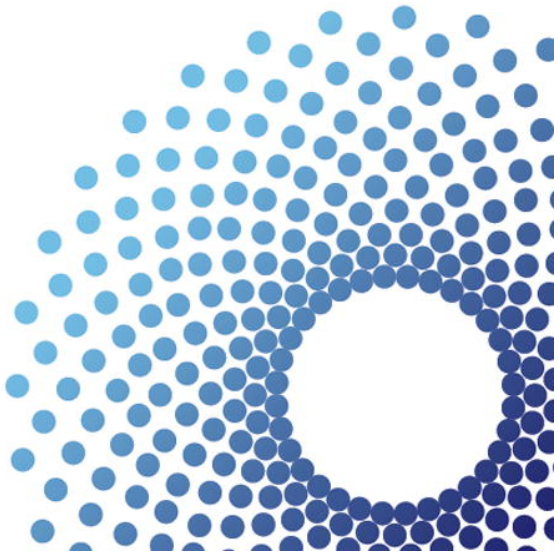
Vol. 77, Issue 1
July 2007
ISSN 0168-8227

DIABETES
RESEARCH AND
CLINICAL PRACTICE
Official Journal of the International Diabetes Federation Western Pacific Region



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Diabetes Research and Clinical Practice 77 (2007) 58–61
DIABETES RESEARCH AND CLINICAL PRACTICE
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Association of sulfonylurea receptor 1 genotype with therapeutic response to gliclazide in type 2 diabetes

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Received 31 January 2006; received in revised form 10 September 2006; accepted 6 October 2006
Available online 21 November 2006

Abstract

To investigate the effects of sulfonylurea receptor 1 (SUR1) exon 33 (TCC → GCC, S1369A) polymorphism on responsiveness to gliclazide. About 115 patients with type 2 diabetes were treated with gliclazide for 8 weeks. SUR1 genotypes were tested by Taqman-PCR. After gliclazide treatment, there was association between T/G polymorphism and decrease of HbA1c. G carriers were more sensitive to gliclazide and the decrease of HbA1c was more significant than TT genotype (TT, 0.76% ± 1.70%; TG + GG, 1.60% ± 1.39%, $P = 0.044$). The polymorphism of SUR1S1369A was associated with the therapeutic efficacy of gliclazide.

Keywords: Type 2 diabetes; Polymorphism; Gliclazide

1. Introduction

Type 2 diabetes is a heterogeneous disorder that results from impaired insulin secretion and insulin action [1,2]. The significant association between sulfonylurea receptor 1 (SUR1) gene polymorphisms and type 2 diabetes has been reported [3,4]. Among various hypoglycemic agent, sulfonylureas have been widely used in clinical practice. Sulfonylureas bind to the SUR1 subunit of the ATP-sensitive K^+ (K_{ATP}) channel and cause channel closure, triggering the opening of voltage gated Ca^{2+} channels, enhanced Ca^{2+} entry, and stimulation of insulin release [5,6]. The variability of sulfonylureas response is significant in clinical practice. The association between SUR1 genotype and the therapeutic efficacy of sulfonylureas is unclear. In this study, our aim was to investigate the influence of SUR1 exon 33 (TCC → GCC, S1369A) polymorphism on responsiveness to gliclazide in type 2 diabetes.

2. Materials and methods

2.1. Subjects

A total of 115 patients (64 men and 51 women) with type 2 diabetes were recruited. Diagnosis of diabetes was made according to WHO criteria. Patients with fasting plasma glucose (FPG) ≥7.8 mmol/l were enrolled if they had been treated with diet therapy and physical exercise and not been taking any hypoglycemic agent for 2 months before study. Patients with cardiac, hepatic, renal or other chronic diseases

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doi:10.1016/j.diabres.2006.10.021

were excluded. The study protocol was approved by the Ethical Committee of Anhui Medical University. Written informed consent was obtained from all subjects after they were given a complete description of the study. Gliclazide (Diamicron, company of SERVIER) was started at a dose of 40 mg before breakfast and supper. The dosage was adjusted according to FPG at the 15th day and end of the first month, and was not adjusted at the second month. Another 40 mg dosage was added when FPG was higher than 7.0 mmol/l. The maximal dosage was up to 240 mg/day.

All subjects were asked to continue their previous diet therapy and physical exercise throughout the study. Clinic visits occurred every 2 weeks. Data on fasting finger stick glucose, body weight, diet and physical activity were collected. Neither antihypertensive nor lipid-lowering drugs were allowed before and throughout the study period.

2.2. Biochemical studies

Hemoglobin A1c (HbA1c) was measured by affinity chromatography. FPG was measured using the glucose oxidase method. Total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) were measured via the automatic biochemical analysor. Fasting insulin was measured by radioimmunity. Insulin resistance was estimated by using the homeostasis model assessment (HOMA-IR) score, calculated as fasting insulin (mU/l) × fasting glucose (mmol/l)/22.5.

2.3. Genotyping

Genomic DNA were extracted from peripheral blood leukocytes by the phenol–chloroform method. Genotypic analysis was determined by Taqman-PCR. The forward and reverse primers were 5′-GGGAAGATCCAGATCCAGAACCT-3′, and 5′-CCGTGCTCTGACCTTCTGT-3′. The Taqman probes were VIC-5′-TGCCCTCATCGCCCCT-3′-NFQ, FAM-5′-ATGCCCTCATCTCCCCT-3′-NFQ. The PCR mixture consisted of 2× Universal PCR Master Mix No AmpErase UNG 2.5 μl, 10 ng DNA extract, 0.72 μM primers and 0.16 μM Taqman probe (Applied Biosystems, USA). After one cycle at 95 °C for 10 min, a two-step PCR procedure was used consisting of 15 s at 95 °C and 1 min at 60 °C for 50 cycles. Amplification and data acquisition were carried out using the ABI 7900HT sequence detection system.

2.4. Statistical analysis

Statistical analyses were performed using the SAS software. The χ^2-test was used for Hardy–Weinberg of the genotype. Comparison of results was by *t*-test and ANOVA, except for fasting plasma glucose and HbA1c reduction when we used covariance (ANCOVA) with baseline fasting plasma glucose, HbA1c and dosage as a covariate. Fasting insulin, HOMA-IR and triglyceride were log transformed before parametric analysis.

3. Results

Among the 115 subjects, the frequencies of the genotype TT, TG, GG were 33.0%, 47.0% and 20.0%, respectively. The allele frequencies were in Hardy–Weinberg equilibrium.

At the end of the second month fasting plasma glucose decreased significantly from 10.39 ± 2.55 to 7.80 ± 2.45 mmol/l ($P < 0.001$). HbA1c decreased from $8.79 \pm 1.75\%$ to $7.52 \pm 1.47\%$ ($P < 0.001$).

There were no significant differences in age, body weight, BMI, blood pressure and the plasma lipid profiles according to the genotypes before treatment. The insulin level and HOMA-IR were not significantly different among the genotype at baseline (Table 1). Accordance with a previous report, pooling individuals with the T/G and the G/G genotype were carried out [7]. Although the differences of FPG and HbA1c among the genotype at baseline were not statistically significant,

Table 1
SUR1S1369A genotype and clinical characteristics

	TT	TG	GG	*P*
n	38	54	23	
Age (years)	49.63 ± 9.32	51.02 ± 8.65	48.30 ± 8.24	0.443
Body weight (kg)	63.70 ± 11.34	64.45 ± 12.89	63.98 ± 12.47	0.566
BMI (kg/m^2)	24.60 ± 3.45	25.37 ± 2.75	25.01 ± 2.38	0.432
Systolic blood pressure (mmHg)	125.34 ± 16.78	125.39 ± 18.01	131.00 ± 16.59	0.382
Diastolic blood pressure (mmHg)	83.50 ± 9.06	82.52 ± 12.21	85.13 ± 9.31	0.618
Total cholesterol (mmol/l)	5.60 ± 1.17	5.44 ± 1.15	5.50 ± 1.27	0.819
Triglyceride (mmol/l)	3.14 ± 2.86	2.33 ± 2.11	2.88 ± 2.86	0.309
HDL-C (mmol/l)	1.48 ± 0.32	1.50 ± 0.31	1.48 ± 0.27	0.890
LDL-C (mmol/l)	3.06 ± 1.16	2.93 ± 0.89	2.77 ± 1.09	0.557
Fasting insulin (mU/l)	9.13 ± 5.34	9.26 ± 5.06	10.78 ± 6.58	0.447
HOMA-IR	4.08 ± 2.27	4.14 ± 2.43	4.79 ± 2.48	0.441

Data are means ± S.D.

Table 2
Changes in blood glucose and HbA1c after treatment according to SUR1S1369A genotype

	TT	TG	GG	*P*	TT	TG + GG	*P*
n	38	54	23		38	77	
FPG (mmol/l)							
Before treatment	10.68 ± 2.48	10.09 ± 2.52	10.59 ± 2.74	0.499	10.68 ± 2.48	10.24 ± 2.58	0.315
Change in FPG	2.52 ± 2.08	2.52 ± 2.50	2.98 ± 2.33	0.715	2.52 ± 2.08	2.66 ± 2.45	0.485
HbA1c/%							
Before treatment	8.65 ± 1.70	8.76 ± 1.71	9.10 ± 1.94	0.614	8.65 ± 1.70	8.86 ± 1.78	0.333
Change in HbA1c	0.76 ± 1.70	1.54 ± 1.48	1.72 ± 1.12	0.037	0.76 ± 1.70	1.60 ± 1.39	0.044*

Data are means ± S.D. *$P < 0.05$ vs. TT genotype.

the patients with G allele carriers represented more significant decrease of HbA1c after treatment compared with TT genotype ($P = 0.044$). Decrease in the FPG did no differ among the genotype (Table 2).

These groups were comparable at baseline and the end of study regarding diet composition and time of physical activity. There were no significant changes in body weight, BMI, blood pressure and lipid concentrations according to the genotypes after treatment.

4. Discussion

Pharmacogenetics has become increasingly accepted as an important consideration in the therapeutic decision-making process [8]. Type 2 diabetes mellitus is a multifactorial disorder with both genetic and environmental factors contributing to the development of chronic hyperglycemia [9–11]. Genetic factors play important roles in the pathogenesis of diabetes [10,12]. Sulfonylureas cause hypoglycemia by stimulating insulin release from the pancreatic β-cells. The effects of sulfonylureas are initiated by drug binding to the K_{ATP} channel, a complex that consists of two subunits: the sulfonylurea receptor and an inward rectifier channel protein, located in the plasma membrane of β-cells [13,14]. Interaction of sulfonylurea and receptor induces membrane depolarization, activation of voltage-gated Ca^{2+}channel, and degranulation of insulin-containing vesicles [6]. Our data suggest that after the treatment of gliclazide there is a significant decrease in HbA1c in G allele carriers compared with T/T homozygous individuals. This result strongly argues for the hypersensitivity to sulfonylureas in G allele carriers. Moreover, like other sequence variants of the SUR1 gene [3,15], the T/G polymorphism is located at the highly conserved phosphorylation site of the nucleotide-binding folds-2 (NBF-2) [7], which involved in regulation of the K_{ATP} channel by MgADP [7]. Glucose-induced increase in intracellular ATP induces closure of the K_{ATP} channel, membrane depolarization, Ca^{2+} influx and insulin secretion [16]. The point mutation might enhance the bonding force of SUR1 and ATP, which results in the hypersensitivity of K_{ATP} channel to ATP. However, no significant differences in the decrease of FPG levels could be found. This could be due to the fact that HbA1c is also affected by the postprandial blood glucose.

The frequency of the genotypes in our group was very similar to the previous report in Chinese population and in Danish subjects [2,17]. In accordance with a previous report [7], we found no significant association of the SUR1S1369A polymorphism with BMI and the lipid profiles.

In conclusion, our results suggested that G allele carriers represented more significant improvement of HbA1c level after treatment compared with TT genotype. TT genotype will need to apply more efficacious hypoglycemic agents.

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