HASIL CEK_Variation of CYP2C9 Gene and Glycemic Control in Diabetic Patients: A Literature Review

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Variation of *CYP2C9* Gene and Glycemic Control in Diabetic Patients: A Literature Review

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ABSTRACT

The prevalence of Diabetes Mellitus Type 2 (DMT2) is continuing to increase worldwide. The variety of responses to the oral antidiabetic is influenced by several factors, including genetics, physiology, pathophysiology and the environment. Genetic factors are estimated to contribute 15–30% to differences in metabolism and drug response between individuals. The purpose of this study was to determine the variation of the *CYP2C9* gene in DMT2 patients and its association with glycemic control. The method used in this research was literature review. Keywords used for collecting the articles were "*CYP2C9*, diabetes mellitus, type 2, oral antidiabetic". Article search was conducted on Google Scholar, PubMed and several international journal providers. The inclusion criteria were articles published in the last 20 years (2000–2020) that addressed the variance and polymorphism of *CYP2C9* in DMT2 patients and could be reviewed in full text, including national and international journals. The exclusion criteria in this research were articles that are not original articles. The analysis in this study was performed by describing the qualitative and quantitative results of the journal studies reviewed. We found 13 articles that met the inclusion criteria. The DMT2 patients included in the study were from India, Slovenia, Russia, Mexico, China, Turkey, Egypt, Israel, Greece, Netherlands, Japan, United Kingdom and Germany. Most of the allele variants found were CYP2C9*2 and CYP2C9*3 with heterozygous genotype CYP2C9*1/*2, CYP2C9*1/*3 and heterozygous genotype due to two allele polymorphisms, namely CYP2C9*2/*3. Homozygous genotypes found were CYP2C9*1/*1 (normal genotype) and genotypes due to 2 allele polymorphisms namely CYP2C9*2/*2 and CYP2C9*3/*3. The DMT2 patients with polymorphism experienced better glycemia control than DMT2 patients with the normal genotype. However, those with CYP2C9*2 and CYP2C9*3 polymorphisms experienced higher risk of hypoglycemia.

The DMT2 patients mostly have normal CYP2C9*1/*1 genotype, requiring definition of adjustment of dose of oral antidiabetic to obtain the optimal therapeutic effect. However, the hypoglycaemic risk must be closely monitored for DMT2 patients with CYP2C9*2 and CYP2C9*3.

Keywords: *diabetes mellitus type 2, CYP2C9, review*

1. INTRODUCTION

Epidemiologic data of DMT2 shows an increased prevalence, at a rate of about 21.3 million Indonesian patients in 2030 [1]. Data published in 2013 reported an increased prevalence of DMT2 (based on physician diagnosis in patients with age ≥ 15 years) of 2%, in comparison to data from The Indonesia Basic Health Research in 2018 [2]. Currently, the prevalence in all criteria of ages is lower than prevalence of DMT2 in patients aged ≥15 years old, which is 1.5% [3].

The most common treatment of DMT2 is oral hypoglycemic agents or insulin depending on disease severity [4]. Oral hypoglycemic agents (OHA) commonly used are sulphonylurea, metformin or a combination. Sulphonylureas, such as glibenclamide, has a mechanism to increase insulin secretion by beta cells in the pancreas. On the other hand, metformin has been known to reduce hepatic glucose production (gluconeogenesis). Combination of these drugs is also possible as a treatment if single treatment is not responsive [5]. The metabolic process of OHA results in different response individually and is related to factors such as genetics, physiology, pathophysiology and environmental. In general, genetics accounts for approximately 15–30% of factors that contribute to different responses in metabolic process and response to drug. The CYP2C9 and CYP2C19 are responsible for sulphonylurea metabolism [6], however CYP2C9 is also important in the hydroxylation of glibenclamide.

The purpose of this study is to determine the genotype description of CYP2C9 in DMT2 patients in different countries as a risk factor for this disease. Furthermore, this study will also determine the association between CYP2C9 gene and glycemic control.

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2. METHODS

2.1 Search Strategy

This study used a narrative review method. The database used to search articles in this review were open educational resources and website such as PubMed, MDPI, Google Scholar, DOAJ and Nature. Keywords used to locate target journals are displayed in Table 1 and the process of literature searching is displayed in Figure 1.

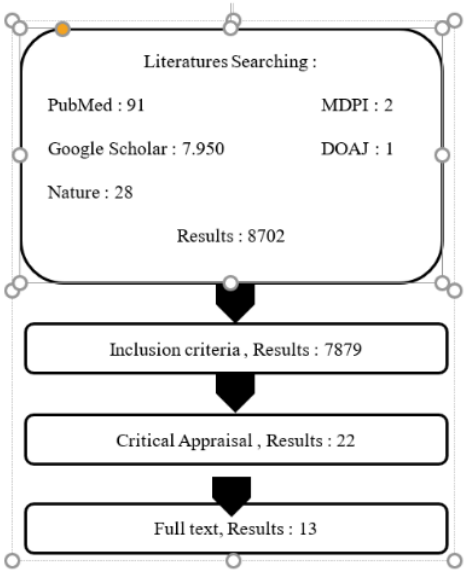

Figure 1. Process of literature searching

2.2. Inclusion and Exclusion Criteria

Inclusion criteria of this study were as follows: (1) articles published in the last 20 years (2000-2020), (2) articles describing CYP2C9 genotype study in patients with Type 2 diabetes mellitus taking oral antidiabetics, (3) articles available as full text, and (4) articles providing outcome therapy (related to diabetic status or hypoglycemic effect). Moreover, the exclusion criteria were non-original articles, such as commentaries, case reports, systematic reviews or meta-analyses. Critical appraisal was conducted to screen the articles based on the research question, internal validity and minimal risk of bias.

2.3. Data Extraction

Data from studies that met the inclusion criteria were extracted independently. We found 7,879 articles that met the inclusion criteria. Regarding the characteristic study, data collected included title, author, the year of publication, number of samples, kind of oral antidiabetic, method of the study, variants genotype in CYP2C9 and outcome therapy, which related to diabetic status (controlled or uncontrolled diabetes) or hypoglycemic effect (Table 1).

Table 1. *Keywords used in databases*

Database	Keywords	Articles found
PubMed	*"diabetes mellitus, type 2" OR "type 2 diabetes mellitus" AND "CYP2C9"*	59
PubMed	*"diabetes mellitus, type 2" OR "type 2 diabetes mellitus" AND "hypoglycemic agent" OR "antidiabetic" OR "sulphonylurea" AND "CYP2C9" AND "blood sugar levels" OR "blood glucose levels"*	15
PubMed	*"CYP2C9" AND "diabetes mellitus type 2" AND "glibenclamide" OR "oral antidiabetic" AND "metformin" OR "oral antidiabetic"*	7
PubMed	*"CYP2C9" AND "antidiabetic" AND "type 2 diabetes patients"*	1
PubMed	*"diabetes mellitus type 2" AND "cyp2c9 polymorphism" AND "oral antidiabetic" AND "effectiveness"*	9
Google Scholar	*"cyp2c9, type 2 diabetes mellitus, antidiabetic oral, fasting glucose levels"*	7.950
Nature	*"type 2 diabetes mellitus, CYP2C9, blood glucose levels"*	28
MDPI	*"CYP2C9" AND "type 2 diabetes mellitus" OR "diabetes mellitus, type 2" AND "sulphonylurea" AND "blood glucose levels"*	2
DOAJ	*"type 2 diabetes mellitus, antidiabetic oral, CYP2C9"*	1
Number of articles found prior to exclusion		8.072

3. RESULTS

We reviewed 13 articles that met the inclusion criteria (Figure 1). All of the articles reviewed were original, 10 of which were cohort studies (76.9%), two cross-sectional studies (15.4%) and one case control study (7.7%). Based on the distribution area or setting place of the journal, articles showed that an even spread in many countries, including India, Slovenia, Russia, Mexico, China, Turkey, Egypt, Israel, Greece, Netherlands, Japan, UK and Germany (Table 2).

Table 2. Result from extraction data

No	The Title, Author, and The year of publication	Number of sample, detail of sample	Method of the study	Variants genotype of CYP2C9	Outcome therapy	Result
1.	Influence of CYP2C9 gene polymorphisms on response to glibenclamide in type 2 diabetes mellitus patients [7]	80 patients : 78 patients: combination treatment (glibenclamide and metformin) 2 patients: monotherapy (glibenclamide)	*cohort*	64 patients: *1/*1	25% controlled diabetes 75% uncontrolled diabetes	Variants genotype CYP2C9 (*1/*2 and *1/*3) is related to controlled diabetes, while normal genotype CYP2C9 (*1/*1) is related to uncontrolled diabetes.
				15 patients: *1/*3 1 patients: *1/*2	50% controlled diabetes 50% uncontrolled diabetes	
2.	CYP2C9, KCNJ11 and ABCC8 polymorphisms and the response to sulphonylurea treatment in type 2 diabetes patients [8]	156 patients : 135 patients: combination treatment (sulfonylurea and metformin) 21 patients: monotherapy (sulfonylurea)	*cohort*	96 patients: *1/*1	18 patients (56.3%) with hypoglycemic 78 patients (62.9%) without hypoglycemic	Association of CYP2C9 (as a gene which metabolize sulphonyilurea) polymorphism and hypoglycaemia episode was not significant in DMT2
				30 patients: *1/*2	7 patients (21.9%) with hypoglycemic 23 patients (18.6%) without hypoglycemic	
				21 patients: *1/*3	5 patients (15.6%) with hypoglycemic 16 patients (12.9%) without hypoglycemic	
				3 patients: *2/*2	0 patients (0%) with hypoglycemic 3 patients (2.4%) without hypoglycemic	
				6 patients: *2/*3	2 patients (6.2%) with hypoglycemic 4 patients (3.2%) without hypoglycemic	
3.	Effect Of Cytochrome P450 2c9 Gene Polymorphisms On Individual Sensitivity To Gliclazide In Patients With Type 2 Diabetes Mellitus [9]	74 patients using monotherapy (gliclazide)		46 patients: *1/*1 14 patients: *1/*2 11 patients: *1/*3 1 patients: *2/*2 2 patients: *2/*3	All patients with variants genotype of CYP2C9 achieved the HbA1c target	Patients with wild-type allele had lower effective dose of gliclazide rather than patients who had a polymorphic allele of CYP2C9, which usually use high dose (90-120 mg) of drug.
4.	CYP2C9*3 gene variant contributes independently to glycemic control in patients with type 2	404 patients : Monotherapy (Glibenclamide) or combination treatment	*cross-section*	CYP2C9*2, variants *1/*1	153 patients has good glycemic control	Variants CYP2C9*3 has a correlation with good glycemic index rather than variants CYP2C9*2

No	The Title, Author, and The year of publication	Number of sample, detail of sample	Method of the study	Variants genotype of CYP2C9	Outcome therapy	Result
	diabetes treated with glibenclamide [10]	(glibenclamide and metformin)			211 patients has poor glycemic control	in DMT2 patients who use glibenclamide. However, there is no significant relationship between CYP2C9*2 variants and good glycemic index in patients who use sulphonylurea.
				CYP2C9*2, variants *1/*2	18 patients has good glycemic control 20 patients has poor glycemic control	
				CYP2C9*2, variants *2/*2	0 patients has good glycemic control 2 patients has poor glycemic control	
				CYP2C9*3, variants *1/*1	154 patients has good glycemic control 224 patients has poor glycemic control	
				CYP2C9*3, variants *1/*3	17 patients has good glycemic control 9 patients has poor glycemic control	
5.	CYP2C9*3 variant is associated with antidiabetes efficacy of gliclazide in Chinese type 2 diabetes patients [11]	746 patients : monotherapy (gliclazide)	*cohort prospective*	CYP2C9*3 : 672 patients: *1/*1	FPG day 1 : 11.3 ± 2.8 FPG day 29 : 8.3 (in mmol/L)	Compare to AA (*1/*1) genotype of CYP2C9, patients with AC (*1/*3) and CC (*3/*3)genotypes had greater reduction of FPG and showed a higher rate of treatment success
				CYP2C9*3 : 72 patients: *1/*3 2 patients: *3/*3	FPG day 1 : 11.0 ± 2.6 (*1/*3) 10.5 ± 1.1 (*3/*3) FPG day 29 : 7.3 (in mmol/L)	
6.	Mild Hypoglycemic Attacks Induced by Sulphonylureas Related to CYP2C9, CYP2C19 and CYP2C8 Polymorphisms in Routine Clinical Setting [12]	108 patients : Monotherapy : glimepiride (n=50) gliclazide (n=46) glipizide (n=12)	*cohort prospective*	CYP2C9 *1/*1	5 patients (33%) with hypoglycemic 54 patients (58%) without hypoglycemic	Frequency of CYP2C9 variants (hetero- or homozygous) higher in patients who reported hypoglycemic incidence rather than who did not. However it did not reach statistical significance.
				CYP2C9 *1/*2 or *1/*3	9 patients (60%) with hypoglycemic 36 patients (39%) without hypoglycemic	
				CYP2C9 *2/*2, *2/*3 or *3/*3	1 patients (7%) with hypoglycemic 3 patients (3%) without hypoglycemic	
7.	Effect of CYP2C9 Gene Polymorphisms	100 patients :	*cohort*	53 patients: *1/*1	21 patients (41.2%) has diabetes control	Although the drug dosage did not differ

No	The Title, Author, and The year of publication	Number of sample, detail of sample	Method of the study	Variants genotype of CYP2C9	Outcome therapy	Result
	on Response to Treatment With Sulfonylureas in A Cohort Of Egyptian Type 2 Diabetes Mellitus Patients [13]	94 patients : combination treatment (metformin and glibenclamide) 6 patients monotherapy (glibenclamide)				significantly among genotypes, group 4 (CYP2C9*2/*3) showed better in control their fasting blood sugar. It can possibly related with the slower metabolism of sulphonylurea and impacts on longer half-life of SU.
				20 patients: *1/*2	8 patients (42%) has diabetes control	
				18 patients: *1/*3	12 patients (70%) has diabetes control	
				9 patients: *2/*3	8 patients (89%) has diabetes control	
8.	Any Polymorphisms of CYP2C9 Affects the Biochemical Profile of Diabetic Patients Receiving Glibenclamide [14]	58 patients : combination treatment (glibenclamide and metformin)	*Observational prospective*	40 patients: *1/*1	Mean of HbA1c : 7.5±0.99 Hypoglycaemia events : 0.2±0.6	Patients with CYP2C9*1/*1 (wild type) and patients with CYP2C9 polymorphism using the similar dosage of glibenclamid and similar glycemic control, however patients with CYP2C9 polymorphism experienced more hypoglycemic episode.
				18 patients with CYP2C9 polymorphism : 12 patients: *1/*2 5 patients: *1/*3 1 patient: *2/*3	Mean of HbA1c : 7.6±1.3 Hypoglycaemia events : 0.6±1.1	
9.	Presence of CYP2C9*3 Allele Increases Risk For Hypoglycemia in Type 2 Diabetic Patients Treated With Sulfonylureas [15]	176 patients : monotherapy (Glimepiridee or Glicazide)	*cohort*	120 patients: *1/*1	55 patients (59.8%) with hypoglycemic 65 patients (77.4%) without hypoglycemic	DTM2 patients who has CYP2C9*3 tend to have increasing risk of hypoglycemia when using sulphonyilureas rather than other variants.
				43 patients: *1/*2	26 patients (28.2%) with hypoglycemic 17 patients (20.2%) without hypoglycemic	
				1 patient: *2/*2	0 patients (0%) with hypoglycemic 1 patients (1.2%) without hypoglycemic	
				11 patients: *1/*3	10 patients (10.9%) with hypoglycemic 1 patients (1.2%) without hypoglycemic	

No	The Title, Author, and The year of publication	Number of sample, detail of sample	Method of the study	Variants genotype of CYP2C9	Outcome therapy	Result
				1 patient: *2/*3	1 patients (1.1%) with hypoglycemic 0 patients (0%) without hypoglycemic	
10.	Cytochrome P450 2C9 *2 and *3 Polymorphisms and the Dose and Effect of Sulfonylurea in Type II Diabetes Mellitus [16]	475 patients : 296 patients : tolbutamida 77 patients : glibenclamide 76 patients : Glimepiridee 26 patients : glyclazide	*cohort prospective*	321 patients : *1/*1	45 patients using tolbutamide therapy : Before : 11.0 mmol/L After : 8.9 mmol/L	Patients with CYP2C9*3 variants experienced decreasing an average of fasting blood glucose after treatment higher than wild-type genotype, however it did not differ significantly. Furthermore, patients with CYP2C9*3 variants needs lower dose of tolbutamide compare to wild-type genotype.
				103 patients : *1/*2, *2/*2	13 patients using tolbutamide therapy : Before : 11.8 mmol/L After : 8.9 mmol/L	
				51 patients : *1/*3,*2/*3	7 patients using tolbutamide therapy : Before : 11.8 mmol/L After : 7.5 mmol/L	
11.	Effect Of CYP2C9 Genetic Polymorphisms on The Efficacy on Pharmacokinetics of Glimepiridee in Subjects With Type 2 Diabetes [17]	134 patients: monotherapy (glimepiride) Further for pharmacokinetic study: 6 patients	*cross sectional*	4 patients: *1/*1	BS pretreatment : 141 BS 8 hour after : 198	The reduction of HbA1c after 6 months treatment is higher in CYP2C9*1*3 rather than CYP2C9*1*1 ($P<0.05$). Long term observation showed that CYP2C9*1*3 have a good response with glimepiridee rather than CYP2C9*1*1.
				1 patient female : *1/*3	BS pretreatment : 126 BS 8 hour after : 117	
				1 patient male : *1/*3	BS pretreatment : 272 BS 8 hour after : 210	
12.	Loss-of-Function CyP2C9 Variants Improve Therapeutic Response to Sulfonylureas in Type 2 Diabetes: a Go-DaRTS Study [18]	1.073 patients: 578 patients using monotherapy (sulphonylurea) 495 patients using combination treatment (sulphonylurea + metformin)	*cohort prospective*	678 patients: *1/*1 346 patients: *1/*2,*1/*3 49 patients: *2/*2, *2/*3,*3/*3	Patients with two copies of the CYP2C9*2 or CYP2C9*3 loss of functions allele showed higher in achieving the target of treatment (3.4 times with p=0.0009) compared to wild allele	Patients with CYP2C9*2 or CYP2C9*3 genotype also showed 0.5% reduction of HbA1c concentration, which better rather than other genotype.
13.	Association between CYP2C9 slow metabolizer genotypes and severe hypoglycemia on medication with sulphonylurea	357 patients using sulphonylurea	*case control*	237 patients: CYP2C9*1/*1 66 patients: CYP2C9*1/*2	337 patients showed better index glycemic control, while 20 patients experienced hypoglycemic events	Patients who experienced hypoglycemic events has higher number of rare genotype (10%), CYP2C9*2/*3 and CYP2C9*3/*3 rather

No	The Title, Author, and The year of publication	Number of sample, detail of sample	Method of the study	Variants genotype of CYP2C9	Outcome therapy	Result
	hypoglycemic agents [19]			5 patients: CYP2C9*2/*2 40 patients: CYP2C9*1/*3 6 patients: CYP2C9*2/*3 3 patients: CYP2C9*3/*3		than patient without hypoglycemia (2%)

The articles showed the relationship between genotype variance with outcome therapy and the effect of therapy such as the hypoglycemia effect after the treatment. The outcome therapy of the articles varied and include factors such as fasting blood glucose (FBG), blood glucose (BG) or Haemoglobin A1c (HbA1C). The FBG is one of glycemic index parameters measured after the patients fasted for at least 8 hours, in comparison to BG that can be measured anytime. HbA1c is measured to determine the average BG within 2–3 months.

4. DISCUSSION

The first study from Surendiran et al. [7] showed that 75% of patients in normal genotype group (CYP2C9*1/*1) had uncontrolled diabetes status and 50% of patients in variants genotype (CYP2C9*1/*2 and CYP2C9*1/*3) also faced uncontrolled diabetes status. The results showed the significant relationship between variants genotype CYP2C9 with controlled diabetes status and between normal genotype with uncontrolled diabetes status. This study also demonstrated that variants genotype is related to good response of diabetic control in patients who use glibenclamide than those in normal genotype. Another outcome is related to hypoglycemic effect with the use of glibenclamide, displaying that variants genotype was not related to adverse effect or hypoglycemic events.

A second study, from Klen et al. [8] showed that there is no significant correlation between variants genotype of CYP2C9 with diabetes index and with hypoglycemic episode. The average HbA1c achieves the target of 7.0±0.9 and hypoglycemic episodes occurred in 32 patients (20.51%). On average, patients with two wild-type alleles faced 0.390±0.982 hypoglycemic events, in comparison to those who faced increased hypoglycemic events (0.550±0.55 in one polymorphic allele and 1.22±2.728 in two polymorphic alleles). Other results from this study included that geriatric patients (>60 years) have a higher risk to face significant hypoglycemic events. Geriatric patients with two wild-type alleles experienced 0.36±0.98 events, while patients with one polymorphic allele experienced 0.79±1.7 events and patients with two polymorphic allele experienced 2.67±4.6 events ($p = 0.014$). This study concluded that the CYP2C9 polymorphism was not related significantly to diabetes index, however CYP2C9 genotype may influence the risk of hypoglycemia in geriatric patients.

The next study discussed the impact of CYP2C9 polymorphism on individual sensitivity to the use of gliclazide [9]. Results of this study showed that 46 patients (62.16%) had normal genotype of CYP2C9 *1/*1 and allele polymorphisms, whether heterozygote (CYP2C9*1/*2, CYP2C9*1/*3, CYP2C9*2/*3) or homozygote (CYP2C9*2/*2), was found in 28 patients (37.84%). This study showed that variants genotype has a correlation with individual response of the drug, and will affect BG. Patients who have polymorphic allele of CYP2C9 (homo- or heterozygous) relate to the decreasing dose of gliclazide and using it as a monotherapy agent for DMT2.

A research study by Castelan-Martinez et al. [10] found that the genotypes and allelic frequencies in Mexican patients were CYP2C9*2 CC, CT, TT and CYP2C9*3 AA, AC. This study showed that DMT2 patients with CYP2C9*3 variants have good glycemic control rather than patients who have CYP2C9*2 variants, and the relationship maintained after adjustment.

Another study from China showed that the largest frequencies of CYP2C9*3 genotype was AA (*1/*1), which is 90.08% [11]. Results of this study showed that the polymorphism of CYP2C9*3 was significantly related to the diabetic index (FBG) as an outcome of DMT2 treatment.

Other study from Turkey showed the impact of CYP2C9 polymorphism on hypoglycemia [12]. Results of this study showed that patients with genotype variants of CYP2C9 tend to experience hypoglycemic effects, highly impacting patients who use gliclazide as a DMT2 treatment.

The next study determined the impact of CYP2C9 polymorphism on response of treatment in Egyptian patients with DMT2 [13]. The genotype frequencies are 53 patients who were carriers of CYP2C9 *1/*1 (wild-type), 20 patients who were carriers of CYP2C9 *1/*2 (heterozygous for

CYP2C9*2), 18 carriers of CYP2C9 *1/*3 (heterozygous for CYP2C9*3) and 9 patient carriers of CYP2C9 *2/*3 (double heterozygous for both mutant alleles). Better diabetes control was observed using FBG and found to be higher in patients with carriers CYP2C9*2/*3 genotype. This study assumed that CYP2C9*2/*3 genotype caused slower SU metabolism and extended its half-life.

A research study from Koren et al. [14], showed that the outcome therapy in each genotype did not differ significantly, however related to hypoglycemic event, patients with CYP2C9 polymorphism experienced higher hypoglycemic events after three months of treatment with glibenclamide (22.2% events in more than two hypoglycemic episodes). Meanwhile, patients with normal genotype only experienced 5% of events during three months of treatment and using the same dosage as others.

A study performed by Ragia, et al. [15] showed that the frequency of patients with CYP2C9 polymorphism was 31.8% from 176 total samples. In this study, patients with genotype polymorphism experienced hypoglycemia higher than other genotypes. Of patients with the CYP2C9*3 allele, 11 patients (12%) experienced hypoglycemia, while only one patient did not. Patients who have CYP2C9*1/*3 genotype showed statistically significant increased hypoglycemia risk after adjusted analysis ($p = 0.011$), however no differences in CYP2C9*2 allele related to hypoglycemic event.

Another study, from Becker et al. [16], aimed to determine the association between CYP2C9 polymorphism with glucose level and prescribed doses of sulphonylureas. Most patients were treated using tolbutamide and a larger genotype frequency is CYP2C9 *1/*1. The result showed that patients who have CYP2C9*3 polymorphism have an average higher number of decreases in FBG after a certain duration of treatment. Although it is not significantly different ($p = 0.11$), CYP2C9*3 patients require lower prescription doses compared to wild-type patients. Furthermore, patients with other genotypes did not differ significantly in term of prescribed doses of tolbutamide compared to wild-type patients.

Results of a study by Suzuki et al. [17] showed that patients with genotype variants CYP2C9*1/*3 have a good response to glimepiride rather those with normal genotype. However, one patient experienced a gain in body weight after treatment with glimepiride.

In research from Zhou et al, [18], patients with genotype CYP2C9*2/*2 or CYP2C9*2/*3 or CYP2C9*3/*3 had a 0.5% better reduction of HbA1c rather than wild-type patients, specifically in CYP2C9*2/*3 genotype. Patients with CYP2C9*2/*3 genotype was known can achieve target treatment 7.54 times ($p = 0.003$) rather than normal genotype. Patients with CYP2C9*2 showed slight overrepresentation in a non-tolerant group, however it still hard to draw the conclusion. In general, CYP2C9 loss-of-function variants relate to the greater response to sulphonylureas and lower rate of failure.

A research study from Holstein et al. [19] showed that 20 DMT2 patients who use sulphonylureas experienced hypoglycemia in the following details: 13 (65%) from patients who had CYP2C9*1/*1, 4 (20%) from patients who had CYP2C9*1/*2, one patient for each genotype CYP2C9*1/*3 (5%), CYP2C9*2/*3 (5%), and CYP2C9*3/*3 (5%), however no hypoglycemic cases in genotype CYP2C9*2/*2. This study also presented that age plays a role in the hypoglycemic event. The mean age of the diabetic control patients (337 patients) was 65 years, while in 20 DMT2 patients who experienced hypoglycemia mean age was 74 years.

In general, result of variants genotype from genotyping analysis on 13 research studies are CYP2C9*2 (rs1799853), CYP2C9*3 (rs1057910) and CYP2C9*1/*1 (wild-type). There are two types of CYP2C9*2 which are homozygous, CYP2C9*2/*2 (consisting of two identical alleles or perform polymorphism in both alleles), and heterozygous, CYP2C9*1/*2 (consisting of two different alleles or perform polymorphism in one allele). Others include CYP2C9*3 with homozygote variant CYP2C9*3/*3 and heterozygous variant CYP2C9*1/*3. Genotype heterozygote CYP2C9*2/*3 also found in some subjects.

The total patients from 13 articles reviewed was 3941 DMT2 patients. Patients with wild-type genotype perform in 72.47% DMT2 patients from the aforementioned articles. Variants genotype CYP2C9*3/*3 is the rarest, which affects only 12 patients from 3941 patients (0.30%). Patients with heterozygous genotypes, such as CYP2C9*1/*2 or CYP2C9*1/*3, affects approximately 971 patients (24.64%), while homozygous genotypes, such as CYP2C9*2/*2, CYP2C9*2/*3 or CYP2C9*3/*3, are found in only 114 patients.

Based on the performed literature review, further studies are needed to find the clear impact of CYP2C9 polymorphism, especially in Indonesia, which has a higher incidence of DMT2. Genetic and other factors can be associated with the patients' response to oral antidiabetics and impact the outcome, whether due to glycemic index or side effect.

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AUTHORS' CONTRIBUTIONS

NM, DAP, INF: search the articles; HD: data extraction; LMH, RM: Critical appraisal; NM, DAP: manuscript draft; INF, LMH, RM: manuscript revision

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