



Akreditasi PP IAI-2 SKP

Pharmacogenomics and Personalized Medicine in Type 2 Diabetes

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Surakarta, Indonesia**ABSTRACT**

Type 2 diabetes mellitus (T2DM) has reached epidemic proportions worldwide and poses a considerable concern for public health. Although a variety of pharmacological treatments is available, but response, doses, and tolerability to drugs are highly variable and monotherapy often failed. A large interindividual variability in drug response has been noticed and contributing factors include age, sex, disease, drug and food interactions, comorbidity, as well as genetic factors. Large variability related to hypoglycemic drug therapy response is often encountered in the clinic. Poor therapeutic outcomes may be caused by variability of individual characteristics. Personalized medicine is an emerging concept for treating diseases, which involves determining specific information of a particular patient and then prescribing specific treatment. Pharmacogenetics holds the promise of bringing personalized medicine to drug dosing decisions, to reduce morbidity and mortality, and to improve life quality for T2DM patients.

Keywords: Type 2 diabetes mellitus, pharmacogenetics, oral diabetics drugs, personalized medicine

ABSTRACT

Diabetes melitus tipe 2 telah merupakan epidemi di seluruh dunia dan menjadi perhatian besar di bidang kesehatan. Meskipun berbagai terapi farmakologis telah tersedia, namun respons, dosis, dan tolerabilitas penderita sangat bervariasi dan monoterapi sering gagal. Terdapat variabilitas besar terkait respons terapi antara individu dan beberapa faktor yang berperan, diantaranya usia, jenis kelamin, penyakit, interaksi obat dengan makanan, komorbiditas, serta faktor genetik. Variabilitas besar terkait respons terapi obat hipoglikemik sering dijumpai di klinik. Respons terapi tidak optimal mungkin karena pemilihan terapi tanpa memperhatikan karakteristik individual. *Personalized medicine* merupakan konsep terkini pemberian terapi. Pada konsep ini, pemilihan jenis terapi mempertimbangkan profil genetik maupun karakteristik individual. Farmakogenetik menjadi kunci mewujudkan *personalized medicine*, sehingga diharapkan dapat mengurangi morbiditas dan mortalitas penyakit, serta meningkatkan kualitas hidup penderita diabetes melitus tipe 2. **Ratih Dewi Yudhani. Farmakogenomik dan Personalized Medicine untuk Diabetes Tipe 2.**

Kata kunci: Diabetes melitus tipe 2, farmakogenetik, obat diabetika oral, *personalized medicine*

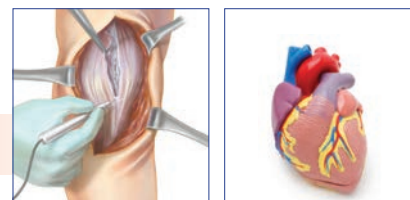
INTRODUCTION

It has been recognized for more than 50 years that genetics differences among people contribute to interindividual differences in the response to many commonly used drugs.⁷ Studies exploring such inherited differences have updated our knowledge, and the focus has been recently shifted from candidate genes (pharmacogenetics) to genome-wide association studies (pharmacogenomics).² Pharmacogenetics is the term used to denote the science about how inherited genetic variants affects the response to drugs, including drug efficacy or adverse

effects.^{4,7} Pharmacogenomics, an approach that has evolved from pharmacogenetics is an apparently new science about how the systematics identification off all human genes, their products, and interindividual variation in expression and function over time may be used to predict the right treatment in individual patient and to design new drug. Pharmacogenomics promises a new drug selection process, which takes into account variation in an individual's genetic makeup to optimize pharmacokinetics and pharmacodynamics to ultimately increase drug efficacy and safety profile. In other words,

creating genetically tailored drug regimens to optimize an individual's response.^{7,9,10}

Diabetes is a multifactorial, heterogenous group of disorders characterized by deficiency or failure in maintaining normal glucose homeostasis.¹ Type 2 diabetes (T2D) is characterized by impaired insulin secretion and decreased insulin sensitivity. T2D accounts for the majority of all diagnosed cases of diabetes in adults, and is typically associated with obesity, sedentary lifestyle, older age, family history of diabetes, and ethnicity.^{2,3} T2D is one of the leading causes



of cardiovascular disease, microvascular complications, and death in the USA and worldwide. Its incidence has been rising steadily over the past few decades, and is predicted to reach epidemic proportions in developing nations.⁴ It is estimated that around 285 million people suffer from type 2 diabetes with projected rise to 438 million in the next 20 years.⁵

Current therapies for diabetes include lifestyle modification and pharmacotherapy with oral antidiabetic drug (OAD) or injected hypoglycemic agents. The goal of all treatment strategies is to maintain near-normal glycemic levels which have shown to decrease the risk of complications.^{1,5} Despite rapid progress in drug development, it is still challenging to achieve good glycemic control in a substantial population even with multiple anti-diabetic treatments.² Type 2 diabetes is a heterogeneous disease with variable clinical features, genetic risk factors, and underlying pathogenic mechanisms. It is also well recognized that great interindividual variability exists in clinical outcomes of hypoglycemic agents. Not every diabetes patient with same age, duration of disease, body mass index, and HbA1c will respond in the same way to a given treatment, and some may have adverse reactions.^{1,6} Variable response of different individuals to pharmacotherapy may be due to many factors, such as age, gender, liver and/or kidney function and co-medications. It could also be partially attributable to polymorphisms (variants that are found in more than 1 percent of the population) in genes encoding drug-metabolizing enzymes, transporters, receptors, and molecules involved in signal transduction. These variants may contribute to the variability in pharmacokinetics (drug absorption, distribution, metabolism, and excretion) and pharmacodynamics (drug target, mechanism of drug action, and drug response) of a specific drug, and thus lead to various efficacy and toxic effects.^{2,7}

These factors may cause poor therapeutic outcomes in certain patients. Since long-term, hyperglycemia is an important contributor of micro- and macrovascular complications, optimization of treatment strategies according to individual features, called personalized medicine, is imperative.^{2,8}

Personalized medicine for diabetes is the use of genetic makeup information to tailor strategies for preventing, detecting, or monitoring diabetes. It represents an approach for defining disease subtypes and defining biomarkers that can identify patients who are most likely to respond, not respond, or at high risk to adverse effects from a specific treatment.^{1,6} Personalized medicine allows personalized drug prescribing with less trial-and-error and less wasted-time.⁶

Pharmacogenetics/pharmacogenomics approaches are considered to be important in the personalized management of glycemia, by providing specific information for drug selection, dose titration, treatment duration, and avoidance of adverse drug reactions for a genetically defined patient subset; they may also shed light on the mechanism of drug action and provide potential therapeutic targets.² It is estimated that about 95% of the variability in drug response is due to genetic differences, accounting for these differences then would be highly beneficial, not only for the health care, but for patient to lessen treatment failures and adverse events.⁹

This review focuses on the examples of pharmacogenomics data related to the type 2 diabetes therapy, particularly the association of sulphonylurea (SU) and biguanides (metformin) treatment outcomes with polymorphisms of drug metabolizing enzymes, drug transporter, and drug target that might lead to the promotion of personalized therapy of type 2 diabetes.

DISCUSSION

A. Pharmacogenomics and Type 2 Diabetes Treatment

1. Sulphonylureas

Sulphonylureas (SUs) are one of the most widely-used oral hypoglycemic agents. The common SUs agent are glicazide, glibenclamide, and glimepiride. Most patients respond well to these drugs, but the efficacy is highly variable; 10-20% patients experience a primary failure which is characterized by a reduction in insulin secretion within the first three months of initiation. These patients do not achieve adequate glycemic control even with the highest recommended dose. In addition, 5-10% patients with T2D who initially respond to SU treatment will subsequently

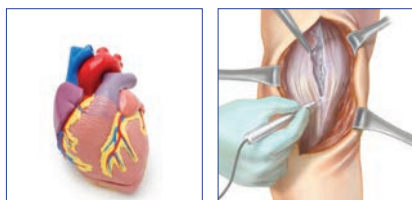
lose the ability to maintain near-normal glycemic levels, called secondary SU failure.^{1,9}

Failure to respond, or deterioration of response to sulphonylurea therapy is known to result from a variety of factors, including poor dietary and/or physical activity compliance, weight gain, reduction of insulin sensitivity, age of onset, or presence of anti-islet cell and glutamic acid decarboxylase antibodies, but the strongest predictor of failure is deterioration of β -cell function. Patients with KCNJ11 and ABCC8 mutations have shown good response with SU compared to metformin.¹ Polymorphisms in TCF7L2 and CYP2C9 gene have also influence the response of SU therapy.⁵ The summary of gene polymorphisms involved in the pharmacogenetics of sulphonylureas can be seen in table 1.

1.1 Role of KCNJ11 and ABCC8 Polymorphisms in Sulphonylurea Response

Sulphonylurea exert their pharmacological actions through specifically binding the regulatory SU receptor (SUR1) subunit of the K_{ATP} channel to induce transformation to the closed state, thereby promoting insulin secretion and reduction in blood glucose. K_{ATP} channels of pancreatic β -cells are composed of a Kir6.2 pore and SUR subunits, which regulate the status of the Kir6.2 pore based on ATP levels and is the target for the SU drug class. Closure leads to membrane depolarization and opening of intracellular voltage-gated Ca^{2+} channels that results in an increase in intracellular $[Ca^{2+}]$, which stimulates insulin vesicle exocytosis and insulin release to reduce blood glucose.^{11,12}

Several studies demonstrate genetic variations among genes that encode for the Kir6.2 pore (KCNJ11 gene), and SUR1 subunits (ABCC8 gene) of pancreatic K_{ATP} channels can alter response to SU therapy, but they were mainly observed in the neonatal diabetic population because that is where these polymorphisms are predominately found. These forms of diabetes can be attributed to genetic variations in the K_{ATP} channel, which results in a decrease in ATP-sensitivity and/or a pore fixed in the open conformation. In general, KCNJ11 and ABCC8 gene polymorphisms alter the K_{ATP} channels sensitivity to ATP or favor an open state leading to a reduction in insulin secretion and



subsequent hyperglycemia.¹² Kir6.2 (KCNJ11 gene) mutation cause dominant neonatal diabetes (ND) by reducing the ability of ATP to block K_{ATP} channel, hyperpolarizing the β -cell, and preventing insulin secretion. Thus, the mutated K_{ATP} channel does not close in response to increased ATP concentrations, however, it could be closed when SU bind to SUR1 by an ATP-independent route. The discovery of the causal role of K_{ATP} channel has enabled ND patient to switch from insulin to SU therapy that significantly improved glycemic control and reduced the risk of diabetic complications.¹²

A common Glu23Lys polymorphism, also known as E23K in KCNJ11 gene, encoding Kir6.2 is associated with T2D development and a recent study found that the carriers of K-allele in the KCNJ11 gene had better therapeutic response to glicazide.^{5,14} Importantly, recent evidence demonstrated that patient with KCNJ11 mutation could be treated more efficiently with SU than with insulin.⁵

The ABCC8 gene encodes the SUR1 subunit which regulated K_{ATP} channel activity. Heterozygous activating mutations in the ABCC8 gene have been characterized as a cause of permanent and transient ND that may present as T2D. Interestingly, a common Ser1369Ala SNP of ABCC8 influenced antidiabetic efficacy of SU in Chinese, but not in German.^{13,15} In addition, this same Ser1369Ala variant of ABCC8 appeared not to be associated with the risk for severe SU-induced hypoglycemia in German and Japanese T2D.^{15,16} Additional polymorphisms of ABCC8 gene, including SNP in exon 16 (-3C/T) and exon 31 (Arg1273Arg) have been also reported to be associated with SU efficacy in European Caucasians.¹⁷

1.2 Role of TCF7L2 Polymorphisms in Sulphonylurea Response

The most promising gene variants affecting the SU response are those involved in drug pharmacodynamics, such as the transcription factor 7-like 2 (TCF7L2). This gene encodes a transcription factor (Tcf-4), that involved in the regulation of cellular proliferation and differentiation.^{5,18} TCF7L2 gene has the strongest association with T2D reported to date. Interestingly, individuals with T2D-associated homozygous TT genotype were less likely to response to SU therapy.^{19,20}

Table 1. Summary of the gene polymorphisms involved in the pharmacogenetics of sulphonylurea⁵

SNP	Study Population	Associated Response Phenotype	Reference
KCNJ11			
▪ Glu23Lys (rs5219)	T2D patients (N=101) treated with glicazide for 6 months	K-allele carriers had significantly higher decrease in HbA1c compared with EE homozygotes	Javorsky, <i>et al</i> , 2012 (14)
▪ 3p+215G>A (rs5210)	Patients with T2D (1.268), 8 weeks of glicazide therapy	Significantly associated with decrease in FPG (Fasting Plasma Glucose)	Feng, <i>et al</i> , 2008 (13)
ABCC8			
▪ Ser1369Ala (rs757110)	Patients with T2D (1.268), 8 weeks of glicazide therapy	Significantly associated with decrease in FPG (Fasting Plasma Glucose)	Feng, <i>et al</i> , 2008 (13)
▪ Exon 16-3C>T (rs1799854)	Patients with T2D (N=228) on SU therapy	Carriers of wild-type CC genotype had significantly lower HbA1c levels compared to patients with TT genotype	Nicolac, <i>et al</i> , 2008 (17)
▪ rg1273Arg (rs1799859)	Patients with T2D (N=228) on SU therapy	Patients with wild-type GG genotype had significantly higher HbA1c levels compared to patients with AA genotype	Nicolac, <i>et al</i> , 2008 (17)
TCF7L2			
▪ rs7903146 C>T	T2D patients (N=87), 6 months with SU therapy in addition to metformin	Significantly higher reduction in HbA1c and FPG in patients with CC genotype compared to the CT and TT genotype	Schröner, <i>et al</i> , 2011 (19)
▪ rs12255372 G>C	T2D patients (N=189), 6 month SU treatment	T allele was significantly more frequent in patients who failed to respond to SU than in the control subjects	Holstein, <i>et al</i> , 2011 (20)
CYP2C9			
▪ *3(Ile359Leu) (rs1057910)	A population-based cohort Rotterdam Study (N=7.983)	Carriers of *3 allele required lower doses of tolbutamide to regulate glucose levels as compared to *1/*1 genotype	Becker, <i>et al</i> , 2008 (21)
▪ *2 (Arg144Cys) (rs1799853)	Population-based GoDARTS study: T2D patients, incident users of SU (N=1.073)	More likely to achieve a treatment HbA1c < 7% (53mmol/mol) than patients with wild-type genotype	Zhou, <i>et al</i> , 2010 (22)
▪ *3 (Ile359Leu) (rs1057910)			

1.3 Role of CYP2C9 Polymorphisms in Sulphonylurea Response

Sulphonylureas (SU's) are mainly metabolized by the enzyme cytochrome P450 (CYP) isoform CYP2C9. A recent population-based Rotterdam study showed that polymorphisms in CYP2C9 gene affected the patient sensitivity to SU.²¹ Recent data from the Go-DART study (Genetics of Diabetes Audit and Research Tayside Scotland) in 1.073 SU treated patients (80% received glicazide) indicated that patients with two copies of the CYP2C9*2 or CYP2C9*3 loss-of-function alleles were 3,4 times more likely to achieve a treatment target of HbA1c level (level of HbA1c < 7%) as compared with wild type carriers resulting in a 0,5% greater reduction in HbA1c.²² CYP2C9*2 and CYP2C9*3 were associated with impaired metabolism and reduced oral clearance of SU. Patients carrying these alleles required lower doses of SU and were more likely to achieve glycemic goals including HbA1c, but were at a higher risk of mild or severe hypoglycemia.²

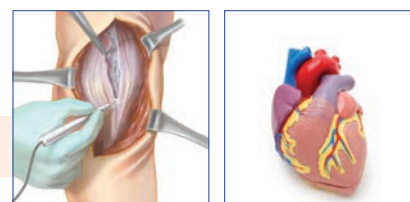
Metformin

The biguanide drug metformin is recommended as the first-line therapy for T2D. Although the full pharmacological action

profile remain unclear, at this point, evidence suggests that the major action of metformin is exerted in the liver, primarily from the activation of adenosine monophosphate-activated protein kinase (AMPK). Activation (phosphorylation) of AMPK is done by serine-threonine kinase 11 (STK11/LKB1), which suppresses hepatic gluconeogenesis, thereby, reducing glucagon-mediated glucose output by the liver.⁹ However, a recent study showed that metformin could also inhibit gluconeogenesis in AMPK-independent way.²³

Metformin is able to exert glucose-lowering actions with a low risk of hypoglycemia, as well as reduced the likelihood of developing macrovascular and microvascular complications, these qualities are what make it an attractive first-line therapy. Despite an exceptional efficacy and safety profile, several T2Ds (about 38%) still fail to reach glycemic goals in metformin therapy.⁹

Metformin is not metabolized but is excreted unchanged in urine by active tubular secretion. There is large variation in metformin renal clearance, and genetic

**Table 2.** Possible role and effect of variation on metformin therapy.⁹

Protein transporter	Coded by	Site	Action	Variants Action
OCT1	SLC22A1 gene	- Hepatocytes - Enterocytes	Mediates metformin uptake, accumulation and pharmacological action in the liver (AMPK activation)	- Decreased hepatic and intestinal metformin uptake and accumulation - Decreased AMPK activation - Increased plasma glucose levels - Lower insulin levels
OCT2	SLC22A2 gene	Renal distal tubule	Facilitate urinary elimination of metformin	- Decreased metformin clearance - Increased plasma concentration
MATE1	SLC47A1 gene	- Bile canalicular membrane of hepatocytes - Renal epithelium	Metformin secretion in bile and urine	May effect glucose lowering effect of metformin
MATE2-K	SLC47A2 gene	Renal epithelium	Metformin excretion in urine	

factors contribute in more than 90%. Its oral absorption, hepatic uptake, and renal elimination are mediated by carrier proteins. The intestinal absorption of metformin is probably mediated by plasma membrane monoamine transporter (PMAT, encoded by SLC29A4 gene), expressed on the luminal side of enterocytes. Organic cation transporter 1 (OCT1, encoded by SLC22A1 gene), expressed in the basolateral membrane of hepatocytes and enterocytes, mediates hepatic, and intestinal metformin uptake. OCT2 (encoded by SLC22A2), expressed primarily at the basolateral membrane in the kidney tubular cells, facilitates uptake of metformin into proximal tubule cells. The multidrug and toxin extrusion transporter 1 (MATE1, encoded by SLC47A1) and MATE2-K (encoded by SLC47A2), located in the apical membrane of the renal proximal tubule cells, facilitate metformin excretion from tubular cells into urine.^{5,9}

The therapeutic response to metformin is highly variable. In patients receiving metformin as an initial treatment for T2D, less than two-thirds achieve desired glycemic control or the HbA1c goal of < 7% (< 53 mmol/mol). This implies that identification of genetic factors associated with treatment effectiveness could be relevant.⁵ Recent studies suggest that interpatient variability in response to metformin therapy could be related to polymorphisms in the OCT genes and/or MATE genes (table 2).⁹

The majority of pharmacogenetic studies

of metformin response have investigated the effects of polymorphisms in the gene encoding OCT1, SLC22A1 gene. OCT1 is necessary for metformin transport into the liver and subsequent metformin activity. Human SLC22A1 gene is highly polymorphic. Reduced-function polymorphisms of the SLC22A1 gene, such as Arg61Cys, Gly401Ser, 420del, and Gly465Arg have been associated with lower effects of metformin in the oral glucose tolerance test.²⁴ Furthermore, a subsequent study in the same SNPs demonstrated an additive increase in renal clearance of metformin with increasing number of reduced-function alleles.²⁵

Replication of results regarding influence of OCT1 low-activity alleles on metformin pharmacokinetics and response, indicated that those variants could be useful pharmacogenetic markers for metformin therapy.⁵ Overall, the information derived from this study demonstrates that polymorphisms of OCT1 genes may modulate an individual's clinical metformin response in human. However, further studies are needed to replicate this effects in larger populations and in various ethnic groups to determine if the effects can be generalized to the overall population of the reduced function allele carriers.⁹

In the other hand, the results of the studies exploring the effect of the only common coding variant in the gene encoding OCT2 (SLC22A2), Ala270Ser (rs316019),

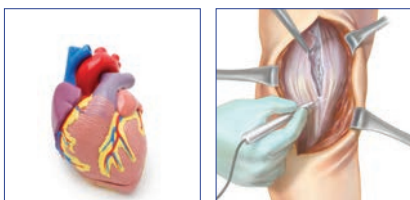
on metformin clearance, have been contradictory. Two studies found significantly reduced renal clearance of metformin in homozygous variant carriers compared to wild-type homozygotes.^{26,27} Interestingly, separate study reported the opposite effect in individuals heterozygous for Ala270Ser variant who had higher metformin renal clearance as compared to the reference group.²⁸ However, given the importance of OCT2 in metformin pharmacokinetics, further pharmacogenetic studies are needed.

A preliminary study in the incident metformin users from the population-based Rotterdam study cohort assessed the influence of variations in MATE1-encoding gene, SLC47A1, on the HbA1c-lowering effect of metformin. From 12 tagging SNPs analyzed, the rs2289669 G>A in intron 10 was associated with greater reduction in HbA1c levels.²⁹ Moreover, a recent study analyzed the effect of the MATE2-K gene (SLC47A2) polymorphism on glycemic response to metformin in newly diagnosed T2D patients (105). A common 5'-UTR variant, g.-130- G>A (rs12943590), was associated with enhanced promoter activity and weaker response to metformin, assessed by the relative HbA1c change.³⁰

B. Benefit of Personalized Medicine for Diabetes

The evidence has been accumulating to show that pharmacogenetics/pharmacogenomics has the potential to improve the management of T2D and the effective OAD (oral antidiabetic drug) prescribing. Several variants related to drug-metabolizing enzymes, drug-transporters, drug target, and diabetes risk genes have been linked to interindividual differences in the OAD treatment outcomes. As summarized here, significant pharmacogenetic evidence has demonstrated an association between specific gene polymorphisms and interindividual variability in OAD therapeutic and side effects. Identification of drug-genotype interaction in pharmacogenetic studies of the OAD treatment might have clinical implications in the near future resulting in selection of more specific personalized therapy in T2D.⁵

In addition, the potential benefit of a personalized medicine approach to diabetes is the possibility of earlier interventions to



prevent or treat the disease by using screening genetic tests. Patients who are at high risk for a chronic disease such as diabetes usually experience a prolonged asymptomatic period before the onset of the disease. Patients who are identified by genetic testing to be at high risk for diabetes can be directed to preventive measures, such as lifestyle modifications or medications, to delay or prevent the disease. Genetic tests and biomarkers can be utilized for predicting diagnosis and for monitoring the course of diabetes.⁶

Personalized medicine allows for personalized drug prescribing with less trial and error, and less time wasted with an inadequate response or with side effects, and will be a great benefit and will become an increasingly important part of the fight against diabetes.⁶ The result would be a better treatment outcome.

CONCLUSIONS

Interindividual differences in the therapeutic efficacy as well as adverse effects of OADs may be significantly affected by genetic determinants. The main aim of pharmacogenomics on type 2 diabetes therapy is to understand the role of individual's genetic makeup in how is the efficacy, as well as side effects of a particular drug. Small genes differences between different population groups, or between families within a population group can mean different reaction to medicine. Understanding this can help tailor future drugs to better suite a particular individual or group (personalized medicine).

Pharmacogenomics has provided a greater understanding of biological mechanisms that cause or contribute to interindividual variability in response of oral antidiabetic

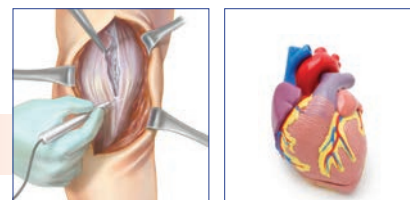
therapy. SNPs in gene encoding the subunits of K_{ATP} channel and hepatic metabolizing enzyme CYP2C9 have been shown to alter individual sensitivity to SU therapy. In addition, OCT1, OCT2, MATE1 and MATE2 SNPs have shown to alter metformin's pharmacokinetics an ability to inhibit glucose output from the liver and may help explain variability in response.

Pharmacogenomics has become a revolutionary approach for defining an individual's clinical response to drug therapy. However, there are still many ethical, social, economic, legislative, and research protocol issues that need to be sorted out before personalized medicine becomes customary in clinical practice. Nevertheless, advances are rapidly closer to clinical practice to be implicated in the management of many complex diseases, including type 2 diabetes.

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CONTINUING PROFESSIONAL DEVELOPMENT



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