HASIL CEK_Genotype of Potassium Inwardly Rectifying Channel, Subfamily J, Member 11 (KCNJ 11) Gene and Glycaemia Control in Diabetic Patients: A Narrative Review

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Genotype of Potassium Inwardly Rectifying Channel, Subfamily J, Member 11 (KCNJ 11) Gene and Glycaemia Control in Diabetic Patients: A Narrative Review

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ABSTRACT

There are several factors that may affect the body response to the medicine and the drug response. One of the factors is the genetic variations. Some genes are predicted to have significant roles in oral antidiabetic response. This review is intended to define the role of Potassium inwardly rectifying channel, subfamily J, member **11 (***KCNJ11)* genotypes to the glycemia control in Diabetes melitus type 2 (DMT2) patients. We conducted literature review using keywords "genotype description, kcnj11 gene, blood sugar level, diabetes melitus type 2" in Pubmed, Science Direct, BMC, PMC and Google Scholar database. Among the fourteen articles, we found that the most alleles studied was: rs5219 and rs5215. The homozygous wildtypes of rs5219 have no correlation with the risk of DMT2. However, the correlation between the allele of rs5219 and the medication response are still unclear. Furthermore, the correlation of alleles of rs5215 and the risk of DMT2 and medication response are still contradictive. The future studies are still needed to confirm the correlation between allele of rs5219, rs5215 and the risk of DMT2 and medication response.

Keywords: Provide KCNJ11, Diabetic, medication, response

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INTRODUCTION

Diabetes melitus type 2 (DMT2) is the metabolic disturbance indicated with the increase of Blood Sugar Level (BSL) due to the insulin resistance (1). DMT2 caused the sixth of death in the world in 2016 (2). The number of DMT2 in Indonesia is getting increase yearly and will reach 21.3 juta penduduk pada tahun 2030 (3). Genetic studies are needed of define the risk factor of genetic in DMT2. The results of genetic studies can be used to design prevention strategic and treatment (4). The *Genome Wide Association Study* (GWAS) reported some genes as the risk factors of DMT2, such as: *ABCC8, KCNJ11, PPARγ, UII, TCF7L2, CDKAL1, CDKN2A/B, IGF2BP2, HHEX/IDE, FTO*, dan *SLC30A8*(5–9). One of the gene associated with DMT2 is *potassium inwardly rectifying channel (KCNJ11).* This gen has a role in the expression of Kir6.2, the subdomain of integrated protein K_{ATP} *channel*, β pancreatic cell with the function of K^+ selective membrane (4). The KCNJ11 expressed the K+ ion channel which sensitive to the ATP and has significant role in controlling the insulin secretion (10). The polymorphism of *KCNJ11* related to rs5219, describes the substitution of glutamate to lysine which can cause the decrease sensitivity of KATP. This situation can open the channel more frequent and inhibit the insulin secretion (11)(12). Some previous studies found that genes variation can be the risk factor of DMT2 and some are associated with the glycaemic control (9,12). The aim of this narrative review is to describe the role of *KCNJ11* gene as the risk factors of DMT2 and its association with the glycaemia control.

MATERIAL AND METHODS

Materials

We found 5.290 articles from PubMed (446), *Google Scholar* (4.202), *Science Direct* (59), DOAJ, *BioMed Central* (44), dan *Europe PMC* (529) that were accessed during June 2020. After the critical appraisal, we identified 14 articles relevant to the topic. The study outcomes were Fasting Blood Glucose (FBG), Blood Sugar Level (BSL) and HbA1C (Hemoglobin A1c).

METHOD

This review used a narrative review. The articles were found from *PubMed, Science Direct,* and *Google Scholar*. The inclusion criteria for the articles were full text articles and published from 2010 to 2020. Exclusion criteria was no genotype variations discussed in the article. The PICO were *"Genotype Description"* AND *"KCNJ11 gene"* OR *"ABCC8"* AND *"Blood Sugar Level" OR Diabetes Mellitus Type 2.* From the 5290 articles, we extracted 3797 articles due to the year limitation (2010-2020). The next procedures were selecting the articles based on the review objective and we got 29 articles. After the critical appraisal, we identified 14 articles met the criteria (Table 1).

RESULTS AND DISCUSSION

We found 15 articles which conducted in Egypt, Syrian, Mexico, Gaza, Russia, Iran, Kirgizstan and Indonesia. Table 2 shows the results of articles review. All of the studies are original articles with 9 studies of case control, 4 studies of RCT and 1 study of cross-sectional design. The total number of subjects participated in all studies were 3918, with 3129 among them are the DMT2 patients and the rests were subjects in control groups. We identified these SNPs; rs5219 (E23K dan Glu23Lysy), rs5218 (A190A), rs5216 (L267L), rs1800467 (L270V) and rs5215 (I337V).

The study of Gonen et al, 2012 in Turkish population, shows that the CC genotype of L5216, GA genotype of E23K, CC genotype of L267L and AA genotype of I337V are dominantly found in the case group. In the case group, the frequency of heterozygous and homozygous mutant is high (13). The study of Abed et al, 2013, in Gaza population, presents that KK genotype has high proportion in case

group (83%) and EE genotype has high proportion ing control group (61.8%) (14).The study of Klen, et al, 2014, finds that the risk of hypoglycaemia is dominantly found in the heterozygous type of rs5215 and rs5219 (48.7% and 48.7%, respectively). However, the statistical analysis does not show the significant association between the genotypes and hypoglycemia risk (15). According to this result, the *KCNJ11* polymorphism have no association with treatment and hypoglycaemia risk. The study of Li et al, 2014, in 108 DMT2 patients treated with glicazide for 16 weeks, shows that subjects with KK genotype has better response for glicazide, compared to EE and EK genotypes. During the treatment, the carriers of K show the lower BGL and HbA1C compared to the carrier E (16). These results are consistent to study by Rastegari et al, 2015, in 40 DMT2 patients. The study shows that subjects with K allele carriers have higher risk of DMT2 risk and the healthy subjects have E allele carrier (17). In Russian population of DMT2, the prevalence of E and K alleles are 36.6% and 63.4%, respectively. The proportion of EE, EK and KK were 41%, 44.8% and 14.2%, respectively. Ghanem, et al, 2016 (18), also finds that the proportion of KK in the DMT2 group was higher than its proportion in the control group, even thought there was no significant association. The study conducted by, Rodriguez-rivera, et al, 2017, in Mexican-Mestizo population. The highest proportion genotype is EK (45.3%) (19).

Isakova, et al, 2018 in Kirgiztan population presens that K allele has high proportion in DMT2 group than in the control group (44% vs 32.6%)(20). Sanchez-Ibara, et al, 2018 presents that the rs5219 has significant effect to the sulfonylurea response and the rs5215 did not have significant effect to sulfonylurea response. The individu with KK genotype of rs5219 has higher HbA1C level than other genotypes (21). Regarding to the drug response, some previous studies present the correlation between gene variants and drug response. The response of repaglinide and rosiglitazone were found influenced by *CYP2C8, SLCO1B1, PAX4* and *PSMD6* genes (22–25). The *KCNJ11* and *ABCC8* variants are more related to the sulfonylurea response (26). The clearance of sulfonylurea also associated with variants of *CYP2C9*2* and **3* (27,28). However, rs11212617 has association with the metformin response. The *SLC22A1* gene, is a marker for efficacy and excretion of metformine (29,30).

The other study by Muhammad, et al, 2018 also shows that the KK genotype has higher proportion in DMT2 patients than in the control group (15.4%) (31). The study of Makhzoom, et al 2019, in Suriah shows that DMT2 patients had 80% of genotype KK than in the control group (32). This results also supported by the study results of Sunita, et al, 2020 (33). Table 3 summarizes the KCNJ11 genotype's role in the DMT2 disease and the treatment. Most of the studies in this review confirmed that the genotype KK of KCNJ11 gene is related to the DMT2 disease risk. It caused by the mechanism of insulin secretion defect and mechanism of potassium channel affected by the lysin (10,34). One of the studies described the proportion of K allele among different population. The higher proportion is shown by China population and the lower proportion is shown by Mauretanian population (40% vs 19%, respectively). Generally, the proportion of K allele in North African is around 20%, in the Asian around 36%-40% and 37-39% in Caucasian (32). This proportion is appropriate to the incidence of DMT2 over the world with China, North African and Europe as the top highest prevalence of DM in the world (35). In various population, the individu with KK genotype has an increased risk of DMT2 as 1.25 to 3.8 times with the recessive models (9,12,16,17,32,36,37). The DMT2 is a disorder which is not only caused by genetic, but also influenced by some others factors like diet, exercise and other lifestyle. The previous study in China, designed the epidemiology and genetic risk factors as the predictors of DMT2. More than 80 loci of genetic variants, combined with epigenetic, gene-environment interactions, and environment factors are considered as the DMT2 risk factors (38). Thus, in the future, the study of genetic polymorphism in DMT2, based on the ethnicities must be consider the other possible risk factors, like lifestyle and environmental support. The limitation of this review is according to the data we have, it is recommended to learn about other SNPs of *KNJ11* and its role in the future. We suggest using Scifinder for the literatures search.

CONCLUSION

Our study finds that the genotypes of KK of rs5219 increased the risk of DMT2. However, the association of this SNPs with antidiabetic drug response and hypoglycemia risk must be explored in the future studies.

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CONFLIST OF INTEREST

All authors have no conflict of interests

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Table 1: The results of articles searching

Database	Key words	Articles found
PubMed	*"genotype description" AND "KCNJ11 gene" OR "ABCC8" AND "Blood Sugar Level"*	59
PubMed	*"genotype description" AND "KCNJ11 gene" OR "ABCC8" AND "diabetes mellitus"*	368
PubMed	*"diabetes mellitus type 2") AND "KCNJ11 gene" AND "genotype description"*	1
PubMed	*"genotype description" AND "KCNJ11 gene" AND "diabetes mellitus"*	2
PubMed	*"genotype KCNJ11" AND "Diabetes mellitus type 2" AND "blood sugar level"*	16
Google Scholar	*"Genotype Description KCNJ11 gene Diabetes Mellitus type 2"*	4.200
Google Scholar	"Deskripsi Genotip Gen KCNJ11 pada Diabetes Mellitus type 2"	2
Science Direct	*"Genotype Description KCNJ11 gene Diabetes Mellitus type 2"*	59
DOAJ	*"type 2 diabetes mellitus and genotype KCNJ11 gene"*	10
BioMed Center	*"type 2 diabetes mellitus and genotype KCNJ11 gene"*	44
Europe PMC	*"Diabetes Mellitus type 2 and KCNJ11 polymorphism"*	529
Total number of articles		5.290

Table 2: Studies related to the KCNJ11 gene and its glycaemic control

Author, year, country	Title	Number of subjects	Method	SNPs related	Results
Gonen, et al (2012) Turki	Effects of Single Nucleotida Polymorphism in K(ATP) channel genes on Diabetes in Turkish Population	Case group: 169 Control group: 119	Case-control	rs2519 (E23K); rs5218 (A190A); rs5216 (L267L); rs1800467 (L270V); rs5215 (I337V)	The subjects with heterozygous are dominant in case group.
Abed, et al (2013) Gaza	Single Nucleotide Polymorphism E23K of *KCNJ11* Gene and Other Risk Factors Associated with Type-2 Diabetes Mellitus In Gaza	Case group: 100 Control group: 100	Case-control	E23K	The subjects with K allele have risk factors of DMT2
Klen, (2014) Slovenia	*CYP2C9, KCNJ11* and *ABCC8* polymorphisms and the response to sulphonylurea treatment in type 2 diabetes patients	21 DMT2 patient with sulfonilurea 35 DMT2 patients with sufonilurea + metformin	RCT	rs5219 (Lys23Glu) rs5215 (Val250Ile)	rs5219 has no association with hypoglycemia
Li, (2014) China	*KCNJ 11*; E23K variant is associated with the therapeutic effect of sulphonylureas in Chinese type 2 diabetic patients	108 DMT2 patients treated with glicazid	RCT	rs5219	Subjects with K allele show high response to glicazid
Nikitin, et al (2015) Russia	Association of *FTO, KCNJ11, SLC30A8,* and *CDKN2B* polymorphism with type 2 diabetes mellitus	Case group: 440 Control group: 246	Case control	rs2519	Subjects with KK genotype shows higher risk of DMT2
Rastegari, et al (2015) Iran	Association of KCNJ11 (E23K) gene polymorphism with susceptibility to type 2 diabetes in Iranian patients	40 DMT2 patients	case-control	rs5219	Subjects with KK genotype shows higher risk of DMT2
Sorokina, et al (2016) Moskow	Evaluation of An Association Between Rs5219 Polymorphism of KCNJ11 Gene And The Risk Of Type 2 Diabetes Mellitus	1050 DMT2 patients	RCT	rs5219	Subjects with K allele have higher risk of DMT2
Ghanem, et al (2016) Mesir	Association between KCNJ11 & ABCC8 Genetic Polymorphism and Type 2 Diabetes in Egyptian Patients	Case group: 53 Control group: 30	case-control	rs5219 (E23K)	The genotypes show no association with DMT2 risk

Rodríguez-Rivera, et al (2017) Meksiko	Identification of genetic variants in pharmacogenetic genes associated with type 2 diabetes in a Mexican-Mestizo population	247 DMT2 patients	RCT	rs2519 (E23K)	Subjects with heterozygous show higher risk of DMT2
Isakova, et al (2018) Kirgistan	*ADIPOQ*, *KCNJ11* and *TCF7L2* polymorphisms in type 2 diabetes in Kyrgyz population: A case-control study	Case group: 114 Control group: case group: 114 Control group: 109	case-control	rs5219	Subjects with K allele have higher risk of DMT2
Sanchez-Ibarra, et al (2018) Meksiko	Genotypic and Phenotypic Factors Influencing Drug Response in Mexican Patients with Type 2 Diabetes Mellitus	495 DMT2 patients	Cross sectional	Glu23Lys	Subjects with wildtype and homozygous mutant have higher level of HbA1C
Muhammad, et al (2018) Indonesia	Polymorphism Genes Sulfonylurea Receptpr-1 and Potassium Inwardly- Rectifying Channel Subfamily J Member 11 as a Risk Factor for Type 2 Diabetes Mellitus in Ethnic of Makassar	Case group: 52 Control group: 52	case-control	E23K	Subjects with EK genotype have protecting effect for DMT2 risk
Makhzoom, (2019) Siria	Association of *KCNJ11* rs5219 gene polymorphism with type 2 diabetes mellitus in a population of Syria: a case-control study	Case group: 6 Control group: 63	case-control	rs5219	Subjects with K allele have higher risk of DMT2
Sunita, et al (2020) Indonesia	Polymorphism E23K *KCNJ11* Gen as a Risk Factor of Diabetes Mellitus in Serawai Tribe of Bengkulu	Case group: 50 Control group: 50	Case-control	E23K	Subjects with K allele have higher risk of DMT2

Table 3: The KCNJ11 genotypes' role in the DMT2 disease and the treatment

rs id	Genotype' role	Genotype' role	Genotype' role
rs5219 (E23K)	GG has no risk to DMT2	GA has no risk to DMT2	AA has a risk to DMT2
rs5219 (E23K)	EE has low risk to DMT2 and has response to glicazide	EK has risk to DMT2 and has response to glicazide	KK has high risk to DMT2 and has response to glicazide
rs5219 (E23K)	CC has no association with drug response and hypoglycemia risk and low risk to DMT2	CT has no association with drug response and hypoglycemia risk and has risk to DMT2	TT has no association with drug response and hypoglycemia risk and high risk to DMT2 DMT2
rs5219 (Glu23Lys)	CC has low response to sulfonylurea and high risk to DMT2	CT has high response to sulfonylurea and has risk to DMT2	TT has low response to sulfonylurea and high risk to DMT2
rs5219 (Glu23Lys)	GluGlu has low risk to DMT2	GluLys has risk to DMT2	LysLys has high risk to DMT2
rs5218 (A190A)	C/C has no association with DMT2	C/T has no association with DMT2	T/T has no association with DMT2
rs5216 (L267L)	C/C has no association with DMT2	C/G has no association with DMT2	-
rs1800467 (L270V)	C/C has no association with DMT2	C/G has no association with DMT2	G/G has no association with DMT2
rs5215 (I337V)	A/A has low risk to DMT2	A/G has low risk to DMT2	G/G has low risk to DMT2
rs5215 (I337V)	TT has no association with drug response and hypoglycaemia risk	TC has no association with drug response and hypoglycaemia risk	CC has no association with drug response and hypoglycaemia risk

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