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The Relationship between Methylenetetrahydrofolate Reductase C677T Gene Polymorphism and Diabetic Nephropathy in Croatian Type 2 Diabetic Patients

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ABSTRACT

Methylenetetrahydrofolate reductase (MTHFR) polymorphism has been shown to be associated with the development of diabetic nephropathy in many ethnic groups. In this study, we examined the correlation between MTHFR C677T polymorphism and microalbuminuria in patients with diabetes mellitus type 2 in Croatian patients. 85 patients with diabetes mellitus type 2 were recruited. Patients were classified into two groups – with and without diabetic nephropathy according to urinary albumin excretion rate in urine collected during 24 hours. The C677T genotype was determined by real-time PCR analysis. The genotype frequencies were CC 36,5%, CT 42,3% and TT 21,2% in diabetic patients without nephropathy versus CC 39,4%, CT 45,4% and TT 15,2% in those with nephropathy. There was no statistically significant difference in allele distribution between patients with nephropathy and those without ($p=0,788$). Our study did not show a correlation between mutations in the MTHFR gene and diabetic nephropathy in Croatian patients. Diabetic nephropathy is influenced by multiple risk factors which can modify the importance of MTHFR polymorphism in its development.

Key words: allele distribution, methylenetetrahydrofolate reductase mutations, type 2 diabetes mellitus, diabetic nephropathy, genetic polymorphism, Croatia

Introduction

Diabetes mellitus is the most frequent chronic metabolic disease characterised by complications on blood vessels, nerves and basal membranes of different tissues¹. The number of people with diabetes is constantly increasing because of many reasons: aging of the population, population growth, urbanization which includes sedentary lifestyle and lack of physical activity and significant increase of prevalence of obesity². It is assumed that the number of the diseased will increase from about 285 million adults in 2010 to 439 million adults in 2030³. The number of people with diabetes in Croatia is also in-

creasing, and diabetes is one of the leading causes of death in Croatia^{4,5}.

Diabetic nephropathy is a serious complication of diabetes mellitus and the leading cause of chronic renal disease and end stage renal failure^{6,7}. The etiology of diabetic nephropathy is multifactorial and involves not only chronic hyperglycaemia and arterial hypertension, but also environmental factors and genetic susceptibility.

5,10-methylenetetrahydrofolate reductase (MTHFR) is one of the key enzymes in the metabolism of homo-

cysteine, where it catalyses homocysteine remethylation to methionine. The thermolabile form of this enzyme was discovered two decades ago⁸. The autosomal recessive point mutation C677T in the MTHFR gene leads to a valine-to-alanine substitution at amino acid 226. The result of this mutation is decreased activity and increased thermolability of this enzyme⁹. There are three possible genotypes in the case of the MTHFR C677T polymorphism. The CC genotype is referred to as »wild type«, the CT genotype is described as »heterozygous« and the TT genotype as the »homozygous variant«. Many studies showed that patients who are homozygous for C677T MTHFR mutation are predisposed to elevated homocysteine levels in plasma compared with heterozygous or wild type¹⁰.

The »homocysteine hypothesis of arteriosclerosis« was first proposed in 1969 by McCully¹¹. Since then, in addition to established risk factors, epidemiologic data and many studies showed that elevated plasma homocysteine concentration is an independent risk factor for vascular disease^{12–20}. Recent in vitro studies indicate that homocysteine enhances the expression of VEGF (vascular endothelial growth factor), which is a pro-angiogenic factor with a known role in the pathogenesis of diabetic nephropathy^{21,22}. Based on this evidence, it can be considered that the polymorphism of C677T gene for MTHFR as basis for hyperhomocystinaemia could be involved in the development of diabetic nephropathy.

Many authors came to the conclusion that genetic polymorphism of the MTHFR gene can have different influence on homocysteine metabolism and on the risk of diabetic nephropathy in different ethnic groups. It was assumed that homocysteine metabolism could be modified by genetic factors which can vary among different populations^{7,21,24–26}. On the other hand, some studies did not prove such connection^{23,27}.

The aim of this study is to determine the correlation between MTHFR C677T polymorphism and microalbuminuria as an early sign of diabetic nephropathy in patients with diabetes mellitus type 2 in Croatian patients.

Subjects and Methods

Subjects

The subjects included in the study were men and women who were ≥ 18 years old and hospitalized in the Medical Department during 2009. All included patients were diagnosed with diabetes mellitus type 2 based on 1999 WHO and EASD & ESC classification and guidelines^{28,29}. All of the patients on haemodialysis were excluded from the study in order to exclude the influence of renal failure on homocysteine metabolism. The Hospital Ethics Committee approved the study, and the informed consent was obtained from all included participants. The general data about all included subjects were recorded, including age, gender, body weight, blood pressure. The venous blood samples were collected for measurement of glycosylated haemoglobin (HbA1c) and plasma venous

glucose level, and additional blood samples for MTHFR C677T genotype analysis and analysis of total homocysteine level were taken. Patients were classified into two groups- with diabetic nephropathy or without it according to urinary albumin excretion rate in urine collected during 24 hours. Diabetic nephropathy was defined as micro- or macroalbuminuria (≥ 30 mg/24 h), whereas normal albumin excretion rate was defined as < 30 mg/24 h^{30,31}.

Determination of MTHFR genotype

The blood samples were taken from fasting subjects and placed into vacutainer tubes containing EDTA. Leukocyte DNA was isolated from whole-blood samples (QIAamp DNA Blood Mini Kit). The C677T mutation in the MTHFR gene was analyzed by polymerase chain reaction (real-time PCR) of genomic DNA using the following primer pairs: MTHFR-F: 5'-CCT CAA AGA AAA GCT GCG TGA-3' and MTHFR-R: 5'-AAG CAC TTG AAG GAG AAG GTG TC-3'. The analysis was conducted on »Taqman 7300 Real Time PCR System«, Applied Biosystems. According to the increase of the signal of the defined essay, the SDS 1.3.1. Software 7300 Real Time PCR System defined whether the samples were homozygous for the wild type (C/C), heterozygous (C/T) or homozygous for the mutation (T/T).

Homocysteine level measurement

The blood samples were taken into vacutainer tubes containing EDTA during standard procedure. The homocysteine level was determined by fluorescence polarization immunoassay technology (FPIA) on AxSYM homocysteine machine, using AxSYM Homocysteine Reagent Pack according to manufacturer's instructions (Abbot). According to the manufacturer's package insert, hyperhomocystinaemia was defined as the homocysteine level higher than $16.00 \mu\text{mol/L}$ for men, and higher than $20.44 \mu\text{mol/L}$ for women³².

Statistical analysis

The qualitative parameters are presented as absolute numbers and percentages. The quantitative data are presented as median and range. The differences between qualitative parameters were tested by χ^2 test, using Yates correction in 2x2 tables. The differences in quantitative data between two groups were tested by non-parametric Mann-Whitney U test.

The statistical analysis was performed using Statistica 6.0 software. In all tests, statistical significance was taken at nominal $p < 0.05$ for all comparisons.

Results

Eighty-five patients participated in the study, thereof 38 men (44.7%) and 47 women (55.3%). Out of 85 studied patients, 33 (38.8 %) had evidence of microalbuminuria (Table 1). The differences between qualitative parameters were tested by χ^2 test, using Yates correction in 2x2

tables. The differences in quantitative data between two groups were tested by non-parametric Mann-Whitney U test. There were no differences between patients with and without diabetic nephropathy in terms of gender, body weight, systolic blood pressure, plasma glucose level and glycosylated haemoglobin. Differences between those with and without nephropathy were noted for age and homocysteine level.

In the analyzed group, 32 patients (37.65%) had the C/C allele, whereas 37 (43.53%) were heterozygous (C/T) and 16 (18.82%) were homozygous for the C677T mutation (T/T). There was no statistically significant difference in allele distribution between patients with nephropathy and those without (Table 2). Because of the dependency of homocysteine level on the patient's gender, the statistical analysis of the correlation between the MTHFR

C677T mutation and the homocysteine level was performed separately for males and for females^{32–36}.

There was no statistically significant difference in the homocysteine level considering the MTHFR genotype (Table 3). In the group of males it is only noted that the homocysteine level was somewhat higher in the group of homozygotes (T/T), and the lowest in the group »wild type« (C/C). This difference is notable, but not statistically significant.

Discussion and Conclusion

In this study, we analyzed the correlation of MTHFR C677T gene polymorphism with diabetic nephropathy in the population. MTHFR genotype and allele frequencies

TABLE 1
CLINICAL CHARACTERISTICS OF PATIENTS CLASSIFIED INTO TWO GROUPS – WITH DIABETIC NEPHROPATHY AND WITHOUT IT

| | AER | | p value |
|---------------------------------|------------------|------------------|---------|
| | <30 mg/24h, N=52 | ≥30 mg/24h, N=33 | |
| Gender | | | |
| – male | 22 (42.3%) | 16 (48.5%) | 0.738 |
| – female | 30 (57.7%) | 17 (51.5%) | |
| Age (years) | 65 (41–88) | 71 (39–88) | 0.022 |
| Body weight (kg) | 80 (52–157) | 80 (65–150) | 0.533 |
| Blood pressure-systolic (mm Hg) | 135 (90–220) | 140 (110–170) | 0.239 |
| tlparHomocysteine (μmol/L) | 12.5 (6.4–25.3) | 15.2 (4.4–27.7) | 0.023 |
| Glucose level (mmol/L) | 8.8 (4.3–19.8) | 9.6 (3.8–24.3) | 0.334 |
| Glycosylated haemoglobin (%) | 8.0 (6.1–12.2) | 7.9 (6.1–14.7) | 0.821 |

AER – albumin excretion rate

TABLE 2
METHYLENETETRAHYDROFOLATE REDUCTASE (MTHFR) C677T GENOTYPES (NUMBER OF SUBJECTS AND PERCENTAGES) IN PATIENTS WITH AND WITHOUT DIABETIC NEPHROPATHY

| MTHFR C677T genotype | Albumin excretion rate | | p value |
|----------------------|------------------------|------------------|---------|
| | <30 mg/24h, N=52 | ≥30 mg/24h, N=33 | |
| Homozygous (T/T) | 11 (21.2%) | 5 (15.2%) | 0.788 |
| Heterozygous (C/T) | 22 (42.3%) | 15 (45.4%) | 0.788 |
| »Wild type« (C/C) | 19 (36.5%) | 13 (39.4%) | 0.788 |

MTHFR – methylenetetrahydrofolate reductase

TABLE 3
THE CORRELATION BETWEEN METHYLENETETRAHYDROFOLATE REDUCTASE (MTHFR) C677T MUTATIONS AND THE HOMOCYSTEINE LEVEL

| Homocysteine level (μmol/L) in: | MTHFR | | | Mann-Whitney U test | |
|---------------------------------|-----------------|-----------------|-----------------|---------------------|-------------|
| | T/T | C/T | C/C | T/T vs. C/C | C/T vs. C/C |
| All patients | 13.7 (7.9–25.3) | 13.1 (6.4–25.1) | 13.4 (4.4–27.7) | p=0.6777 | p=0.937 |
| Male | 14.9 (9.5–25.3) | 13.1 (6.4–25.1) | 10.1 (4.4–27.7) | p=0.0829 | p=0.137 |
| Female | 13.1 (7.9–17.3) | 13.4 (7.4–23.0) | 15.2 (8.0–21.6) | p=0.3798 | p=0.535 |

MTHFR – methylenetetrahydrofolate reductase

were not different between type 2 diabetic patients with and without nephropathy. This finding concurs with that of Eroglu et al. who reported that the MTHFR gene polymorphism is not associated with the development of diabetic nephropathy in Turkish type 2 diabetic patients³⁷. Similar results were obtained in Japanese population^{23,38}.

Unlike the above examples, many published research papers pointed to the relationship between the MTHFR gene polymorphism and the development of diabetic nephropathy. The results of the research on Tunisian population clearly showed that homozygosity for C677T and hyperhomocysteinemia were associated with diabetic nephropathy⁷. These findings are in agreement with observations in the Chinese population according to the research of Sun and associates from 2004 and 2006 and based on which authors concluded that MTHFR C677T polymorphism could represent a genetic risk factor for diabetic nephropathy in Chinese type 2 patients²⁴. Another research in the Chinese Han population showed similar results³⁹. The confirmation of these results was also obtained in Lebanese and Polish patients, but the results of another research on the Polish population speak in favor of relationship between MTHFR polymorphism and diabetic nephropathy only in male patients^{40–42}. Finally, a meta-analysis of 15 available studies that analyzed the association between diabetic nephropathy and MTHFR C677T showed heterogeneity between studies and a marginal correlation between development of diabetic nephropathy and genetic polymorphism²¹.

It is evident that all above mentioned studies and reports were conducted on different populations. Since genetic factors can vary among different human groups, ethnic variations of the genetic polymorphism of the MTHFR gene could explain the variety of results in different populations.

From the results of our study it is obvious that patients in the group with diabetic nephropathy were statistically significantly older than in the normoalbuminuric group. This result is not unexpected, since older age is associated with reduced kidney function and creatinine clearance, as well as with higher probability of longer duration of diabetes and its chronic complications.

The present study also shows that individuals with microalbuminuria had higher plasma homocysteine compared with patients with normoalbuminuria. There is no statistically significant difference in the homocysteine level considering MTHFR polymorphism, in the whole study population, or in separate groups of men and women. Observing separately the group of men, a somewhat higher medium homocysteine level (14.9 $\mu\text{mol/L}$) is evident in the group of homozygotes (T/T), and the lowest in the group of »wild types« (10.1 $\mu\text{mol/L}$). This difference is probably not statistically confirmed due to a relatively small number of patients. In the female part of the population such a trend is not evident.

Some studies state that hyperhomocysteinemia is positively correlated with diabetic nephropathy. The study conducted by Chico et al showed the results similar to ours – patients with both types of diabetes and nephropathy had higher plasma homocysteine levels than the patients without nephropathy²⁵. One Australian research showed that patients with microalbuminuria had higher levels of homocysteine than those with normoalbuminuria⁴³. Another study suggests significant correlation of plasma homocysteine level with microalbuminuria, but only in patients with diabetic nephropathy who had C677T polymorphism⁴⁴. In contrast, the findings published by Soares et al did not find meaningful difference between the subjects when homocysteine levels were assessed according to the MTHFR genotype⁴⁵. The differences between these results could be a consequence of the diversity of laboratory methods, different analyzed sample sizes, different nutritional status or could be genetically determined.

In conclusion, our study did not show a correlation between MTHFR polymorphism and diabetic nephropathy in Croatian patients. However, the possibility that MTHFR polymorphism could be a risk factor for nephropathy cannot be completely excluded because diabetic nephropathy is influenced by multiple risk factors which can modify the importance of MTHFR polymorphism in its development. To detect that correlation it would be necessary to conduct larger additional studies in patients with diabetic nephropathy.

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POVEZANOST POLIMORFIZMA C677T GENA ZA METILENTETRAHIDROFOLAT REDUKTAZU I DIJABETIČKE NEFROPATIJU U BOLESNIKA SA ŠEĆERNOM BOLESTI TIP 2 U HRVATSKOJ

SAŽETAK

Polimorfizam gena za metilentetrahidrofolat reduktazu (MTHFR) je povezan s razvojem dijabetičke nefropatije u mnogim etničkim skupinama. U ovoj studiji istraživali smo povezanost između polimorfizma C677T gena za MTHFR i mikroalbuminurije u bolesnika sa šećernom bolesti tip 2 u hrvatskih bolesnika. Osamdeset pet bolesnika sa šećernom bolesti je obrađivano i svrstano u dvije skupine – sa dijabetičkom nefropatijom i bez nje, ovisno o vrijednostima izlučenog albumina u 24-satnom urinu. Mutacija C677T gena za MTHFR određena je metodom izolacije DNA i alel specifične lančane reakcije polimeraze (PCR). Raspodjela genotipova u skupini bolesnika s normoalbuminurijom bila je: CC 36,5%, CT 42,3% i TT 21,2%, dok je u skupini bolesnika sa mikroalbuminurijom bila: CC 39,4%, CT 45,4% i TT 15,2%. Nije bilo statistički značajne razlike među grupama u distribuciji C677T genotipova ($p=0,788$). Naše istraživanje nije pokazalo povezanost između mutacije gena za metilentetrahidrofolat reduktazu i dijabetičke nefropatije u hrvatskih bolesnika. Mnogostruki čimbenici mogu modificirati značajnost utjecaja polimorfizma MTHFR na nastanak dijabetičke nefropatije.