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Possible role of IL-6 and TIE2 gene polymorphisms in predicting the initial high transport status in patients with peritoneal dialysis: an observational study

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ABSTRACT

Objectives: The aim of this study was to investigate the effect of interleukin (IL)-6 and TIE2 gene polymorphisms on baseline peritoneal transport property.

Design: An observational study.

Setting: Renji Hospital in Shanghai, China.

Participants: This study included 220 patients with continuous ambulatory peritoneal dialysis (PD).

Outcome measures: Patients were divided into 2 groups based on the results of an initial peritoneal equilibration test performed within 3 months of starting PD therapy: group 1 consisted of low/low average transporters (n=123), and group 2 consisted of high/high average transporters (n=97). We genotyped TIE2 and IL-6 polymorphisms and analysed their effects on baseline transport status.

Results: The genotype AT in IL-6 Rs13306435 and the genotype CC in TIE2 Rs639225 were both negatively associated with a higher initial peritoneal transport status (IL-6 Rs13306435: OR=0.408, 95% CI 0.227 to 0.736; TIE2 Rs639225: OR=0.188, 95% CI 0.044 to 0.806).

Conclusions: IL-6 and TIE2 polymorphisms are associated with baseline peritoneal transport property.

Strengths and limitations of this study

- This study was the first study to explore the possible association between TIE2 gene polymorphisms and the characteristics of peritoneal transport.
- This was also the first study to confirm the association between the interleukin (IL)-6 polymorphism and baseline peritoneal transport among the Chinese Han population.
- We used a convenient and non-invasive method to study the initial high transport status in patients with peritoneal dialysis.
- The TA genotype of rs13306435 present in only 7% of the total population; therefore, it is not the main determinant of peritoneal transport in most patients.
- We did not examine dialysate IL-6/TIE2 concentration to investigate its relationship with single nucleotide polymorphisms.

INTRODUCTION

Peritoneal dialysis (PD) is an effective renal replacement therapy for patients with end-stage renal disease (ESRD).[1] Patients undergoing PD have significantly different small solute transport rates. The standard peritoneal equilibration test (PET) proposed by Twardowski *et al*[2] in 1987 is the most widely used method to assess the peritoneal small solute transport rate. Patients can be divided into four types: high (H), high average (HA), low average (LA) and low (L) based on PET results. Studies have shown an association between high transport status and poor outcome.[3–6] The results of a meta-analysis[7] have indicated that for every 0.1 increase in the dialysate over plasma ratio for creatinine (D/P Cr), the relative risks for mortality and technique failure increase by 1.15 and 1.18, respectively. Compared with the mortality of the low transport group, that of the LA, HA and high transport groups increased by 21.9%, 45.7% and 77.3%, respectively. As technology advances, new peritoneal dialysate (icodextrin)[8–11] and automated PD (APD)[12–14] have been shown to improve the prognosis of high transporters. However, in developing countries, icodextrin and APD cannot be widely used for patients with PD. Initial high transport is still an important factor that influences the outcome of these patients without icodextrin

or APD. Therefore, it is important to know the baseline peritoneal transport property before starting PD therapy. We can advise probable high transporter patients to choose haemodialysis (HD) or renal transplantation for renal replacement therapy. Researchers have attempted to find non-invasive biomarkers to predict the baseline peritoneal membrane function before starting dialysis. Previous studies found that age, gender and complications such as hypertension, diabetes and malnutrition might influence transport characteristics.[1] However, they are not sufficient to predict high transport status.

In recent years, many studies have shown that genetic variants may play an important role in mechanisms contributing to the baseline variability in peritoneal transport.[15–20] It has been suggested that chronic inflammation mediated by various inflammatory cytokines may have an effect on peritoneal transport.[21] Studies have shown that the interleukin (IL)-6 level in peritoneal dialysates is associated with the peritoneal solute transport rate in patients with dialysis.[22–24] A polymorphism of IL-6 (Rs13306435) is reported to correlate with baseline peritoneal transport status in Caucasian and Korean patients.[15 19] An increase in the effective solute exchange area caused by peritoneal vascular proliferation is also an important factor for high peritoneal transport status.[25] TIE2 is the receptor of angiogenin (Ang) 1 and 2. Ang/Tie2 has been confirmed to play an important role in angiogenesis in the peritoneum.[26] The angiogenesis of the peritoneum induced by PD can be inhibited using sTie2/Fc in a uremic rat model.[27] Therefore, it is possible that the genetic polymorphisms of IL-6 and TIE2 might be involved in the mechanism of high peritoneal transport status. This study aimed to determine whether TIE2 and IL-6 gene polymorphisms have an effect on the baseline peritoneal transport property and explore its possible role in predicting initial high transport status.

MATERIALS AND METHODS

Patient selection

All patients with PD having an initial PET performed within 3 months of starting PD therapy were included. Those who switched from failed renal allograft or maintenance HD were excluded. Two hundred and twenty patients with continuous ambulatory PD in the Peritoneal Dialysis Center, School of Medicine, in Shanghai Jiaotong University were enrolled in the study. Written informed consent was obtained from each patient.

Study of peritoneal transport

A standard PET was performed for each of the enrolled patients. Dialysate as well as plasma creatinine and glucose levels were measured at 4 hours using 2 L of 2.5% glucose dialysis fluid. Creatinine dialysate to plasma ratios at 4 hours (D/P Cr) were calculated. Patients were classified into four types based on the D/P Cr value: H (D/P Cr>0.8), HA (D/P Cr 0.66–0.8), LA (D/P Cr 0.5–0.65) and low transporters (D/P Cr<0.5). Then they were divided into two groups: group 1 consisted of L/LA transporters, and group 2 consisted of H/HA transporters. The residual urine volume was assessed after 24 hours of urine collection. Weekly peritoneal Kt/V (peritoneal Kt/V) and residual urine Kt/V (urine Kt/V) were calculated and presented as total weekly Kt/V (total Kt/V).

DNA extraction and genotyping

DNA was extracted from whole blood using a DNA purification kit (Promega, USA). The single nucleotide polymorphisms (SNPs) of IL-6 and TIE2 were genotyped by a single base primer extension assay. The genomic DNA flanking the SNP was amplified by PCR using forward and reverse primer pairs (tables 1 and 2), and standard PCR reagents in a 10 µL reaction volume containing a 20 ng DNA sample, 0.4 µmol of each primer, a 10× PCR buffer, 0.4 µmol dNTPs (Generay Biotech, China), 10 mmol $MgCl_2$ and 0.25 units HotStarTaq DNA Polymerase (QIAGEN, Germany). After 40 cycles of PCR (MJ Research PT-100), the products were purified by 2 U shrimp alkaline phosphatase (SAP) and 2 U exonuclease I (Epicentre). The purified amplification products (2 µL) were added into a SNaPShot Multiplex Ready reaction mixture (Applied Biosystems) containing 1 µL of genotyping primer for the primer extension reaction (tables 1 and 2). The primer extension reaction was carried out with 25 cycles at 96°C for 10 s, 50°C for 5 s and 60°C for 30 s. The reaction products were purified by 0.5 U SAP. The final reaction samples (0.5 µL) were added into 9.25 µL Hi-Di formamide (Applied Biosystems) and 0.25 µL GS-120 LIZ (Applied Biosystems). The mixture was incubated at 95°C for 5 min and then analysed by electrophoresis using the ABI Prism 3730xl DNA analyser (Applied Biosystems). Results were analysed using GeneScan analysis software (Applied Biosystems).

Table 1 Primer sequences of IL-6 for genotyping using SNapShot assay

SNP	PCR-L	PCR-R	Target
rs1800795	AACCTCCTCTAAGTGGGCTG	GGTGGGGCTGATTGGAAAC	TCCCCCTAGTTGTGTCTTGC
rs1800796			CCAGGCAGTTCTACAACAGCC
rs13306435	GAAGGGTCCTACTCAGAGCA	GTTGGGTCAGGGGTGGTTAT	TTCCTTCAGGCAAAGAATCTAGA

IL, interleukin; SNP, single nucleotide polymorphism.

Table 2 Primer sequences of TIE2 for genotyping using the SNapShot assay

SNP	PCR-L	PCR-R	Target
rs10967717	TTTCCTCTGGTGGGTAGGAA	GGGCTACTGGGATCTCTGAC	GAGGAGTATAATGATTTCCTCAGGC
rs657867			CCACATGGTTTGAATTGGGA
rs639225	TTCTTCCTCCTCAACCAGAAA	TCACATCAACGTGCTGGTCT	CAATATTGTCCAAGAAATCACAGC
rs542913	ACGGGTGGGTCTGTTTCTC	GAGGCTTGCCTAAGGGAAAT	CATTCTCCTTTGCACATTTGC
rs3737188	GATTGTCCCGAGGTCAAGAG	TTTCCCAGGGCACACAGTAT	TTGTCCCGAGGTCAAGAGGTGTA
rs2273719	TGGCACTGTTTGTCTTCCAG	ACCGGCTGACTTTGCTAGAG	AGGCACACCCTACTGCGG
rs2273718			AGTCTGTAGCCCTGGGGCA
rs10967789	ATGGGCTGAAATCAGAATGC	AACCTGTACTATCAGGGTCATTG	AATGCTATTAAATGTTTTCCTGTGT
rs9987817	CTGGGTGACATTTGGGAGAC	CACTCCTGGATGAGACGTGA	GATGAGACGTGAGTAGGCAAGA

SNP, single nucleotide polymorphism.

Statistical analysis

Statistical analysis was conducted using SPSS V.17.0. All categorical data were presented as absolute counts or percentages, and mean and SD were provided for continuous data. To compare the differences between two baseline transport groups, categorical data were analysed by Fisher's exact test and continuous variables were analysed by an unpaired t-test. Logistic regression analysis was applied to determine whether polymorphism of IL-6 and TIE2 affected the baseline peritoneal transport status. p Values of <0.05 were considered statistically significant.

RESULTS

Clinical parameters between different transport groups

In total, 220 patients were enrolled in this study. The average age of the patients was 52.54±14.56 years; the male-to-female ratio was 118:102 and the average body mass index was 21.83±3.47 kg/m^2. Residual renal function was 3.98±3.47 mL/min. The causes of ESRD were as follows: chronic glomerulonephritis (n=71; 32.3%), diabetic nephropathy (n=32; 14.5%), hypertensive nephropathy (n=9; 4.1%) and other/unknown (n=107; 48.6%). Based on the first PET results, there were 97 patients (44.1%) in the H/HA group, and 123 patients (55.9%) in the L/LA group. Comparisons of clinical characteristics between the two groups are shown in table 3.

Distribution of IL-6 and TIE2 polymorphisms in different transport groups

The distributions of IL-6 and TIE2 genotypes in the peritoneal transport groups are summarised in tables 4 and 5. Distributions of the 24 alleles (12 polymorphisms) were within the Hardy-Weinberg equilibrium. For the IL-6 polymorphism, there was a statistically significant correlation between the AT genotype of rs13306435 and the peritoneal transport group (p=0.023). For the TIE2 polymorphism, the distribution of rs10967789 and

Table 3 Comparison of clinical characteristics and peritoneal parameters between the peritoneal transport groups of 220 patients with peritoneal dialysis

	L/LA (n=123)	H/HA (n=97)	p Value
Age (year)	52.85±14.94	52.27±14.42	0.761
Male (%)	68 (55.3)	60 (61.8)	0.291
BMI (kg/m^2)	21.82±3.58	21.85±3.03	0.939
DM (%)	22 (17.8)	23 (23.7)	0.266
Hypertension (%)	94 (68.1)	75 (70.1)	0.740
Periods between operation and initial PET (d)	48 (39, 69)	47 (35, 68)	0.924
Haemoglobin (g/L)	104.60±22.67	99.13±21.29	0.056
Serum albumin (g/L)	36.37±4.7	34.8±5.33	0.017
hs-CRP (mg/L)	2.65 (0.71, 3.83)	2.58 (1, 3.86)	0.657
ACEI/ARB (%)	64 (52)	53 (54.6)	0.624
D4/D0 (glucose)	0.44±0.08	0.34±0.08	<0.01
D/P Cr	0.55±0.08	0.74±0.07	<0.01
RRF (mL/min)	4±2.92	3.95±2.63	0.901
Npcr (g/(kg.d))	1.05±0.6	0.96±0.26	
UF (mL)	160 (−200, 520)	80 (−45, 500)	0.004
Urine volume (mL)	1000 (560, 1400)	1000 (500, 1500)	0.217
Kt/V	2.23±0.58	2.20±0.56	0.647

ACEI; ACE inhibitors; ARB, angiotensin-receptor blockers; BMI, body mass index; DM, diabetes mellitus; D/P Cr, dialysate over plasma ratio for creatinine; H, high; HA, high average; hs-CRP, high-sensitive C reactive protein; L, low; LA, low average; PET, peritoneal equilibration test; RRF, residual renal function; UF, ultrafiltration.

Table 4 IL-6 gene polymorphisms in two groups

	L/LA (n=123)	H/HA (n=97)	p Value
Rs13306435			
AT	14	3	0.023
TT	109	94	
Rs1800796			
CC	77	61	0.986
CG	37	28	
GG	9	8	
Rs1800795			
GG	121	96	0.506
GC	2	1	

IL, interleukin; H, high; HA, high average; L, low; LA, low average.

Table 5 TIE2 gene polymorphisms in two groups

	L/LA (n=123)	H/HA (n=97)	p Value
Rs10967717			
AA	15	16	0.652
AG	56	47	
GG	52	34	
Rs10967789			
CC	90	83	0.039
CG	33	14	
Rs2273718			
AG	14	4	0.081
GG	109	93	
Rs2273719			
AA	4	2	0.868
AG	36	27	
GG	83	68	
Rs3737188			
CC	6	1	0.373
CT	44	31	
TT	73	65	
Rs542913			
CC	100	80	0.403
CT	22	17	
TT	1	0	
Rs639225			
CC	40	18	0.047
CT	53	46	
TT	30	33	
Rs657867			
AA	112	87	0.732
AG	11	10	
Rs9987817			
CC	97	74	0.730
CT	22	22	
TT	4	1	

H, high; HA, high average; L, low; LA, low average.

rs639225 genotypes differed significantly between the two groups (p=0.039 and 0.047, respectively).

Parameters for peritoneal solute transport rate for different genotypes

We further compared the peritoneal solute transport rate among groups with the three SNPs (rs13306435, rs10967789 and rs639225). We found no statistically significant difference in the data of D/P Cr and D/D0 glucose (the ratio of dialysate glucose concentrations at 0 and 4 hours) among different genotypes (table 6).

Roles of IL-6 and TIE2 gene polymorphisms in predicting initial peritoneal high transport status

With possible clinical factors controlled in a multiple logistic regression model, the genotype AT in IL-6 Rs13306435 and CC in TIE2 Rs639225 were both negatively associated with a higher initial peritoneal transport status (IL-6 Rs13306435: OR=0.408, 95% CI 0.227 to 0.736; TIE2 Rs639225: OR=0.188, 95% CI 0.044 to 0.806; table 7).

DISCUSSION

The relationship between gene polymorphisms and disease has been receiving greater attention from researchers. It has been shown that SNPs of IL-6 may influence the development of cardiovascular disease,[28] cancer,[29 30] fractures[31] and autoimmune diseases.[32–34] In contrast, there is less available research regarding TIE2 gene polymorphisms, except for a study on the relationship between rs638203/rs639225 and vascular malformations.[35]

In this study, we investigated the effect of genetic polymorphisms of IL-6 and TIE2 on the baseline peritoneal transport property. Results showed that IL-6 and TIE2 gene polymorphisms were both negatively associated with initial high transport status. The genotypes of rs13306435 and rs639225 were shown to be independent predictors of initial high transport status in patients with PD.

Initial transport status can determine the patients' dialysis prescription, which may influence the outcome for patients with PD. Previous studies have shown an association between initial high transport status and poor outcome. Although icodextrin and APD have been shown to improve the prognosis of high transporters, most of the patients with PD in developing countries are unable to use them. In China, for instance, icodextrin has not been approved for sale yet, and few patients can afford the cost of APD therapy. Therefore, predicting

Table 6 The parameters for peritoneal solute transport rate according to different genotypes

IL-6 Rs13306435	AT	TT	p Value
D/P creatinine	0.61±0.99	0.63±0.12	0.357
D/D0 glucose	0.41±0.092	0.39±0.085	0.424
TIE2 Rs639225	CC	CT/TT	
D/P creatinine	0.61±0.11	0.64±0.11	0.056
D/D0 glucose	0.40±0.09	0.39±0.08	0.518
TIE2 Rs10967789	CC	CG	
D/P creatinine	0.64±0.12	0.61±0.09	0.187
D/D0 glucose	0.39±0.09	0.40±0.06	0.839

D/P, dialysate over plasma ratio; IL, interleukin.

Table 7 Multivariate logistic regression model to identify factors associated with high/high average transport status

	OR	95% CI	p Value
TIE2 Rs639225 (CC vs CT/TT)	0.188	0.044 to 0.806	0.024
IL-6 Rs13306435 (AT vs TT)	0.408	0.227 to 0.736	0.043
Age	0.966	0.930 to 1.004	0.081
Male	1.401	0.519 to 3.788	0.506
DM	3.28	0.952 to 11.360	0.060
Periods between operation and initial PET (d)	0.996	0.987 to 1.005	0.401
hs-CRP(mg/L)	1.081	0.964 to 1.212	0.182
Serum albumin (g/L)	0.898	0.796 to 1.014	0.083
TIE2 Rs10967789 (CC vs CG)	1.061	0.371 to 1.632	0.197
Haemoglobin (g/L)	0.984	0.796 to 1.014	0.192

DM, diabetes mellitus; hs-CRP, high-sensitive C reactive protein; IL, interleukin; PET, peritoneal equilibration test.

the baseline transport status is important to select a better treatment strategy. Our study provided a potential solution to predict initial high transport status before beginning PD.

There have been several genetic studies of peritoneal solute transport rate in patients with PD. Polymorphisms of endothelial nitric oxide synthase,[16] receptor of advanced glycation end products[17] and transforming growth factor-βl[18] were reported to be involved in baseline transport status. In 2005, Gillerot *et al*[15] showed that the SNP of IL-6 (rs1800795) influenced baseline peritoneal permeability in Caucasian patients with PD. Additionally, Hwang *et al*[19] reported that the rs1800795 polymorphism was associated with dialysate IL-6 concentration and baseline peritoneal transport status in Korean patients with PD. However, for the Chinese Han population, the minor allele frequency (MAF) of rs1800795 was reported to be very low (MAF=0.02). Thus, it might not be appropriate to directly apply these results to this population. Our finding is similar to those of the aforementioned studies. This supports the role of the IL-6 polymorphism in predicting baseline peritoneal transport.

Angiogenesis in the peritoneum could directly increase the effective solute exchange area and influence the transport characteristics. Previous studies have found that polymorphisms of vascular endothelial growth factor were not associated with initial peritoneal transport type.[15 17] Ang/Tie2 has recently been confirmed to play an important role in angiogenesis in the peritoneum.[26] Whether the polymorphisms of TIE2 are involved in initial peritoneal transport status remains unknown. In this study, we carefully selected nine SNPs with MAF>0.05 in the Chinese Han population to investigate their possible role in predicting high transport status. The results showed that TIE2 could be a new factor in predicting the baseline transport type. This is the first study to explore the possible association between TIE2 gene polymorphisms and characteristics of peritoneal transport. Rs639225 is located in exon 13 of TIE2. A study reported its association with venous malformation and presumed that this polymorphism might cause abnormal splicing of *TIE2* into a defective protein.[28] Functional validation of this polymorphism is warranted in the future.

There are some limitations to our study. The TA genotype of rs13306435 presents in only 7% of the total population; therefore, it is not the main determinant of peritoneal transport in most patients. Additionally, this study was conducted at a single centre and the number of cases was limited; increasing the sample size would improve this study. Research has shown that the IL-6/TIE2 concentration was associated with baseline transport status. We hypothesised that the SNPs may participate in the formation of high transport status by influencing the dialysate IL-6/TIE2 concentration. We did not examine the dialysate IL-6/TIE2 concentration in this study. As shown in table 6, we did not find any statistically significant difference in the data of D/P Cr and D/D0 glucose between the different genotypes. We believe that this may be due to the limited sample size.

In conclusion, IL-6 and TIE2 polymorphisms are associated with baseline peritoneal transport property. A functional study of the polymorphisms is required in the future.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval Ethical committee of Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China.

Data sharing statement The technical appendix, statistical code and data set are available from the corresponding author.

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