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Review Article

# Homocysteine and venous thromboembolism—Is there any link?

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ABSTRACT

Homocysteine is an intermediary product of methionine metabolism. The level of homocysteine is controlled by two pathways—remethylation and transsulphuration. Elevated homocysteine level may result from deficiency or impaired function of enzymes and cofactors in these pathways. Homocystinuria is a rare genetic disease with extreme hyperhomocysteinemia and is associated with the occurrence of arterial and venous thrombotic events at young age. Therefore, homocysteine has been considered a risk factor for vascular diseases.

Plasma homocysteine level is influenced by many factors, genetic as well as environmental. Mild hyperhomocysteinemia is quite common. The role of homocysteine in venous thrombosis has been studied less extensively than its role in arterial diseases and nowadays it seems quite controversial. In vitro, it is possible to demonstrate multiple prothrombotic action of homocysteine. However, the results of epidemiologic studies are not so clear. Most of them found an association of hyperhomocysteinemia with venous thromboembolism (VTE) but the association was quite weak and moreover, it was much weaker in prospective than in retrospective studies. It is not quite clear whether elevated homocysteine level is the cause of thromboembolic event or the consequence of it. It is also possible that hyperhomocysteinemia plays a role in the pathogenesis of VTE only as an additional risk factor in the presence of other thrombophilic disorders.

However, some data confirm hyperhomocysteinemia as a risk factor for recurrent VTE. Some smaller studies have also found association of hyperhomocysteinemia with venous thrombosis at unusual sites.

Homocysteine level can be lowered by vitamin supplementation, especially with folic acid and vitamin B12. So far, the benefit of lowering homocysteine level in primary and secondary VTE prevention has not been clearly proven.

Currently, there is not enough evidence to support the necessity of testing homocysteine level in VTE patients, neither is sufficient evidence of the benefit of vitamin supplementation in mild or moderate hyperhomocysteinemia. Therefore, such testing and supplementation should be performed only in selected cases.



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## 1. Introduction

Venous thromboembolism (VTE) is a multifactorial disease, with many inherited and acquired risk factors and their interaction playing a role in the etiopathogenesis. One of important risk factors is thrombophilia. It is defined as a tendency to form thrombi in veins or arteries but the term is used more frequently in association with venous thrombosis. Hyperhomocysteinemia is often included in the list of thrombophilic disorders [1]. However, there is much disagreement concerning the importance of homocysteine level testing and potential management of hyperhomocysteinemia in VTE patients.

## 2. Homocysteine metabolism

Homocysteine, a sulfur-containing amino acid, is an intermediary product of methionine metabolism (methionine is an essential amino acid, abundant in animal proteins). Homocysteine is formed intracellularly by demethylation of dietary methionine. Plasma homocysteine level is controlled by two metabolic pathways – remethylation to methionine and transsulphuration to cysteine – Fig. 1. Remethylation is the predominant metabolic pathway which is important for the regulation of fasting level while transsulphuration pathway regulates elevated homocysteine levels, e.g. postprandially or after methionine load.

Remethylation has two alternative pathways in humans.

(a) The predominant one is vitamin B12 (cobalamin) dependent, it occurs in all tissues including vascular endothelium. This pathway is connected with folate cycle.
(b) The additional remethylation pathway is less important, it is bound to hepatocytes.

In transsulpuration pathway, vitamin B6 is required as a cofactor [2–4].

## 3. Hyperhomocysteinemia and its causes

The determinants of homocysteine level include genetic and physiologic factors, life style, nutrition, various diseases and medication. The level increases with age (from childhood to old age approximately doubles), after adolescence it is slightly higher in men, decreases in pregnancy. Homocysteinemia also depends on renal function and creatinine synthesis. Healthy life style and sufficient vitamin consumption in the diet or in the form of vitamin supplements (especially those containing folic acid) lead to reduction of homocysteine level, as well as folate-fortified diet (e.g., folate fortification of grain products, implemented in the US) [5]. However, mild hyperhomocysteinemia is found in individuals with alternative diet, vegetarians and vegans, respectively, as a consequence of vitamin B12 deficiency [6]. There are also ethnic and regional differences in homocysteine level. Therefore, the reference limits for homocysteinemia should not be strictly defined but should be interpreted with respect to the mentioned determinants. The value of 15 μmol/L is considered as the upper reference limit for the age of 15–65 years; 20 μmol/L for the age above 65 years; and 10 μmol/L for children and pregnant women while these limits should be

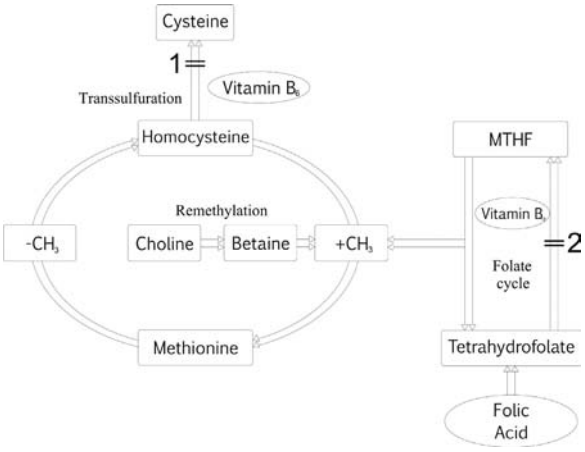


**Fig. 1 – Scheme of homocysteine metabolism—according to Key NS, Mc Glennen RC [4]. 1—catalyzed by cystathionine beta-synthase (CBS). 2—catalyzed by methylentetrahydrofolate reductase (MTHFR). In the remethylation pathway, betaine (trimethylglycine) or N-5-methyltetrahydrofolate. (MTHF) serve as methyl (CH3) group donors. Folic acid is a source of tetrahydrofolate; vitamin B12 is a cofactor in the folate cycle. In the transsulphuration pathway, vitamin B6 works as a cofactor.**