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Association of CYP2C9*2 Allele with Sulfonylurea-Induced Hypoglycemia in Type 2 Diabetes Mellitus Patients: A Pharmacogenetic Study in Pakistni Pashtun Population.

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Abstract : Polymorphism in cytochrome P450 (CYP) 2C9 enzyme is known to cause significant inter-individual differences in drug response and occurrence of adverse drug reactions. Different alleles of the CYP2C9 gene have been identified but the notable alleles responsible for reduced enzyme activity are CYP2C9*2 and CYP2C9*3. No pharmacogenetic data is available on CYP2C9*2 and CYP2C9*3 alleles in Pakistani population. In Pakistan pharmacogenetics which examines the relationship between genetic factors and drug response, are in the early stages of development. We for the first time investigated the association between the CYP2C9 variant alleles CYP2C9*2 and CYP2C9*3 and the incidence of hypoglycemia in diabetic patients who were receiving the sulfonylurea medications. A total of n=400 individuals of Pashtun ethnicity were recruited from ten different districts of Khyber Pakhtunkhwa, Pakistan to participate in the study. The study participants were divided into two distinct groups: the case group (n=200) and the control group (n=200). The case group consisted of individuals with Type 2 Diabetes Mellitus (T2DM) who were receiving sulfonylurea medications and experience hypoglycaemia with it whereas the control group included individuals with T2DM who were receiving sulfonylurea medication but did not experience sulfonylurea-induced hypoglycaemia (SIH). Blood samples were obtained from study participants following informed consent. DNA was isolated from whole blood samples using Wiz-Prep DNA extraction kit. Following DNA isolation, CYP2C9 alleles were genotyped using MassARRAY sequencing platform at centre of genomics Rehman Medical Institute (RMI). The frequency of CYP2C9*2 (low activity allele) was more frequent in the diabetic patients with SIH compared to the control group (17.5% vs. 6.0%, p=0.021). The frequency of its corresponding genotype CYP2C9*1/*2 was higher in cases compared to control group (10% vs. 6% with P=0.036), same was true for genotype CYP2C9*2/*2 (7% vs. 3.5 % with P=0.028). Logistic regression analysis evident potential association of CYP2C9*2 allele and its genotypes with SIH. When adjusted for confounding factors such age, weight, sex, daily dose of sulphonylurea and triglyceride level the association between the CYP2C9*2 allele and hypoglycemia remains consistent. Confounding factors played no role in SIH because both groups (cases and controls) were closely matched in term of age, weight, sex, mean daily dose of sulphonylurea and trigyleride levels. Our study suggests that genetic information about a patient's CYP2C9 gene/enzyme can potentially assist physicians in prescribing the most suitable and safest drug based on their genetic make-up.

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1. Introduction:

Type 2 diabetes mellitus (T2DM) is considered 21st century epidemic [1]. It affects approximately 537 million people worldwide, including 19.4 million in Pakistan [2]. Sulfonylureas are a class oral anti-diabetic medication frequently used in the management of T2DM [3]. The mechanism of action of sulfonylureas involves stimulating the release of insulin from pancreatic beta cells, which leads to a reduction in blood glucose level [4]. However sulfonylurea drugs secretes insulin independent of blood glucose level as a consequence, patients with T2DM undergoing sulfonylurea therapy are at high risk of developing hypoglycemia (lower blood sugar level than the normal) that have potentially severe consequences [5]. Hypoglycemia poses a greater risk and can be more dangerous and life-threatening for individuals with T2DM and concurrent cardiovascular complications [6]. Known risk factors for sulfonylurea-induced hypoglycemia (SIH) includes low haemoglobin (Hb)A1c, old age, long duration of diabetes, co-morbid conditions (like congestive heart failure, coronary artery disease, ischemic heart disease and renal insufficiency), taking multiple medications (poly-pharmacy),use of long-acting sulfonylurea preparations as well as pharmacogenetic factors [7, 8]. Genetic polymorphisms in the enzymes responsible for metabolizing sulfonylurea affects pharmacokinetics and pharmacodynamics of these drugs, leading to altered drug metabolism, clearance rate and drug action. Individual genetic makeup is a critical factor in drug selection and determining the appropriate drug dose. Some individuals metabolize the drug slowly, resulting in higher levels of the drug in their bloodstream over time, which can lead to a prolonged hypoglycemic action. On the other hand, individuals who metabolize sulfonylureas rapidly experience lower drug levels, potentially leading to reduced efficacy and a higher risk of treatment failure [9, 10].

Cytochrome P450 (CYP450) enzymes play a vital role in drug metabolism. These The CYP450 enzymes are primarily present in the liver, but also present in other tissues, including the pancreas, kidneys and gastrointestinal tract [11]. The Human Genome Project has identified at total of n=57 human CYP450 enzymes; a significant portion of drug metabolism is carried out by a subset of these enzymes. Approximately 90% of drugs are metabolized by six major CYP enzymes, namely CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 [12]. The commonly used second-generation sulfonylureas, such as glibenclamide, glipizide, and glimepiride, are primarily metabolized by the cytochrome P450 (CYP) 2C9 enzyme [13]. Two well-known genetic variants of the CYP2C9 gene are CYP2C9*2 (Arg144Cys) and CYP2C9*3 (Ile359Leu). These variants lead to amino acid substitutions in the CYP2C9 enzyme, resulting in lower/decreased enzyme activity [14, 15]. Different phenotypes (normal metabolizers, intermediate-metabolizers and poor metabolizers) exist based on the genotypes of CYP alleles [16]. Patients who carry two identical copies of the wild-type CYP alleles (CYP2C19*1/*1) are classified as normal metabolizers. In this case, metabolizing ability of enzyme is optimal. Heterozygous genotypes, where one copy of the allele is wild-type and the other copy is a reduced-function or loss-of-function allele (*1/*2 and *1/*3), or homozygous genotypes with two copies of reduced-function alleles (*2/*2), result in an intermediate-metabolizers phenotype. In this case, individual's exhibit reduced enzyme activity compared to normal metabolizers. Homozygous genotypes with two copies of loss-of-function alleles (*3/*3) or heterozygous genotypes with one copy of one copy of reduced-function and other of loss-of-function alleles (*2/*3) are classified as poor metabolizers. These individuals have significantly impaired or absent enzyme activity, resulting in a significant impact on drug metabolism [16, 17].

Genetic information about patient's CYP2C9 enzymes helps physicians to prescribe the most suitable and safest drugs based on individual genetic make-up. The CYP2C9 enzyme is responsible for metabolizing approximately 13% of clinically available drugs [18]. In Pakistan, where over 2.6 billion unit doses of drugs are dispensed annually, it is estimated that more than 332 million unit doses are metabolized by the CYP2C9 enzyme. According to a study, around 20% of Pakistan's

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population carries a CYP2C9 genotype that contains at least one low activity allele. This indicates that over 66 million doses of drugs dispensed annually in Pakistan may not have the desired effects for patients with a low activity CYP2C9 allele. For drugs that require activation through the CYP2C9 enzyme, patients with a low activity allele may experience a lack of response. Conversely, if a drug is inactivated by CYP2C9, increased frequency and severity of adverse effects could be expected in individuals with a low activity allele [19]. In Pakistan Pharmacogenomic data about cytochrome P450 enzymes is very limited. The frequencies of CYP2C9*2 and CYP2C9*3, which are responsible for the low activity of the enzyme, are not known in the Pakistani cohort. The aim of the present case-control study was to Screen the Patients with T2DM from Pakistani Pashtun population for low activity enzyme alleles and assess its possible role in SIH. Our study is an important step towards understanding the genetic factors influencing drug response in the studied population.

2. Material and methods

2.1. Case and control definition

The cases were defined as individuals with T2DM who have experienced hypoglycemia while being treated with sulfonylurea medications. Hypoglycemia refers to a condition where blood sugar levels drop below normal. On the other hand, the controls were individuals with T2DM who are receiving treatment with sulfonylurea medications but have not experienced hypoglycemia. The cases and controls we differentiated by their response to the sulfonylurea treatment in terms of experiencing hypoglycemia.

2.2. Subject selection

A total of 400 individuals (T2DM/controls n= 200 and T2DM patients with SIH/cases n= 200) of Pashtun ethnicity belonging from seven districts (Peshawar, Mardan, Charsadda, Bannu, Kohat, Dir and swat) of Khyber Pakhtunkhwa, Pakistan participated in the study. Patients with and without SIH were registered at the endocrinology units of three tertiary care hospitals: Lady Reading Hospital (LRH) Peshawar, Hayatabad Medical Complex (HMC) Peshawar, and Khyber Teaching Hospital (KTH) Peshawar. These hospitals likely provided specialized care for patients with endocrine disorders, including type 2 diabetes mellitus (T2DM). To ensure accurate comparisons, the cases (T2DM patients with SIH) were matched with the control group (T2DM) in terms of age, gender, and ethnicity. Written informed consent was obtained from all the participants to ensure their voluntary participation in the study. In the case of illiterate or uneducated patients, the informed consent form was read and explained to them in the local Pashtu language. If the patient agreed to participate, a relative or attendant signed the consent form on their behalf. Detailed demographic information and clinical parameters of the patients were collected using a carefully designed proforma. These parameters likely included relevant medical history, current medications, renal function/glomerular filtration rate, BMI, triglyceride levels, HbA1c level, and other factors that could potentially influence the development of SIH. Inclusion criteria for cases were as follows (i) T2DM with SIH; (ii) Patient of age in range of 30 to 80 years and (iii) Patient from Pashtun population. Individuals with mental disorders, age below 30 years, and those presenting with chronic infections like HCV, HBV, or malignancies were excluded from the study.

2.3. Ethical approval

The study acquire the ethical approval from the ethical committee of the Department of Pharmacy, University of Peshawar, with the approval number 907/PHAR. All procedures conducted during the study adhered to the principles outlined in the Helsinki Declaration of 1975.

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2.4. Collection of blood samples

Blood samples were collected from the study individuals by a trained nurse using aseptic procedures. The blood was drawn from the median cubital vein, typically located in the inner elbow area. Three milliliters of whole blood were collected from each participant using EDTA tubes, which were properly labeled to ensure accurate identification and traceability of the samples. After collection, the EDTA tubes containing the blood samples were stored at a temperature of -10°C to preserve the integrity of the samples until further analysis or testing.

2.5. DNA Extraction and Quantification

Deoxyribonucleic acid (DNA) was extracted from 200 microliters (µl) of whole blood samples obtained from cases and controls. The Wiz-Prep DNA extraction kit (Wiz-Prep no. W54100) was used for the extraction process, following the guidelines provided by the manufacturer provided with the kit. After successful DNA extraction, the quantification of the extracted DNA was conducted using the Invitrogen Qubit™3, a fluorometer-based system designed specifically for DNA quantification. The final DNA concentration was adjusted to 5 ng/µL.

2.6 SNPs selection and Genotyping

Well-known genetic variants of the CYP2C9 gene, namely CYP2C9*2 (Arg144Cys) and CYP2C9*3 (Ile359Leu), were selected to assess its role in SIH. These variants are known to cause amino acid substitutions in the CYP2C9 enzyme, leading to decreased enzyme activity. The genotyping of the selected variants were performed using the Sequenom MassARRAY genotyping platform at centre of Genomics, Rehman medical institute (RMI) Peshawar via collaboration. The Sequenom MassARRAY genotyping method is a high-throughput genotyping technology that utilizes matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) to accurately and efficiently genotype genetic variations.

2.7. Statistical analysis

The statistical analysis was carried out using IBM SPSS (Statistical Package for Social Sciences) version 24. The key variables selected for analysis included gender, advanced age, BMI, GPR, concurrent medications, triglyceride levels, geographical area (districts), smoking status, lifestyle, exercise, diet, occupation, and the selected genetic variants in CYP2C9. To assess the genetic variants conformity with the Hardy-Weinberg equilibrium (HWE), a chi-square (χ^2) test was performed. The HWE test evaluates whether the observed genotype frequencies in the population differ significantly from the expected frequencies. To determine the difference in the distribution of allelic and genotypic frequencies between the cases (T2DM patients with SIH) and the control (T2DM patients), χ^2 test was used. To examine the association between the selected genetic variants in CYP2C9 gene with hypoglycemia, binary logistic regression test was performed. Logistic regression is a statistical technique used to analyze the relationship between independent variables (genetic variants) and a binary dependent variable (hypoglycemia). A probability value (p-value) of less than 0.05 was considered statistically significant.

3. Results

3.1. Study Subjects Characteristics

Detail socio-demographics, biochemical features and co-morbidities prevalence in study subjects (cases and controls) are given in table 1, 2 and 3. A total of n=400 confirmed diabetic patients (200 each with and without SIH) of age in range of 30 to 80 years were included in this study. No significance difference ($p>0.05$) in mean age and weight of cases vs. controls were observed. Among the study participants 84 % were male and 16% were females. Moreover 76% of the participants were married, whereas 24% were unmarried. Forty six percent (46%) of participants

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were cigarette smoker while 29% of the study participants were non-smokers. The use of Naswar (a local smokeless tobacco product) use was reported high in study participants. It is worth noting that a significant proportion of the study subjects were illiterate and came from lower socio-economic background. Additionally, almost all patients (95%) we reported to have positive family history of T2DM. Co-morbidities prevalence were slightly frequent in T2DM patient with SIH compared controls but the difference was not significant statistically (P>0.05) details given in table 2. The two groups showed no notable variations in sulfonylurea mean daily dose (p = 0.998 for glimepiride & p = 0.761 for gliclazide, respectively) urea level (P=0.213), creatnine level (P=0.982) and HbA1C (p = 0.991) details listed in table 3.

Table 1. Socio-demographic characteristics of cases and controls.

Variables	Cases n (f)	Control n (f)	P-value
Gender			
Male	165 (82.5%)	173 (86.5%)	0.061
Female	35(17.5%)	27 (13.5%)	
Mean age (yrs)	58 ± 12:40	56 ± 13:43	0.605
Mean weight (Kg)	62.64 ± 6:07	59.55 ± 8:32	0.213
Address			
Peshawar	45 (22.5%)	16 (16%)	
Charsadda	31 (15.5%)	13 (13%)	
Mardan	22 (11.0%)	13 (13%)	
Kohat	12 (6.0%)	11 (11%)	
Swabi	19 (9.5%)	4 (4%)	
Nowshera	17 (8.5%)	5 (5%)	0.318
Bannu	18 (9.0%)	10 (%)	
karak	5 (2.5%)	2 (25%)	
Dir	16 (11%)	10 (2%)	
Swat	15 (7.5%)	10 (10%)	
Occupation			
Business	30 (15.0%)	6 (6.0%)	
Govt. servant	37 (18.5%)	27 (27.0%)	
Retired	35 (17.5.0%)	30 (30.0%)	0.058
Farming	25 (12.5%)	10 (10.0%)	
House wife	40 (20.0%)	15 (15.0%)	
Labor	33 (16.5%)	12 (12.0%)	
Family Hx of T2DM			
Yes	133 (66.5%)	175 (63%)	0.004
No	67 (33.5%)	25 (25%)	
Marital status			
Single	71 (35.5%)	43 (34%)	0.138
Married	129 (64.5%)	157 (57%)	
Smoking			
Yes	104 (52.0%)	80 (80%)	0.063
No	96 (48%)	20 (20%)	
Naswar			
Yes	130 (65.0)	153 (76.5%)	0.061
No	70 (35.0%	47 (23.5%)	

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Diet and drug compliance			
Yes			
No	127 (63.5.5%)	42 (42%)	0.012
	73 (36.5)	58 (58%)	
Socioeconomic status			
Good	52 (26.0%)	34 (34%)	
Average	102 (51.0%)	53 (53%)	0.314
Below	46 (23%)	13 (13%)	

N=number; f= frequency; kg=kilogram; yr=year; Hx=history.

Table 2. Co-morbidities prevalence in study participants.

Co-morbid disease	Frequency (f)		P-value
	Cases (n=200)	Controls (n = 200)	
Hypertension	112.0%	102.5%	0.071
IHD	21.0%	18.0%	0.311
Renal Failure	5.0%	3.0%	0.412
Retinopathy	61.0%	58.91%	0.112
HBV	0.00%	0.00%	0.000
HCV	0.00%	0.00%	0.000

IHD: Ischemic heart disease; HCV: Hepatitis C virus; HBV: Hepatitis B virus.

Table 3. Bio-chemical characteristics of study participants.

Variables	Cases (n=200)	Controls (n=200)	P-value
Total cholesterol (mg/dL)	265.25±15.37	259.23±12.54	0.076
LDL- cholesterol (mg/dL)	125.4±14.12	121.62±8.91	0.118
HDL- cholesterol (mg/dL)	58.2±7.01	62.1±5.22	0.132
Triglycerol (mg/dL)	158.3±10.5	156.2±9.15	0.184
Urea (mg/dL)	41.44 ± 15.20	39.50 ± 17.97	0.213
Creatinine (mg/dl)	0.94 ± 0.15	0.92 ± 0.21	0.982
HBA1C (%)	7.60 ± 5.55	7.39 ± 1.46	0.911
Mean daily dose of Glimepiride (mg)	5.13 ± 1.56	5.13 ± 1.54	0.998
Mean daily dose of Gliclazide (mg)	108.09 ± 44.37	105.00 ± 34.06	0.761

Mg/dL: milligram per decilitre; mg: milligram LDL: low density lipoprotein; HDL: high density lipoprotein.

3.2. Allelic frequencies

Te allelic frequencies of CYP2C9*1, CYP2C9*2, and CYP2C9*3 in cases and controls are listed in table 4. The notation CYP2C9*1 refers to the wild-type allele, *1 allele represents the reference

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sequence of the gene. In the studied population we reported that 84.0% of cases and 91.5% of controls carry the CYP2C9*1/wild type allele. The CYP2C9*2 low activity allele was more frequent in the diabetic patients with SIH compared to the control group (17.5% vs. 6.0%). On the other hand, CYP2C9*3 (loss of enzyme activity) allele was present in 7 (3.5%) of diabetic patients with SIH and in 5 (2.5%) of individuals of control group.

Table 4. Allelic distribution/frequencies of CYPC19*2 and CYPC19*3 in cases and controls.

CYP2C9 Alleles	Phenotypes	Cases n(f)	Controls n(f)	OR (95%Cl)	Crude P-value	Adjusted P-value
CYP2C9*1	wild-type/no effect	158(84.0%)	183(91.5%)	Ref	Ref	Ref
CYP2C9*2	Decreases enzyme activity	35 (17.5%)	12(6.0%)	0.102 (0.08–3.08)	0.021	0.031
CYP2C9*3	Loss of enzyme activity	07(3.5%)	5(2.5%)	0.041 (0.02-2.21)	0.101	0.091

N=number; f=frequency.

3.3. Genotype frequencies

The prevalence of CYP2C9*1/*1, *1/*2, *2/*2, *2/*3 and *3/*3 genotypes are listed in table 5. The frequency of CYP2C9*1/*1 (reference genotype) between the cases and controls was (79% vs. 89%), whereas the frequency of genotype *1/*2 was higher in cases compared to control group (10% vs. 6% with P=0.036), same was true for genotype *2/*2 (7% vs. 3.5 % with P=0.028), in contrast the genotype *1/*3 was under presented in cases compared to control group (1% vs. 1.5%) with P-value of 0.344. Genotypes *2/*3 and *3/*3 were not reported either in cases or controls.

Table 5. Genotype frequencies of CYPC19*2 and CYPC19*3 in cases and controls.

CYP2C9 Genotypes	Phenotypes	Type of Genotype	Cases n(f)	Controls n(f)	OR (95%Cl)	Crude P-value	Adjusted P-value
CYP2C9 *1/*1	Normal metabolizer	Hom	158(79%)	178(89%)	Ref	Ref	Ref
CYP2C9 *1/*2	Intermediate metabolizer	Het	20 (10%)	12(6.0%)	1.21 (1.81–3.02)	0.036	0.039
CYP2C9 *1/*3	Intermediate metabolizer	Het	2 (1.0%)	3 (1.5%)	0.94 (0.77–1.15)	0.344	0.231
CYP2C9 *2/*2	Intermediate metabolizer	Hom	20 (7%)	7 (3.5%)	2.83 (1.69–3.00)	0.028	0.031
CYP2C9 *2/*3	Poor metabolizer	Het	---	---	---	---	--
CYP2C9 *3/*3	Poor metabolizer	Hom	---	---	---	---	---

Ref: reference/ wild type; hom: homozygous; het: heterozygous.

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3.4. Risk of hypoglycemia in CYP2C9 carriers

Our study reported higher carriage rate of low activity allele CYP2C9*2 in case group compared to control (OR = 0.102, 95% confidence interval (CI): 0.08–3.08, P = 0.021 (table 4. The frequency of CYP2C9 genotypes that lead to impaired CYP2C9 function (*1/*2 and *2/*3) was also detected higher in cases than controls (Table 5). Logistic regression analysis with hypoglycemia status as the dependent variable and CYP2C9 genotypes (*1/*2 and *2/*3) as contributing variables; estimated CYP2C9*1/*2 and CYP2C9*2/*2 genotype as risk factors of SIH. The confounding factors such as age, triglyceride levels, urea level, creatinine level, and renal impairment (decreased GFR) were found uniform in cases and controls and the association between the CYP2C9*2 allele/genotypes and hypoglycemia remains consistent even after adjusting for the confounding factors. This implies that observed association is independent of these factors for details please consider table 5.

4. Discussion

Pakistan is one among the most populous countries of the world, with a population of over 220 million people. The country has a rich cultural and ethnic heritage, with various ethnic groups contributing to its genetic diversity. Despite of one of the largest population in the world, there is a scarcity of pharmacogenomic studies investigating genetic variations in different enzymes/genes that could alter drug response [19]. Cytochrome P450-2C9 (CYP2C9) an important enzyme is involved in the biotransformation and clearance of many drugs including oral sulphonylureas. Different alleles of the CYP2C9 gene have been identified, with some alleles associated with reduced enzyme activity and others associated with increased activity. Individuals carrying alleles associated with reduced CYP2C9 activity may metabolize drugs, such as sulfonylureas, more slowly, leading to higher drug levels and an increased risk of adverse effects, including hypoglycemia. [20]. In the present study, we investigated the association between CYP2C9*2 and *3 alleles, and its genotypes with SIH in T2DM patients who were being treated with the sulfonylureas drugs like glimepiride or gliclazide. The findings of our study suggest that the presence of the CYP2C9*2 allele and its corresponding genotypes CYP2C9*1/*2 and CYP2C9*2/*2 plays a key role in predisposing patients receiving sulfonylurea treatment to hypoglycemia. Furthermore, our study reported that the CYP2C9*3 allele was present at a ratio of 3.5% vs. 2.5% in cases vs. control. The frequency of CYP2C9*3 allele was found approximately uniform in cases vs. controls and doesn't accounts for SIH in the studied population. We also considered several additional factors that could potentially influence the distribution and clearance of sulfonylureas, thereby affecting the occurrence of hypoglycemia. These factors included age, cholesterol levels, creatanine level, and renal impairment. Importantly, the study found no significant differences in these parameters between the cases (patients who experienced hypoglycemia) and the controls (patients who did not experience hypoglycemia). This suggests that the observed association between the CYP2C9*2 allele and hypoglycemia is independent of these factors and likely attributed to the genetic variation itself. Previous studies also reported association CYP2C9*2 allele and its genotypes with SIH [21, 22].

Studies investigating the effect of CYP2C9 variants on the risk of sulfonylurea-related hypoglycemia are relatively limited, and the results from the available studies have been inconsistent [23].Some studies have reported an association between CYP2C9 reduced-function alleles and an increased risk of hypoglycemia in T2DM patients taking sulfonylureas. These findings suggest that individuals with specific CYP2C9 genotypes may have a higher susceptibility to hypoglycemia when treated with sulfonylurea drugs [24, 25]. However, other studies have not detected any evidence of an association between CYP2C9 variants and sulfonylurea-related hypoglycemia [26, 27]. This lack of consistency in findings may be due to various factors, including differences in study design, such as variations in the definition of hypoglycemia, the age of the study population, the specific sulfonylureas included in the analysis, and the statistical power resulting from small sample sizes.

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Sulphonylurea induced hypoglycemia is a critical concern in the treatment of diabetes. It can lead to various complications, ranging from discomfort and reduced adherence to therapy to severe morbidity and mortality [28, 29]. Minimizing the occurrence of hypoglycemic episodes is essential for providing safe and effective treatment to diabetes patients. Genotyping for CYP2C9 genetic variations can be particularly valuable, especially during the initiation of sulfonylurea treatment. Certain CYP2C9 genotypes are associated with reduced enzyme activity, leading to slower metabolism of sulfonylureas and an increased risk of drug accumulation and subsequent hypoglycemia. By identifying patients with CYP2C9 genotypes that predict low enzyme activity, genotyping can aid in preventing medication overdose and subsequent hypoglycemic episodes [30, 31, 32]. This information allows healthcare providers to adjust the dosage or choose alternative treatment options that are less likely to cause adverse effects in individuals with specific genotypes. Personalized medicine approaches, such as genotyping, can contribute to more precise and tailored therapies, minimizing the risk of adverse drug events and optimizing treatment outcomes for patients with diabetes.

5. Conclusion

In the present case-control perspective study we explored the association of the CYP2C9*2 allele (known to have low enzyme activity) with sulfonylurea-induced hypoglycaemia (SIH) in the studied population. The CYP2C9*1/*2 and CYP2C9*2/*2 genotypes, as well as the CYP2C9*2 allele, were found more prevalent in cases (individuals experiencing SIH) compared to controls (individuals without such adverse reactions). It is important to note that further research and replication studies are needed to confirm and validate these findings. Additionally, the clinical implications of this association should be carefully considered in terms of personalized medicine, drug dosing, and patient management strategies for individuals with this reduced function allele and genotypes.

6. Limitations

The study included participants from Pashtun ethnic cohort only; inclusion of study participants from other Pakistani sub-populations such as Sindhi, Punjabi and Balochi, would have enhance the diversity and generalizability of the study findings. We focused CYP2C9 gene variants only there are some other interesting Cytochrome P450 (CYP450) genes that affect many drugs metabolism and clearance. The sample size was limited to 400 individuals. Despite of the mentioned limitations the present study first of its kind in pakistani Pashtun population identified important Pharmacogenetic risk variants in CYP2C9 genes associated with sulphonylurea induced hypoglycemia.

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Conflict of interest: none to declare.

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