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The impact of IRS1 rs1801278 polymorphism on patients with type 2 diabetes mellitus treated with glibenclamide

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Abstract

Background: The insulin receptor substrate 1 (IRS1) plays a vital role in the intracellular signaling of insulin upon insulin binding to its receptor. Glibenclamide is a commonly prescribed drug for the treatment of type 2 diabetes mellitus. This research aims to investigate the influence of IRS1 rs1801278 single nucleotide polymorphism (SNP), on the interindividual variations in metabolic and glycemic parameters among Iraqi patients with type 2 diabetes mellitus treated with glibenclamide.

Methods: This cross-sectional study, conducted from September 2024 to September 2025, enrolled 160 Iraqi patients diagnosed with type 2 diabetes mellitus and they were taking glibenclamide as a monotherapy for at least three months. Some biochemical parameters, including glycemic indices, lipid profile, and liver and kidney functions, were assessed. Genotyping of the IRS1 rs1801278 (C/G) SNP was done using allele-specific polymerase chain reaction technique.

Results: The frequencies of IRS1 rs1801278 genotypes were 75% for CC, 16.25% for CG, and 8.75% for GG. Patients with the GG genotype exhibited higher levels of fasting blood glucose, HbA1c, and insulin resistance, and a significantly altered lipid profile.

Conclusions: The IRS1 rs1801278 SNP is significantly associated with poor glycemic control and altered lipid profile. These results suggest that genetic variation in IRS1 could be associated with differences in metabolic and glycemic profiles in individuals with type 2 diabetes and underscore the clinical relevance of the IRS1 rs1801278 SNP in the Iraqi population.

دراسة في تعدد الاشكال الجيني لجين ركيزة مستقبلة الأنسولين وتأثيره على فعالية دواء كليبنكلاميد في علاج مرضى السكري النوع الثاني العراقيين.

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الخلاصة

المقدمه: يلعب البروتين الركيزة لمستقبل الإنسولين1 (Insulin Receptor Substrate-1; IRS1) دورًا محوريًا في مسارات الإشارة داخل الخلية بعد ارتباط الإنسولين بمستقبله. ويُعد دواء الغليبينكلاميد من الأدوية الشائعة الاستخدام في علاج داء السكري من النوع الثاني. تهدف هذه الدراسة إلى تقصي تأثير تعدد الأشكال الوراثية المعروف بـ IRS1 rs1801278في التباين الفردي للاستجابات الأيضية ومؤشرات التحكم السكري لدى المرضى العراقيين المصابين بداء السكري من النوع الثاني والمعالجين بالغليبينكلاميد.

طرائق العمل: أُجريت هذه الدراسة المقطعية خلال الفترة من أيلول 2024 إلى أيلول 2025، وشملت 160 مريضًا عراقيًا مشخصين بداء السكري من النوع الثاني، كانوا يتلقون الغليبينكلاميد كعلاج أحادي لمدة لا تقل عن ثلاثة أشهر. جرى تقييم عدد من المؤشرات الكيميائية الحيوية، بما في ذلك مؤشرات التحكم السكري، وصورة الدهون في الدم، ووظائف الكبد والكلى. كما تم تحديد الأنماط الجينية لـتعدد الاشكال الوراثية IRS1 rs1801278 (C/G)باستخدام تقنية تفاعل البوليميريز المتسلسل النوعي للأليل (Allele-Specific Polymerase Chain Reaction).

النتائج: بلغ تواتر الأنماط الجينية لـ IRS1 rs1801278 نسبة 75% للنمط CC، و16.25% للنمط CG، و8.75% للنمط GG. وأظهر المرضى الحاملون للنمط الجيني GG مستويات أعلى من سكر الدم الصيامي، والهيموغلوبين السكري(HbA1c) ، ومقاومة الإنسولين، إضافة إلى اضطراب ملحوظ إحصائيًا في صورة الدهون مقارنة بالأنماط الجينية الأخرى.

الاستنتاجات: يرتبط تعدد الأشكال الوراثية IRS1 rs1801278 ارتباطًا مهماً بسوء التحكم السكري واضطراب استقلاب الدهون. وتشير هذه النتائج إلى أن الاختلافات الجينية في جين IRS1قد تسهم في التباين في المؤشرات الأيضية ومؤشرات السيطرة على سكر الدم لدى الأفراد المصابين بداء السكري من النوع الثاني، مما يؤكد الأهمية السريرية لتعدد الأشكال الوراثية rs1801278في السكان العراقيين.

1. Introduction

Diabetes mellitus is a chronic condition characterized by abnormal carbohydrate metabolism along with other metabolic dysfunctions that result in hyperglycemia and disruption of fat and protein metabolism (Gomez-Diaz, 2023; Jubair et al., 2024). Glibenclamide and other sulfonylurea drugs exert their antidiabetic effects through increased insulin secretion from pancreatic beta-cells (Seino et al., 2017). Insulin binds to a specific insulin receptor in the cells of the liver, skeletal muscles, adipose tissues, and other organs and tissues. Binding of insulin to its receptor initiates a signaling pathway that results in the transport of glucose-transporting channels to the cell surface. Glucose transporting channels transport glucose from blood into the cell cytoplasm, where glucose undergoes metabolism (Mohan et al., 2022; Saltiel, 2021). The insulin receptor substrate 1 (IRS1) gene located on chromosome 2p36.3 encodes the insulin receptor substrate protein, which is an endogenous insulin substrate that plays a pivotal role in the cellular insulin signaling cascade by transmitting the signal between the insulin receptor and phosphoinositide 3-kinase. As IRS-1 is phosphorylated on the insulin receptor, it binds to other proteins, which leads to an increase in the translocation of glucose transporter type 4 (GLUT4) into the outer membrane of cells, which ultimately increases glucose uptake from the blood into these cells (Qi et al., 2011).

Polymorphisms in the IRS1 gene, as reported in previous researches, could be associated with altered insulin signaling and insulin resistance, possibly resulting in interindividual variability in metabolic parameters among diabetic patients as well as affecting their responsiveness to the pharmacological treatment with the antidiabetic agent glibenclamide (Aljabali, 2024; Shaw, 2011). This research aims to investigate the impact of the rs1801278 SNP on Iraqi patients with type 2 diabetes mellitus and their responsiveness for treatment with glibenclamide.

2. Materials, Patients and Methods

2.1. Patients' Constant and Enrollment

This cross-sectional study adheres to Helsinki Declaration, it is approved by the Scientific and Ethical Committee of the College of Pharmacy, University of Kerbala (reference number: 2024HU8). Written informed consent was obtained from all participants prior to enrollment. Participants were asked to complete a specially designed questionnaire that collected information on demographic characteristics, family history of diabetes, dietary habits, weight, height, side effects experienced by using glibenclamide therapy, and medical history, such as duration of diabetes, duration of treatment, and concomitant diseases.

A total of 160 Iraqi patients diagnosed with type 2 DM were recruited at the Center of Diabetes and Endocrinology, Kerbala, Iraq, from September 2024 to September 2025. Eighty of the subjects were males, and the other 80 were females. The diagnosis of the patients was based on the American Association of Diabetes 2024 criteria (Committee, 2023). The patients' ages range from 40 to 67 years old and they had been taking glibenclamide as a monotherapy for at least 3 months.

2.2. Patient Inclusion Criteria

Patients with type 2 diabetes mellitus aged over 40 years who had been administered glibenclamide as monotherapy for a minimum of three months and exhibited no evident comorbidities.

2.3. Patient Exclusion Criteria

Patients were excluded from the study if they met any of the following criteria:

Presence of serious or life-threatening conditions, including malignancy, chronic kidney disease, liver disease, cardiovascular disease, anemia, or hemoglobinopathies.

History of recent surgery within the preceding two months.

Use of concomitant medications known to interfere with the pharmacological action or bioavailability of glibenclamide.

2.4 Blood Collection

All the participants were fasting for about 8 hours before the venous blood was drawn from them. Five milliliters of blood were drawn; 3 mL were stored in a gel tube and centrifuged to obtain blood serum, which was used later for the biochemical analysis. The remaining 2 mL of the blood were stored in EDTA tubes for the genetic analysis and estimation of HbA1c. The blood was stored at less than −20°C for 2 months till the time of the genetic analysis.

2.5. Genetic Analysis

The genomic DNA was extracted using the Presto Gene aid extraction kit according to the manufacturer's protocol. A total of 100µL of the genomic DNA was obtained from each blood sample. A nanodrop (The Thermo Scientific Nanodrop, Thermo Fisher Scientific, USA) was used to identify the concentration and purity of the extracted DNA.

Allele-specific polymerase chain reaction (PCR) was performed using PCR-thermal cycler Veriti, Thermo Fisher Scientific/USA to detect the rs1801278 (C>G) SNP. The lyophilized primers were provided by Pioneer Company, Korea. The forward primer sequences for the C allele and G allele are 5-TAGGCCTGCAAATGCTAGCAGCCCC-3, 5-TAGGCCTGCAAATGCTAGCAGCCCG-3, respectively, while the reverse primer sequence is 5-GCTGCTCAGACCAATAGCCGCCT-3. The rs1801278 SNP lies on exon 1 of the IRS1 gene, the primers were designed using the NCBI database with the accession number (IRS1/NM_005544.3/NP_005535.1).

The PCR reaction mixture volume was 25µL in total; the volume of the mixture components was as follows: 12µL of Accupower PCR Premix (Pioneer Company, Korea), 2µL (100 ng/µL) of the extracted DNA, 1.5µL (10pmol/L) of the forward primer, 1.5µL (5pmol/µL) of the reverse primer, and 8µL of nuclease-free water. The PCR program was as follows: in stage 1 of the PCR process, the DNA strands undergo denaturation at 95° for 3 minutes; in stage 2, annealing takes place and the temperature changes three times in a cycle that is repeated thirty times; the first part of the cycle, the temperature remains at 95° for 34 seconds; in the second part, the temperature is 67° for 30 seconds, while in the third part, the temperature is 72° for 50 seconds; and in stage 3, the final annealing occurs, and the temperature is 72° for 7 minutes.

Electrophoresis was performed utilizing a 1.5% (wt./v.) agarose gel pre-stained with ethidium bromide in tris-borate ethylenediaminetetraacetic acid (TBE) buffer for the detection of PCR amplicons. Given the sample size, the study was sufficiently powered to detect moderate effect sizes; however, smaller differences may not have been detected. Genotyping quality control included the use of negative controls in each PCR run and duplicate genotyping of randomly selected samples, showing complete concordance and the overall genotyping call rate exceeded 98%.

2.6. Biochemical Analysis

The blood serum collected in the gel tube was used to estimate the biochemical parameters, such as fasting blood glucose, insulin, urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) concentrations, while HbA1c was estimated using 100 µL of the blood collected in the EDTA tube.

Fasting blood glucose was assessed using the enzymatic indicator test based on the Trinder reaction, quantified by the production of a pink quinonimine dye via the Glucose GOD-PAP kit, Biorex Diagnostics, United Kingdom. HbA1c is measured by an enzymatic test that quantifies glycated hemoglobin in the whole blood via protease and fructosyl-peptide oxidase reaction, resulting in hydrogen peroxide, which is then quantified spectrophotometrically (Enzymatic HbA1c Reagent kit, Mindray, China). Insulin concentration is quantified by immunoassay to detect human insulin in human serum or plasma with chemiluminescent microparticle immunoassay (CMIA) technology using the Architect Insulin kit from Abbott, Germany.

Triglyceride, LDL, HDL, urea, creatinine, AST, and ALT were assayed using specific kits from Biorex Diagnostics Company, United Kingdom. The VLDL was calculated as follows: triglycerides (mg/dL) /5 (Friedewald et al., 1972). Homeostasis model assessment-insulin resistance (HOMA-IR) was calculated as follows: fasting insulin (µIU/ml) × fasting glucose (mg/dl)/405 (Matthews et al., 1985).

2.7. Statistical Analysis

The statistical program for the social sciences (SPSS) version 22 (IBM, Chicago, IL, USA) has been used to analyze the data. To compare the three groups of the study subjects, a one-way analysis of variances (one-way ANOVA) was conducted. To account for multiple comparisons across biochemical and glycemic parameters, p-values were adjusted using Bonferroni test. Regarding the genetic model, the genotype groups treated as categorical variable; each group was independent group. The goodness of fit test was used to test

the distribution of alleles and genotypes according to Hardy–Weinberg equilibrium, and the chi-square value was obtained. A significant difference between the means was regarded at $P < 0.05$.

3. Results

3.1. Demographic Characteristics, Family History of Diabetes, Dietary habits, and Medical History of Enrolled Patients

The demographic characteristics of the patients under this study, family history of diabetes, dietary habits, and medical history, such as duration of diabetes, duration of treatment, side effects experienced by using glibenclamide therapy and concomitant diseases, are displayed in Table1. The study included 160 Iraqi diabetic patients, of whom 80 were male and 80 were female. The hypoglycemia side effect experienced by glibenclamide therapy exhibited a distribution ratio of 39% among the patients, while a family history of DM and cardiovascular disease occurred in almost one-third of the patients.

Table1: The Demographic Characteristics and Medical History of The Study Subjects

Character		Frequency (%) (n:160)
Age (years) (Mean ± SD)		50.55 ± 6.26
Duration of DM (years) (Mean ± SD)		6.94 ± 5.57
Duration of treatment (years) (Mean ± SD)		5.20 ± 5.78
Sex	Male	80 (50)
	Female	80 (50)
Family history of DM	Yes	62 (38.75)
	No	98 (61.25)
Hypoglycemia	Yes	63 (39.38)
	No	97 (60.62)
GI issues	Yes	44 (27.5)
	No	116 (72.5)
Allergy	Yes	30 (18.75)
	No	130 (81.25)
CVD	Yes	64 (40)
	No	96 (60)
Weight gain	Yes	39 (24.37)
	No	121(75.63)
n: Number of the studied subjects, SD: Standard deviation, BMI: Body mass index, DM: diabetes mellitus. GI: gastrointestinal, CVD: cardiovascular disease.		

3.2. Allele Distribution of the rs1801278 (C>G) SNP, and Goodness of Fit Test

The rs1801278 (C>G) SNP was genotyped using allele-specific PCR. The C allele is considered the reference allele, while the G allele is considered the alternative allele. The patients were divided into three groups according to their detected genotype (CC, CG, and GG). PCR amplicons appeared as bands of 390 bp, as shown in Fig.1. The distribution of genotypes for the rs1801278 (C>G) SNP was 75% for CC, 16.25% for CG, and 8.75% for GG, while the distribution of the alleles was 0.83 for C and 0.17 G allele as shown in Table2. The goodness-of-fit test revealed a deviation from Hardy–Weinberg equilibrium for the genotype distribution of the IRS1 rs1801278 (C/G) SNP in the type 2 DM patients (Table2.).

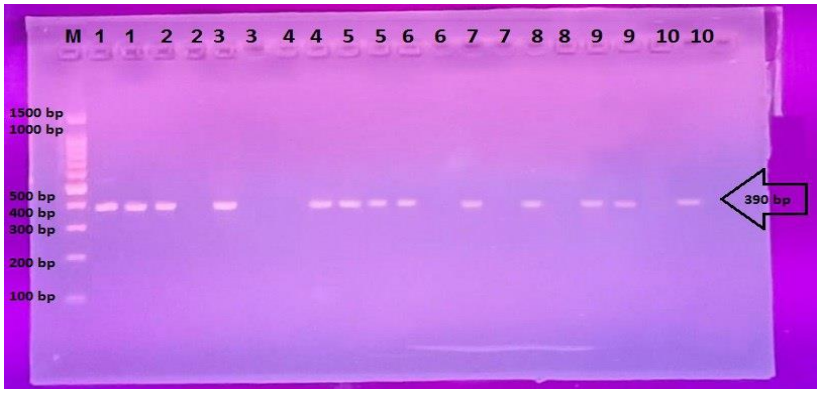

Figure1: The agarose gel electrophoresis for identifying rs1801278 (C >G) SNP using allele specific PCR. M: DNA ladder, samples 1, 5, and 9 represent the heterozygous mutant type (CG), samples 4, and10 represent the homozygous mutant type (GG), and samples 2, 3, 6, 7, and 8 shows the wild type (CC).

Table2: The Allele and Genotype Distribution for The Rs1801278 (C/G) SNP Among the Study Subjects

Genotype (n: 160)	Frequency (%)	Chi squared	P value
CC (wild type)	120 (75)	28.177	0.0001
CG (heterozygous mutant type)	26 (16.25)		
GG (homozygous mutant type)	14 (8.75)		
Allele	Frequency		
C	0.83		
G	0.17		
The goodness of fit test was used with p<0.05 considered significantly different, n: Numbers of the study subjects.			

3.3. Analyzing the Association Between the rs1801278 (C/G) SNP and Age, Body Mass Index (BMI), and Some Biochemical Parameters

The association between the rs1801278 (C/G) SNP and age, body mass index (BMI), and some biochemical parameters, including glycemic indices, lipid profile, and liver and kidney functions, is presented in Table3. The age and BMI did not show significant differences among the three groups of patients. Regarding the glycemic indices, HbA1c, fasting blood glucose, insulin concentration, and HOMA-IR showed significant increasing in the GG group compared to the other groups (P= 0.01, 0.04, 0.003 and 0.0002 respectively). In contrast, creatinine did not show a significant difference, whereas urea showed a significant increasing in the GG group. Both AST and ALT did not show significant differences between the patients' groups. All lipid profile parameters, including TG, TC, HDL, LDL, and VLDL, exhibited significant increasing in GG group compared to the wild and heterozygous mutant type groups (P= 0.03, 0.0002, 0.02, 0.01 and 0.03 respectively).

Table3: The Association Between Rs1801278 (C/G) SNP and The Biochemical Parameters

Parameter	CC (n=120) Mean ±SD	CG (n=26) Mean ±SD	GG (n=14) Mean ±SD	P value
Age	50.74years ± 6.11	50.84years ± 7.32	48.42years ± 5.47	0.41
BMI	27.71 ± 4.42	29.17 ± 5.02	27.50 ± 4.21	0.30
HbA1c	8.77% ± 2.02	8.91% ± 1.43	10.45% ± 2.65	0.01*b, c
FBS	211.31 mg/dL ± 98.92	207.23 mg/dL ± 64.8	278.21 mg/dL ± 108.2	0.04*b, c
AST	26.35 U/L ± 13.77	26.82 U/L ± 11.7	27.60 U/L ± 8.17	0.93
ALT	20.85 U/L ± 11.64	24.57 U/L ± 18.89	23.53 U/L ± 9.76	0.35
Urea	28.11 mg/dL ± 8.9	28.52 mg/dL ± 7.0	34.75 mg/dL ± 8.12	0.02*b, c
Creatinine	1.12 mg/dL ± 3.48	0.76 mg/dL ± 0.28	0.87 mg/dL ± 0.37	0.83

TG	183.39 mg/dL ± 101.86	174.47 mg/dL ± 84.92	257.39 mg/dL ± 140.21	0.03*[b, c]
HDL	36.61 mg/dL ± 10.89	35.38 mg/dL ± 17.96	27.28 mg/dL ± 11.25	0.02[*b, c]
LDL	83.24 mg/dL ± 27.53	73.803 mg/dL ± 27.32	100.83 mg/dL ± 24.40	0.01[*b, c]
VLDL	36.37 mg/dL ± 20.56	34.9 mg/dL ± 16.98	51.47 mg/dL ± 28.04	0.03[* b, c]
Total cholesterol	181.69 mg/dL ± 46.88	180.3 mg/dL ± 52.2	246.7 mg/dL ± 57.26	0.00002[*b, c]
Insulin	13.65 µIU/mL ± 16.56	18.75 µIU/mL ± 14.85	28.55 µIU/mL ± 15.92	0.003[*b]
HOMA-IR	7.78 ± 12.91	9.81 ± 8.20	22.91 ± 16.78	0.0002[*b, c]

* Post-hoc test: a: CC vs. CG, b: CC vs.GG, c: CG vs. GG. A one-way ANOVA test was used with $p<0.05$ considered significantly different. The data is represented as mean ± standard deviation, n: numbers of the study subjects, BMI: body mass index, HbA1c: hemoglobin A1C, FBS: fasting blood sugar, HOMA-IR: homeostatic model assessment for insulin resistance, AST: aspartate aminotransferase, ALT: alanine aminotransferase, TG: triglycerides, HDL: high-density lipoprotein, LDL: low-density lipoprotein, VLDL: very low-density lipoprotein.

4. Discussion

The goodness-of-fit test revealed a deviation from Hardy–Weinberg equilibrium for the genotype distribution of the IRS1 rs1801278 (C/G) SNP in the type 2 DM patients (Table2). Since all the study subjects are diabetic patients and, the study was conducted in a single clinical center this deviation may reflect disease-related selection or an association between this locus and type 2 diabetes susceptibility. In order to exclude the technical error in genotyping process strict experimental techniques and, genotyping quality control included the use of negative controls in each PCR run and duplicate genotyping of randomly selected samples, showing complete concordance that was employed with a call rate exceeded 98%. Further studies on the Iraqi population involving larger sample sizes and including healthy control groups are warranted to confirm these findings.

Our results indicated significant differences in HbA1c, fasting blood glucose, insulin levels, HOMA-IR, urea, and lipid profile among the different IRS1 rs1801278 (C>G) genotype carriers (CC, CG, and GG). A subsequent pairwise comparison utilizing the post hoc test indicated that the significant differences observed among genotypes were predominantly due to the GG genotype carriers, who exhibited elevated mean values of fasting glucose, HbA1c, insulin concentration, HOMA-IR, urea, TG, LDL, VLDL, and TC, while the GG genotype carriers had lower HDL levels. These results indicate that the GG genotype may be associated with increased insulin resistance and modified metabolic function in compared with CG and CC genotype carriers (Table3).

Age, BMI, and liver enzymes did not display any significant differences among the patients' groups. This demonstrates that these variables did not drive the observed differences in the glycemic indices of the patients, and this strengthens the internal validity of this study.

Several studies have reported that the IRS1 gene polymorphism can have an effect on insulin resistance and glucose tolerance (Alharbi et al., 2014; Omar et al., 2021; Prudente et al., 2014). In a previous animal study, IRS1 whole-body knockout mice exhibited reduced glucose tolerance (Araki et al., 1994; Tamemoto et al., 1994). Our results support the hypothesis that IRS1 polymorphisms may contribute to inter-individual variability in the biochemical and glycemic parameters, thus variability in the response to glibenclamide.

The elevated TG, TC, VLDL, and LDL, along with reduced HDL, observed in the carriers of the GG genotype could be explained by the fact that the GG genotype carriers show the worst glycemic control and could be linked to the development of a worse diabetic dyslipidemia state than the CC and the CG genotype carriers. Previous research found that rs1801278 SNP carriers had a higher atherogenic lipid profile, indicating a possible involvement of the IRS1 gene in the development of lipid abnormalities linked to coronary artery disease (Baroni et al., 1999).

The elevated serum urea levels in individuals with the GG genotype may reflect indirect effects mediated through altered insulin signaling and renal function, as previously reported in studies linking IRS1 variants to renal metabolic changes in diabetes (Lavin et al., 2016; Thameem et al., 2012).

Conclusion

The present findings demonstrate that, among Iraqi patients with type 2 DM receiving glibenclamide, the carriers of the homozygous mutant type (GG) of the IRS1 rs1801278 SNP exhibited poorer glycemic control and altered lipid profiles compared with the CC, and CG genotypes carriers. These observations highlight the need for further large-scale and functional studies to clarify the biological implications of this genetic variant. Moreover, the results suggest that genetic variation in IRS1 could contribute to inter-individual differences in metabolic outcomes among treated patients.

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