Letter to the Editor

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Thrombosis and Risk Factors: A Comment

Tromboz ve Risk Faktörleri: Bir Yorum

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To the Editor,

We read with great interest the recent publication by Akar related to thrombosis and risk factors, in which he reached in conclusion that in case of need only homocysteine (Hcy) levels should be routinely analyzed and not the 5, 10-methylenetetrahydrofolate reductase (MTHFR) 677 T polymorphism [1]. The methylation of Hcy to methionine is catalyzed by the MTHFR enzyme. As far as is known, genetic deficiency of MTHFR is one cause leading to increased plasma Hcy levels [2]. But, it should not be forgotten that Hcy rises in many acquired and genetic conditions (Table) [3]. There are three main indications for determining plasma total Hcy: (a) to diagnose homocystinuria; (b) to identify individuals with or at risk of developing cobalamin or folate deficiency; (c) to assess total Hcy as a risk factor for cardiovascular and other disorders [4]. There is an involved question in this point: Is increased plasma total Hcy level related to both venous and arterial occlusive disease? And, if is it true, are polymorphism and mutation of MTHFR directly playing a role to augment the level of Hcy for cardiovascular disease (CVD)? As reviewed elsewhere, moderately increased plasma Hcy is associated with venous and arterial occlusion [5]. Moreover, as it is known, the presence of MTHFR 677C→T polymorphism is a strong risk factor for increased plasma Hcy level but not for CVD [4]. In a metaanalysis including 11.162 CVD cases and 12.758 controls, with high Hcy levels in a state of low folate levels, the TT genotype was associated with a 16% increase in coronary heart disease risk [6]. Concordantly, previous studies had shown that the MTHFR 677C→T polymorphism is only associated with high Hcy levels or increased CVD risk in a setting of low folate status [6]. Hence, at higher dietary intakes of folate, the effect of the MTHFR 677C→T genotype has no adverse effect on plasma Hcy levels or on subsequent risk of CVD. The results support the hypothesis that impaired folate metabolism, resulting in high Hcy concentrations, plays a causal role in the occurrence of CVD. In view of cost effectiveness, do not investigate routinely MTHFR 677C→T polymorphism in the general or CVD population seems to be reasonable, but the other mutations of MTHFR could be still influential for high plasma Hcy levels.

In conclusion, even if some researchers contradict, provided that folate status is adequate, there is little clinical value of screening for MTHFR 677C→T genotype in the general population for prediction of venous and arterial occlusive disorders and high Hcy levels of course.

Conflict of Interest Statement

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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Table 1: Causes of Elevated Homocysteine Levels

CAUSES	EFFECT
Vitamin deficiency	
Cobalamin deficiency	Mild to severe
Folate deficiency	Mild to severe
Disease	
Renal failure	Mild to moderate
Posttransplantation	Mild to moderate
Hypothyroidism	Mild
Acute lymphocytic leukemia	Mild
Drugs and toxins	
Alcohol abuse	Mild to severe
Methotrexate and other antifols	Mild to severe
Cyclosporine A	Mild
Nitrous oxide toxicity	Mild to severe
Genetic disorders	
Cystathionine β-synthase deficiency	
Homozygous state	Severe
Heterozygous state	Mild or none
Hereditary disorders of cobalamin	
Metabolism, transport, or absorption	Mild to severe
Hereditary disorders of folate	
Metabolism, transport, or absorption	Mild to severe
Methylene tetrahydrofolate reductase polymorphisms (homozygous C677T or A1298C mutations)	Mild or none
Physiologic and lifestyle factors	
Male sex	Mild
Aging	Mild
Coffee drinking	Mild
Smoking	Mild

Modified from Carmel R. Megaloblastic Anemias: Disorders of Impaired DNA Synthesis. In: Greer JP, Foerster J, Rodgers GM, Paraskevas F, Glader B, Arber DA, Means RT Jr, eds. Wintrobe's Clinical Hematology. 12th ed. Philadelphia: Lippincott Williams & Wilkins, 2009: 1143-72.

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Reply

Thrombosis and Risk Factors

I read the comment of Toprak et al. on my letter to the Editor appeared in a recent issue of the journal with great interest [1]. They pointed a missing point in my letter and then focused on the effect of folate metabolism on homocysteine and metihelenetetrahydrofolate gene polymorphism at 677 C to T extensively [1]

I would like to express my thanks to Toprak et al. giving a chance to explain my view on this matter once more.

As it is well known that there is a continuing debate on homocysteine metabolism, MTHFR SNP's and folate metabolism and there are several published reviews on this subject not reaching to a conclusion.

Recently we reported that MTHFR 677 T has an influence on Hcy levels in Turkish population. But also we found another possible MTHFR gene haplotype, which does not have an effect on Hcy levels [2].

Furthermore, there are also rare novel SNPs published within the MTHFR 677 region with an allele frequency of 1 in 3000-4000 sample, including MTHFR 678 C-A (Ala222Ala) in Turkish population [3-5] which may lead to erroneous technical reporting.

Since our first publication on homocysteine related gene polymorphisms in Turkish population in 1998 [6], and the others following the first paper, I reached to a conclusion that without determining homocysteine levels, analyzing MTHFR 677C-T solely at the DNA level is unnecessary, not cost effective and does not have any clinical value especially in Turkish population.

So, only homocysteine levels should be routinely analyzed and not the MTHFR 677 T SNP alone. If any cause of high homocysteine levels could not be found, then MTHFR 677 T analysis can be performed.

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