Relationship between URAT1 Gene Polymorphism and Uric Acid-Lowering Effect of Losartan in Hypertensive Patients with Hyperuricemia

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To investigate the relationship between urate iransporter-1 gene polymorphism and the uric acid-lowering effect of losartan in hypertensive patients complicated with hyperuricemia, polymerase chain reaction-restriction fragment length polymorphism was used to identify the genotypes of 100 hypertensive patients with hyperuricemia and 100 healthy controls. The experimental group patients received oral administration of 100 mg losartan for 14 d. Blood pressure, uric acid, creatinine, blood urea nitrogen, triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, small and dense low-density lipoprotein cholesterol and fasting plasma glucose were measured before and after treatment. There was no significant difference in the frequency distribution of alleles and genotypes of rs7929627, rs75786299 and rs3825017 between the two groups. After treatment, the levels of uric acid, creatinine, blood urea nitrogen and fasting plasma glucose were significantly decreased and the levels of uric acid and creatinine in hypertensive patients with hyperuricemia were significantly lower than those with TT genotype ($p<0.05$). The rs7929627, rs75786299, and rs3825017 of the URAT1 gene could affect the uric acid-lowering effect of losartan.

Key words: Hypertension, hyperuricemia, URAT1, genetic polymorphism, losartan

Recent studies have reported that hyperuricemia was one of the risk factors for cardiovascular disease[1-3]. For hypertensive patients complicated with hyperuricemia, it is necessary not only to reduce blood pressure, but also to reduce the level of serum uric acid (UA) to achieve a good therapeutic effect. Losartan has both antihypertensive and UA level lowering effects and is the main drug for the treatment of hypertension complicated with hyperuricemia. The mechanism is achieved by inhibiting the urate transporter 1 (URAT1) on the proximal renal tubules brush border cells. URAT1 was a highly specific electrically neutral urate exchanger, which can reabsorb the Ur and secrete a small amount of Ur, so as to regulate the concentration of serum Ur and promote the balance. Therefore, a large number of studies have focused on the relationship between URAT1 gene single nucleotide polymorphism (SNP) and human hyperuricemia[4-6]. Many studies have pointed out that URAT1 gene SNP was associated with primary hyperuricemia, and its multiple site mutations may be the candidate genes for hyperuricemia[7-10]. Previous studies have shown that URAT1 gene rs7929627, rs75786299, rs3825017 polymorphisms were closely related to the Ur levels in the body, but the correlation with the Ur-lowering effect of losartan has not been reported. The purpose of this study was to investigate the relationship between URAT1 gene polymorphism and the effect of losartan on reducing Ur in patients with hypertension complicated with hyperuricemia. At the same time, this study detects the changes of sd LDL-c indexes in hypertension patients complicated with hyperuricemia treated with losartan, so as to provide the experimental basis for losartan to regulate lipid metabolism through URAT1 gene and provide guidance for clinical medication.

A total of 100 patients with hyperuricemia complicated with hypertension treated in the department of cardiology in the Shidong Hospital from 2018 to 2019 were selected as the experimental group, 46 males and 54 females, with an average age of 65±12 y. At the same time, 100 healthy patients were selected as the control group, including 48 males and 52 females, with an average age of 63.2±15.3 y. Inclusion criteria

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of patients with hypertension complicated with hyperuricemia were, age of 45-70 y, systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg meeting the diagnostic criteria of hypertension, the level of serum UA in males higher than 7 mg/dl (416 μM), the level of serum UA in females higher than 6 mg/dl (357 μM) meeting the diagnostic criteria of hyperuricemia. Exclusion criteria were those patients with normal UA, secondary hypertension, congestive heart failure, transient ischemic attack, hepatic and renal insufficiency caused by nephropathy. One hundred patients in the experiment group received oral administration of 100 mg losartan for 14 d. All the subjects signed the informed consent form before participating in the study. The equipment used were, automatic UV spectrophotometer Q3000 (Thmorgan), gradient PCR (Olabo), UVP gel solo (Bio-Rad), high-speed refrigerated centrifuge (Beckman Coulter), PCR primer (General BioSystems), LA Taq DNA polymerase (Detai Biologics), 100-1000 base pairs DNA marker (Beijing Dingguo Changsheng Biotechnology) and automatic biochemical analyser (Beckman Coulter).

Fasting venous blood was collected before and after taking losartan and the contents of UA, creatinine (CR), blood urea nitrogen (BUN), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), small and dense low-density lipoprotein cholesterol (sd LDL-C) and fasting plasma glucose (FBG) were measured. At the same time, the patient's blood pressure was recorded. A total of 1 ml venous blood was collected after 12-14 h of fasting (EDTA used as an anticoagulant). Genomic DNA was extracted and stored at -20° according to the procedure of the QIAamp DNA Blood Midi Kit (Qiagen, Germany). Mass Array platform integrating iPLEX and Mass Array technology was used for genotyping. This technique contained 5 major steps, initial locus specific PCR amplification was performed, followed by shrimp alkaline phosphatase was used to neutralize the uncombined deoxynucleotides (dNTPs) and UEP extension reaction was performed. Resin was used to purify excess ionic compounds, and finally MALDI-TOF mass spectrometry was used to analyze the distinct mass of extended primer, which could trace the alternate alleles.

Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used for genotyping. Referring to the NCBI database and designing the corresponding primers combined with Premier Primer 5.0 software, the rapid detection technique of multiple gene point mutations was used to detect the 3 SNP loci of the screened URAT1 gene. PCR reaction system contained 2.5 μl 10 PCR buffer (containing Mg^{2+}), 2μl deoxy-nucleoside triphosphate, 0.7 μl primers, 1.5 μl DNAs template, 0.2 μl Taq polymerase. The primers used in this study were as follows, rs7929627F-AAATTCAGCTTTCCCGGGAGGT, rs7929627R TACTCAAGGGGCCCAGAAGAGG, rs75786299F GCCTAAGGGTGAGCCTGGAGAC, rs75786299R GGGCTCTGCACCTTGAGTCATC, rs3825017F GGGCTCTGCAGGAGGCATAGAT, rs3825017R CTCTGTGTGGGCTTGGGTCACT. The differences in the 3 SNP loci of the URAT1 gene between the two groups were analyzed. The changes of UA, CS, BUN, TG, TC, HDL-C, LDL-C, sd LDL-C and FBG before and after losartan administration in hypertensive patients complicated with hyperuricemia group were analyzed, and then the correlation between the alleles of each SNP locus and the changes in these indices. The effect of each SNP locus of URAT1 gene on the effectiveness of losartan was analyzed. In this study, SPSS 22.0 software was used for statistical analysis and the numerical value was expressed in the form of mean±standard deviation (SD). The chi-square test was used to analyze the distribution of URAT1 genotypes. One-way ANOVA was used to analyze the difference, and t-test was used to compare the data before and after treatment. $p<0.05$ indicates that the difference is statistically significant. According to the comparative analysis of the clinical data of the 2 groups, there was no significant difference in age, sex ratio, BMI, TG, HDL-C, LDL-C, and sd LDL-C between the two groups. There were significant differences in UA, CR, BUN, TC and FBG between the 2 groups ($p<0.05$, Table 1).

The genotypes of rs7929627, rs75786299, and rs3825017 loci of URAT1 gene in the control group were in accordance with the HWE balance test ($\chi2=0.12$, P=0.56; $\chi2=0.09$, P=0.76; $\chi2=0.56$, P=0.82). The results of statistical analysis showed that there was no significant difference in allele and genotype frequency distribution of rs7929627, rs75786299, and rs3825017 between the 2 groups (Table 2).

The clinical characteristics of hypertensive patients with hyperuricemia before taking losartan were studied. The results showed that there was no significant difference in basic clinical data among rs7929627, rs75786299, and rs3825017 genotypes of URAT1 gene ($p>0.05$, Table 3). Comparison of clinical indices of 100 hypertensive patients complicated with

hyperuricemia before and after taking losartan demonstrated that the levels of UA, CR, BUN and FBG decreased significantly after treatment ($p<0.05$). However, there were no significant differences in other indices, such as TG, TC, HDL-C, LDL-C, and sd LDL-C before and after treatment (Table 4). In order to analyse the relationship between the genotypes of rs7929627, rs75786299, and rs3825017 of the URAT1 gene and the efficacy of losartan, the difference of detection indices and the reduction before and after treatment were compared. The results showed that the decreased level and extent of UA and CR in hypertensive patients with hyperuricemia (TC/CC) were significantly lower than those in patients with TT genotype (Table 5).

In recent years, due to improvement of the economic level great changes have taken place in people's way of life. There are more and more patients with hypertension and the incidence of hypertension complicated with hyperuricemia is also increasing. A large number of studies have pointed out that the patients with hypertension complicated with hyperuricemia were related to metabolic diseases such as hypertension, diabetes and cardiovascular and cerebrovascular diseases[11-14]. The results of this study showed that compared to the general biochemical indices of the 2 groups, most of the biochemical indices in the experimental group were higher than those in the control group. There was no significant difference in age, sex ratio, BMI, TG, HDL-C, LDL-C, and sd LDL-C between the two groups. However, there were significant differences in UA, CR, BUN, TC and FBG between the 2 groups. A number of studies have pointed out that losartan exerted a dose-dependent reduction in the level of serum UA[15-17]. The mechanism of losartan in reducing UA depended on the excretion of its parent compound. Several studies have also shown that losartan plays a role in reducing UA by reducing URAT1 mRNA levels[18-19]. Some studies have pointed out that in patients with hypertension, a functional mutation of URAT1 would abolish the UR-lowering effect of losartan, while the normal gene still would contribute to the reduction of UA[20]. Therefore, the change of URAT1 gene function on the mechanism of losartan-induced reduction of UA was still the key to the treatment of hypertension complicated with hyperuricemia. The purpose of this study was to study the relationship between URAT1 gene polymorphism and the UA reducing effect of losartan in hypertensive patients complicated with hyperuricemia. URAT1 gene located on chromosome 11q13 consisted of 10 exons, 9 introns, and 12 transmembrane domains. The total length is 2642 base pairs, the coding region is 1659 base pairs, which encodes a membrane transporter protein of 555 amino acids. URAT1 contains two kinds of spliced protein, protein a (553 amino acids) and protein b (332 amino acids). Compared to protein a, protein b lacks 221 amino acids. It is speculated that this special structure may affect the reabsorption of UA by renal tubules. Previous studies have shown that multiple site polymorphisms of URAT1 gene were closely related to the level of UA in the body and the results of DNA amplification and sequencing showed that there were some differences in the frequencies of TT, TC, and CC at different sites[21]. In this investigation, the polymorphisms of rs7929627, rs75786299, and rs3825017 of the URAT1 gene were analysed. The results showed that there was no significant difference in allele and genotype frequency distribution of

TABLE 1: COMPARISON OF CLINICAL DATA BETWEEN TWO GROUPS

Clinical data	Control group	Experimental group	P
Male/female	48/52	46/54	0.456
Age (y)	63.2±15.3	65±12	0.203
BMI (kg/m^2)	24.65±3.1	23.48±2.6	0.103
UA (μM)	289±68	506±92	0.000
CR (mM)	47±32	96±18	0.000
BUN (mM)	4.9±0.9	6.8±2.4	0.000
TG (mM)	1.58±0.99	1.67±0.68	0.062
TC (mM)	3.7±0.34	6.0±0.56	0.001
HDL-C (mM)	1.23±0.37	1.06±0.22	0.674
LDL-C (mM)	2.56±0.45	3.06±0.52	0.108
sd LDL-C (mM)	1.13±0.21	1.32±0.18	0.134
FBG (mM)	4.8±0.8	8.9±0.6	0.000

TABLE 2: DISTRIBUTION CHARACTERISTICS OF GENOTYPE AND ALLELE FREQUENCY OF URAT1 SNP LOCI IN THE TWO GROUPS

Loci	SNP	Control group	Experimental group	x^2	P
	TT	222 (22.4)	238 (24.0)	1.332	0.876
	TC	454 (45.9)	426 (43.0)	1.441	0.545
rs7929627	CC	312 (31.7)	326 (33.0)	0.454	0.434
	T	846 (42.7)	968 (48.9)	0.874	0.843
	C	1134 (57.3)	1012 (51.1)	2.910	0.433
	TT	310 (31.3)	338 (34.1)	1.733	0.342
	TC	425 (42.9)	450 (45.5)	0.939	0.123
rs75786299	CC	255 (25.8)	202 (20.4)	0.343	0.439
	T	1086 (54.8)	1126 (56.9)	0.594	0.234
	C	894 (45.2)	854 (43.1)	0.383	0.530
	TT	268 (27.1)	288 (29.1)	1.000	0.083
	TC	348 (35.2)	404 (40.8)	0.545	0.294
rs3825017	CC	372 (37.7)	296 (30.1)	0.324	0.204
	T	886 (44.7)	964 (48.7)	0.232	0.504
	C	1094 (55.3)	1016 (51.3)	1.403	0.249

TABLE 3: CLINICAL DATA OF DIFFERENT GENOTYPES OF SNP IN THE EXPERIMENTAL GROUP BEFORE LOSARTAN TREATMENT

Clinical data	rs7929627			P	rs75786299			P	rs3825017			P
	TT	TC	CC		TT	TC	CC		TT	TC	CC	
Male	13	15	18	0.103	12	16	18	0.332	17	15	14	0.803
Female	21	19	14	0.203	16	19	19	0.232	20	18	16	0.434
Age (y)	62.8±15.9	66.4±13.86	63.8±12.87	0.098	67.0±12.5	63.7±10.9	64.8±14.7	0.065	62.5±11.8	66.8 ±13.7	67.3 ±13.4	0.555
BMI (kg /m^2)	24.8±3.1	23.9±3.1	25.3±1.5	0.394	24.5±2.6	23.6±2.0	23.2±3.0	0.098	23.5±3.6	23.6 ±1.4	23.3 ±1.6	0.384
UA (μM)	506±92	506±92	506±92	0.934	506±92	506±92	506±92	0.202	506±92	506 ±92	506 ±92	0.102
CR (mM)	96±18	96±18	96±18	0.239	96±18	96±18	96±18	0.102	96±18	96 ±18	96 ±18	0.302
BUN (mM)	6.7±2.1	6.8±2.4	7.0±3.4	0.503	6.6±4.5	7.1±3.8	7.3±3.0	0.124	6.8±2.4	6.5 ±2.9	6.9 ±2.0	0.233
TG (mM)	1.69±0.48	1.777±0.55	1.58±0.99	0.403	1.69±0.44	1.69±0.55	1.70±0.31	0.116	1.66±0.59	1.67 ±0.47	1.68 ±0.43	0.119
TC (mM)	5.8±0.7	6.1±0.6	6.2±0.5	0.322	6.0±0.56	6.0±0.6	6.0±0.6	0.493	6.3±0.3	6.1 ±0.8	5.8 ±0.4	0.125
HDL-C (mM)	1.13±0.25	1.11±0.30	1.22±0.24	0.232	1.34±0.10	1.21±0.17	1.11±0.25	0.503	1.22±0.21	1.19 ±0.18	1.03 ±0.27	0.432
LDL-C (mM)	3.03±0.42	3.08±0.42	3.09±0.46	0.329	3.23±0.41	3.03±0.32	3.03±0.02	0.493	3.05±0.45	3.06 ±0.48	3.07 ±0.90	0.443
sd LDL-C (mM)	1.38±0.09	1.36±0.32	1.32±0.16	0.401	1.35±0.14	1.39±0.12	1.40±0.13	0.223	1.33±0.19	1.30 ±0.16	1.38 ±0.22	0.221
FBG (mM)	8.7±0.3	8.7±0.5	8.6±0.5	0.089	9.0±0.3	9.1±0.6	8.8±0.7	0.594	8.5±0.9	8.2 ±0.9	8.8 ±0.5	0.332

TABLE 4: COMPARISON OF CLINICAL DATA BEFORE AND AFTER TAKING LOSARTAN IN EXPERIMENTAL GROUP

Indexes	Before	After	P
UA (μM)	506.56±92.33	438.56±56.86	0.000
CR (mM)	96.67±18.45	84.35±16.98	0.000
BUN (mM)	6.8±2.4	5.4±2.3	0.000
TG (mM)	1.68±0.67	1.75±0.45	0.342
TC (mM)	6.0±0.56	6.8±0.24	0.127
HDL-C (mM)	1.08±0.24	1.06±0.22	0.321
LDL-C (mM)	3.07±0.54	3.89±0.42	0.123
sd LDL-C (mM)	1.32±0.18	1.34±0.22	0.158
FBG (mM)	8.9±0.6	7.2±0.4	0.000

TABLE 5: COMPARISON OF CLINICAL INDICES OF PATIENTS WITH DIFFERENT SNP GENOTYPES IN THE EXPERIMENTAL GROUP BEFORE AND AFTER TREATMENT

Indices	rs7929627			P	rs75786299			P	rs3825017			P
	TT (34)	TC (34)	CC (32)		TT (28)	TC (35)	CC (37)		TT (37)	TC (33)	CC (30)	
ΔUA	123.54 ±46.87	7.86 ±9.84	1.85 ±4.07	0.000	119.56 ±65.87	8.96 ±6.76	1.00 ±5.76	0.000	113.54 ±76.94	6.86 ±9.24	1.24 ±8.43	0.000
ΔCR	8.67 ±12.34	6.35 ±7.89	2.65 ±3.48	0.001	9.01 ±15.98	5.87 ±2.84	2.19 ±3.02	0.000	9.02 ±14.65	5.98 ±7.67	2.25 ±3.03	0.002
ΔBUN	0.83 ±1.24	1.26 ±0.89	0.76 ±1.42	0.342	0.84 ±1.54	1.12 ±0.79	0.73 ±1.58	0.124	0.79 ±1.45	1.38 ±0.79	0.69 ±1.56	0.125
ΦUA	23.54% ±13.67%	1.36% ±3.67%	1.5% ±3.6%	0.000	23.46% ±12.87%	1.42% ±3.48%	1.67% ±4.65%	0.000	24.76% ±14.73%	1.40% ±3.24%	1.8% ±2.9%	0.001
ΦCR	8.79% ±14.56%	6.73% ±7.84%	2.64% ±5.98%	0.000	9.02% ±16.78%	6.44% ±7.02%	2.43% ±5.55%	0.000	8.99% ±15.73%	6.42% ±8.03%	2.33% ±5.01%	0.002
ΦBUN	12.03% ±18.76%	14.54% ±13.33%	2.43% ±5.66%	0.118	12.58% ±18.55%	13.88% ±12.67%	2.09% ±4.78%	0.095	13.56% ±19.06%	13.95% ±12.99%	2.68% ±5.99%	0.065

rs7929627, rs75786299, and rs3825017 between the experimental group and the control group. Although there was no significant difference in the distribution of alleles and genotypes of rs7929627, rs75786299, and rs3825017 loci between the experimental group and the control group, and there was no significant difference in the basic clinical data of URAT1 gene SNP locus genotypes before treatment, UA, CR, BUN, and FBG decreased significantly after treatment. In addition, the extent of reduction of UA and CR in hypertensive patients with hyperuricemia (TC/CC) were significantly lower than those in patients with TT genotype.

To sum up, this study found that 3 loci of URAT1 gene, rs7929627, rs75786299, and rs3825017 could affect the UA-lowering effect of losartan. Therefore, the treatment of hypertension complicated with hyperuricemia can be determined according to the genetic characteristics of rs7929627, rs75786299, and rs3825017 of the URAT1 gene.

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Conflict of interest:

All authors report no conflicts of interest in this work.

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