

Review Article

Homocysteine and Folic Acid Prescription Effects on Cardiovascular Diseases

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Abstract:

Introduction: Homocysteine, is a sulfhydryl-containing amino acid that is typically present in very small amounts in all cells of the body. Many investigations have indicated hyperhomocystenemia as a risk factor, which is correlated with complications such as atherosclerosis, cardiovascular disease (CVD), and stroke. The aim of the present work was to review different studies for the lowering effect/s of folic acid supplementation on plasma homocysteine levels.

Methods: An academic search was conducted in number of electronic databases such as EMBASE, PubMed, and etc. for the key words; homocysteine , vitamin B12 , vitamin B6 , folic acid (vitamin B9) and cardiovascular diseases during years 2004 to 2018.

Findings: Review of the selected papers indicated that increased homocysteine levels as a risk marker for cardiovascular diseases, is associated with atherosclerotic outcomes. In addition, it is considered a higher risk of coronary artery disease in patients with chronic renal dysfunction. In apparent contrast, however, another study indicated no risk reduction in homocysteine-lowering trials based on prescription of folic acid and concluded that intake of high amounts of folic acid may be beneficial via the homocysteine lowering, but may also be harmful via destabilization the atherosclerotic plaque.

Conclusion: The authors conclude uncertainty of whether or not folic acid means of homocysteine lowering forms of therapy will reduce the risk of CVD remains a main focus of future research works.

Key words: Homocysteine, Methionine, Cysteine, Atherosclerosis, Cardiovascular Disease.

Introduction:

Homocysteine, is a sulfhydryl-containing amino acid that is typically present in very small amounts in all cells of the body. It is produced in the normal biosynthesis of the amino acids methionine and cysteine (1) through two pathways: remethylation, which requires folic acid (vitamin B9) and vitamin B12 coenzymes; and trans-sulfuration, which

requires pyridoxal-5'-phosphate; the vitamin B6 coenzyme (2). Total concentration of homocysteine in plasma of healthy humans (fasting) is low and its level is between 5.0 and 15.0 $\mu\text{mol/L}$ when assessed with HPLC or 5.0-12.0 $\mu\text{mol/L}$ when immunoassay methods are used (3). Data from a number of laboratories suggest that mild elevations of homocysteine in plasma are a risk factor for

(CVD) (2), however, the definition of hyperhomocysteinemia differs between studies (1). It is defined as a medical condition characterized by an abnormally high level of homocystein (above 15 $\mu\text{mol/L}$) in the blood (1,4).

The prevalence of hyperhomocystenemia may vary significantly between populations, and most likely depend on age, diet, and genetic background as well (1). Increasing age, male sex, smoking, coffee consumption, high blood pressure, unfavorable lipid profile, high creatinine and faulty diet are some of the factors associated with increased homocysteine level (5). On the other hand, physical activity, moderate alcohol consumption, good folate and vitamin B12 status are associated with lower homocysteine level. It is reported that vegetarians may be at a higher risk of hyperhomocysteinemia due to low plasma B12 level but the difference is likely to be insignificant. (5).

Hyperhomocysteinemia may arise from genetic defects of enzymes involved in homocysteine metabolism (6,7). However, nutritional deficiencies of folate (vitamin B9), vitamin B12 and to a lesser extent, vitamin B6 that are essential cofactors in homocysteine-methionine metabolism may also give rise to it (6,7). Therefore, a person with a nutritional deficiency that leads to low blood concentrations of the aforementioned is at increased risk of hyperhomocysteinemia as well (3). In addition, use of various drugs, alcohol, tobacco, coffee as well as several other diseases such as renal and thyroid dysfunction, cancer, and diabetes are believed to be associated with moderately elevated homocysteine concentration (1,8). The major route of homocysteine clearance from plasma

is the kidney and the rise is due to defective metabolism of homocysteine by the kidney (7). Total homocysteine level are found to be considerably higher in patients with chronic renal disease, than the moderately raised concentrations commonly found in patients with vascular disease. This may be the probable cause that contributes to the high incidence of vascular complications in patients with chronic renal failure (7). Furthermore, atherosclerosis is the most common pathological process that leads to (CVD). There has been an indication towards a significant correlation between hyperhomocystenemia and (CVD) and its complications such as heart attacks and strokes (1,7). It is believed that hyperhomocystenemia leads to endothelial cell damage, reduction in the flexibility of vessel deposition of plasma lipids in plaques, fibrosis and calcification of plaques (1,7,9). Hyperhomocystenemia may also lead to an enhancement of the adverse effects of risk factors like hypertension, smoking, lipid and lipoprotein metabolism, as well as promotion of the development of inflammation (7,9). It is also possible that enhanced arterial stiffness in hyperhomocystenemia might be attributed to homocysteine related LDL atherogenesis (10).

Methods:

The papers for the present review were identified by searching a number of electronic databases including; PubMed, Scopus, Scientific Information, and EMBASE during years 2004 to 2018 for the key word such as homocysteine , vitamin B12 & B6 , folic acid (vitamin B9) and cardiovascular diseases .

Discussion:

Several cross-sectional and case control studies have pointed towards a clear correlation between total serum homocysteine and the incidence of coronary and vascular disease (11,12). In addition, increased homocysteine level is found to be associated with atherosclerotic outcomes as well as an independent risk marker for (CVD) (7). Moreover, subgroup analyses in other studies showed that elevated homocysteine was associated with higher risk of coronary artery disease in patients with chronic renal dysfunction (5,7,12). In apparent contrast, however, another study indicated no risk reduction in homocysteine-lowering trials. These trials were mainly based on prescription of folic acid and were concluded that intake of high amounts of folic acid may be beneficial via the homocysteine lowering, but may also be harmful via destabilization the atherosclerotic plaque (13,14). Furthermore, B vitamins were shown to reduce homocysteine without improving endothelial dysfunction (1).

Apart from being part of the antioxidant defense system, some vitamins also play a role as enzyme cofactors (9). Vitamin B6, B12 and folic acid (vitamin B9) are essential cofactors in homocysteine-methionine metabolism. Therefore, low vitamin B availability (B6, B12 and folic acid) leads to impaired re-methylation of homocysteine to methionine and thus to homocysteine accumulation (9). It has been shown that increased homocysteine level was associated with atherosclerotic outcomes and risk of stroke in elderly individuals (1,11). However, lowering homocysteine level by B vitamin supplementation has been failed to

demonstrate beneficial effects in cardiovascular diseases and this has been proven to be true in many other research works (9,14-17).

Conclusion:

At present there is a controversy regarding the significance of homocysteine as a risk factor for CVD and stroke and whether patients should be screened for homocysteine routinely. Therefore, it is concluded uncertainty of whether or not folic acid means of homocysteine lowering forms of therapy will reduce the risk of CVD remains a main focus of future research work.

References:

1. Faeh D, Chioloro A, Paccaud F. Homocysteine as a risk factor for cardiovascular disease: should we (still) worry about it? *Swiss Med Wkly*. 2006; 136:745–56.
2. Schaffer A, Verdoia M, Casetti E, et al. Relationship between homocysteine and coronary artery disease. Results from a large prospective cohort study. *Thromb Res*. 2014; 134:288-93.
3. Baszczuk A, Kopczynski Z. Hyperhomocysteinemia in patients with cardiovascular disease. *Postepy Hig Med Dosw*. 2014; 68:579.
4. Guo H, Chi J, Wang P. Influence of folic acid on plasma homocysteine levels and arterial endothelial function in patients with unstable angina. *Indian J Med Res*. 2009; 129 (3):279-84.
5. Shenov V, Mehendale V, Prabhu K, Shetty R, Rao P. Correlation of serum homocysteine levels with the severity of coronary artery

disease. *Ind J Clin Biochem.* 2014; 29(3):339–44.

6. Curro M. Gugliandolo A. Gangemi C. et al. Toxic effects of mildly elevated homocysteine concentrations in neuronal like cells. *Neurochem Res.* 2014; 391:485-95.

7. Hankey GJ. Ekelboom JW. Homocysteine and vascular disease. *Lancet.* 1999; 354:407-13.

8. Palmieri EA. Fazio S. Lombardi G. Biondi B. Subclinical hypothyroidism and cardiovascular risk: a reason to treat? *Treat Endocrinol.* 2004;3 (4):233-44.

9. Mangge H. Becker K. Fuchs D. Gostner JM. Antioxidants, inflammation and cardiovascular disease. *World J Cardiol.* 2014 ;6(6):462–77.

10. Zhang S. Yong –Yi B. Luo LM. et al. Association between serum homocysteine and arterial stiffness in elderly: a community based study. *J Geriatr Cardiol.* 2014;11 :32-8

11. Okura T. Mlyoshi K. Irita J. et al. Hyperhomocysteinemia is one of the risk factors associated with cerebrovascular stiffness in hypertensive patient, especially elderly males. *Naturecom Sci Rep.* 2014;4: 5663.

12. Veeranna V. Zalawadiya SK. Niraj A. Pradhan J. Ference B. Burack RC. et al. Homocysteine and reclassification of cardiovascular disease risk. *J Am Coll Cardiol.* 2011; 58:1025–33.

13. Blom HJ . Y Smulders Y. Overview of homocysteine and folate metabolism. With special references to cardiovascular disease and neural tube defects. *J Inherit Metab Dis.* 2011; 34:75-81.

14. Clarke R. Halsey J. Lewington S. et al. Effects of lowering homocysteine levels with B vitamins on cardiovascular disease, cancer,

and cause-specific mortality. *Arch Intern Med.* 2010; 170(18).

15. Chysant SG. Chysant GS. The current status of homocysteine as a risk factor for cardiovascular disease: a mini review. *Expert Rev Cardiovasc Ther.* 2018; 16(80):559-565.

16. Martí-Carvajal AJ. Sola I. Lathyris D. Dayer M. Homocysteine-lowering interventions for preventing cardiovascular events. *Cochrane Database Syst Rev.* 2017; Aug 17; 8:CD006612.

17. Djuric D. Jakovljevic V. Zivkovic V. Srejovic Homocysteine and homocysteine-related compounds: an overview of the roles in the pathology of the cardiovascular and nervous systems. *Can J Physiol Pharmacol.* 2018 ;96(10):991-1003.