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Clinical Pharmacogenomic of Metformin in Egyptian Patients with Insulin Resistance

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Abstract

Pharmacogenomics is rapidly developing and expanding as a key element of precision medicine, in which the association between individual genetic variabilities and drug disposition and therapeutic responses are investigated. The aim of this study was to explore the association of genetic mutation and /or polymorphism of genes related to therapeutics used in the treatment of insulin resistance IR. This study was aimed to investigate the association of rs2289669 variants in SLC47A1 gene response to metformin after 6 months follow up in Egyptian patients with insulin resistance IR. This study included 70 patients from those attending the outpatient clinics Diabetic Department, National Institute of Diabetes and Endocrinology in the period from 03/02/2022 to 1/2/2023 approved (NO. IDE 00272). Metformin 1000 mg and Vildagliptin 50 mg were given as treatment for 6 months, Genotyping of the rs2289669 variant of SLC47A1 gene was performed using the restriction fragment length polymorphism–PCR (RFLP–PCR) method. **Results** as regarding decrease in HbA1c, TC, TC/HDL, LDL/HDL there was significant difference between the three different genotypes GG, GA, AA of SLC47A1 rs2289669 variant (P<0.05).also there was no significant difference in response of glycemic and lipid parameters to metformin 1000 mg among different genotypic groups after 6 months (p > 0.05) Except HbA1c, TC, TC/HDL, LDL/HDL there was significant difference between the three different genotypes of SLC47A1 rs2289669 variant (P<0.05) . The study results indicate that effects of variation in SLC47A1 (rs2289669) on the clinical efficacy of metformin were important in treatment of insulin resistance.

Keywords: Metformin; Insulin Resistance; Pharmacogenomics; rs2289669; SLC47A1

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1. Introduction

Insulin resistance (IR) is defined as a decreased response of cells to insulin. IR is observed when a decrease in prolonged elevated blood glucose levels to a particular concentration of insulin is disturbed. In the state of IR, the lowering of plasma glucose to physiological levels requires more insulin. This condition, called hyperinsulinemia, begins with the development of IR [1]. Insulin resistance, also

known as impaired insulin sensitivity, is the result of decreased reaction of insulin signaling to blood glucose levels. This state is observed when muscle cells, adipose tissue, and liver cells, improperly respond to a particular concentration of insulin. Insulin resistance and related increased plasma insulin levels (hyperinsulinemia) may cause metabolic impairments, which are pathological states observed in obesity and type 2 diabetes mellitus [1]. Precision medicine is a newly emerging approach that patients are given personalized care based on their unique genetic and lifestyle characteristics [2]. Pharmacogenomics, a part of precision medicine, is the study of how genes affect a person's response to drugs.

This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to variations in a person's genes [3]. Pharmacogenomics is rapidly developing and expanding as a key element of precision medicine, in which the association between individual genetic variabilities and drug disposition and therapeutic responses are investigated [3]. Genetic differences were found to affect not only the occurrence of disease and its progression, but also the form and dosage of medication used, the degree of therapeutic effectiveness, and the risk of adverse drug reactions which can aid in the development of individually tailored therapies [2]. Identifying genetic variants linked to altered drug response can be a major concern in diabetes research [4]. The biguanide metformin has been used for its glucose lowering effect since 1957 in Europe and since 1995 in the USA. Yet despite being the most frequently prescribed anti diabetic treatment worldwide, its mechanism of action remains largely elusive. The pharmacokinetics and response to metformin reveal a wide inter individual variability.

The polarity of metformin makes it dependent on membrane transporters for cellular uptake and secretion. The main metformin transporters are solute carrier family 22 members (SLC22A) 1 and 4 (also known as OCT1 and OCTN1, respectively), multidrug and toxin extrusion protein (MATE) 1 and 2, and the plasma membrane monoamine transporter hENT4 (also known as PMAT) [5]. The SLC47A1 and SLC47A2 genes may mediate the transport and excretion of metformin. Some variants of these genes can affect the glycemic response to metformin. Given the importance of SLC47A1 gene role in metformin response, there were not many investigations on the SLC47A1 gene and response to metformin. The SLC47A1 gene encodes the multi-drug and toxic excretion 1(MATE1) protein, which plays a key role in the transport and excretion of metformin [5]. This study was aims to investigate the association between variant in the SLC47A1 gene rs2289669 variant and response to metformin after 6 months follow up in the Egyptian patients with insulin resistance IR.

2. Subjects and Methods

This study was carried out at National Institute of Diabetes and Endocrinology, included 70 patients from those attending the outpatient clinics Diabetic Department, National Institute of Diabetes and Endocrinology. According to the clinical examination, laboratory findings result, subjects sharing in this study were insulin resistance group: this group included 70 patients with insulin resistance (normal patient).

2.1. Exclusion criteria (Excluded subjects)

Patients with type 1 diabetes, gestational diabetes, severe diabetic polyneuropathy (DPN), high risk of urogenital infections, diabetes complications, malignancies, renal insufficiency (moderate to severe, eGFR < 30), and systemic inflammatory disease will be excluded. Furthermore, we excluded the patients with a history of diabetic foot ulcer, diabetic ketoacidosis, Fournier gangrene, recurrent urinary tract infections (UTI), recurrent mycotic infections of urogenital tract, and cancer as well as pregnant or breastfeeding women, Patient received insulin injection, patients with history of autoimmune disease, patients with insulin resistance (HOMA IR ≤ 2.9), and patients with age <18 years OR >65 years.

2.2. Inclusion criteria (Included subjects)

Patients with insulin resistance (HOMA IR >2.9), patients with diabetes mellitus, prediabetes mellitus, patients were treated with sitagliptin, vildagliptin, linagliptin, alogliptin, and patients aged 30-65 years. Metformin in a daily dose of 1000 mg, was added to the previous treatment with vildagliptin 50 mg.

All patients group were subjected to the following:

Informed consent was obtained from each participant, demographic, age, gender, onset of DM, duration of disease. Full history taking, complete clinical examination and Laboratory investigation including Anthropometric measurements: Weight (KG), Height (M) and Body mass index (KG/M^2), Systolic blood pressures SBP (mm Hg), diastolic blood pressure DBP (mm Hg) and heart rate pulse (bpm).There are two routine laboratory tests and fasting blood sugar (FBS), and fasting blood insulin, HbA1c, and lipid profile such as total cholesterol (TC), low-density lipoprotein (LDL), high -density lipoprotein (HDL), triglycerides (TG),creatinine, urea, measured at baseline and followed for 6 months for each patient after entering study.

2.3. Method of genotyping

1. DNA Extraction

Genomic DNA was isolated from peripheral blood leukocytes by standard salting out method.

2. Genotyping (RFLP method)

Genotyping for (rs2289669) variations was performed using the restriction fragment length polymorphism–PCR (RFLP–PCR) method. For polymerase chain reaction amplification, the following primers (Invitrogen, California, USA) were used: -forward 5-TCAGTTTCCACAGTAGCGTCG-3 and reverse 5-GACACTG- GAAGCCACACTGAA-3. A Perkin Elmer Gene Amp 9700 PCR System (Applied Biosystems, Foster city, CA, USA) was used for the amplification. PCR conditions were as follows: initial denaturation at 95 °C for 10 min; followed by 30 cycles of denaturation at 95 °C for 30 s; annealing at 58 °C for 30 s; primer extension for 30 s at 72 °C; and final extension at 72 °C for 10 min.

3. Variant of rs2289669

The PCR products were digested with Taq I restriction endonuclease. The digestion of 211 bp amplicon of rs2289669 (AA) genotype resulted in 21 and 190 bp fragments; the (GG) genotype remained 211 bp; while the heterozygous genotype (GA) 21, 190, 211 bp fragments.

2.4. Statistical analysis

For the entire study cohort, data were collected for all analyzed parameters and tabulated. Raw data were coded, transformed into coding sheets, managed, and stored into SPSS program (SPSS package version 22 for Windows, Chicago, IL, USA © 2013). Genotypes and alleles frequencies were compared between responder and non-responder groups and by Chi-square test. Fisher's exact test was used if cell expected frequencies were < 5.

Data were grouped into two main categories:

Qualitative categorical variables (Genotypes, alleles, gender): Descriptive statistics including Genotype and allele frequency distributions were used to describe different characteristics.

Quantitative variables (All measured biochemical parameters): Descriptive statistics including mean, standard deviation, standard error "SEM", were used to describe different characteristics. To test the significance of results for the continuous data variables among three different groups, one way ANOVA .and among two different groups, unpaired student t-test. All P-values were two-tailed (Two-sided) and the significance of results was set at 5% level of significance (P-value < 0.05 was considered as statistically significant) (Norman and Streiner, 2000). Statistical analysis was applied to the insulin resistance IR patients (№ = 70) who classified according to their genotypes (GG=47, GA=17, AA=6) at the base line and after 6 months. Classification of the patients into the Responders (R) and the Nonresponders (NR) according to % alterations in the glycemic and lipid parameters according to the rule.

$$\%\ Alteration = \frac{(paramter\ after\ 6\ months - parameter\ at\ basline)}{paramter\ at\ baseline} x\ 100$$

3. Results and discussion

3.1. Results

The baseline anthropometric measures of 70 patients with insulin resistance were measured and compared before metformin 1000 mg therapy. As indicated in Table 1, there was no significant difference in baseline demographic profiles and anthropometric measures among different genotypic groups (GG (47), GA (17), and AA (6)) of SLC47A1 rs 2289669 variant in 70 insulin resistance patients (p > 0.05). After 6 months demographic profiles and anthropometric measures of 70 patients with insulin resistance were measured and compared after metformin 1000 mg therapy. As indicated in Table 2, there was no significant difference in demographic profiles and anthropometric measures among different genotypic groups after 6 months (p > 0.05) Except DBP there was significant difference between the three different genotypes of SLC47A1 rs2289669 variant. In table (3), there was no significant difference between all patients before and after metformin 1000 mg treatment regarding glycemic and lipid parameters (p > 0.05) Except TC, TC/HDL, LDL/HDL there was significant difference between all patients before and after metformin 1000 mg treatment regarding glycemic and lipid parameters (p < 0.05). In table (4) there was no significant difference in response of glycemic and lipid parameters to metformin 1000 mg among different genotypic groups after 6 months (p > 0.05) Except HbA1c, TC, TC/HDL, LDL/HDL there was significant difference between the three different genotypes of SLC47A1 rs2289669 variant (P<0.05).

3.2. Discussion

The field of pharmacogenomics is still in its early stages of development. Currently, its utilization is very restricted, although novel methodologies are being investigated in clinical trials [6]**.** The objective of this study was to investigate the correlation between genetic mutation and polymorphism of SLC47A1 gene with the effectiveness of metformin which used to treat insulin resistance (IR), the aim of the study was to investigate the association SLC47A1 rs2289669 polymorphisms and their influence on metformin efficacy in Egyptian patients with Insulin resistance. In our study, there was no significant difference in baseline anthropometric measures among different genotypic groups GG (47), GA (17), AA (6)) of SLC47A1 rs 2289669 variant in 70 insulin resistance patients (p > 0.05), [5] investigated whether this same variation in GLP1R could affect T2DM patients' responses to DPP-4 inhibitors. They showed allele and genotype distributions of rs3765467 in study population. G was major allele, whereas A was minor allele in this group. The genotype distribution did not deviate from Hardy–Weinberg equilibrium (P=0.939). Clinical characteristics of the study participants at baseline. The mean duration of diabetes was 9.3 years, and the HbA1c level was the ~8.2%.

After 24 weeks of DPP-4 inhibitor add-on treatment, fasting blood glucose levels and HbA1c values significantly decreased (from 155.5±44.8mg/dL to 133.7±34.7, P< 0.001 for HbA1c). In addition, total cholesterol and triglyceride levels also decreased significantly. In our study, there was no significant difference between all patients before and after metformin 1000 mg treatment regarding glycemic and lipid parameters (p > 0.05) Except TC, TC/HDL, LDL/HDL there was significant difference between all patients before and after metformin 1000 mg treatment regarding glycemic and lipid parameters (p < 0.05). In a study by [7]], a total of 267 T2DM patients and 182 healthy subjects were enrolled to explore the allele frequencies and genotype frequencies of SLC22A1 rs594709 & SLC47A1 rs2289669 polymorphisms. BMI (25.10 ± 2.74 kg/m2 versus 23.98 ± 2.94 kg/m2 , p < 0.001), waist circumference (87.40 ± 8.56 cm versus 81.72 ± 9.52 cm, p < 0.001), waist-to-hip ratio (0.91 ± 0.06 versus 0.85 ± 0.07, p < 0.001), FBG (8.91 ± 3.40 mmol/L versus 5.11 ± 0.57 mmol/L, p < 0.001) and, TG (3.12 ± 3.71 mmol/L versus 1.85 ± 6.82 mmol/L, p < 0.05) in T2DM patients were significantly higher than those of healthy subjects.

Moreover, HDL-C level (1.32 ± 0.64 mmol/L versus 1.51±0.45 mmol/L, p < 0.001) in T2DM patients was significantly lower than that in healthy subjects. No significant differences were found in hip circumference, TC, and LDL-C level between two groups. In a study by [7], a frequency of the SLC22A1 rs594709 and SLC47A1 rs2289669 polymorphisms in T2DM patients and healthy subjects, both SNPs agreed with Hardy Weinberg equilibrium in each group (p > 0.05). Minor allele frequencies (MAFs) of SLC22A1 rs594709 in T2DM group and healthy control were 26.78% and 28.57%, respectively. MAFs of SLC47A1 rs2289669 were, respectively, 47.19% and 46.97% in T2DM patients and healthy subjects. No significant differences were found in allele frequencies (p = 0.555 for rs594709; p = 0.950 for rs2289669) and genotype frequencies (p = 0.927 for rs594709; p = 0.669 for rs2289669) between T2DM patients and healthy controls.

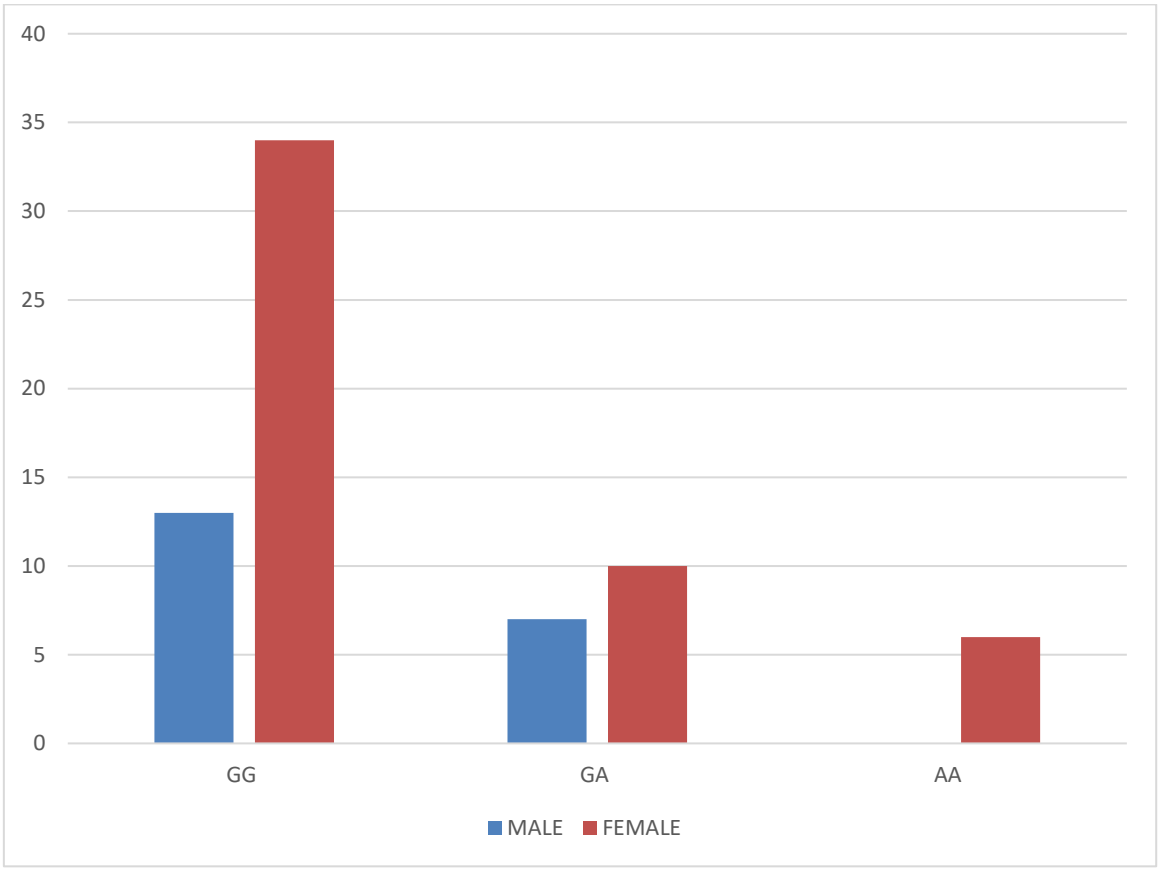

Fig. (1): Gender of different genotypes of SLC47A1 rs2289669 variant in 70 IR patients

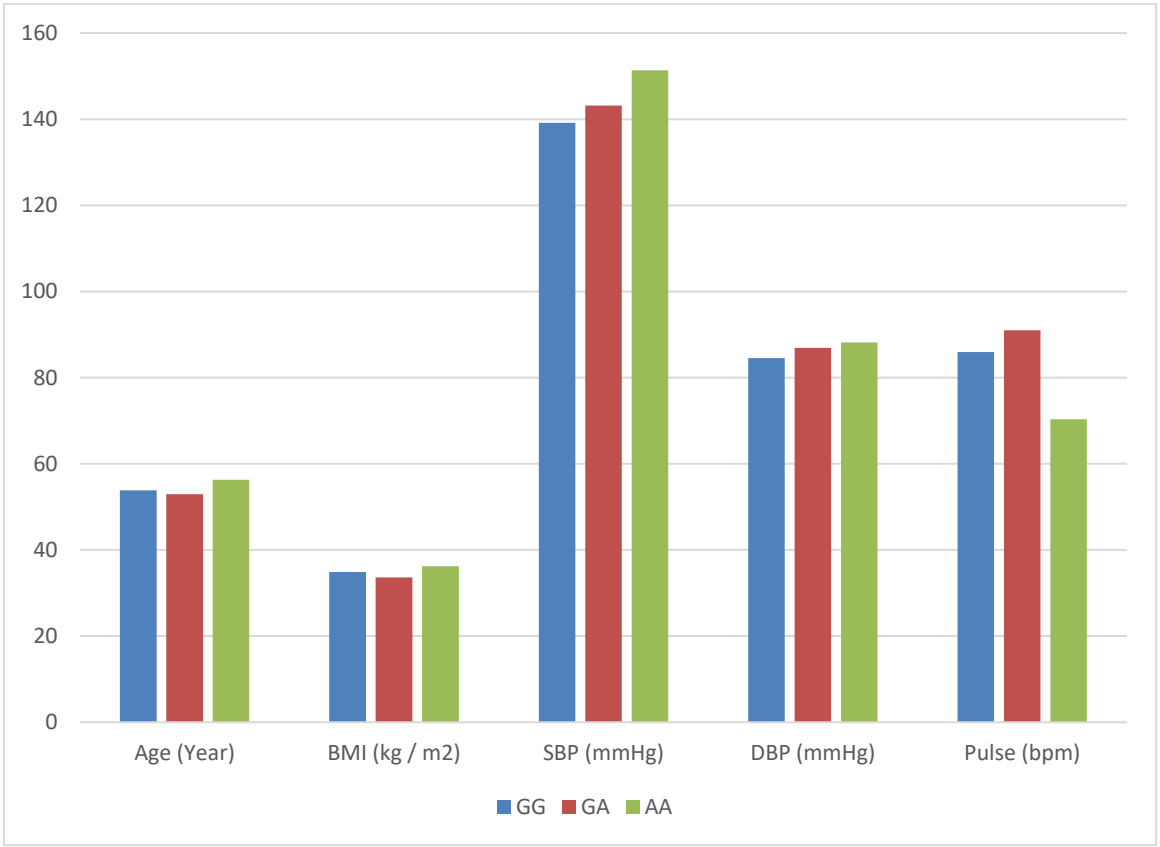

Fig. (2): Baseline Characteristics Anthropometric measures of different genotypes of SLC47A1 rs2289669 variant in 70 IR patients.

Table (1): Baseline characteristics anthropometric measures of different genotypes (GG (47), GA (17), and AA (6)) of SLC47A1 rs 2289669 variant in 70 insulin resistance patients

Variables	GG (47)	GA (17)	AA (6)	P-Value
Gender	Male (13)	Male (7)	Male (0)	0.154^{NS}
	Female (34)	Female (10)	Female (6)	
Age (Year)	53.81 ± 7.08 53.81 ± 1.03	52.94 ± 8.78 52.94 ± 2.13	56.33 ± 8.16 56.33 ± 3.33	0.645 ^{NS}
BMI (kg / m^2)	34.89 ± 7.87 34.89 ± 1.14	33.62 ± 6.13 33.62 ± 1.48	36.26 ± 4.86 36.26 ± 1.96	0.713^{NS}
SBP (mmHg)	139.15 ± 18.98 139.15 ± 2.77	143.18 ± 20.61 143.18 ± 4.99	151.33 ± 21.23 151.33 ± 8.67	0.323^{NS}
DBP (mmHg)	84.55 ± 13.12 84.55 ± 1.91	86.94 ± 12.66 86.94 ± 3.07	88.17 ± 16.04 88.17 ± 6.54	0.712^{NS}
Pulse (bpm)	85.98 ± 12.54 85.98 ± 1.83	91.00 ± 17.76 91.00 ± 4.30	70.33 ± 8.28 70.33 ± 3.83	0.09^{NS}

SLC47A1, solute carrier family 47 member 1; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table (2): After 6 months Demographic profiles and Anthropometric measures of different genotypes (GG (47), GA (17), and AA (6)) of SLC47A1 rs 2289669 variant in 70 insulin resistance patients

Variables	GG (47)	GA (17)	AA (6)	P-Value
Gender	Male (13)	Male (7)	Male (0)	0.154^{NS}
	Female (34)	Female (10)	Female (6)	
BMI (kg / m^2)	33.42 ± 3.87 33.42 ± 0.56	33.85 ± 3.82 33.85 ± 0.92	33.35 ± 5.06 33.35 ± 2.06	0.924^{NS}
SBP (mmHg)	133.30 ± 15.62 133.30 ± 2.27	139.62 ± 10.68 139.62 ± 2.59	137.46 ± 9.35 137.46 ± 3.81	0.273^{NS}
DBP (mmHg)	83.92 ± 11.00 83.92 ± 1.60	94.62 ± 12.84 94.62 ± 3.11	89.23 ± 6.84 89.23 ± 2.79	0.005^{S}
Pulse (bpm)	85.11 ± 12.93 85.11 ± 1.88	81.55 ± 9.93 81.55 ± 2.41	74.65 ± 13.11 74.65 ± 5.35	0.123^{NS}

Table (3): glycemic and lipid parameters before and after Metformin 1000 mg in all patients (n=70).

Variables	Baseline	6 months	p-value
BMI (kg / m2)	34.70 ± 7.23 34.70 + 0.86	33.52 ± 3.91 33.52 ± 0.46	0.120^{NS}
HbA1c %	8.99 ± 2.85 8.99 ± 0.34	8.75 ± 2.33 8.75 ± 0.27	0.355^{NS}
HOMA-IR	6.61 ± 5.82 6.61 ± 0.69	6.85 ± 4.83 6.85 ± 0.57	0.761^{NS}
HOMA-B	99.59 ± 408.68 99.59 ± 48.84	54.13 ± 43.40 54.13 ± 5.18	0.317^{NS}
TC	230.61 ± 61.91 230.61 ± 7.40	215.09 ± 32.39 215.09 ± 3.87	0.034^{S}
TC/HDL	6.77 ± 4.27 6.77 ± 0.51	5.56 ± 1.51 5.56 ± 0.18	0.020^{S}
LDL/HDL	4.12 ± 2.19 4.12 ± 0.26	3.37 ± 1.28 3.37 ± 0.15	0.003^{S}

Table (4): Response of glycemic and lipid parameters to metformin 1000 mg treatment of different genotypes (GG (47), GA (17), and AA (6)) of SLC47A1 rs 2289669 variant in 70 insulin resistance patients

Parameter		GG	GA	AA	Total	P-value
response of BMI to metformin 1000mg	responders	33	7	5	45	0.06^{ns}
	Non-responders	14	10	1	25	
response of HbA1c to metformin 1000mg	responders	31	6	1	38	0.01^{s}
	Non-responders	16	11	5	32	
response of Homa-IR metformin 1000 mg	responders	25	6	2	33	0.349^{ns}
	Non-responders	22	11	4	37	
response of Homa B to metformin 1000 mg	responders	21	7	2	30	0.858^{ns}
	Non-responders	26	10	4	40	
response of TC to metformin 1000 mg	responders	34	10	1	45	0.024^{S}
	Non-responders	13	7	5	25	
response of TC/HDL to metformin 1000 mg	responders	36	11	1	48	0.011^{S}
	Non-responders	11	6	5	22	
response of LDL/HDL to metformin 1000 mg	responders	34	17	1	47	0.022^{S}
	Non-responders	13	10	5	23	

In our study there was no significant difference between all patients before and after metformin 1000 mg treatment regarding glycemic and lipid parameters ($p > 0.05$) Except TC, TC/HDL, LDL/HDL there was significant difference between all patients before and after metformin 1000 mg treatment regarding glycemic and lipid parameters ($p < 0.05$). Additionally, in a study by [7] found a significant SNP-SNP interaction between SLC47A1 rs2289669 and SLC22A1 rs594709, which affected the improvement of insulin resistance and blood lipid induced by metformin therapy. Among SLC22A1 rs594709 AA genotypes, patients with SLC47A1 rs2289669 AA genotype showed significantly higher decrease in FBG ($p = 0.015$), PINS ($p = 0.041$), and HOMA-IR ($p = 0.014$) than GA or GG genotypes, while, among SLC22A1 rs594709 G allele carriers, patients with SLC47A1 rs2289669 AA genotype showed a greater decrease in TC ($p = 0.013$) than GA or GG genotypes**.** Previously, Caucasians population-based study by [8] in diabetic patients revealed that rs2289669 G/A in SLC47A1 gene associated with the therapeutic efficacy of metformin.

The decrease in HbA1c was greater in AA homozygotes compared with the GA + GG genotype patients after metformin treatment. The effect of SLC47A1 rs2289669 polymorphism on pharmacodynamics ($n = 202$) and pharmacokinetics ($n = 28$) of metformin was also evaluated in Chinese patients and showed that AA genotype patients had a better glucose lowering effect after one-year follow-up. As for pharmacokinetics parameters, AA genotype patients had higher AUC12h and lower renal clearance and renal clearance by secretion. Thus, it is possible that the effect of the rs2289669 polymorphism on metformin glucose lowering efficacy was caused partly or completely by a reduced renal excretion and increased metformin plasma levels. However, in [7-8] study, they did not find SLC47A1 rs2289669 polymorphism correlated with metformin glucose lowering effect but was associated with the reduction of TC and LDL-C. This result was like long-term metformin and sulphonyl urea combination therapy study by [9] carried out in Slovenia.

Their results suggested that SLC47A1 rs2289669 genotype not associated with HbA1c levels but significantly associated with cholesterol levels in metformin-treated T2DM patients even after adjustment for renal function. In contrast to previous studies, sample size, period of metformin treatment, and different races were all possible reasons leading to different results. Replication studies in a relatively large population in a multi-ethnic diabetic cohort are needed to confirm SLC47A1 rs2289669 polymorphism effect on metformin efficacy both in glycemic control and in lipid profiles. Furthermore, [7] found that there was an interaction between SLC47A1 rs2289669 and SLC22A1 rs594709, which affected the blood glucose, insulin level, insulin resistance improvement, and blood lipid after metformin treatment. Among SLC22A1 rs594709 AA genotype patients, SLC47A1 rs2289669 AA genotype patients showed a better glycemic control compared with G allele carriers, while, among SLC22A1 rs594709 G allele carriers, patients with SLC47A1 rs2289669 AA genotype showed a better metformin efficacy in blood lipid than GA or GG genotypes.

In our study there was no significant difference in response of glycemic and lipid parameters to metformin 1000 mg among different genotypic groups after 6 months ($p > 0.05$) Except HbA1c, TC, TC/HDL, LDL/HDL there was significant difference between the three different genotypes of SLC47A1 rs2289669 variant ($P<0.05$), Interaction between SLC22A1 and SLC47A1 polymorphisms and metformin response had been reported previously [9]]; the effect of the SLC47A1 rs2289669 polymorphism on the decrease of HbA1c by metformin was larger in incident users with the SLC22A1 rs622342 CC genotype than in incident users with the AA or AC genotype patients. Both rs622342 and rs594709 are in intron regions of SLC22A1 gene. The interaction is possibly due to the genetic mutations in SLC22A1 and SLC47A1 altering the function of OCT1-mediated influx and MATE1-mediated efflux. As OCT1 transports metformin into the hepatocyte and MATE1 transports metformin out of the hepatocyte into the bile, altered OCT1 and MATE1 function may be able to influence intracellular metformin concentrations and glucose lowering function of metformin. Further replication and mechanism studies are needed to illustrate influences of SLC22A1 and SLC47A1 polymorphisms on metformin efficacy.

4. Conclusions

Future approaches will move from evidence-based medicine to personal-based medicine, and we will have to use pharmacogenetic methods to achieve better treatments to determine the effectiveness of drug treatments and prevent side effects. We face an increase in number of insulin

resistance patients in coming years, using these methods can be very helpful and reduce cost of medication for the patients and health system. The study results indicate that effects of variation in SLC47A1 (rs2289669) on the clinical efficacy of metformin were important in treatment of insulin resistance.

Recommendation

We recommend increase the sample size and make the study from multicenter.

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