

[ ORIGINAL ARTICLE ]

## A Variation in the *ABCC8* Gene Is Associated with Type 2 Diabetes Mellitus and Repaglinide Efficacy in Chinese Type 2 Diabetes Mellitus Patients

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### Abstract:

**Objective** Previous studies have suggested that variations in the *ABCC8* gene may be closely associated with T2DM susceptibility and repaglinide response. However, these results have not been entirely consistent, and there are no related studies in a Chinese population, suggesting the need for further exploration. The current study investigated the associations of the *ABCC8* rs1801261 polymorphism with type 2 diabetes mellitus (T2DM) susceptibility and repaglinide therapeutic efficacy in Chinese Han T2DM patients.

**Methods** A total of 234 T2DM patients and 105 healthy subjects were genotyped for *ABCC8* rs1801261 polymorphism by a polymerase chain reaction-restriction fragment length polymorphism assay. A total of 70 patients with the same genotypes of *CYP2C8*\*3 139Arg and *OATP1B1* 521TT were randomized to orally take 3 mg repaglinide per day (1 mg each time before meals) for 8 consecutive weeks. The pharmacodynamic parameters of repaglinide and biochemical indicators were then determined before and after repaglinide treatment.

**Results** The frequency of *ABCC8* rs1801261 allele was higher in T2DM patients than in the control subjects (22.6% vs.11.0%,  $p<0.01$ ). After repaglinide treatment, T2DM patients carrying genotype CT showed a significantly attenuated efficacy on FPG ( $p<0.01$ ) and HbA1c ( $p<0.01$ ) compared with those with genotype CC.

**Conclusion** These results suggested that the *ABCC8* rs1801261 polymorphism might influence T2DM susceptibility and the therapeutic effect of repaglinide in Chinese Han T2DM patients. This study was registered in the Chinese Clinical Trial Register on May 14, 2013 (No. ChiCTR-CCC13003536).

**Key words:** *ABCC8*, gene polymorphism, type 2 diabetes mellitus, repaglinide, sulfonylurea receptor 1, insulin secretion

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### Introduction

Type 2 diabetes mellitus (T2DM) and its associated complications pose a major global healthcare burden. It is estimated that 592 million people worldwide will be affected by diabetes by the year 2035, and a majority of the affected will be Asians (1, 2). T2DM is generally recognized as a

multifactorial, polygenic disease (3). Genetic factors play an important role in the development of T2DM (4). Polymorphisms in genes encoding proteins involved in the pancreatic  $\beta$ -cell function, insulin function and glucose metabolism might influence the susceptibility of T2DM (5, 6).

Among these genes, the ATP-binding cassette superfamily transporter family C8 (*ABCC8*) has come under attention (7). It has been reported that sulfonylurea receptor 1

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(SUR1) encoded by the *ABCC8* gene is of great significance in the pancreatic  $\beta$ -cell function. Because the adenosine triphosphatase (ATP)-sensitive potassium ( $K^+$ ) channels ( $K_{ATP}$ ) on the islet  $\beta$ -cell membrane are composed of ion channels formed by SUR1 and Kir16.2, SUR1 plays an important role in modulating ATP-sensitive potassium channels and insulin release (8). Pathogenic mutations in the SUR1 gene can cause various types of diabetes, such as hyperinsulinemic hypoglycemia of infancy and T2DM (9). Thus, abnormal SUR1 (*ABCC8*) can lead to disturbance of potassium channel and insulin secretion (10). It has been reported that *ABCC8* rs1801261 polymorphisms are correlated with the risk of T2DM in Danish and Canadian populations (11, 12). However, four previous studies involving Dutch Caucasian, English, North Indian and Finnish populations have showed that the *ABCC8* rs1801261 site is not associated with the risk of T2DM (13-16). These results are not entirely consistent, and there are no related studies in Chinese populations, underscoring the need for further exploration.

Furthermore, most T2DM patients often eventually require hypoglycemic agents in order to maintain an acceptable glycemic level and to reduce the risk of development and progression of disease complications (17). However, an identical antidiabetic therapy regimen might bring in various therapeutic responses and sometimes even serious adverse reactions, which is partly a result of genetic factors (18). Repaglinide is an insulin secretagogue that is widely used in the treatment of T2DM in clinical practice. It can enhance insulin secretion from pancreatic  $\beta$ -cells by combining with SUR1, thereby inhibiting  $K_{ATP}$  channels and activating calcium ( $Ca^{2+}$ ) channels (19, 20). It is often combined with metformin to treat T2DM patients who fail sulfonylurea treatment by reducing postprandial hyperglycemia (21).

Recently, more attention has been gradually given to the presence of considerable interindividual variability in repaglinide therapeutic efficacy (22). Some researchers have attributed this to the genetic polymorphisms of cytochrome P450 2C8 (*CYP2C8*) and organic anion-transporting polypeptide 1B1 (*OATP1B1*) because of their influence on the pharmacokinetic process of repaglinide (23, 24). In addition, it has been found that *KCNJ11*, *KCNQ1*, *NOS1AP*, *NAMPT*, *NeuroD1* and other genetic polymorphisms can affect the efficacy of repaglinide (25-29). However, these studies have been unable to fully elucidate the mechanism of action by which the same repaglinide therapy results in various therapeutic responses. By targeting islet  $\beta$ -cells, repaglinide might produce various therapeutic effects, depending on the genetic polymorphism of *ABCC8*.

In summary, repaglinide can bind to SUR1 to stimulate insulin release in pancreatic  $\beta$ -cells. *ABCC8* gene coding SUR1 may therefore play a critical role in glucose metabolism, and *ABCC8* gene polymorphisms may be related to T2DM susceptibility and individual differences in the effects of repaglinide. The present study investigated the association between *ABCC8* rs1801261 polymorphisms and T2DM in Chinese T2DM patients and explored the effects of these

polymorphisms on repaglinide efficacy in order to provide a genetic pharmacology basis for gene-directed individualized medication.

## Materials and Methods

### Subjects

A total of 234 unrelated T2DM patients (mean age: 49.94  $\pm$  0.79 years; 140 men and 94 women) and 105 healthy controls (mean age: 46.60  $\pm$  1.19 years; 62 men and 43 women) were enrolled in this study. The case group and healthy control group were collected from the Department of Endocrinology and Physical Examination of the Affiliated Hospital of Xuzhou Medical College. For the allocation of the participants, a computer-generated list of random numbers was prepared by an investigator with no clinical involvement in the trial. The study was registered in the Chinese Clinical Trial Register (No. ChiCTR-CCC13003536) and performed in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical College. Written informed consent was obtained from each subject before the study.

T2DM was diagnosed according to the 1999 World Health Organization Criteria for hyperglycemia, as follows: fasting plasma glucose (FPG)  $\geq$  7.0 mmol/L and/or 2-hour plasma glucose post-oral glucose tolerance test (2-h PG)  $\geq$  11.1 mmol/L. Patients who participated in this study had a body mass index (BMI) of 18.5-30 kg/m<sup>2</sup> and had not received an insulin secretagogue and/or agonists or inhibitors of *CYP2C8*, *CYP3A4* and *OATP1B1* in the past 3 months. The exclusion criteria were receiving insulin treatment, pregnancy or lactation, and a history of ketoacidosis, acute myocardial infarction, congestive heart failure, trauma or liver/kidney diseases. The inclusion criteria for healthy control subjects were (i) a BMI of 18.5-30 kg/m<sup>2</sup> and (ii) normal glucose levels (FPG < 6.1 mmol/L and 2-h PG level < 7.8 mmol/L). Control subjects with high blood pressure and hyperlipidemia were excluded from this study.

### Clinical laboratory tests

T2DM patients received repaglinide (trade name: Novo; Novo Nordisk, Copenhagen, Denmark) 1 mg at 15 minutes before meals orally 3 times a day for 8 weeks. During treatment, their diet and exercise habits remain unchanged. Anti-hypertensive drugs or hypolipidemic drug users continued to take their current medications with the dose unchanged. Venous blood samples were collected after fasting overnight and again 2 hours after a standard breakfast (100 g sugar-free steamed bread). Parameters were measured before and eight weeks after repaglinide administration.

### Clinical observation index and determination method

Plasma glucose and lipid profiles, including triglyceride (TG), total cholesterol (TC), low-density lipoprotein chole-

**Table 1. Clinical Characteristics of Type 2 Diabetes Mellitus Patients and Healthy Subjects.**

| Parameter                | Healthy controls | T2DM patients | p value              |
|--------------------------|------------------|---------------|----------------------|
| N (male/female)          | 105 (62/43)      | 234 (140/94)  | 0.892 <sup>b</sup>   |
| Age (years)              | 47.13±1.078      | 49.81±0.789   | 0.053                |
| BMI (kg/m <sup>2</sup> ) | 23.52±0.32       | 25.98±0.26    | 0.000 <sup>**a</sup> |
| WHR                      | 0.82±0.008       | 0.92±0.004    | 0.000 <sup>**a</sup> |
| FPG (mmol/L)             | 5.22±0.05        | 9.58±0.17     | 0.000 <sup>**a</sup> |
| TC (mmol/L)              | 4.77±0.91        | 5.29±0.09     | 0.006 <sup>**a</sup> |
| TG (mmol/L)              | 1.27±0.09        | 2.46±0.18     | 0.000 <sup>**a</sup> |
| HDL-c (mmol/L)           | 1.33±0.03        | 1.41±0.03     | 0.367 <sup>a</sup>   |
| LDL-c (mmol/L)           | 2.69±0.05        | 3.16±0.07     | 0.000 <sup>**a</sup> |

Data are given as mean±standard error. p values are determined by Student's *t*-test. \**p*<0.05, \*\**p*<0.01. <sup>a</sup>p values are determined by Mann-Whitney U test. <sup>b</sup>p values are determined by Pearson chi-square test. BMI: body mass index, WHR: waist to hip ratio, FPG: fasting plasma glucose, TG: triglyceride, TC: total cholesterol, HDL-c: high-density lipoprotein-cholesterol, LDL-c: low-density lipoprotein-cholesterol

terol (LDL-c) and high-density lipoprotein cholesterol (HDL-c), were detected using a Roche Cobas8000 analyzer (Roche, Basel, Switzerland). The levels of plasma insulin and glycated hemoglobin (HbA1c) were measured using an electrochemiluminescence assay (Roche, Shanghai, China) and high-performance liquid chromatography assay, respectively. The BMI and waist circumference to hip circumference ratio (WHR) were calculated as follows: BMI=body weight (kg)/height (m)<sup>2</sup>; WHR=waist circumference/hip circumference. The steady-state model of insulin resistance index (HOMA-IR) was calculated as follows: FPG (mmol/L)×FINS (mU/L)/22.5.

### Genotyping analyses

Genomic DNA was isolated from peripheral blood leukocytes using a SiMax Genome DNA kit (Sbsbio, Shanghai, China). In the present study, genotyping was performed using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay. For amplification of *ABCC8* rs1801261 site PCR primer sequence: forward primer: 5'-AGCACCTGGAGGGAGTTGA-3'; reverse primer: 5'-TCCCTCTTAAGTGGTCCTCC-3'. PCR products of the *ABCC8* rs1801261 polymorphism were digested with BsiE1 (NEB, Beijing, China). The amplified DNA fragments were digested by BsiE1 (NEB). The polymorphism of CYP2C8\*3 Arg139Lys was also genotyped by a PCR-RFLP assay, where the following primers were used: 50-AGGCAATTCCTCAATATCTC-30 (sense) and 50-CTCCTCCACAAGGCAGTGA-30 (antisense). The resultant DNA products were digested by BseRI (NEB). The OATP1B1 T521C genotypes were detected by the amplification refractory mutation system (ARMS) using the following four primer pairs: forward primer: 50-AAGTAGTTAAATTTGTAATAGAAATGC-30, reverse primer: 50-GTAGACAAA GGGAAAGTGATCATA-30; forward primer for wild-type genotype: 50GGGTCATACATGTGGATATAAGT-30, reverse primer for mutant variants: 50-AAGCATATTACCCATGAA

CG-30. All obtained DNA fragments were separated by 2% agarose gel electrophoresis followed by ethidium bromide staining and visualization with UV transillumination.

### Statistical analyses

The allele frequencies were determined by gene calculating, and Hardy-Weinberg equilibrium tests were performed. Statistical analyses were performed using the SPSS software program (version 21.0 for Windows; IBM, NY, USA). The baseline characteristics in T2DM patients and healthy subjects were performed using a two-sample *t*-test (27). The paired Student's *t*-test and a one-way analysis of variance (ANOVA) were performed to assess the effects of repaglinide on the metabolic parameters of subjects with various genotypes. Variables with a normal distribution were analyzed by the two-sample *t*-test or one-way ANOVA, while those with a skewed distribution were analyzed by the Mann-Whitney U test or Kruskal-Wallis test (30). All continuous variables were summarized as the mean and standard deviation. Statistical power was calculated using the PASS software program (<http://www.ncss.com>). A value of *p*<0.05 was considered statistically significant.

## Results

### Clinical characteristics

The clinical and biochemical characteristics of all participants are listed in Table 1. The values of BMI, WHR, FPG, TC, TG and LDL-c were higher in patients with T2DM than in healthy subjects (all *p*<0.01). However, no significant differences were found between the two groups in the age, sex distribution or plasma HDL-c concentration.

### Allelic frequency analyses

In the present study, 234 T2DM patients (140 men and 94 women) and 105 healthy subjects (62 men and 43 women) were genotyped for the *ABCC8* rs1801261 polymorphism. The genotype distribution in each group was consistent with the Hardy-Weinberg equilibrium, and the samples were representative (*p*>0.05). The C allele frequency of *ABCC8* rs1801261 was 77.4% in T2DM patients and 89.0% in healthy subjects (Table 2). In this study, there were significant differences between T2DM patients and healthy controls in the allelic frequencies of *ABCC8* rs1801261 polymorphisms (*p*<0.01).

### Assessment of baseline parameters in T2DM patients with different *ABCC8* rs1801261 genotypes

In the present study, the baseline clinical characteristics of the 234 T2DM patients with different *ABCC8* rs1801261 genotypes were analyzed by a one-way ANOVA or the Kruskal-Wallis test. There was no association between *ABCC8* rs1801261 polymorphisms and the sex, age, WHR, BMI, FPG, PPG, fasting serum insulin (FINS), postprandial serum insulin (PINS), HOMA-IR, HbA1c, TG, TC or

**Table 2. Comparison of Genotype and Frequencies of *ABCC8* rs1801261 Polymorphism between Type 2 Diabetes Mellitus Patients and Healthy Subjects.**

| Genotypes              | Healthy controls (n=105) (%) | T2DM patients (n=234) (%) | p value  |
|------------------------|------------------------------|---------------------------|----------|
| <i>ABCC8</i> rs1801261 |                              |                           |          |
| CC                     | 82 (78.10)                   | 128 (54.70)               | 0.000**b |
| CT                     | 23 (21.90)                   | 106 (45.30)               |          |
| Alleles                |                              |                           |          |
| C                      | 187 (89.00)                  | 362 (77.40)               | 0.000**b |
| T                      | 23 (11.00)                   | 106 (22.60)               |          |

The allelic frequencies are indicated in absolute values (percentage).

<sup>b</sup>p values were determined by Pearson chi-square test. \*\*p<0.01.

**Table 4. Clinical Characteristics of T2DM Patients before and after Repaglinide Treatment.**

| Parameter      | Before treatment | After treatment | p value            |
|----------------|------------------|-----------------|--------------------|
| FPG (mmol/L)   | 10.09±0.30       | 7.12±0.20       | 0.000**d           |
| PPG (mmol/L)   | 16.96±0.53       | 10.98±0.32      | 0.000**d           |
| FINS (mU/L)    | 21.31±3.40       | 15.04±2.04      | 0.974 <sup>d</sup> |
| PINS (mU/L)    | 97.10±18.99      | 73.92±10.63     | 0.781 <sup>d</sup> |
| HOMA-IR        | 8.82±1.36        | 4.32±0.53       | 0.000**d           |
| HbA1c (%)      | 9.46±0.23        | 7.05±0.11       | 0.000**            |
| TC (mmol/L)    | 5.36±0.19        | 4.85±0.13       | 0.004**            |
| TG (mmol/L)    | 2.34±0.23        | 1.93±0.15       | 0.015 <sup>d</sup> |
| HDL-c (mmol/L) | 1.40±0.06        | 1.35±0.06       | 0.401 <sup>d</sup> |
| LDL-c (mmol/L) | 3.21±0.14        | 3.08±0.13       | 0.326 <sup>d</sup> |

Data are expressed as mean±standard error. p values are determined by paired-samples Student's t-test. <sup>d</sup>p values are determined by Wilcoxon matched-pair signed-rank test. \*\*p<0.01. \*p<0.05.

FPG: fasting plasma glucose, PPG: postprandial plasma glucose, FINS: fasting serum insulin, PINS: postprandial serum insulin, HOMA-IR: homeostasis model assessment for insulin resistance, HbA1c: glycated hemoglobin, TG: triglyceride, TC: total cholesterol, HDL-c: high-density lipoprotein-cholesterol, LDL-c: low-density lipoprotein-cholesterol

LDL-c. However, significant differences were observed among these patients in terms of the HDL-c (Table 3).

### Effects of *ABCC8* rs1801261 polymorphisms on the efficacy of repaglinide in T2DM patients

To exclude the potential influence of OATP1B1 and CYP2C8\*3 genetic polymorphisms, 70 T2DM patients with different *ABCC8* rs1801261 genotypes but the same OATP1B1 521TT and CYP2C8\*3 139Arg genotypes (60 CT carriers and 10 CC carriers) were randomly selected to participate in the present study. After 8 weeks of repaglinide therapy, these patients showed markedly declined values for FPG (p<0.01), PPG (p<0.01), HbA1c (p<0.01), TC (p<0.01), TG (p<0.05) and HOMA-IR (p<0.01) compared with before treatment (Table 4). The effects of repaglinide on FPG were weaker in *ABCC8* rs1801261 CT heterozygotes than in CC genotype carriers (p<0.01, Table 5, Figure a), and patients with CC genotypes had significantly lower HbA1c levels than those with the CT genotype (p<0.05, Ta-

**Table 3. The Baseline of Characteristics in T2DM Patients with Various *ABCC8* rs1801261 Genotypes.**

| Parameter                | <i>ABCC8</i> rs1801261 genotypes |             | p value             |
|--------------------------|----------------------------------|-------------|---------------------|
|                          | CC                               | CT          |                     |
| N (male/female)          | 128 (75/53)                      | 106 (65/41) | 0.672 <sup>b</sup>  |
| Age (years)              | 50.12±1.04                       | 49.44±1.20  | 0.672               |
| BMI (kg/m <sup>2</sup> ) | 26.10±0.34                       | 25.73±0.38  | 0.502 <sup>a</sup>  |
| WHR                      | 0.92±0.05                        | 0.91±0.05   | 0.829 <sup>a</sup>  |
| FPG (mmol/L)             | 9.72±0.24                        | 9.33±0.23   | 0.350 <sup>a</sup>  |
| PPG (mmol/L)             | 15.61±0.38                       | 15.84±0.39  | 0.499 <sup>a</sup>  |
| FINS (mU/L)              | 22.18±2.65                       | 21.40±2.87  | 0.322 <sup>a</sup>  |
| PINS (mU/L)              | 81.83±10.21                      | 94.97±14.91 | 0.887 <sup>a</sup>  |
| HOMA-IR                  | 8.88±1.03                        | 8.48±1.09   | 0.256 <sup>a</sup>  |
| HbA1c (%)                | 9.07±0.19                        | 8.90±0.18   | 0.592 <sup>a</sup>  |
| TC (mmol/L)              | 5.27±0.11                        | 5.26±0.14   | 0.712 <sup>a</sup>  |
| TG (mmol/L)              | 2.48±0.28                        | 2.40±0.18   | 0.899 <sup>a</sup>  |
| HDL-c (mmol/L)           | 1.44±0.03                        | 1.35±0.04   | 0.030 <sup>*a</sup> |
| LDL-c (mmol/L)           | 3.22±0.09                        | 3.05±0.10   | 0.291 <sup>a</sup>  |

Data are given as mean±standard error. p values are determined by Student's t-test. <sup>a</sup>p values are determined by Mann-Whitney U test. <sup>b</sup>p values are determined by Pearson chi-square test. \*p<0.05.

BMI: body mass index, WHR: waist to hip ratio, FPG: fasting plasma glucose, PPG: postprandial plasma glucose, FINS: fasting serum insulin, PINS: postprandial serum insulin, HOMA-IR: homeostasis model assessment for insulin resistance, HbA1c: glycated hemoglobin, TG: triglyceride, TC: total cholesterol, HDL-c: high-density lipoprotein-cholesterol, LDL-c: low-density lipoprotein-cholesterol

ble 5, Figure b).

## Discussion

Polymorphisms of genes related to insulin secretion and resistance might influence the susceptibility of T2DM and the therapeutic efficacy of repaglinide. This present study with newly identified Chinese type 2 diabetes patients showed that the variant of rs1801261 in *ABCC8* was associated with the susceptibility of T2DM and the efficacy of repaglinide in Chinese Han T2DM patients.

Variants in the gene *ABCC8* have been reported to be associated with defects in the β-cell mass and/or β-cell function, leading to reduced insulin secretion (31). Several pharmacogenomic studies have demonstrated that mutations in *ABCC8* genes are the most common cause of neonatal T2DM (32), a topic that has received intense focus in T2DM research, and previous studies have shown that variants in these genes encoding Kir6.2 and SUR1 are associated with susceptibility to T2DM (33).

In contrast to findings in Danish and Canadian populations, we found that the frequency of T allele of *ABCC8* rs1801261 in our T2DM patients was significantly higher than that of healthy control group (p<0.01) (Table 2), suggesting that *ABCC8* rs1801261 gene polymorphisms might be related to T2DM incidence in the Han population in China and that the risk T-allele is a risk factor for T2DM. The results also showed that the CC genotype of *ABCC8*

**Table 5. Effects of Different *ABCC8* rs1801261 Genotypes on the Clinical Characteristics of Type 2 Diabetes Mellitus Patients before and after Repaglinide Treatment.**

| Parameter             |        | CC          | CT           | p value              |
|-----------------------|--------|-------------|--------------|----------------------|
| N (male/female)       |        | 10 (6/4)    | 60 (39/21)   | 0.760 <sup>b</sup>   |
| FPG (mmol/L)          | Before | 11.35±1.00  | 9.88±0.30    | 0.085                |
|                       | After  | 6.58±0.40   | 7.22±0.22    | 0.267                |
|                       | DV     | -4.77±0.78  | -2.66±0.32   | 0.008 <sup>**a</sup> |
| PPG (mmol/L)          | Before | 17.89±1.54  | 16.81±0.56   | 0.479                |
|                       | After  | 10.70±0.35  | 11.03±0.37   | 0.720                |
|                       | DV     | -7.19±1.57  | -5.78±0.65   | 0.283 <sup>a</sup>   |
| FINS (mU/L)           | Before | 14.78±7.29  | 22.40±3.78   | 0.360 <sup>a</sup>   |
|                       | After  | 9.73±1.04   | 15.94±2.36   | 0.840 <sup>a</sup>   |
|                       | DV     | -5.05±7.32  | -6.46±2.93   | 0.127 <sup>a</sup>   |
| PINS (mU/L)           | Before | 44.67±18.12 | 105.83±21.79 | 0.254 <sup>a</sup>   |
|                       | After  | 52.88±12.52 | 77.43±12.19  | 0.675 <sup>a</sup>   |
|                       | DV     | 8.21±21.47  | -28.40±15.41 | 0.322 <sup>a</sup>   |
| HOMA-IR               | Before | 6.78±3.36   | 9.16±1.50    | 0.568 <sup>a</sup>   |
|                       | After  | 2.78±0.26   | 5.08±0.80    | 0.401 <sup>a</sup>   |
|                       | DV     | -4.00±3.35  | -4.08±1.23   | 0.906 <sup>a</sup>   |
| HbA <sub>1c</sub> (%) | Before | 10.52±0.64  | 9.28±0.24    | 0.057                |
|                       | After  | 7.10±0.31   | 7.04±0.12    | 0.843                |
|                       | DV     | -3.42±0.41  | -2.24±0.20   | 0.026 <sup>*</sup>   |
| TG (mmol/L)           | Before | 1.46±0.16   | 2.49±0.26    | 0.179 <sup>a</sup>   |
|                       | After  | 1.67±0.40   | 1.97±0.17    | 0.347 <sup>a</sup>   |
|                       | DV     | 0.21±0.36   | -0.52±0.16   | 0.247 <sup>a</sup>   |
| TC (mmol/L)           | Before | 4.98±0.31   | 5.43±0.21    | 0.406                |
|                       | After  | 4.67±0.39   | 4.89±0.34    | 0.562                |
|                       | DV     | -0.31±0.38  | -0.54±0.18   | 0.681 <sup>a</sup>   |
| HDL-c (mmol/L)        | Before | 1.39±0.07   | 1.39±0.06    | 0.953                |
|                       | After  | 1.46±0.18   | 1.33±0.06    | 0.498                |
|                       | DV     | 0.07±0.21   | -0.06±0.08   | 0.464 <sup>a</sup>   |
| LDL-c (mmol/L)        | Before | 3.26±0.29   | 3.20±0.15    | 0.884                |
|                       | After  | 3.22±0.39   | 3.05±0.14    | 0.660                |
|                       | DV     | -0.04±0.40  | -0.15±0.15   | 0.797                |

Data are given as mean±standard error. p values represent statistical difference among the two different genotypes assessed by Student's t-test. <sup>a</sup>p values are determined by Mann-Whitney U test. <sup>b</sup>p values are determined by Pearson chi-square test. \*p<0.05, \*\*p<0.01.

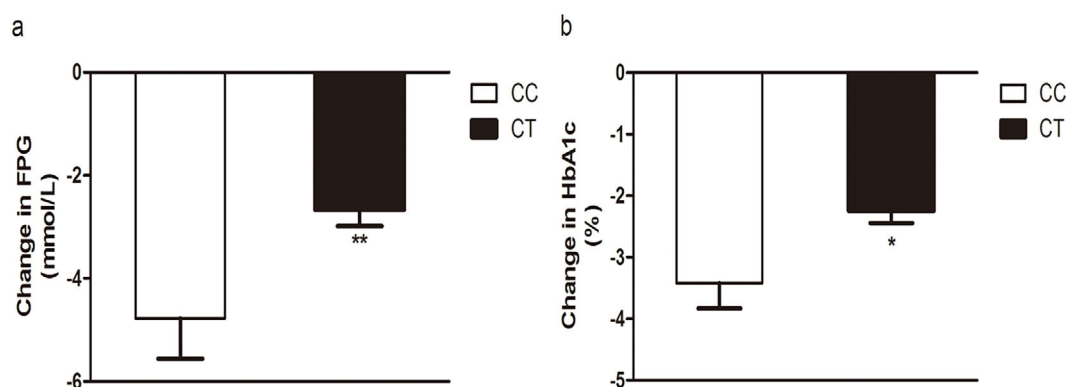
DV: differential values (the difference between the pre- and post-administration values), FPG: fasting plasma glucose, PPG: postprandial plasma glucose, FINS: fasting serum insulin, PINS: postprandial serum insulin, HOMA-IR: homeostasis model assessment for insulin resistance, HbA<sub>1c</sub>: glycated hemoglobin, TG: triglyceride, TC: total cholesterol, HDL-c: high-density lipoprotein-cholesterol, LDL-c: low-density lipoprotein-cholesterol

rs1801261 polymorphism resulted in higher HDL-c levels than the CT genotype in patients with T2DM (p<0.05) (Table 3).

*ABCC8* rs1801261 polymorphisms are located in the *ABCC8* gene exon region. The SNP changes the C allele to the T allele (ACC→ACT) but does not result in any change in the threonine amino acid at 759 residues (Thr759Thr). Weisnagel et al. found that T allele carriers of the *ABCC8* rs1801261 locus had lower insulin levels than noncarriers (12), suggesting a correlation between *ABCC8* rs1801261 polymorphisms and insulin secretion. In addition, it has been shown that rs1801261 polymorphisms are associ-

ated with the function of β-cells, and the CT genotype in T2DM patients results in a lower level of insulin secretion than the CC genotype (34). Therefore, mutations in the *ABCC8* gene may affect the biological function of SUR1 in insulin secretion, thereby influencing the occurrence and development of T2DM.

Polymorphisms of genes involved in drug metabolisms, such as cytochrome P450 (CYP) 2C8 (35) and organic anion-transporting polypeptide 1B1 (OATP1B1), may influence the efficacy of repaglinide and the incidence of adverse effects (36). To exclude the impact of OATP1B and CYP2C8 genetic polymorphisms on the response to



**Figure.** Changes in FPG and HbA1c in T2DM patients after treatment with repaglinide. Changes in fasting blood glucose (FPG; post-administration levels minus pre-administration levels) and glycated hemoglobin (HbA1c; post-administration levels minus pre-administration levels) in type 2 diabetes mellitus patients with different *ABCC8* rs1801261 genotypes after treatment with repaglinide. Data are expressed as the mean with the standard error of the mean (n=70). \*p<0.05, \*\*p<0.01 compared with the CC genotype group.

repaglinide, participants with the same OATP1B1 521TT and CYP2C8\*3 139 Arg genotypes but different *ABCC8* rs1801261 genotypes were randomly selected. After eight consecutive weeks of repaglinide treatment, the levels of FPG, 2-HPG, HbA1c, TC, TG and HOMA-IR were significantly lower in these T2DM patients, indicating that repaglinide can improve the blood sugar and lipid metabolism values.

C/C homozygotes of the *ABCC8* exon16-3T/C variant reportedly responded better to repaglinide with regard to insulin sensitivity than those with the T/C or T/T genotypes; however, no significant effect of the *ABCC8* exon16-3T/C variant on repaglinide treatment was noted (37). The results of another study were not consistent, but C allele carriers were found to be more likely to develop higher TG concentrations after 6 months than noncarriers (38). However, the effect of *ABCC8* exon16-3T/C variants on the therapeutic efficacy of repaglinide has not been reported, and this should be explained by future functional research on the polymorphisms of *ABCC8* in addition to a population study.

In the present study, the association between *ABCC8* rs1801261 and repaglinide efficacy was examined. The results showed that repaglinide treatment had attenuated efficacy on the FPG in patients with the CT genotype of *ABCC8* rs1801261 (p<0.01). Patients with the CC genotype of *ABCC8* rs1801261 have shown a significant reduction in the levels of FPG than in patients with the CT genotype, suggesting that repaglinide is less effective in reducing postprandial blood glucose in T2DM patients who carry the T-allele.

## Conclusion

Our findings will aid in the development of better strategies for predicting therapeutic efficacy and controlling blood glucose in T2DM patients carrying different *ABCC8* genotypes. However, more detailed genetic and functional inves-

tigations will be needed in order to examine the effects of *ABCC8* variants on repaglinide therapy and provide more experimental evidence supporting patient-tailored therapy.

**The authors state that they have no Conflict of Interest (COI).**

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