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Research Article
Impact of Solute Carrier Family 47 Member 1 Gene Polymorphism Detection on Therapeutic Effect of Diabetes

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Abstract

Background and Objective: At present, some clinical treatment programs are using the known gene theory to study the relationship between gene polymorphism and drug efficacy and safety with the goal of drug effect and safety. As SLC47A1 (Solute carrier family 47 members 1, SLC47A1) was a transporter for diabetes treatment drug metformin. We conducted a statistical analysis of the SLC47A1 genetic testing results and diabetes patients data in the department of endocrinology in the second quarter of 2019 in our hospital to explore the impact of SLC47A1 gene polymorphism on the treatment of diabetes. **Materials and Methods:** We investigated 372 cases of SLC47A1 gene test reports and patient medical records, collected information on gender, age, diabetes type, complications and the relationship between genotype and biochemical indicators before and after metformin treatment and perform statistical analysis on it. **Results:** GG genotype had the highest incidence in men, <30 years or type 2 diabetes patients, GA genotypes had the highest incidence in men, >30 years or type 2 diabetes patients and AA genotype had the highest incidence in men, <30 years or type 1 diabetes. Besides, the complications that each genotype tended to occur were also significantly different. At the same time, compared with the biochemical parameters before the guidance, the biochemical parameters after the guidance were significantly improved. **Conclusion:** The guidance of SLC47A1 gene polymorphism on metformin medication could improve diabetes treatment effect and patients with AA genotype had the best treatment effect.

Key words: SLC47A1 gene polymorphism, genetic testing, diabetes, blood biochemical examination, therapy effect

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

T2DM diabetes is a chronic disease characterized by elevated blood glucose[1]. Metformin is currently the most widely used oral hypoglycemic agent in the world. It can increase the sensitivity of surrounding tissues to insulin, insulin-mediated glucose utilization and glucose utilization by non-insulin-dependent tissues[2,3].

Studies have found that there were individual differences in the treatment of diabetic patients with metformin and approximately 29-38% of patients could not obtain the ideal hypoglycemic effect[4,5]. Metformin was a substrate of various multi-specific solute carrier organic cation transporters[6]. These transporters included MATE1 (multidrug and toxin extrusion protein 1, MATE1) which was expressed in the proximal tubules of the kidney and the brush border membrane on the lumen side of the liver tubules. It participated in the *in vivo* disposal of metformin and was responsible for the excretion of cationic drugs including metformin in renal tubular epithelial cells. It was closely related to the metabolism of metformin *in vivo*[7]. The SLC47A1 gene encodes MATE1, so it was speculated that the SLC47A1 gene polymorphism may affect the metabolism of MATE1 in the body, causing changes in metformin excretion and then affecting the hypoglycemic effect of metformin. According to reports, SLC47A1 (rs2289669) gene polymorphism was related to the drug response of metformin[8]. The A allele was more effective, while the G allele was worse[9]. Compared with GA+GG genotype patients after metformin treatment, the reduction of AA genotype HbA1c was greater. Studies had shown that the effect of rs2289669 gene polymorphism on the hypoglycemic effect of metformin may be partially or completely due to decreased renal excretion and increased plasma metformin levels[10]. However, some studies had shown that the SLC47A1 rs2289669 genotype had nothing to do with HbA1c levels[11]. The different results may be related to the sample size that there need replication studies were needed in a relatively large number of multi-ethnic diabetes cohorts to confirm the effect of the SLC47A1 rs2289669 polymorphism on the efficacy of metformin in blood glucose control.

To further enrich the data, we will further analyze the relationship between the distribution of gene polymorphism in our hospital and the efficacy of metformin, aiming to provide evidence for gene-oriented TDM personalized medicine.

MATERIALS AND METHODS

Study area: The starting and ending time of the project was from April, 1-June 30, 2019 and there was no age limiting. In the end, there were 372 genetic testing data.

Common materials: Our research plan was mainly divided into 4 parts: (1) Enrollment of diabetic patients, (2) SLC47A1 gene detection in diabetic patients, (3) Clinical pharmacists provided clinical guidance reports for the clinician on metformin medication based on the results of genetic testing, (4) Clinician would adjust metformin medication according to the report and (5) Analyzing the patient's parameters before and after medication guidance to determine the treatment effect of SLC47A1 testing on metformin personalized medication guidance. The above-mentioned had been made into a flow chart, please refer to Fig. 1 for details.

Population material: This research protocol was ethically reviewed and approved by the Medical Ethics Committee of Yijishan Hospital of Wannan Medical College (No.: 2014 Lunshenxin No. 25). The data was about the data of TDM patients before receiving treatment in our hospital. The specific detailed inclusion and exclusion criteria were that the patients would accept metformin therapy after they were evaluated by a doctor. The diagnostic criteria of TDM should meet the "1999 WHO Diabetes Diagnostic Criteria".

Genetic testing process

Experimental materials

Instrument: L998A fluorescence detector (Xian Tian Long Technology Co., Ltd. Xian, China). Reagents: Nucleic acid purification reagents (Beijing Huaxia Times Gene Technology Development Co., Ltd. Beijing, China), Gene Test General Reagent, (Beijing Huaxia Times Gene Technology Development Co., Ltd. Beijing, China), 10×ammonium chloride solution (Beijing Huaxia Times Gene Technology Development Co., Ltd. Beijing, China).

Process: We first extracted DNA from the patient's blood and then detected the genotype of SLC47A1 on the L998A fluorescence detector and the instrument detection method was PCR - Restriction Fragment Length Polymorphism. Quality control would be done before the experiment and the test on the same day would only start when the three genotypes of each gene were accurate.

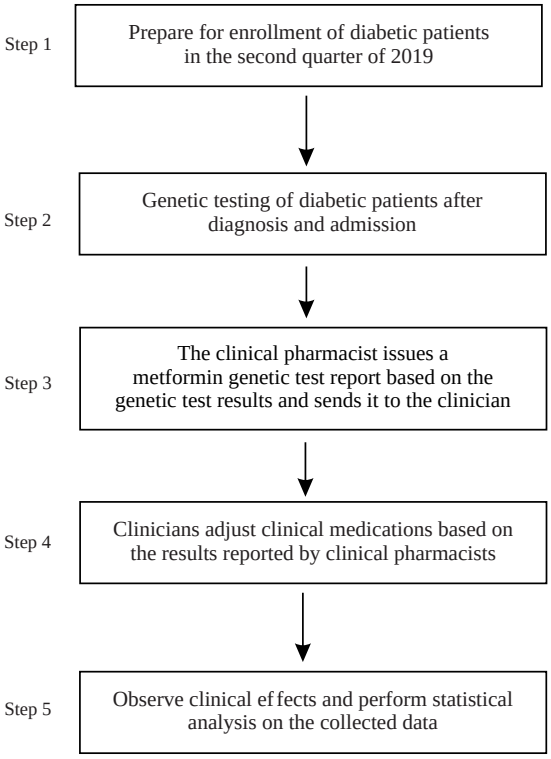

Fig. 1: Basic process of metformin medication based on genetic testing
Whole process was divided into 5 steps and they were in close contact, any step could be indispensable

Process of individualized metformin medication guided by genetic testing: SLC47A1 has three gene genotypes, each gene genotype corresponding to three different metformin treatments. The clinical pharmacist will give a specific medication report for metformin based on the result and the patient's clinical data. If the patient's genotype is GG, The sensitivity to metformin is poor and the hypoglycemic response is reduced, consider increasing the dose of metformin or using metformin combined with sulfonylureas or other hypoglycemic drugs. If the patient's genotype is GA, the sensitivity to metformin is moderate and the hypoglycemic effect is moderate. For a moderate response rate, if the patient has higher requirements for glucose control, consider increasing the dose of metformin or use metformin combined with sulfonylureas or other hypoglycemic drugs. If the patient's genotype is AA, It has good sensitivity to metformin and good hypoglycemic response. The responsiveness is better and metformin can be selected alone.

Biochemical parameters testing process

Experimental materials: Test paper (Shengshi Dong Tang Technology Development Co., Ltd. Jiangsu, China), Fully automatic bioanalysis machine (Sheng shi dong tang Technology Development Co., Ltd. Jiangsu, China).

The biochemical parameters of diabetic patients were mainly detected by hospital biochemical testing equipment.

Statistical analysis: Data were analyzed using SPSS 24.0 for windows (SPSS Inc., Chicago, IL, USA). Data were presented as Means±SEM. The chi-square test or Fisher's exact test was used to compare categorical variables. Statistical significance was defined as *p<0.05, **p<0.001 and ***p<0.001.

RESULTS

Demographic features of patients and genotype distribution: Genetic testing to guide clinical medication required the participation of doctors, pharmacists and patients and for a specific working process, please refer to Fig. 1. We first made statistics on the basic characteristics of patients. In the second quarter, a total of 372 patients with diabetes before receiving treatment were tested for SLC47A1 gene rs2289669 polymorphism in our hospital as shown in Table 1, there were 258 males (69.35%) and 114 females (30.65%). Among male patients, GA genotype accounted for the highest proportion, reaching 42.64% and among female patients, GG genotype accounted for the highest proportion, reaching 36.84%. However, there was no significant difference in the distribution of the three genotypes between male patients and female patients. In addition, patients were mainly over 30 years old, accounting for 95.70% and GA genotype patients account for the largest proportion, reaching 40.73% and patients under 30 years of age had the most GG genotype patients, accounting for 56.25%. Similarly, there was no significant difference in the distribution of the three genotypes between the two groups of patients over 30 and under 30. Among the patients, type 2 diabetes accounted for 94.62%, among them, GA genotype patients accounted for the highest proportion, 39.20%, type 1 diabetes only accounted for 5.38% and GA and AA patients accounted for the highest proportion, reaching 35%. At the same time, we found that GG genotype had the highest incidence in males, <30 years old or type 2 diabetes patients, GA genotype had the highest incidence in males, >30 years old or type 2 diabetes patients, The AA genotype had the highest incidence in men, <30 years old or type 1 diabetes. There was no significant difference in the distribution of the three genotypes between type 1 diabetes and type 2 diabetes. We also counted the diabetes-related complications of the three genotypes and discovered that the genotypes of three different genes had significant statistical differences in the impact of some diabetes-related

Table 1: Comparison of the distribution of SLC471 genotype in 372 diabetics with different clinical features

		SLC471G>A Genotype (case %[b])				
Clinical	Case (%)[a]	GA (%)	GG (%)	AA (%)	χ^2	p-value
Sex						
Male	258 (69.35)	110 (42.64)	98 (37.98)	50 (19.38)	3.853	0.1456
Female	114 (30.65)	40 (35.09)	42 (36.84)	32 (28.07)		
Age (year)						
>30	356 (95.70)	145 (40.73)	141 (39.61)	70 (19.66)	5.16	0.0758
<30	16 (4.30)	2 (12.5)	9 (56.25)	5 (31.25)		
Types						
I	20 (5.38)	7 (35.0)	6 (30.0)	7 (35.0)	1.374	0.5032
II	352 (94.62)	138 (39.20)	131 (37.22)	83 (23.58)		

We compared the distribution characteristics of different genotypes in gender, age and diabetes types. As a result, its distribution in gender, age and disease types had no significant difference, (a) Percentage of cases in the total and (b) Percentage of cases in the group

Table 2: Complications of three different SLC471 genotype

	SLC471G>A genotype case (%)				
Clinical parameters	GA (150)	GG (140)	AA (82)	χ^2	p-value
Hypertension	66 (44)	40 (28.57)	32 (39.02)	7.554	0.0229*
Hyperuricemia	21 (14)	11 (7.86)	4 (4.88)	5.898	0.0524
Peripheral vascular disease	16 (10.67)	2 (1.43)	6 (7.32)	10.37	0.0056**
Hyperlipidemia	38 (25.33)	14 (10)	18 (21.95)	11.82	0.0027***
Diabetic foot disease	3 (2)	3 (2.143)	2 (2.44)	0.04862	0.976
Diabetic nephropathy	20 (13.33)	12 (8.57)	18 (21.95)	7.959	0.0187*
Diabetic peripheral neuropathy	36 (24)	16 (11.43)	24 (29.27)	12.09	0.0024***
Diabetic retinopathy	12 (8)	6 (4.28)	6 (7.32)	1.786	0.4095
Diabetic ketosis	16 (10.66)	6 (4.28)	4 (4.88)	5.257	0.0722
Urinary tract infection	6 (4)	0 (0)	0 (0)	9.026	0.011*
Bilateral carotid arteriosclerosis	28 (18.67)	8 (5.71)	16 (19.51)	12.78	0.0017***
Fatty liver	2 (1.33)	10 (7.14)	2 (2.44)	7.257	0.0265*
Diabetic eye disease	8 (5.33)	2 (1.43)	2 (2.44)	3.745	0.1537
Coronary heart disease	4 (2.67)	0 (0)	0 (0)	5.984	0.0502

Complications included hypertension, hyperuricemia, peripheral vascular disease, hyperlipidemia, diabetic foot disease, diabetic nephropathy, diabetic peripheral neuropathy, diabetic retinopathy, diabetic ketosis, urinary tract infection, bilateral carotid arteriosclerosis, fatty liver, diabetic eye disease, coronary heart disease and different complications have significant differences in the distribution of different genotypes,*p<0.05, **p<0.01 and ***p< 0.001

complications. Patients with GA genotypes had higher rates of hypertension (66 patients in total), peripheral vascular disease (16 patients in total), hyperlipidemia (38 patients in total), urinary tract infection (6 patients in total) while patients with GG genotypes only had higher rates of fatty liver (10 patients in total). Meanwhile, diabetic nephropathy (18 patients in total), diabetic peripheral neuropathy (24 patients in total) and bilateral carotid arteriosclerosis (16 patients in total) were prone to occur in patients with AA genotypes. However, there was no significant statistical difference in the effect of genotypes on hyperuricemia, diabetic foot disease, diabetic retinopathy, diabetic ketosis, diabetic eye disease and coronary heart disease (Table 2).

Therapeutic effect after metformin medication guidance: After the pharmacist send the genetic test results to the clinician, the doctor adjusted the medication according to the guidelines and finally, the clinical pharmacist performed statistical analysis on the experimental data and clinical data which concluded biochemical examinations. Biochemical examinations included GLU (Glucose, Glu), 2h-GLU (Blood glucose two hours after a meal, 2h-GLU), C-P (c-peptide, C-P), 2h-CP (c-peptide 2 hrs after a meal, 2h-CP), HbA1a (Hemoglobin A1a, HbA1a), HbA1b (Hemoglobin A1b, HbA1b) and HbA1c (Hemoglobin A1c, HbA1c), which were routine examination items for hospitalized diabetic patients. We counted the differences in the changes of the above indicators before and after the treatment of metformin as the treatment was guided by the genetic test results. In Table 3, the mean value of GLU before and after the guidance was decreased from 8.36±3.16-7.80±3.68 mmol L^{-1} and the mean value before and after the guidance was high but the level of Glu decreased from a moderate increase to a slight increase and the lowest value before and after the guidance dropped from 4.31-4.07 mmol L^{-1} and the highest value dropped from 16.97-15.97 mmol L^{-1}. It preliminarily shows that SLC47A1 genetic testing has achieved certain results in controlling blood sugar levels. In addition, the mean value of 2h-GLU

Table 3: Therapeutic effect after gene testing medication guidance

Clinical parameters	Before guidance	After guidance	p-value
GLU	8.36±3.16	7.80±3.68	0.2169
2h-GLU	13.93±4.94	14.62±6.15	0.5145
CP	1.07±0.73	1.27±0.90	0.1649
2h-CP	2.32±1.67	3.50±2.83	0.0007**
HbA1a	0.77±0.22	0.82±0.13	0.1264
HbA1b	1.14±0.31	0.58±0.13	<0.0001***
HbA1c	9.38±2.48	7.90±2.09	0.0001***

Glu, 2h-Glu, CP, 2h-CP, HbA1a, HbA1b and HbA1c. These parameters are routine checks for diabetic patients after admission items. **p<0.01, ***p<0.001. Glu: Glucose, 2h-Glu: Glucose 2 hrs after a meal, C-P: C-peptide, 2h-CP: C-peptide 2 hrs after a meal, HbA1a: Hemoglobin A1a, HbA1b: Hemoglobin A1b and HbA1c: Hemoglobin A1c

increased from 13.93±4.94 mmol L^{-1} before guidance to 14.62±6.15 mmol L^{-1} but the highest value decreased from 23.92 mmol L^{-1} before treatment to 22.1 mmol L^{-1}. It could also show that the treatment has made some progress. The mean value of CP value was 1.07±0.73 ng mL^{-1}, which increased to 1.27±0.90 ng mL^{-1}, the mean value of 2h-CP increased from 2.32±1.67-3.5±2.83 but the highest value of CP decreased from 5.22-3.3 ng mL^{-1}. The highest value of 2h-CP increased from 7.93-13.09, which indicates that the secretory function and reserve function of β cells have not been restored. The mean value of HbA1a increased from 0.77±0.22% before guidance to 0.82±0.13% after guidance. However, the lowest value did not change and the highest value fell from 1.5-1.1%, which preliminarily shows that the level of blood glucose control is of little significance. However, the mean value of HbA1b decreased from 1.14±0.31-0.58±0.13% and the mean value of HbA1c decreased from 9.38±2.48-7.90±2.09%, both of which decreased significantly. And the highest value of HbA1b before and after the guidance dropped from 1.8-1.2% and the lowest value also dropped from 0.6-0.5%. At the same time, the highest value of HbA1c before and after the guidance dropped from 18-14%. It was confirmed that blood glucose was well controlled and it was further confirmed that the SLC47A1 gene test can effectively control blood sugar levels. As the levels of HbA1b and HbA1c depended on the blood glucose level and the duration of hyperglycemia. It shows that after the instruction, the blood glucose level has been well controlled within a period. Therefore, we concluded that the guidance of metformin gene test results was beneficial to the improvement of the treatment effect.

Influence of SLC47A1 gene polymorphism on the guidance of metformin medication: We conducted a statistical analysis of the effect of metformin treatment under the guidance of SLC47A1 gene polymorphism and found that before and after the guidance of GG genotype patients, the mean value of GLU decreased from 8.48±3.00-8.42±3.60 mmol L^{-1} and the mean value of 2h-GLU decreased from 13.96±4.96-13.44±5.92 mmol L^{-1}. Meanwhile, the highest value of GLU increased from 14.95-15.02 mmol L^{-1} and also the highest value of 2h-GLU increased from 27.13-30.95 mmol L^{-1}. At the same time, the lowest value of 2h-GLU increased from 3.21-5.82 mmol L^{-1}. In addition, the level of GLU before and after the guidance was moderately elevated, indicating that the blood glucose level of patients with the GG genotype had not been controlled. At the same time, the highest value of CP before and after the guidance was reduced from 3.95-1.01 ng mL^{-1} and the highest value of 2h-CP was reduced from 6.82-1.4 ng mL^{-1} but the mean value of CP was increased from 1.08±0.75-1.47±1.11 ng mL^{-1} and the mean value of 2h-CP increased from 2.26±1.4-3.41±1.77 ng mL^{-1}, there was no significant difference, indicating that the secretory function and reserve function of pancreatic β cells had not been improved. In addition, the value of HbA1a increased from 0.78±0.23-0.87±0.14% and the value of HbA1c decreased from 9.23±2.09-8.33±3.02%. There was no significant difference, so there was no statistical significance. However, the mean value of HbA1b decreased from 1.17±0.34-0.57±0.08% ($p<0.0001$) and the highest value was reduced from 1.8-0.7% and the lowest value was reduced from 0.6-0.5%. There was a significant difference, indicating that the blood glucose had been obtained a certain degree of control in the recent period. In summary, it is concluded that SLC47A1 gene testing guidance could control the blood glucose level of patients with GG genotype but the effect was not obvious (Table 4). In the GA genotype data, before and after the guidance, the mean value of Glu increased from 8.17±3.20-8.18±4.06 mmol L^{-1} and the 2h-GLU value increased from 14.21±4.45-16.34±6.52 mmol L^{-1}. At the same time, the lowest value increased from 1.29-2.19 mmol L^{-1} and the highest value of 2h-GLU increased from 23.81-26.36 mmol L^{-1} and also the lowest value increased from 4.0 -7.34 mmol L^{-1}, indicating that the blood glucose of GA genotype patients had not been controlled. In addition, the mean value of CP increased from 1.03±0.73-1.07±0.80 ng mL^{-1} and the mean value of 2h-CP increased from 2.31±1.79-3.38±2.44 ng mL^{-1},

Table 4: Therapeutic response to metformin according to solute carrier family 47, member A1 (SLC47A1) rs2289669 GG genotype

Parameters	Before guidance	After guidance	p-value
GLU	8.48±3.00	8.42±3.60	0.6928
2h-GLU	13.96±4.96	13.44±5.92	0.4974
CP	1.08±0.75	1.47±1.11	0.215
2h-CP	2.26±1.4	3.41±1.77	0.0665
HbA1a	0.78±0.23	0.87±0.14	0.7576
HbA1b	1.17±0.34	0.57±0.08	<0.0001***
HbA1c	9.23±2.09	8.33±3.02	0.0999

***p<0.001, Glu: Glucose, 2h-Glu: Glucose 2 hrs after a meal, C-P: C-peptide, 2h-CP: C-peptide 2 hrs after a meal, HbA1a: Hemoglobin A1a, HbA1b: Hemoglobin A1b and HbA1c: Hemoglobin A1c

Table 5: Therapeutic response to metformin according to the solute carrier family 47, member A1 (SLC47A1) rs2289669 GA genotype

Parameters	Before guidance	After guidance	p-value
GLU	8.17±3.20	8.18±4.06	0.8927
2h-GLU	14.21±4.45	16.34±6.52	0.1947
CP	1.03±0.73	1.07±0.80	0.8703
2h-CP	2.31±1.79	3.38±2.44	0.0218*
HbA1a	0.76±0.23	0.84±0.11	0.1813
HbA1b	1.13±0.32	0.58±0.09	<0.0001***
HbA1c	9.37±2.54	8.26±2.01	<0.0001***

*p<0.05, ***p<0.001, Glu: Glucose, 2h-Glu: Glucose 2 hrs after a meal, C-P: C-peptide, 2h-CP: C-peptide 2 hrs after a meal, HbA1a: Hemoglobin A1a, HbA1b: Hemoglobin A1b and HbA1c: Hemoglobin A1c

Table 6: Therapeutic response to metformin according to the solute carrier family 47, member A1 (SLC47A1) rs2289669 AA genotype

Parameters	Before guidance	After guidance	p-value
GLU	8.63±3.25	6.74±2.90	0.0074**
2h-GLU	13.32±5.86	10.89±3.60	0.1493
CP	1.14±0.72	1.63±0.95	0.127
2h-CP	2.39±1.68	3.92±4.74	0.0247*
HbA1a	0.77±0.20	0.72±0.13	0.1537
HbA1b	1.15±0.30	0.6±0.22	<0.0001***
HbA1c	9.55±2.73	6.68±1.24	0.0003***

*p<0.05, **p<0.01, ***p<0.001, Glu: Glucose, 2h-Glu: Glucose 2 hrs after a meal, C-P: C-peptide, 2h-CP: C-peptide 2 hrs after a meal, HbA1a: Hemoglobin A1a, HbA1b: Hemoglobin A1b and HbA1c: Hemoglobin A1c

there was no significant difference and statistical significance, indicating that the secretory function and reserve function of β cells had not been improved. Besides, the mean value of HbA1a increased from 0.76±0.23-0.84±0.11% with no significant difference. However, the HbA1b value decreased from 1.13±0.32-0.58±0.09% ($p<0.0001$) and the highest value decreased from 1.8-0.7% and also the lowest value decreased from 0.6-0.5%. At the same time, the HbA1c value decreased from 9.37±2.54 -8.26±2.01% ($p<0.0001$) and the highest value dropped from 15.6-14 %. It was shown that the blood glucose level of GA genotype patients had been controlled to a certain extent (Table 5). In the AA genotype data, the levels of Glu, HbA1b and HbA1c had been decreased significantly ($p<0.01$). Before and after guidance, the mean value of Glu decreased from 8.63±3.25 -6.74±2.90 mmol L^{-1} ($p< 0.01$) and the highest value decreased from 19.09-13.2 mmol L^{-1}. Meanwhile, the mean value of 2h-GLU decreased from 13.32±5.86-10.89±3.60 mmol L^{-1} and the highest value decreased from 26.68-21.25 mmol L^{-1}, indicating that the patient's blood glucose was well controlled. In addition, the mean value of CP increased from 1.14±0.72-1.63±0.95 ng mL^{-1} and the mean value of 2h-CP increased from 2.39±1.68-3.92±4.74 ng mL^{-1}, indicating the secretion and reserve function of pancreatic β cells were not improved. Besides, the mean value of HbA1a decreased from 0.77±0.20-0.72±0.13% and the highest value also decreased slightly from 1.2-1.1%. Also, the mean value of HbA1b decreased from 1.15±0.30-0.6±0.22% ($p<0.0001$) and the highest value was reduced from 1.8-0.7% and also the lowest value was reduced from 0.6-0.5%. In addition, the mean value of HbA1c decreased from 9.55±2.73-6.68±1.24 % ($p< 0.001$) and the highest value also decreased from 15.6-14%. In summary, after medication guidance, the blood glucose level of patients with AA genotype had been effectively controlled. (Table 6). In addition, after the guidance, the CP and 2h-CP levels of patients did not decrease, indicating that the guiding effect of gene polymorphisms could only control blood glucose and could not improve the secretory function and reserve function of pancreatic β cells significance. In this study, the patients with the AA genotype had the best effect on

blood glucose control and the GLU, HbA1b and HbA1c parameters were all significantly down-regulated, followed by the GA group in which HbA1b and HbA1c were significantly down-regulated. There was little effect in the GG group. Only HbA1b decreased significantly. It showed that the medication guidance of patients with AA and GA genotype was of the best effect. Therefore, we concluded that the SLC47A1 gene polymorphism could guide metformin drug treatment to obtain a good therapeutic effect. Among them, the homozygous mutant genotype AA can obtain a better therapeutic effect than the GA genotype and the GG genotype.

DISCUSSION

This study showed that the three genotypes have no significant differences in gender, age and disease types but there were significant differences in the propensity for complications of patients with each genotype, which has not been reported. In addition, our department has formulated the principles of SLC47A1 genetic testing on guiding clinical medication. Besides, the clinical parameters 2h-CP, HbA1b and HbA1c were significantly reduced after treatment that it is indicating that genetic testing is effective in guiding clinical medication. In comparison with the other two genotypes, only the AA gene patients had the greatest decline in clinical parameters, which were Glu, 2h-CP, HbA1b and HbA1c.

There was no significant difference in the demographic characteristics of patients with the three genotypes in this study. However, HbA1b or HbA1c levels in patients with AA genotype and GA genotype decreased significantly after medication guidance, which was consistent with the results of other studies[12-17] and Rui He and other scholars refer to Pharmacokinetic parameters of metformin indicated that patients carrying MATE1 homozygous A had a higher area under the plasma concentration versus time curve (AUC12h) but lower renal clearance (CLR) and renal clearance by secretion (CLSR) than other patients (all $p<0.01$). In other words, SLC47A1 rs2289669 G>A variants improve the glucose-lowering effect of metformin by slowing its excretion in type 2 diabetes populations[12]. We have not done this work. Meanwhile, At the same time, Liang *et al*. found that compared with participants with a homozygous G allele, those carrying the minor A allele had significantly greater HbA1c reduction. This is also consistent with our research[13]. In addition, Liang *et al*.[13]. also researched SLC22A1 and SLC22A2. Compared with our research, their research is more comprehensive and it is believed that only SLC47A1 affects the level of HbA1c[14]. On the opposite, Xiao *et al*.[16] considered that SLC22A1 rs594709 and SLC47A1 rs2289669 polymorphisms may influence metformin efficacy together in Chinese T2DM patients[16]. However, other scholars have found that patients with GA genotype have the greatest reduction in HbA1C. This is inconsistent with our research results[15]. Some studies found that the clinical response to metformin was not associated with the rs2289669 polymorphisms in the SLC47A1 genes coding for the MATE transporters[11]. However, these research documents only reflected in HbA1b or HbA1c levels. In our study, the Glu level of patients with AA genotype was also significantly reduced which was more convincing. Meanwhile, CP and 2h-CP did not improve significantly, indicating that the secretory function and reserve function of pancreatic is let β cells have not been improved. Besides, this study also studied the complications that patients with each genotype tended to occur, all that was also a supplement to the previous research.

Genetic testing has broad application prospects in the clinical field. Through genetic testing, patients could better understand their own risk of disease and also accept diagnose and treatment early at the beginning of the disease and minimize the damage caused by the disease in the end. At the same time, clinical pharmacists need to propose a more effective and safe medication adjustment plan based on the results of genetic testing. The development of drug genetic testing in my country has also been recognized by clinicians and patients. In 2015, scientists put forward "To achieve precisely targeted therapy for specific patients and diseases with personalized medicine as the core and genome sequencing and bioinformatics technology as the basis" in China. With the rapid development of genetic testing technology and big data, the popularization of genome sequencing data and the increase of genetic databases, gene-oriented personalized medicine has become an important content of hospital pharmacy, which is known as a breakthrough direction for future hospital pharmacy work with therapeutic drug monitoring, adverse reaction monitoring and pharmacists in-depth clinical work.

Genetic testing technology is now mature but the uncertainty of the relationship between genotype and phenotype is the current difficulty for genetic testing to guide clinical medication. For example, what does the ATCG combination represent in the DNA sequence? What does it have to do with our health? Based on current research, the relationship between genotype and phenotype of most monogenic diseases has been studied comprehensively but the single-gene disease is relatively simple and the corresponding relationship is relatively easy to study. However, the incidence of monogenic diseases is rare,

people are often concerned about complex diseases with high incidence. Complex diseases (tumour, diabetes and cardiovascular diseases, etc.) usually involve many gene interactions and environmental factors. Therefore, the application of genetic testing in the risk estimation of complex diseases has more obvious limitations.

The genetic testing industry has become an important part of the national "precision medicine" strategic plan. As we all know, the change of genotypes causes changes in disease phenotypes and the medication adjustment plan adopted on each genotype and phenotype is the primary problem that clinical pharmacists need to solve at present. Meanwhile, some patients suffer from several diseases at the same time and need to take multiple drugs. In this case, how to consider the relevant drug adjustment plan? Therefore, pharmacists must strengthen the learning of relevant knowledge and technology, carry out the work of drug genetic testing more smoothly and orderly and make it more and more perfect.

CONCLUSION

Compared with the biochemical parameters before the guidance, the biochemical parameters after the guidance were significantly improved. In addition, in all gene-phenotype patients, only patients with AA genotype had the best improvement in biochemical parameters. In short, SLC47A1 gene polymorphism guides metformin medication can improve diabetes treatment effect and patients with AA gene-phenotype have the best treatment effect.

SIGNIFICANCE STATEMENT

This study discovered the SLC47A1 gene polymorphism guides metformin medication can improve diabetes treatment effect that can be beneficial for diabetes patients. This study will help the researchers to uncover the critical areas of Genetic testing technology guides disease treatment that many researchers were not able to explore. Thus a new theory on gene polymorphism can improve disease treatment effect may be arrived at.

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