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Impact of *MTHFR* C677T gene polymorphism and vitamins intake on homocysteine concentration in the Polish adult population

Anna Waśkiewicz[1], Walerian Piotrowski[1], Grażyna Broda[1], Agnieszka Sobczyk-Kopciol[2], Rafał Płoski[3]

[1]Department of Cardiovascular Diseases Epidemiology, Prevention and Health Promotion, Institute of Cardiology, Warsaw, Poland
[2]Department of General Biology and Parasitology, Medical University of Warsaw, Warsaw, Poland
[3]Department of Medical Genetics, Medical University of Warsaw, Warsaw, Poland

Abstract

Background: Homocysteine (Hcy) levels are modulated by nutritional and genetic factors, among which is the enzyme 5,10-methylenetetrahydrofolate reductase (*MTHFR*).

Aim: To determine the effects of the *MTHTR* C677T polymorphism, as well as the intake of folate, vitamins B_6 and B_{12} on serum Hcy concentration in the Polish population.

Methods: Within the framework of the National Multicentre Health Survey (WOBASZ), a representative sample of the whole Polish population aged 20–74 was screened in 2003–2005. Vitamins intake, Hcy level and known *MTHTR* C677T genotype were available for 1,561 men and 1,712 women.

Results: In the Polish population, T/T, C/T and C/C genotype frequencies were 10%, 43% and 47%, respectively in men, and 9%, 42% and 49%, respectively in women. The T/T genotype was associated with increased levels of Hcy (13.14 μmol/L in men, and 9.77 μmol/L in women) compared to the C/C and C/T genotypes (10.18 and 8.77, respectively), after adjustment for age, methionine, coffee and alcohol intake, smoking and drugs used. In a multivariable linear regression model, among subjects with the T/T genotype, the only factor influencing Hcy was age in women. In the case of the other groups (C/C and C/T), there was a relationship between Hcy and age, alcohol consumption, drugs used, folate and vitamin B_6 in men, and age, smoking, coffee consumption, drugs used, folate and vitamin B_{12} in women.

Conclusions: The T/T genotype is associated with higher levels of Hcy (29% in men, and 11% in women) compared to other genotypes. Nutritional factors affect Hcy levels only in the C/C and C/T *MTHFR* genotypes.

Key words: *MTHFR* C677T, folate, vitamin B_6, vitamin B_{12}, homocysteine

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INTRODUCTION

Hyperhomocysteinaemia has been suggested as an independent risk factor for cerebral, coronary and peripheral atherosclerosis [1–3]. Hyperhomocysteinaemia may also play an important role in the induction of ischaemic stroke and in the deterioration of the general condition of patients with chronic heart failure [4–6]. Increased homocysteine (Hcy) concentrations can result from genetic defects that alter enzymes involved in Hcy remethylation or transsulphuration, and the deficiency of some vitamins because they also participate in the degradation pathway of this amino acid [7].

The 5,10-methylenetetrahydrofolate reductase (*MTHFR*) is an enzyme crucial for the remethylation of Hcy into methionine. A common polymorphism in *MTHFR* is the substitution of cytosine (C) for thymine (T) at nucleotide 677, which converts alanine to valine residue. The C677T mutation decreases *MTHFR* activity [8, 9]. The Hcy metabolism is dependent on such vitamins as folic acid, pyridoxal phosphatase

Address for correspondence:
Anna Waśkiewicz, M.Sc., Ph.D., Institute of Cardiology, ul. Alpejska 42, 04–628 Warszawa, Poland, e-mail: awaskiewicz@ikard.pl
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Table 1. Prevalence of C677T genotypes and alleles of the *MTHFR* gene in the Polish population

Men				Women			
Prevalence of genotypes							
T/T	C/T	C/C	χ^2	T/T	C/T	C/C	χ^2
158 10.12%	673 43.11%	730 46.77%	0.02*	161 9.40%	709 41.41%	842 49.19%	1.85*
Prevalence of alleles							
T		C		T		C	
31.7%		68.3%		30.2%		69.8%	

*There is 1 degree of freedom and the 5% significance level for 1 degree of freedom is 3.84, and since the χ^2 value is less than this, the null hypothesis that the population is in Hardy-Weinberg frequencies is not rejected.

and cobalamine, acting as co-substrates in the two interconnected metabolic pathways of transsulphuration and remethylation [10, 11].

The objectives of this study were to establish the genetic prevalence of the *MTHFR* C677T polymorphism and to evaluate the effects of this genotype, as well as the intake of folate and vitamins B_6 and B_{12}, on Hcy concentrations in the Polish population.

METHODS

Study population

The study population data came from the Polish National Multicentre Health Survey (the WOBASZ Project), a cross-sectional study on the prevalence and control of classical and genetic cardiovascular disease (CVD) risk factors. The WOBASZ study was conducted in 2003–2005 by the Institute of Cardiology in Warsaw in co-operation with five medical universities in Poland, on a representative random sample of the Polish population aged 20–74 years (6,392 men and 7,153 women). The response rates were 74.3% and 79.3% for men and women, respectively. Dietary intake and serum Hcy level analyses were performed in 50% of the subjects sampled.

The aims and methods of the WOBASZ Project as well as the sampling procedure have been described in detail in papers published previously [12, 13]. The study was approved by the Medical Ethics Committee of the National Institute of Cardiology in Warsaw. Each participant gave two written consents: one for assessment of conventional CVD risk factors and the other for taking a blood sample for DNA isolation and genetic analyses.

Assessment of vitamin intake

Dietary habits were evaluated by the 24-hour recall method. The folate, B_6 and B_{12} intake was calculated from the 'Polish Food Composition Tables'. Additionally, data on vitamin supplementation were collected. Vitamin intake from food and from supplements, as well as vitamin losses due to technological processes and related to the preparation of meals was included in all analyses.

Homocysteine level

Serum Hcy concentration was determined by an immunoenzymatic method using an IMMULITE 1 analyser and reagents manufactured by the DPC company.

DNA extraction and genotyping

The 10 mL blood samples for DNA extraction were drawn and stored at –70°C until DNA was isolated by a salting-out method. The *MTHFR* genotyping was performed by real time polymerase chain reaction using Assay on Demand reagents (Life Technologies) and an ABI Prism 7500 apparatus (Applied Biosystems). Genotyping tests were performed in the Department of Medical Genetics in the Medical University of Warsaw.

For this report, complete data (dietary intake, Hcy levels and DNA genotyping) were available for 1,561 men and 1,712 women.

Statistical analyses

The SAS software (version 9.2) was used for all statistical analyses. Logarithmic transformation was applied for Hcy, because the concentrations of this variable were not distributed normally. Comparisons of the mean of continuous variables were done using Student's *t*-test and frequencies of discrete variables were evaluated using the χ^2-test. A Hardy-Weinberg equilibrium for *MTHFR* genotypic frequencies was also assessed with the χ^2-test. The prediction of log (Hcy) outcome based on independent variables was done using multiple linear regression analysis and R^2 was estimated. A two-sided p value < 0.05 was considered as significant.

RESULTS

The *MTHFR* C677T genotype distribution and allele prevalence in the Polish population are presented in Table 1. The T/T genotype was detected in approximately 10% and the T allele in 30% of the analysed group.

The prevalence of hyperhomocysteinaemia was the only significant difference between the various *MTHFR* C677T genotypes regarding CVD risk factors and vitamin intake. The

Table 2. Characteristics (means and proportions) of the Polish population by C677T variant of *MTHFR*

Parameter	Men			Women		
	T/T	C/C+C/T	P	T/T	C/C+C/T	P
N	158	1,403		161	1,551	
Current smokers [%]	36.1	40.6	NS	23.6	23.1	NS
Hypertensive subjects (WHO criteria) [%]	45.9	40.1	NS	29.8	32.1	NS
Hypercholesterolaemic subjects (cholesterol ≥ 190 mg/dL) [%]	70.6	67.7	NS	63.6	64.6	NS
Obese or overweight subjects (BMI ≥ 25 kg/m^2) [%]	65.1	60.2	NS	47.7	51.8	NS
Diabetic subjects (glucose > 7 mmol/L) [%]	8.3	8.0	NS	4.1	7.3	NS
Hyperhomocysteinaemic subjects (> 12 μmol/L) [%]	52.5	25.8	< 0.0001	22.4	14.9	0.0129
Total cholesterol [mg/dL]	210	211	NS	206	211	NS
LDL cholesterol [mg/dL]	125	129	NS	126	128	NS
HDL cholesterol [mg/dL]	53.3	52.5	NS	60.5	59.6	NS
Triglycerides [mg/dL]	172	153	NS	125	119	NS
Folate intake [μg/day]	275	286	NS	220	218	NS
Vitamin B_6 intake [mg/day]	2.07	2.15	NS	1.50	1.46	NS
Vitamin B_{12} intake [μg/day]	6.22	5.56	NS	4.12	3.52	NS
Folate intake* [μg/day]	283	289	NS	256	232	NS
Vitamin B_6 intake* [mg/day]	2.13	2.33	NS	1.95	1.97	NS
Vitamin B_{12} intake* [μg/day]	6.37	5.60	NS	4.42	3.66	NS

*Dietary intake and supplementation

Table 3. Mean plasma Hcy levels by C677T variant of *MTHFR*

	Homocysteine concentration [μmol/L]			
	Men		Women	
Model A*				
MTHFR T/T	13.12	p < 0.0001	9.69	p = 0.0027
MTHFR C/C+C/T	10.18		8.76	
Model B**				
MTHFR T/T	13.14	p < 0.0001	9.77	p < 0.0001
MTHFR C/C+C/T	10.18		8.77	

*Geometric means adjusted for age; **geometric means adjusted for age, methionine, coffee and alcohol intake, smoking and drugs used (metformin, fibrates and diuretics)

percentage of hyperHcy subjects in T/T genotype carriers was double in men, and 1.5 times higher in women, than in non-carriers (Table 2). However, independently of the C677T variant of the *MTHFR* polymorphism, the Polish adult population was characterised by a high prevalence of subjects with elevated CVD risk factors (hypertensive, hypercholesterolaemic, obese or overweight subjects) as well as by high average levels of total cholesterol, LDL-cholesterol and triglycerides. Regarding the analysed vitamins, low average folate intake and adequate to recommended B_6 and B_{12} intake were reported.

The T/T genotype was associated with increased Hcy (by approx. 29% in men and 11% in women) compared to C/C and C/T. This correlation was preserved after adjusting for confounding variables (age, smoking, drugs used [metformin, fibrates and diuretics], methionine, coffee and alcohol intake) (Table 3).

We assessed the independent impact of selected vitamins on Hcy, in particular the *MTHFR* C677T genotype (Table 4). It has been noted that among subjects with the T/T polymorphism, the only factor influencing Hcy was age in women. However, in the case of other groups (C/C and C/T genotypes) there was a relationship between age, alcohol consumption, drugs used, folate and B_6 intake in men; and age, smoking, coffee consumption, drugs used, folate and B_{12} intake in women.

DISCUSSION

The Hcy metabolism represents an interesting model of gene-environment interaction, and the WOBASZ Project was one

Table 4. Multivariable linear regression analysis between selected factors and Hcy concentration by C677T variant of *MTHFR*

	Men		Women	
	Regression coefficient	P	Regression coefficient	P
***MTHFR* T/T**				
Age	0.00213	NS	0.00995	< 0.0001
Smoking	0.13696	NS	0.09906	NS
Coffee intake	0.0002756	NS	–0.00002672	NS
Alcohol intake	–0.0002259	NS	–0.00208	NS
Drugs used	–0.12241	NS	0.09516	NS
Folate intake	–0.00006839	NS	–0.00003838	NS
Vitamin B_6 intake	0.01375	NS	–0.02392	NS
Vitamin B_{12} intake	–0.0006422	NS	–0.00516	NS
$R^2 \times 100$	4.7%	NS	23.5%	< 0.0001
***MTHFR* C/C+C/T**				
Age	0.00599	< 0.0001	0.00780	< 0.0001
Smoking	0.02905	NS	0.06107	0.0010
Coffee intake	–0.000023	NS	–0.0001025	0.0128
Alcohol intake	0.00115	0.0063	–0.00512	NS
Drugs used	0.07701	0.0118	0.06008	0.0271
Folate intake	–0.0001184	0.05	–0.0000412	0.0285
Vitamin B_6 intake	–0.00693	0.0101	–0.0005152	NS
Vitamin B_{12} intake	–0.0009646	NS	–0.00194	0.05
$R^2 \times 100$	11.2%	< 0.0001	16.3%	< 0.0001

of the few to include in the analysis the concentration of this amino acid, genotypes as well as vitamin intake.

Homocysteine is formed from methionine and is either catabolised in the vitamin B_6-dependent transsulphuration pathway or remethylated into methionine. This latter reaction is catalysed by the methionine synthase, which requires 5-methyltetrahydrofolate as substrate and vitamin B_{12} as co-factor; 5-methyltetrahydrofolate is formed by the reduction of 5,10-methylenetetrahydrofolate by *MTHFR*, which is a regulating enzyme in Hcy methabolism. A 677C-T mutation was detected in the *MTHFR* gene and homozygosity for this genotype was associated with a decreased specific enzyme activity and elevated Hcy.

The results of our study showed that in Poland the prevalence of the T/T polymorphism (approx. 10%) and of the T allele (approx. 30%) is comparable to other European and North American countries. The percentage of subjects with this genotype/allele has been found to be 11% (allele 45%) among Hungarians [14], 6% in Croatia [15] and 12–13% in UK [16]. In Italy [8], a significant difference exists depending on the region of the country. The results of *MTHFR* genotyping in different European populations from the European Atherosclerosis Research Study-II [17] showed an overall T allele prevalence of 32%; it was though significantly lower in the Baltic countries than in other regions of Europe. In North America [15], it was 35%. It is estimated that the T/T genotype rarely occurs in African-Americans [18], whereas among healthy Japanese [19] its prevalence is 14.7%. The data from one of the few studies of these problems performed in Poland [20] showed that, in controls, the prevalence of this polymorphism was 4.4% and of the T allele 21.5%. In contrast to most studies [16, 21, 22], we were unable to confirm an association between the *MTHTR* C677T genotype and other conventional risk factors such as total, LDL, and HDL cholesterol.

In the Polish population, subjects who are T/T homozygotic had a higher concentration of Hcy (by approx. 29% among men and 11% among women) compared to other subjects and after excluding other factors that might have influenced the level of this amino acid. In general, in most projects there has been a relationship observed between the *MTHFR* C677T polymorphism and elevated Hcy; however, in some, this relationship was limited only to people with low folate in their blood. A study performed in the Netherlands [23] indicated that homozygosity for the 677C-T *MTHFR* mutation, especially in combination with a low folate status, predisposed to high plasma concentration of Hcy. In Italy [21], in individuals with folate levels below the median, Hcy was significantly increased not only in T/T homozygotes (by 59%) but also in C/T heterozygotes (by 21% on average). However, the apparently causal relationship between genotype and serum folate levels indicates that in a proportion of individuals in the higher Hcy range, lower folate levels are not necessarily attributable to dietary

insufficiency alone but are, at least in part, a direct result of the reduced activity of the thermolabile enzyme.

The correlations mentioned above refer to the vitamin concentration in blood rather than to its content in the diet. In the WOBASZ Project, the blood concentration of vitamins was not assessed.

Our study assessed the effects of dietary factors on Hcy level in various *MTHFR* C677T genotypes. In subjects with the T/T genotype, the only factor influencing Hcy level was age in women. In 90% of the adult Polish population (genotypes C/C and C/T), there was a relationship found between Hcy and age, alcohol consumption, drugs used, folate and vitamin B_6 in men; and age, smoking, coffee consumption, drugs used, folate and vitamin B_{12} in women.

Unfortunately, the average consumption of folate in the Polish adult population was rather low: almost 80% of men and 90% of women had insufficient folate intake [24]. The result of the WOBASZ study showed that although the average daily food ration of an adult Pole is within the recommended daily intake of vitamins B_6 and B_{12}, the percentage of subjects whose diet did not meet the recommendations of these components ranged from 16% to 51%, depending on gender and the type of vitamin.

CONCLUSIONS

The T/T genotype is independently associated with a higher concentration of Hcy (increase of 29% in men, and 11% in women) compared to other genotypes. Nutritional factors affect Hcy level only in the C/C and C/T *MTHFR* genotypes. The results of our study suggest that flour should be fortified with folic acid, which could contribute to lowering Hcy among people with the C/C or C/T *MTHFR* gene polymorphism (i.e. 90% of the population).

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Conflict of interest: *none declared*

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Wpływ polimorfizmu genu *MTHFR* C677T i spożycia wybranych witamin na stężenie homocysteiny w populacji polskiej

Anna Waśkiewicz[1], Walerian Piotrowski[1], Grażyna Broda[1], Agnieszka Sobczyk-Kopciol[2], Rafał Płoski[3]

[1]Zakład Epidemiologii, Prewencji Chorób Układu Krążenia i Promocji Zdrowia, Instytut Kardiologii, Warszawa
[2]Zakład Biologii Ogólnej i Parazytologii, Uniwersytet Medyczny, Warszawa
[3]Zakład Genetyki Medycznej, Uniwersytet Medyczny, Warszawa

Streszczenie

Wstęp: Metabolizm homocysteiny (Hcy) jest interesującym przykładem genetyczno-środowiskowych interreakcji. Stężenie tego aminokwasu zależy od mutacji genów uczestniczących w szlaku przemian Hcy i spożycia witamin (foliany, witaminy B_6 i B_{12}). Kluczowym polimorfizmem reduktazy metylenotetrahydrofolianu (MTHFR), która uczestniczy w remetylacji Hcy, jest zamiana cytozyny (C) na tyminę (T) w pozycji 677, kodująca sekwencję aminokwasów, w której alanina ulega zamianie na walinę. Polimorfizm ten prowadzi do zmniejszenia aktywności enzymu i w konsekwencji do wzrostu stężenia Hcy, szczególnie u osób będących homozygotami dla allelu T.

Cel: Celem pracy było ustalenie częstości występowania polimorfizmów genu *MTHFR* C677T w populacji polskiej i zbadanie zależności między tymi poliformizmami oraz czynnikami żywieniowymi (foliany, witaminy B_6 i B_{12}) a stężeniem Hcy.

Metody: W ramach Wieloośrodkowego Ogólnopolskiego Badania Stanu Zdrowia Ludności (WOBASZ) przeprowadzonego w latach 2003–2005 przebadano reprezentatywną próbę mieszkańców Polski w wieku 20–74 lat. W niniejszej pracy uwzględniono osoby, u których oznaczono stężenie Hcy, polimorfizm genu *MTHFR* oraz oceniono sposób żywienia. Łącznie wszystkie analizowane dane były dostępne w przypadku 1561 mężczyzn i 1712 kobiet.

Wyniki: Wśród mieszkańców Polski rozpowszechnienie polimorfizmu T/T, C/T i C/C genu *MTHFR* przedstawiało się następująco 10%, 43% i 47% u mężczyzn oraz odpowiednio 9%, 42% i 49% u kobiet, a częstość występowania alleli T wynosiła 30% niezależnie od płci. Analizowany polimorfizm nie różnicował poziomu klasycznych czynników ryzyka chorób układu sercowo-naczyniowego (cholesterol, LDL, HDL, triglicerydy, BMI) oraz częstości występowania nadciśnienia tętniczego, hipercholesterolemii oraz nadwagi i otyłości. Polimorfizm T/T wiązał się ze wzrostem stężenia Hcy (o 29% u mężczyzn i o 11% u kobiet) w porównaniu z genotypami C/C+C/T po skorygowaniu względem wieku, palenia tytoniu, spożycia kawy i alkoholu, zawartości metioniny w diecie oraz stosowania leków, takich jak metformina, fibraty i diuretyki. Średnie stężenie Hcy u homozygot T/T wynosiło 13,14 μmol/l u mężczyzn i 9,77 μmol/l u kobiet, a w przypadku pozostałych polimorfizmów odpowiednio 10,18 μmol/l i 8,77 μmol/l. Oceniono również wpływ czynników żywieniowych na stężenie Hcy w poszczególnych polimorfizmach genu *MTHFR* C677T. U osób będących homozygotami T/T (10% populacji) czynniki żywieniowe nie determinowały stężenia Hcy. W przypadku pozostałych polimorfizmów C/C+C/T stężenie Hcy było uwarunkowane spożyciem folianów u obu płci, witaminy B_6 u mężczyzn i B_{12} u kobiet. Jednocześnie wśród mieszkańców Polski, niezależnie od polimorfizmu genu *MTHFR* C677T, zanotowano niedobór spożycia folianów, które łącznie z suplementacją wynosiło 283–289 μg u mężczyzn i 232–256 μg u kobiet (zalecany poziom: 320–400 μg/dz.). Średnia zawartość w diecie witaminy B_6 (2,13–2,33 mg/dz. u mężczyzn i 1,95–1,97 mg/dz. u kobiet) oraz B_{12} (odpowiednio 5,6–6,4 μg/dz. i 3,7–4,4 μg/dz.) była zgodna z zalecanymi poziomami.

Wnioski: W populacji dorosłych Polaków polimorfizm T/T genu *MTHFR* wiąże się ze wzrostem stężenia Hcy o 29% u mężczyzn i o 11% u kobiet. Czynniki żywieniowe wpływały na Hcy jedynie u osób o genotypie C/C+C/T genu *MTHFR* C677T.

Słowa kluczowe: *MTHFR* C677T, foliany, witaminy B_6 i B_{12}, homocysteina

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Adres do korespondencji:
dr inż. Anna Waśkiewicz, Instytut Kardiologii, ul. Alpejska 42, 04–628 Warszawa, e-mail: awaskiewicz@ikard.pl
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