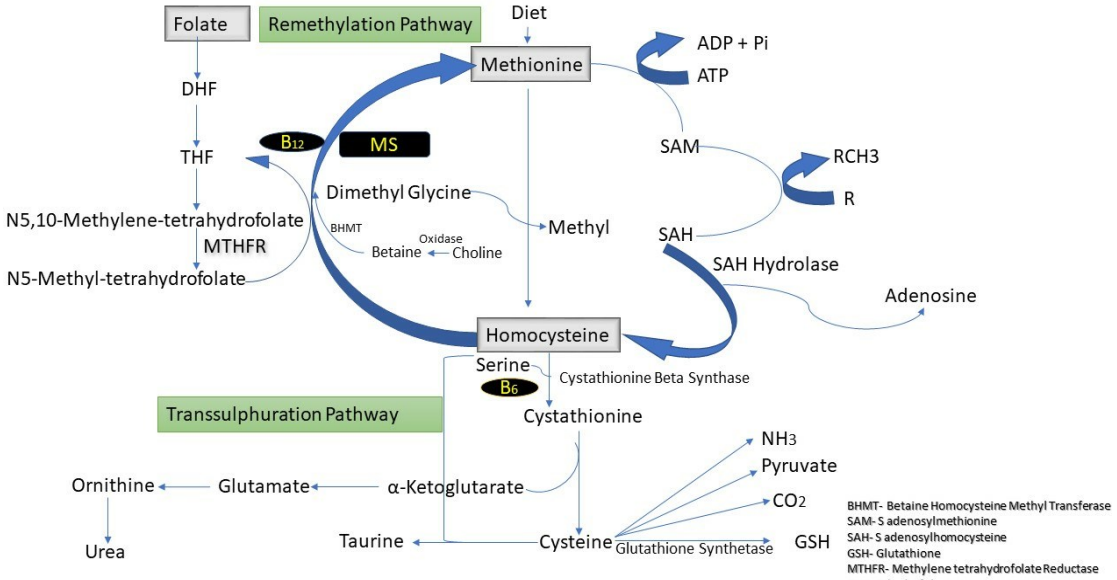

Figure1 : Synthesis and Metabolism of Homocysteine