Hyperhomocysteinemia and liver steatosis: Modification of "the chicken or the egg?" dilemma to the liver

Hiperhomosisteinemi ve karaciğer yağlanması: Eski ikilemin "yumurta mı tavuk mu?" karaciğere uygulanması

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INTRODUCTION

Homocysteine (Hcy) is a sulfur-containing amino acid that is formed as an intermediary in methionine metabolism (1). Extensive evidence shows that elevated plasma Hcy concentration, a reflection of impaired cellular metabolism, can be considered as an independent risk factor for atherothrombotic vascular disease (2). This condition has been observed in 20% to 30% of patients with premature arteriosclerosis and in 21% of the general population above a certain age (3,4). Three enzymes utilize Hcy as a substrate: methionine synthase (MS) and betaine-homocysteine methyltransferase (BHMT), which convert Hcy back to methionine, and cystathionine β-synthase (CBS), the first enzyme in the transsulfuration pathway (1) (Figure 1). The distribution of Hcy among them depends on metabolic conditions: when methionine is relatively deficient, remethylation of Hcy is favored, whereas in situations of methionine excess, the transsulfuration pathway prevails (1,2). *S*-Adenosylmethionine (AdoMet), the first metabolite of methionine, modulates the flow of Hcy through these metabolic pathways; increased levels of AdoMet activate CBS and inhibit the activity of MS and BHMT (1,5). Impairment of Hcy remethylation or transsulfuration leads to hyperhomocysteinemia. Such situations may develop as a consequence of genetic defects in the enzymes MS, CBS or methylenetetrahydrofolate reductase (MTHFR) (the enzyme that synthesizes the MS cosubstrate 5-methyltetrahydrofolate) (2,3). Nutritional deficiencies in vitamin B_6, the cofactor of CBS, or folates and vitamin B_{12}, cosubstrate and cofactor of MS, can also lead, along with impaired renal function, to hyperhomocysteinemia (2-4).

The liver plays a central role in the synthesis and metabolism of Hcy, given the fact that the majority of dietary methionine is metabolized in this organ, where ≈85% of the whole body capacity for transmethylation resides (1,5). Accordingly, the liver displays a specific pattern of expression of genes involved in methionine and Hcy metabolism. There are two genes coding for methionine adenosyltransferase (MAT), the enzyme that converts methionine into AdoMet: one (MAT1A) is expressed exclusively in the liver, and a second gene (MAT2A) is expressed in all tissues (5). BHMT and CBS expression is confined mainly to the liver, whereas MS is widely expressed (1). Thus, it is conceivable that in situations of liver damage, alterations in Hcy may occur. In fact, hyperhomocysteinemia has been reported in chronic alcoholics and in patients with alcoholic cirrhosis, as well as in experimental models of liver damage (6-10). Although there is extensive evidence about the above-mentioned genetic and nutritional determinants for hyperhomocysteinemia, knowledge of the molecular basis of the alteration in Hcy metabolism in liver injury is still limited.

The pathological mechanisms by which elevated Hcy promotes atherothrombotic vascular diseases are not completely known (2,3). Endothelial injury, which can lead to altered nitric oxide (NO) production and impaired platelet modulating activity, has been demonstrated (11-13). In addition, Hcy promotes DNA synthesis and collagen production in vascular smooth muscle cells (VSMCs), cholesterol production by hepatic cells and lymphocyte DNA hypomethylation (14-17). These observations suggest a multifactorial mechanism of action for Hcy that may take place not only at the vascular level but on a variety of cellular backgrounds.

Impaired liver function leads altered the metabolism of methionine and homocysteine, sulfuric acid involved in methionine metabolism, belongs to the group of intra-

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Geliş Tarihi: 16.07.2011 • **Kabul Tarihi:** 08.12.2011

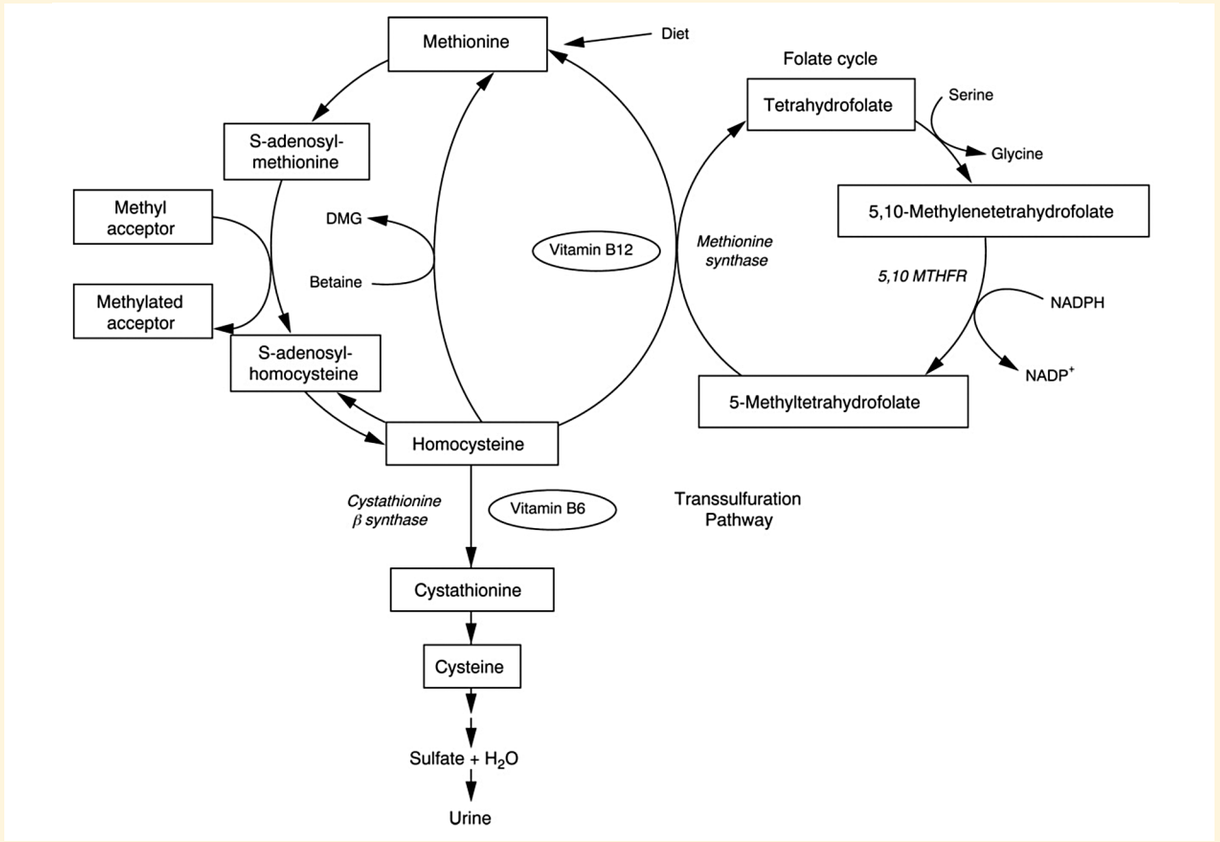

Figure 1. The transsulfuration and re-methylation pathway of Homocysteine. (MTHFR: methylenetetrahydrofolate reductase, MS: methionine synthase, CS: cystathionine ß-synthase, CL: cystathionine γ liase, BHMT: betaine-homocysteine methyltransferase, MT: methyltransferase, SA-Me: *S*-Adenosylmethionine, SAH: *S*-Adenosylhomocysteine, THF: tetrahydrofolate, DMG: Dimethyl glisin, GSH: glutation) (1).

cellular thiols. The observations of Garcia-Tevijano et al. (18) suggested that impaired liver function could be a novel determinant in the development of hyperhomocysteinemia and that there was a role for elevated Hcy levels in the development of liver fibrosis (18).

The hyperhomocysteinemia-induced steatosis model may explain why only some, but not all, hepatitis C virus (HCV)-infected patients develop steatosis, and why only a minority of patients, e.g. those with higher Hcy levels, accumulate a greater amount of fat in the liver. Hyperhomocysteinemia may result from a MTHFR C677T polymorphism (19). In that study, it was shown that the polymorphism of the MTHFR gene at position 677, which has a prevalence of 12%-15% for the TT genotype in the general population, was associated with both hyperhomocysteinemia and a greater degree of steatosis in chronic hepatitis C patients. It was estimated that the relative risk of developing more severe steatosis was six-fold higher for patients with the CT genotype and 20-fold higher for those with the TT genotype (19).

Hyperhomocysteinemia is frequent in the Caucasian population (more than 15%) and its role in vascular pathology has been clearly established (20). In hepatology, experimental data in transgenic mice deficient in Hcy metabolism enzymes have shown the presence of severe liver steatosis with occasional steatohepatitis (21). In humans, many studies have found a correlation between Hcy and steatosis or even non-alcoholic steatohepatitis (NASH) (22,23). Some authors have suggested a discriminating threshold to differentiate simple steatosis from NASH. In chronic hepatitis C, preliminary data have shown that hyperhomocysteinemia is an independent risk factor for steatosis or even fibrosis (19). The physiopathological mechanism has now begun to be better understood. On one hand, there is a strong correlation between Hcy and insulin resistance whatever its etiology (24-26). On the other hand, Hcy has a direct effect on the liver, resulting in over-expression of SREBP-1 and favoring steatosis (27). It stimulates proinflammatory cytokine secretion such as nuclear factor (NF) kappa B, in-

creasing the risk of NASH (28,29). Finally, Hcy could increase the risk of fibrosis by stimulating tissue inhibitor of metalloproteinases (TIMP)-1 (30). Moreover, HCV induces hypomethylation of STAT 1 and could decrease the antiviral activity of interferon (31). Results from in vitro studies have shown that the normalization of STAT 1 methylation by bringing betaine and S-AdoMet (which belongs to the Hcy cycle) restores the antiviral activity of interferon. These data should be confirmed to evaluate the importance of Hcy dosage in the diagnosis of NASH. Finally, treatment of hyperhomocysteinemia could have favorable consequences in steatopathies and HCV infection. Betaine has been shown to be the safest, least expensive and most effective in attenuating ethanol-induced liver injury (32). Betaine, by virtue of aiding in the remethylation of Hcy, removes both toxic metabolites (Hcy and S-adenosylhomocysteine), restores S-AdoMet level, and reverses steatosis, apoptosis and damaged proteins accumulation.

Based on the results of these data, the question of which one causes the other in the etiological link between liver steatosis and hyperhomocysteinemia calls to mind the age-old dilemma "which came first, the chicken or the egg?".

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