



## METHYLENETETRAHYDROFOLATE REDUCTASE GENE POLYMORPHISMS IN CARDIOMETABOLIC DISEASES

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*Although there is growing evidence that C677T polymorphism of the methylenetetrahydrofolate reductase (MTHFR) gene could be considered a risk factor for cardiometabolic diseases associated with elevated levels of homocysteine, the clinical impact and efficiency of therapy remain a matter of debate. The role of A1298C polymorphism of MTHFR in these diseases is still not clearly defined. Most of the studies have shown the correlations between homozygosity for the T677 allele of the MTHFR gene and homocysteine-related cardiometabolic diseases including the metabolic syndrome, diabetes mellitus, ischemic cardiopathy, stroke, and venous thromboembolism. The proposed pathological mechanism of hyperhomocysteinemia involves prothrombotic effects and endothelial dysfunction. Therapy with vitamins B may decrease the homocysteine level in cases with C677T polymorphism whereas the reducing effect on cardiovascular events is not significant. **Biomed Rev 2008; 19: 49-52.***

**Key words:** homocysteinemia, methylenetetrahydrofolate reductase polymorphisms, cardiometabolic diseases

### INTRODUCTION

The methylenetetrahydrofolate reductase (MTHFR) gene has been mapped to chromosomal region 1p36.3. MTHFR C677T polymorphism results from a C to T transition at the nucleotide position 677 in DNA, leading to the substitution of alanine (C) to valine (T) residue at position 226 in the protein; this results in a decreased basal activity of the enzyme by 50% (1). Numerous studies have shown the association

between homozygous genotype MTHFR 677TT and hyperhomocysteinemia. Due to its multiple roles in different cellular pathways, the amino acid homocysteine is a unique candidate for the study of different cardiometabolic and age-related pathological conditions, namely atherosclerosis, obesity, diabetes mellitus and the metabolic syndrome (1,2) as well as dementia and epilepsy (3,4). The role of homocysteine in

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predicting risk for atherothrombotic vascular disease has been evaluated in several observational studies in a large number of patients. Hence hyperhomocysteinemia is considered the "cholesterol of nineties" due to the impact on early atherosclerosis; it is established from a large body of studies that even mildly hyperhomocysteinemia is an independent risk factor for cardiovascular diseases (2).

MTHFR represents one of the key enzymes in homocysteine metabolism, involved in remethylation pathway: the conversion of homocysteine to methionine, using the methyl donor provided by the reduction of 5,10-methylene-tetrahydrofolate to 5-methyl-tetrahydrofolate by this enzyme. The intracellular concentration of homocysteine is maintained at low level by remethylation (requiring folate and B12 vitamin as co-factors) and transsulfuration reactions (requiring B6 vitamin as co-factor). The remethylation pathway contributes predominantly to maintenance of the normal fasting homocysteine level whereas the transsulfuration maintains especially the post-prandial concentration (5).

The interrelations between homocysteine, MTHFR polymorphisms, vitamins B and folate deficiencies in cardiometabolic diseases are complex. MTHFR polymorphisms result in hyperhomocysteinemia especially when the folate level is low. A recent American study, the third National Health and Nutrition Examination Survey (NHANES III), showed a significant association between low serum folate and increased homocysteine levels in cases with MTHFR C677T genotype as well as the significant decreasing of homocysteinemia concentration by moderate daily folic acid intake. The authors showed the reduction of the impact of MTHFR 677C->T on homocysteine levels by moderate administration of folic acid (6). However, some authors showed an independent effect of MTHFR polymorphisms in atherothrombosis and a weak correlation between folate level and homocysteinemia (7). A recent French study showed that 677TT genotype is associated with elevated homocysteine plasma concentration in men, but not in women (5). Some authors showed that not only homozygosity for MTHFR C677T, but also the compound heterozygosity for C677T/A1298C may result in mild hyperhomocysteinemia (8).

### **MTHFR IN METABOLIC SYNDROME**

The metabolic syndrome is a cluster of factors accumulated in one individual, diagnosed in the presence of at least 3 of the following anthropometric and cardiometabolic risks: waist

circumference more than 102 cm in men and more than 88 cm in women, blood pressure  $\geq$  130/85, triglyceride level more than 150 mg/dl., HDL-cholesterol  $\leq$  40 in men,  $\leq$  50 in women, fasting glucose  $\geq$  110 mg/dl. (according to NCEP-ATP III guidelines) (9). A recent study showed that patients with homozygous MTHFR genotype for T allele are at higher risk for insulin resistance with increasing central adiposity, which is independent of age, gender, body mass index, or metabolic syndrome diagnosis (10).

Several studies showed an association between hypertension, hyperhomocysteinemia and C677T MTHFR polymorphism. It was suggested that this genetic defect could be a factor explaining the increased cardiovascular risk for hypertensive patients by elevated homocysteinemia. However, a direct association between C677T MTHFR polymorphism and hypertension could not be confirmed, indicating that other factors modulate the association between hyperhomocysteinemia and essential hypertension (11).

### **MTHFR IN DIABETES MELLITUS**

During the last decades, several studies have shown that there may be a link between elevated concentrations of plasma homocysteine and insulin resistance (12). High levels of homocysteinemia and a positive association with microalbuminuria were identified in patients with type 2 diabetes mellitus (13). Studies in rats showed that insulin resistance was associated with hyperhomocysteinemia and changes involving the enzymes of homocysteine metabolism; a stimulation of insulin-induced elimination of methionine was proposed as a possible explanation of this association (14). Other study failed to demonstrate a significant correlation between increased levels of homocysteine and type 1 diabetes mellitus; no significant differences were found in homocysteinemia related to the metabolic control of diabetes (based on glycohemoglobin values) (15). Some authors showed insulin as an independent and significant factor for the variance of homocysteine level, especially in young obese patients (16).

A recent study aimed to determine whether MTHFR C677T and methionine synthase reductase MTRR polymorphisms could be considered risk factors for early microvascular disease in adolescents with type 1 diabetes; the authors concluded that survival without retinopathy was reduced in cases with combined MTHFR 677TT and MTRR 66GG genotype. They also showed that homozygosity for MTHFR 677 TT was related to earlier onset of retinopathy (17).

### MTHFR IN OBESITY

Obesity as well as overweight was associated with hyperhomocysteinemia; some studies showed a significant association between C677T polymorphism and obesity/overweight. However, a study published in 2008 (18), based on 3 longitudinal studies, The British Women's Heart and Health Study, the Avon Longitudinal Study of Parents and Children and the Copenhagen City Heart Study, failed to demonstrate a significant association between this genetic defect and obesity and showed that the initial positive correlation with homozygosity for MTHFR 677TT was a chance finding (19).

### MTHFR IN CARDIOVASCULAR DISEASES

Hyperhomocysteinemia is considered an independent cardiovascular risk factor; several studies showed that MTHFR C677T genotype is positively associated with arterial and venous thrombotic disease (20,21). On the other hand, MTHFR C677T polymorphism was not significantly associated with cardiovascular diseases (22,23) or venous thrombosis (24).

The second common mutation of MTHFR gene was described in 1998 and consists of an A to C transition at nucleotide 1298 (A1298C) leading to a glutamate to alanine substitution in the MTHFR protein with a decrease in MTHFR activity, especially in homozygous.

### THERAPY WITH B VITAMINS

There are controversies regarding the benefit of vitamins B and folate administration in patients with MTHFR polymorphisms and hyperhomocysteinemia; most of the studies show a decrease in homocysteine levels but not in cardiovascular events (2,7,25,26). Recently was shown that routine screening and therapy of hyperhomocysteinemia with folic acid and vitamins B is not recommended; furthermore, a causal relationship between increased levels of homocysteine and cardiovascular diseases was not confirmed by randomised controlled trials (27,28). A future direction regarding folate therapy could be based on the understanding of (i) caveolae/caveosome-mediated potocytosis of folate (29) and (ii) nitric oxide metabolism (30).

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