PRACA ORYGINALNA

Influence of erythropoietin gene promoter polymorphism rs 1617640 on the incidence and progression of chronic kidney disease; a family-based study

Wpływ polimorfizmu rs 1617640 promotora genu erytropoetyny na występowanie i progresję przewlekłej choroby nerek; badania rodzinne

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ABSTRACT

INTRODUCTION

The aetiology of chronic kidney disease (CKD) and its progression are multifactorial in nature. A number of reports have demonstrated the non-haematological local protective properties of erythropoietin in different tissues, including those in the kidneys. The primary goal of the reported, family-based study was to assess the influence of rs 1617640 erythropoietin gene promoter polymorphism on the incidence and progression of CKD.

MATERIAL AND METHODS

For that purpose, 109 patients with CKD (72.5% with chronic interstitial nephritis and 27.5% with chronic glomerulonephritis) and their parents were examined. At the time of the study, the mean glomerular filtration rate was 28.2 ml/min and 53.2% patients were maintained on renal replacement therapy. Fluorescence labelled probes of the TaqMan Pre-designed SNP Genotyping Assay (Applied Biosystems Company) were used for rs1617640 polymorphism investigation.

RESULTS

The genome distribution of rs 1617640 polymorphism of the erythropoietin gene promoter was: 48.6% AC, 25.7% AA and 25.7% CC patients. Based on Transmission Disequilibrium Test results, the bordeline statistical significance of preferential C allele transfer from parents to their affected children with glomerulonephritis was observed.

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CONCLUSIONS
No influence of rs 1617640 promoter polymorphism of the erythropoietin gene on the incidence of CKD in the course of chronic interstitial nephritis was observed. The bordeline significance of preferential C allele transfer in patients with glomerulonephritis suggests association between rs1617640 and CKD of this aethiology.

KEY WORDS
chronic kidney disease, erythropoietin gene promoter polymorphism, family-based study

STRESZCZENIE

WSTĘP
Etiologia przewlekłego uszkodzenia nerek oraz jego progresji jest wieloczynnikowa. Prace ostatnich lat dowodzą znaczenia pozaszpikowego miejscowego działania ochronnego erytropoetyny w wielu tkankach, w tym także w nerkach.
Celem pracy była ocena w modelu rodzinnym wpływu polimorfizmu rs1617640 promotora genu dla erytropoetyny na rozwój i progresję przewlekłej choroby nerek.

MATERIAŁ I METODY
Badania przeprowadzono w grupie 109 chorych na przewlekłą chorobę nerek w przebiegu przewlekłego śródmiąższowego zapalenia nerek (72,5%) i przewlekłego kłębuszkowego zapalenia nerek (27,5%) oraz u 218 ich biologicznych rodziców. W momencie prowadzenia badania średnia filtracja kłębuszkowa (GFR) wynosiła 28,2 ml/min, a 53,2% chorych było leczonych nerkozastępczo. Genotypowanie polimorfizmu rs1617640 w promotorze genu erytropoetyny wykonano, wykorzystując znakowane fluorescencyjnie sondy z zestawu TaqMan Pre-designed SNP Genotyping Assay firmy Applied Biosystems.

WYNIKI
Analizując rozkład genotypów badanego polimorfizmu, stwierdzono: u 48,6% chorych genotyp AC, a u pozostałych chorych w równym procencie (po 25,7%) genotyp AA i CC. W teście TDT (Transmission Disequilibrium Test) wykazano na granicy istotności statystycznej przekazywanie preferencyjne allelu C w grupie chorych z przewlekłym kłębuszkowym zapaleniem nerek.

WNIOSKI
Nie obserwowano wpływu polimorfizmu rs1617640 genu promotora dla erytropoetyny na występowanie przewlekłego uszkodzenia nerek w przebiegu przewlekłego środmiąższowego zapalenia nerek. Stwierdzone na granicy istotności statystycznej, preferencyjne przekazywanie allelu C w grupie chorych na przewlekłe kłębuszkowe zapalenie nerek, sugeruje związek rs1617640 z przewlekłą chorobą nerek o tej etiologii.

SŁOWA KLUCZOWE
przewlekła choroba nerek, polimorfizm promotora genu dla erytropoetyny, badania rodzinne.

INTRODUCTION

Erythropoietin (Epo) is a glycoprotein with the main biological task of hypoxia-provoked erythropoiesis in bone marrow [1]. Besides its observed influence on erythroblastic line differentiation and maturation, erythropoietin is also known for its strong procoagulant role, resulting from direct effects exerted on blood platelets and vascular endothelium. All these activities control the correct erythrocyte

count, thus ensuring proper oxidation of all tissues. Studies, performed in recent years, have provided much evidence for the many extramedullar activities of this substance, currently categorised to class 1 cytokines. Under hypoxic conditions, erythropoietin stimulates the proliferation, migration and angiogenesis of vascular endothelial cells [2,3,4]. It has been found that Epo acts locally via a tissue protective receptor (TPR) as an antagonist of proinflammatory cytokines, formed in consequence of a lesion (inflammatory condition, injury) or metabolic stress. Epo reduces the flow of inflammatory cells to the injured site and suppresses apoptosis [5]. While acting locally, it simultaneously activates tissue-specific stem cells and progenitor endothelial cells to repair tissue lesions [6,7]. In order to trigger the cascade of local activities, the Epo concentration must be higher than that in haematopoiesis, therefore, the positive, local effects of Epo may be somewhat limited by simultaneous activation of the procoagulation pathway [8, 9, 10]. The conducted observations of the pleiotropic activity of erythropoietin have aroused great expectations for possible future applications of this substance as a factor effectively reducing various tissue pathologies [11,12,13,14].

The cytoprotective role of erythropoietin in the kidneys attracts a particular amount of interest [3,15,16,17,18,19,20]. Chronic kidney disease (CKD) is a serious population-affecting issue [21]. The influence of various pathological factors progressively damages the renal parenchyma, leading to the development of renal failure in a fairly high percent of otherwise often oligosymptomatic patients [22]. Numerous studies have proven the important role of genetic factors in nephropathy aetiology [23,24,26]. In 2008, Tong et al. published a remarkable report about the relevance of erythropoietin gene promoter polymorphism rs 1617640 in the development of microangiopathic complications of diabetes mellitus, including diabetic nephropathy [27].

The primary goal of the reported study was to discover any influence of erythropoietin gene promoter polymorphism rs 1617640 on chronic kidney disease (in the course of primary glomerulopathy and chronic interstitial nephritis) development and progress, based on parent-offspring trio results.

MATERIAL AND METHODS

A group of 327 subjects, including 109 children with chronic kidney disease and their 218 parents were included in the study, making 109 triplets altogether. All the studied patients or their legal guardians provided conscious consent to participate in the study (submitted by parents, when their children were under 16, and both by parents, and children at the age of 16–18 years). Prior to the onset of the study, its protocol was approved by the Ethics Committee of the Medical University of Silesia in Katowice.

There were 109 patients in the study group in the mean age of 15.5 (± 6.45) years and with a mean BMI (body mass index) of 19.1 (± 3.5) kg/m^2, including 48 (44%) females and 61 (56%) males. Chronic glomerulonephritis was the cause of chronic kidney disease in 30 (27.5%) patients, while 79 (72.5%) patients suffer from chronic interstitial nephropathy, the latter diagnosed in 62 (78%) patients as a medical condition secondary to a concomitant urinary tract defect. In 24 (22%) patients, the diagnosis was obtained from renal biopsy.

At the time of the study, the mean concentration of creatinine in the study group was 4.66 (± 3.0) mg/dl, which when converted to glomerular filtration by the Schwartz and MDRD (Modification of Diet in Renal Disease) formulas, respectively for children below 18 and adults, gave the median value of 28.2 ml/min. During the study, 51 (46.8%) patients were conservatively treated. In that group, the mean creatinine concentration and GFR (glomerular filtration rate) were 2.77 (± 1.0) mg/dl and 36.0 (± 15.2) ml/min, respectively. The remaining 58 patients underwent renal replacement therapy: continuous ambulatory peritoneal dialysis (CAPD) was conducted among 33 (56.9%) patients, while haemodialysis (HD) among 17 (29.3%) patients, and 8 (13.8%) patients underwent kidney transplantation. At the time of the study, the mean serum creatinine concentrations and GFR were 6.78 (± 2.7) mg/dl and 12.49 (± 4.17) ml/min respectively in the CAPD group; 7.93 (± 2.24) mg/dl and 12.04 (± 3.45) ml/min respectively in the HD group and 1.08 (± 0.13) mg/dl and 80.5 (± 13.4) ml/min respectively in the kidney transplantation group. During the time of the study, 42 (38%) patients experienced hypertension, out of whom 30% reported it in their

medical histories, already when the kidney disease was diagnosed.
With the available medical records of the patients at hand, the progression of chronic kidney disease was evaluated, taking into account the rise of serum creatinine concentration and GFR decline in time. The mean observation time period was 7.1 (± 5.7) years for the entire study group. The mean value of the first documented serum creatinine concentration was 2.25 (± 2.36) mg/dl. For statistical analysis, the patients were divided into the following two subgroups: with rapid and slow CKD progression. The first group included patients with the onset of renal replacement therapy within a 5-year observation period from the diagnosis of CKD in stage 2 and/or with a doubled serum creatinine concentration, while the 1/serum creatinine concentration index was below 0.3. The other patients were categorised as a group with a slow CKD progression course. The group with slow CKD progression course included 55 (50.5%) patients, while the group with rapid disease progression amounted to 54 (49.5%) patients.
All the reported studies were carried out at the Laboratory of the Department of Internal Diseases, Diabetology and Nephrology in Zabrze (Medical University of Silesia in Katowice). Both the patients and their biological parents were requested to give blood samples, which were then placed into 4.9 ml S-Monovette tubes from Sarstedt, each containing 6.4 mg of potassium versenate. The genomic DNA was isolated from the peripheral blood leukocytes with a DNA isolation kit from Epicentre Technologies with the authors' modification.
Genotyping of the A/C polymorphism was carried out in a erythropoietin gene promoter with fluorsecence-labelled probes of a TaqMan Pre-designed SNP Genotyping Assay, manufactured by the Applied Biosystems Company and designed for SNP rs 1617640 measurements. The PCR and allele identifications were performed in a 7300 Real Time PCR from the Applied Biosystems Company.
Regarding the aetiology of chronic kidney diseases as the basis for the division of the patients into groups, four subgroups were formed and submitted to statistical analysis: group A – patients with chronic glomerulonephritis (GN), group B – patients with chronic interstitial nephritis (CIN), group B1 – CIN patients without any concomitant urinary system defect, group B2 – CIN patients with a concomitant urinary system defect.
Following the distribution of the collected quantitative data in the Kolmogorov-Smirnov test, they were presented as mean values and standard deviations for the parameters of normal distribution and as median values and as the lower/upper quartile for the parameters which did not fulfil the normal distribution conditions.
The statistical analysis was performed with the Microsoft Office Excel 2003 program and Statistica 7 software package, assuming $p < 0.05$ as a statistically significant value.
The Transmission Disequilibrium Test (TDT) was applied to evaluate the allele transfer from the biological parents to their affected offspring, excluding – as non-informative – those families in which both parents were homozygotes. Any test result which demonstrates a statistically significant deviation from Mendel's distribution of alleles (i.e., 50:50), confirms a relationship of the analysed polymorphism with the studied disease. Calculations of the significance of the sum of transferred alleles vs. the expected values in the studied group was done in McNemar's test.

RESULTS

Taking into consideration the entire study group, the AC genotype was observed in 48.6% of the patients, the AA genotype in 25.7% and CC genotype in 25.7% of the patients; see Table I for the distribution of genotypes in the particular subgroups. Based on the TDT results, we did not reveal any significant relationships among erythropoietin gene promoter polymorphism (rs 1617640) and CKD incidence in patients with chronic interstitial nephritis. The bordeline statistical significance (p=0.09) of preferential C allele transfer from parents to their affected children with glomerulonephritis was observed (Table II).
See Table III for the genotype distribution in the subgroups of patients with a different kidney disease progression rate. Several potential risk factors for more rapid CKD progression were accounted for in a multiple stepwise regression analysis, including the AC heterozygotic genotype, chronic glomerulonephritis as a causative condition for chronic kidney disease, female sex, hypertension at observation

Table I. Distribution of rs 1617640 Epo SNP genotype and allele in study groups
Tabela I. Rozkład genotypów polimorfizmu rs1617640 promotora genu erytropoetyny w grupach badanych

	All patients	Group A	Group B	Group B1	Group B2
AA	28 (25.7%)	8 (26.7%)	20 (25.3%)	4 (23.5%)	16 (25.8%)
CC	28 (25.7%)	10 (33.3%)	18 (22.8%)	3 (17.7%)	15 (24.2%)
AC	53 (48.6%)	12 (40%)	41 (51.9%)	10 (58.8%)	31 (50%)
Allele A	109 (50%)	28 (46.7%)	81 (51.3%)	18 (52.9%)	63 (50.2%)
Allele C	109 (50%)	32 (53.3%)	77 (48.7%)	16 (47.1%)	61 (49.2%)

Group A – chronic glomerulonephritis; B – chronic interstitial nephritis; B1 – chronic interstitial nephritis without urinary tract defect; B2 – chronic interstitial nephritis with urinary tract defect

Table II. Frequency of rs 1617640 EPO SNP allele transmission in study groups (TDT results)
Tabela II. Częstość przekazywania alleli polimorfizmu rs 1617640 promotora genu erytropoetyny w grupach badanych (test TDT)

	Allele A transmitted observed/expected		Allele C transmitted observed/expected		chi²	p
Groups ↓	Yes	No	Yes	No		
All patients	41/49	57/49	57/49	41/49	2.6122	0.1060
Group A	10/14.5	19/14.5	19/14.5	10/14.5	2.7931	0.0947
Group B	31/34.5	38/34.5	38/34.5	31/34.5	0.7101	0.3994
Group B1	6/7	8/7	8/7	6/7	0.2857	0.5930
Group B2	25/27.5	30/27.5	30/27.5	25/27.5	0.4545	0.5002

TDT – Transmission Disequilibrium Test; Group A – chronic glomerulonephritis; B – chronic interstitial nephritis; B1 – chronic interstitial nephritis without urinary tract defect; B2 – chronic interstitial nephritis with urinary tract defect

Table III. Distribution of rs 1617640 Epo SNP genotype depending on aetiology and progression of CKD
Tabela III. Rozkład genotypów polimorfizmu rs1617640 promotora genu erytropoetyny w zależności od etiologii i tempa progresji przewlekłej choroby nerek

	All patients (A + B) n = 109		Group A n = 30		Group B n = 79	
CKD progression	slow	rapid	slow	rapid	slow	rapid
Number of patients	55 (50.5%)	54 (49.5%)	6 (20%)	24 (80%)	49 (62%)	30 (38%)
Genotype AA	16 (29.1%)	12 (22.2%)	0	8 (33.33%)	16 (32.7%)	4 (13.3%)
Genotype CC	15 (27.3%)	13 (24.1%)	2 (33.3%)	8 (33.33%)	13 (26.5%)	5 (16.7%)
Genotype AC	24 (43.6%)	29 (53.7%)	4 (66.7%)	8 (33.33%)	20 (40.8%)	21 (17%)

Group A – chronic glomerulonephritis; B – chronic interstitial nephritis; B1 – chronic interstitial nephritis without urinary tract defect; B2 – chronic interstitial nephritis with urinary tract defect

onset and the age at disease diagnosis. The performed analysis demonstrated that the only factor significantly determining the risk of rapid disease progression was chronic glomerulonephritis as the primary cause of CKD; in this case the risk was 6.53 times higher than in chronic interstitial nephritis (OR = 6.53, 95%Cl = 2.37–18.02, p = 0.0004).

DISCUSSION

The results of population studies indicate the significant role of genetic predisposition to both kidney injury development and progression [23, 28]. Monogenic diseases, inherited by Mendel's principle, make only a marginal per-

cent of all the diseases which may lead to extreme renal insufficiency. Numerous mutations and polymorphisms of many genes are at the base of the majority of kidney diseases. Environmental factors also significantly contribute to the phenotypic pictures of the studies [24].

The demonstration of extramedullar erythropoietin actions throws a new light on the aetiology of injury affecting various organs, including the kidneys, while also providing a new perspective for the application of our knowledge in novel therapeutic strategies [12, 13,14,18,29,30,31,32]. Local erythropoietin actions remain quite independent of the endocrine kidney-bone marrow axis. Epo, via the mechanism of local secretion, exerts protective effects on tissues, influencing among others the angiogenesis and suppressing the apoptosis of cells [32,33].

Tong et al. demonstrated that the T allele of Epo gene promoter rs 1617640 polymorphism was a risk factor for the development of microangiopathic complications in diabetes, including diabetic injury of the kidneys [27]. In the observations of Popov et al., post-cardiosurgical patients with the TT genotype required renal replacement therapy much more often due to acute renal insufficiency, which may suggest that the T allele is a dysfunction risk factor [34].

The reported study aimed to demonstrate the influence of erythropoietin gene promoter polymorphism (rs 1617640) on the development and progression of nephropathy in the course of chronic interstitial nephritis and chronic glomerulonephritis. To our knowledge, it has been the first study of the abovementioned polymorphism in a family model. For that purpose, 109 families were evaluated for the transfer of alleles from two biological parents to their sick offspring. The obtained results did not confirm unequivocally the preliminary hypothesis. The investigated erythropoietin gene polymorphism rs 1617640 was not a significant risk factor for either chronic kidney disease occurrence or its progression in any of the studied subgroups of patients. However, taking into consideration the close-to-significant values of TDT ($p = 0.09$) as found in the patients

with chronic glomerulonephritis, one may expect that a study, performed on a larger population, may reverse the results and provide true evidence for the role of the studied polymorphism in the development of chronic injury.

CONCLUSIONS

In the case of chronic interstitial nephritis, erythropoietin gene promoter polymorphism rs 1617640 is not a risk factor either for the incidence of chronic kidney disease or its progression. The bordeline significance of preferential C allele transfer in patients with glomerulonephritis suggests association between of rs1617640 and CKD of this aethiology.

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