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Characteristics of Metformin Transporter Coding Gene (SLC22A1 rs628031 and SLC47A1 rs2289669) in Healthy Indonesian Subject

(*Karakteristik Gen Penyandi Transporter Metformin (SLC22A1 rs628031 dan SLC47A1 rs2289669) pada Subyek Sehat Orang Indonesia*)

Endang Susilowati*

Pharmacy Department, Politeknik Kesehatan Putra Indonesia Malang, East Java, Indonesia.

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Corresponding Author:
Endang Susilowati
Pharmacy Department
Politeknik Kesehatan
Putra Indonesia
Malang
65123
East Java
Indonesia
email: endang@poltekkespim.ac.id

ABSTRACT

Background: Metformin might be a first therapy for Type 2 diabetes; however, it had a lot of variation in glycemic response. **Objective:** to analyze the frequency of minor alleles of the OCT1 coding gene (SLC22A1 rs628031) and MATE1 coding gene (SLC47A1 rs2289669) as well as the genotypic variation of the interaction of these two genetic polymorphisms in healthy subjects of Indonesia. **Material and Methods:** Through inclusion criteria, the study employed an observational descriptive technique with 70 Indonesian Javanese healthy individuals. Subject health information was obtained from the complete blood routine test, serum glutamic oxaloacetic transaminase/ serum glutamic-pyruvic transaminase (SGOT/SGPT), complete urine test, and serum creatinine tests. All data were compared to the normal range. **Results:** The finding shows that the minor allele frequency on SLC22A1 rs628031 A>G and SLC47A1 rs2289669 G>A respectively at 53% and 36%. There are four SLC22A1 rs628031 and SLC47A1 rs2289669 genetic polymorphism interactions; 16 Wt/Wt (16.75%), 24 Wt/M (25%), 32 M/Wt (33.3%) and 24 M/M (25%). The discovery demonstrates that such minor allele frequencies of the SLC22A1 rs628031 OCT1 and SLC47A1 rs2289669 MATE1 genes in healthy Indonesian subjects are relatively high. The SLC22A1 rs628031 A>G and SLC47A1 rs2289669 G>A respectively at 53% and 36%, almost the same as the minor allele frequencies found in several other Asian countries eg. India, Japan, and China. **Conclusions:** OCT1 coding genes (SLC22A1 rs628031 A>G) were found more dominant than MATE1 coding genes (SLC47A1 rs2289669 G>A) and both alleles are relatively high in healthy subjects of Indonesia, which can be used as information to explore the consequences of different genes' interactions on the Indonesian pharmacokinetic properties, and the efficacy variations of metformin in Type2 DM patients.

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INTRODUCTION

In Indonesia, Type 2 Diabetes Mellitus (Type 2 DM) incidence continues to increase. In 2017 there were 10 million more cases and predicted to reach 183 million in 2045 (International Diabetes Federation, 2019). The Indonesian Type 2 DM population aged over 15 years is estimated to be 10.9% of the population. Type 2 diabetes is characterized by an inefficient utilization of insulin by the body and is frequently connected with weight gain and lack of physical activity (Soelistijo et al., 2019). As in other countries, in Indonesia, metformin is the first-line drug and is the most widely prescribed for Type 2 DM treatment and prescribed by doctors. However, the patient's response to metformin therapy shows considerable inter-individual variability. The results of the BA/BE (Bioavailability/Bioequivalence Test) test by BPOM showed Cmax variation in the range of 1099.89-3412.65 ng/ml (National Agency of Drug and Food Control, 2015), while in DMT2 patients the Cssmin steady-state variation was more than 100 times and Cssmax was more than 15 times (Ningrum, Ikawati, Sadewa, & Ikhsan, 2017b). In other countries, steady-state concentrations of metformin show up to 80-fold differences, with a range of 54-4133 ng/ml (K. H. Christensen et al., 2013) and renal clearance of metformin varying between 300-1000 ml/min (Yin, Tomlinson, & Chow, 2006). More than 30% of individuals on metformin alone may not attain blood glucose control (Cook, Girman, Stein, & Alexander, 2007). Variability in therapeutic response is an important problem because it is related to the safety and effectiveness of a drug.

Metformin is one of the organic cations that are hydrophilic so inter-cell transportation requires membrane transporters. Metformin has been demonstrated to function via AMP-activated protein kinase (AMPK)-dependent and AMPK-independent pathways, including suppression of mitochondrial respiration but also perhaps suppression of mitochondrial glycerophosphate dehydrogenase and lysosomes (Rena, Hardie, & Pearson, 2017). Multidrug and Toxin Extrusion Protein 1 (MATE1) and Organic Cation Transporter 1 (OCT1) are the two main transporters of metformin. OCT1 plays a role in metformin uptake to hepatocytes, while its elimination via the kidney is regulated by MATE1 (Graham et al., 2011). The OCT1 coding gene (SLC22A1) and the MATE1 coding gene (SLC47A1) are known to be polymorphic. Several researchers have discovered that polymorphisms in the OCT1 and MATE1 transporter genes influence metformin sensitivity (M. M. H. Christensen et al., 2015; Shu et al., 2008; Yoon, Cho, Yoo, Kim, & Lee, 2013). In Asia, Single Nucleotide Polymorphism (SNP) in SLC22A1 rs628031 and SLC47A1 rs2289669 was found to be around 50-80% (Itoda et al., 2004; Kang et al., 2007; Sur, 2014) and 20-50% (Becker et al., 2010; He et al., 2015; Itoda et al., 2004; Stocker et al., 2013; Tkáč et al., 2013). SLC22A1 polymorphism is linked to higher AUC, decreased Vd of metformin (K. H. Christensen et al., 2013; Shu et al., 2008; Yoon et al., 2013), as well as enhanced renal discharge

(Tzvetkov et al., 2009). While SLC47A1 polymorphism is associated with the inhibition of renal excretion of metformin characterized by an increase in plasma AUC (Becker et al., 2010; He et al., 2015; Stocker et al., 2013; Tkáč et al., 2013). While in Indonesia, research on polymorphisms of both genes has been carried out in patients with Type 2 DM. Minor allele frequency SLC22A1 rs628031 G>A reaches 60.47% while minor allele frequency SLC47A1 rs2289669 is 61.05% (Ningrum, Ikawati, Sadewa, & Ikhsan, 2017a).

Addressing the several transporters engaged in metformin disposal and its localisation inside the same organ, the analysis of the interaction of the two transporter genetic polymorphisms on the response of metformin can provide a better understanding. SLC22A1 polymorphism is assumed to reduce hepatocyte uptake thereby reducing the hypoglycemic effect of metformin, on the other hand, SLC47A1 polymorphisms inhibit the elimination of metformin in the kidney so that the hypoglycemic effect increases (Becker et al., 2010). OCT1 and MATE1 genotype mapping and their interactions are useful as preliminary information for the study of the polymorphisms of each gene and the interaction between the two genes on the pharmacokinetic and pharmacodynamic responses of metformin. Furthermore, understanding the pharmacogenetics of metformin can be important information for integrating genetic screening in making individual therapeutic and treatment decisions in Type 2 DM patients. Therefore, the objective of this study is to analyze the frequency of minor alleles of the OCT1 coding gene (SLC22A1 rs628031) and MATE1 coding gene (SLC47A1 rs2289669) as well as the genotypic variation of the interaction of these two genetic polymorphisms in healthy subjects of Indonesia.

MATERIAL AND METHODS

Subject

A total of 70 volunteers were recruited from healthy subjects using purposive sampling who lived in Malang-East Java with inclusion criteria: 18-50 years old, male and female, BMI between 18-25 kg/m^2, willing to be involved as research subjects proven by signing the informed consents. Exclusion criteria: high serum creatinine levels (men>1.5 mg/dL, women>1.4 mg/dL), SGOT/SGPT values increased 2 times higher than normal values, pregnant and lactating women, heavy smokers, alcohol drinkers, and a history of drug abuse. The method of sampling was consecutive nonprobability sampling, which was taking the required subjects until the minimum number of subjects was met. The Ethics and Law Committee of Airlangga University Hospital granted ethical approval (registration number 120/KEH/2017).

Methods

Clinical Laboratory Test

Subject health information was obtained from the complete blood routine test, serum glutamic oxaloacetic transaminase and or serum glutamic-pyruvic transaminase (SGOT/SGPT), complete urine test, and serum creatinine tests. All data were compared to the normal range.

Genotype Analysis

DNA isolation was obtained from peripheral blood leukocytes with the procedures from the DNA Isolation Kit (Wizard Genomic DNA Purification Kit from Promega). DNA amplification was conducted by PCR using primers, each for SLC22A1 rs628031 was 5'-TTT CTT CAG TCT CTG ACT CAT GCC - 3' (forward) and 5'-AAA AAA CTT TGT AGA CAA AGG TAG CAC C-3' (reverse), while the primary design of SLC47A1 rs2289669 uses 5′-TCA GTT TCC ACA GTA GCG TCG-3′ (forward) and 5′-GAC ACT GGA AGC CAC ACT GAA-3′ (reverse). The amplification procedure for the SLC22A1 gene was conducted under conditions: 94^0C pre-denaturation temperature for 5 minutes, then 35 denaturation cycles at 94^0C for 30 seconds, 61^0C annealing temperature for 30 seconds, followed by an extension at 72^0C for a minute, final extension at 72^0C for 5 minutes. While PCR genetic amplification of SLC47A1 rs2289669 was conducted under the same conditions, except for annealing at 54^0C. Further, PCR products were sequenced with ABI PRISM® 310 Genetic Analyzer.

RESULTS AND DISCUSSION

Subject Characteristic

This study involved 70 healthy Indonesian Javanese participants consisting of26 male participants aged 23 (± 4.7) years on average and 44 female participants with a median age of 20 years (± 3.4) (Table 1). The BMI average of subjects is 21.9 kg/m^2 ± 1.5. The laboratory test result showed serum creatinine (SCr) levels of subjects in the range of 0.47 to 0.98 mg/dl with an average of 0.74 mg/dl. SGPT/SGOT value of all subjects did not exceed 2 times higher than the normal value. The SGOT value was in the range of 10-27 µ/L, and the SGPT value was in the range of 10-33 µ/L.

Table 1. Sample characteristics in healthy subjects

Characteristics		n =70		BMI Average	serum creatinine (SCr) average	SGPT/SGOT value
		n	Age			
Gender	Male	26	23 years ± 4.7	21.9 kg/m^2 ± 1.5	0.74 mg/dl	10-27 µ/L/ 10-33 µ/L
	Female	44	20 years ± 3.4			

Genetic Variation onOCT1 and MATE1

Genetic variation and minor allele frequencies in both genes are presented in Table 2.

Table 2. Genotype variation of OCT1 (SLC22A1) and MATE1 (SLC47A1) in healthy subjects

Gene	SNP	n =70			Minor Allele Frequency (%)
		AA	Aa	aa	
SLC22A1	rs628031 A>G	18	30	22	53 %
SLC47A1	rs2289669 G>A	38	14	18	36 %

Notation A shows the major variant alleles, and a shows the minor variant alleles. AA, Aa, and aa represent wildtype homozygous, mutant heterozygotes, and mutant homozygotes in order. The frequency of minor alleles of the SLC22A1 rs628031 gene was 53% and the SLC47A1 gene 2289669 was 36%.

Genetic Interaction Variation Characteristic

Seventy healthy subjects were grouped based on the profile of genetic variation of both genes, as shown in Table 3.

Table 3. Interaction type of both genes

	SLC47A1 rs2289669 G>A		
	GG	GA	AA
SLC22A1 rs228969 A>G			
AA	AAGG=11	AAGA= 16	AAAA= 11
AG	AGGG= 22	AGGA= 5	AGAA= 0
GG	GGGG= 0	GGGA= 0	GGAA= 5

There were 6 variations of SLC22A1 rs628031- SLC47A1 rs2289669 genetic polymorphism interaction variation; AAGG, AAGA, AAAA, AGGG, AGGA, GGAA. Notation AAGG were subjects with SLC22A1 wildtype - SLC471 wildtype genotype; AAGA and AAAA were subjects with SLC22A1 wildtype - SLC47A1 mutant genotype; AGGG were subjects with SLC22A1 mutant-SLC471 wildtype genotype; AGGA and GGAA were subjects with SLC22A1 mutant-SLC471 mutant genotype.

SLC22A1 rs628031 and SLC47A1 rs2289669 Genetic Polymorphism Interaction

SLC22A1 rs628031 and SLC47A1 rs2289669 genetic polymorphism interaction variations were presented in Table 4.

Table 4. SLC22A1 rs628031 and SLC47A1 rs2289669 genetic polymorphism interaction

Interaction Type (SLC22A1 – SLC47A1)	Amount n =70	Percentage (%)
Wildtype-Wildtype (AAGG)	11	15.7
Wildtype-Mutant (AAGA, AAAA)	27	38.6
Mutant-Wildtype (AGGG, GGGG)	21	30.0

Table 4 showed shows that among the 70 healthy Indonesian subjects, were four SLC22A1 rs628031 and SLC47A1 rs2289669 genetic polymorphism interactions; 16 Wt/Wt (16.75%), 24 Wt/M (25%), 32 M/Wt (33.3%) and 24 M/M (25%). M = Mutant, and Wt = Wildtype.

The study of the metformin transporter polymorphisms, OCT1 and MATE1, and their relationship to pharmacokinetic and pharmacodynamics responses have been largely conducted. It is related to the high polymorphism of the two transporters in almost all of the world's population. OCT1 polymorphism is associated with decreased metformin hepatocyte uptake resulting in a decrease in hypoglycemic effects. While MATE1 polymorphism is associated with barriers to the excretion of metformin in the kidneys which results in increased plasma metformin levels as hypoglycemic effects.

The connection between the OCT1 coding gene polymorphism (SLC22A1 rs628031) and the MATE1 coding gene (SLC47A1 rs2289669). is described in this work Among the 70 healthy subjects included in the study, 53% of minor allele frequency (MAF) of SLC22A1 rs628031 A> G gene and 36% of minor allele frequency (MAF) of SLC47A1 rs2289669 G> A gene was found. OCT1 was known to be highly polymorphic in a diverse ethnic population. The frequency of minor alleles ranges from 15% - 80% (Chen et al., 2010). While the polymorphism of the SLC47A1 rs2289669 gene in the research is proportional to MAF in Japan, 37.5% (Nies, Damme, Kruck, Schaeffeler, & Schwab, 2016) and MAF variation in the world's population reaches 20-50% (Becker et al., 2010; M. M. H. Christensen et al., 2015; He et al., 2015; Stocker et al., 2013; Tkáč et al., 2013). Compared to the study conducted by (Ningrum et al., 2017a), in Type 2 DM patients, the MAF of both genes in healthy subjects in this study was smaller. In Type 2 DM patients, rs628031 was found at 60.47%, and rs2289669 was found at 61.05% (Ningrum et al., 2017a). While in other studies, There were no significant genetic changes in MAF between healthy people and Type 2 DM patients (Becker et al., 2010; Xiao et al., 2016).

SLC22A1 is a gene present on chromosome 6q26 and stretches around 37 kb. SNP rs628031 on SLC22A1 is a type of nonsynonymous mutation, causing a missense mutation in exon 7 where the amino acid methionine turns into valine at position 408 (Met408Val) (Koehler & Mishra, 2008; Koepsell, Lips, & Volk, 2007). A previous study suggested that Met408Val significantly decrease the reduction of FPG or HbA1c (Becker et al., 2010; Zhou et al., 2015) and was strictly correlated with metformin side effects, according to a survey with 246 Latvian individuals (P = 0.02) (Tarasova et al., 2012). OCT1 polymorphism is thought to cause reduced levels of metformin in hepatocytes as the site of action, with consequences for decreasing the hypoglycemic effect of metformin.

The SLC471 gene is located near chromosome 17p11.2, consisting of 570 amino acids and containing 17 exons (Nies et al., 2016). Study in vitro, rs2289669 (G>A) were demonstrated to minimize or

eliminate transportation activity (Becker et al., 2010; Chen et al., 2010; Ha Choi et al., 2009; Kajiwara et al., 2009; Toyama et al., 2010; Tzvetkov et al., 2009). Several studies suggested that rs2289669 (G>A) variant in SLC47A1 has been proven to have a greater decrease in HbA1C than wildtype (Becker et al., 2010; Tkáč et al., 2013; Xiao et al., 2016). This is linked to MATE1 transcription, which is found in the brush border of the renal epithelium and is involved for metformin clearance via the urine and bile. Barriers to the excretion of metformin increase plasma metformin levels and have an impact on improving metformin efficacy (He et al., 2015).

Four variations of genetic polymorphism interactions (rs628031 and rs2289669) were found, with the most variation of rs628031 wildtype - rs2289669 mutant (AAGA and AAAA) at 38.6%. A Chinese study evaluating the effect of the interaction of SLC22A1 and SLC471 gene polymorphisms on the hypoglycemic effect of metformin showed that among Type 2 DM patients with AA SLC22A1 rs594709 genotype, patients with AA SLC47A1 rs2289669 genotype showed a higher GDP decrease (p=0.015) than patients with G allele (M. M. H. Christensen et al., 2015). Similar data were presented by research on Type2 DM patients in Europe. Among patients, who had a mutation on MATE1 rs2289669, showed a greater effect of HbA1C decrease in patients with OCT1 rs622342 CC genotype compared with patients with AA genotype (p = 0.005) (Becker et al., 2010). Data from these two studies showed that SLC22A1 and SLC47A1 polymorphism interaction, all together, can affect the hypoglycemic effect of metformin in Type 2 DM patients.

Findings show that the minor allele frequencies of the SLC22A1 rs628031 OCT1 and SLC47A1 rs2289669 MATE1 genes in healthy Indonesian subjects are relatively high SLC22A1 rs628031 A>G and SLC47A1 rs2289669 G>A respectively at 53% and 36%, almost the same as the minor allele frequencies found in several other Asian countries. eg. India, Japan, and China. However, when compared with Type 2 DM patients in other studies with the same race, the minor allele frequency of the two genes showed a lower frequency. Minor allele frequency SLC22A1 rs628031 G>A in Type 2 DM patients reached 60.47% while minor allele frequency SLC47A1 rs2289669 was 61.05% (Ningrum et al., 2017a). This research also shows the interaction of polymorphisms in OCT1 and MATE1 genes, which can be used as information to examine the impact of these two genes' interplay on the Indonesian pharmacokinetic profile, and the efficacy variations of metformin in Type2 DM patients.

CONCLUSION

OCT1 coding genes (SLC22A1 rs628031 A>G) was found more dominan than MATE1 coding genes (SLC47A1 rs2289669 G>A) and both alleles are relatively high in healthy subjects of Indonesia, which can be used as information to evaluate the impact of these two genes' interactions on the Indonesian pharmacokinetic profile, and the efficacy variations of metformin in Type2 DM patients.

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CONFLICT OF INTEREST

Authors declare there is no conflict of interest.

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