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PHARMACODYNAMIC OF METFORMIN IN TYPE 2 DIABETES MELLITUS PATIENTS: REVIEW OF THE PRKAA2 AND SLC22A3 GENES

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ABSTRAK

Diabetes melitus tipe 2 (DM tipe 2) merupakan penyakit yang termasuk gangguan metabolisme yang ditandai dengan peningkatan kadar glukosa diatas normal. Peningkatan glukosa ini disebabkan oleh berkurangnya fungsi insulin yang dapat berupa kelainan sekresi insulin, gangguan kerja insulin pada jaringan perifer, atau kedua-duanya. Metformin merupakan salah satu terapi yang direkomendasikan untuk DM tipe 2. AMPK merupakan jalur utama mekanisme metformin. AMPKα2 yang dikodekan oleh gen PRKAA2 merupakan subunit AMPK yang berperan penting dalam aktivasi AMPK. OCT3 yang dikodekan oleh SLC22A3 berperan dalam mekanisme transpor metformin. OCT3 diperlukan dalam farmakokinetik metformin seperti penyerapan dan eliminasi, proses ini menentukan bioavailabilitas metformin, pembersihan, dan efek farmakologisnya. Mutasi pada PRKAA2 dan SLC22A3 menyebabkan variasi efek farmakodinamik dan farmakokinetik metformin pada individu secara langsung. Perubahan-perubahan ini pada akhirnya akan mempengaruhi efektivitas metformin pada pasien DM tipe 2.

ABSTRACT

Pharmacodynamic of Metformin in Type 2 Diabetes Mellitus Patients: Review of The Prkaa2 And Slc22a3 Genes. Type 2 diabetes mellitus (type 2 DM) is a disease including on metabolic disorder that characterized by an increase in glucose levels above normal. This glucose increase is caused by reduced insulin function which can be in the form of abnormalities in insulin secretion, impaired insulin action in peripheral tissues, or both. Metformin is one of the recommended therapies for type 2 DM. AMPK is the main pathway of metformin's mechanism. AMPKα2 encoded by PRKAA2 gene is an AMPK subunit that plays an important role in AMPK activation. OCT3 encoded by SLC22A3 plays a role in the metformin transport mechanism. OCT3 is needed in the metformin pharmacokinetic like absorption and elimination, this process determines metformin bioavailability, clearance, and its pharmacological effects. Mutations in PRKAA2 and SLC22A3 cause variations in the pharmacodynamic effects and pharmacokinetic of metformin in individuals directly. These changes will ultimately affect the effectiveness of metformin in type 2 DM patients.

INTRODUCTION

Type 2 diabetes mellitus (type 2 DM) is a disease caused by increasing levels of glucose in blood due to decrease insulin function which lead to not only abnormalities of insulin secretion but also impaired insulin action in peripheral tissues. Several long-term complications of diabetes among other retinopathy, nephropathy, and neuropathy. Type 2 DM sufferers are at higher risk of experiencing several infectious or contagious diseases such as TB, which can worsen the clinical condition. The most frequent complications experienced by type 2 DM sufferers are complications in the cardiovascular and cerebrovascular systems.[1,2] The prevalence of diabetes in Indonesia is predicted to increase by around 6.9% over 25 years from 2020 from 18.69 million cases to 40.7 million cases in 2045. The prevalence will decrease to 15.68% (39.6 million) if there is an intensive implementation of a program to reduce hyperglycemia, and decrease to 9.22% (23.2 million) if it is accompanied by a risk factor prevention program. The number of deaths due to complications of type 2 DM such as stroke complications, cardiovascular disorders and chronic kidney disease will also increase from 2020 to 2045.[3]

The pathomechanism of type 2 DM occurs through two main processes, including decreased insulin sensitivity in body tissues and dysfunction of pancreatic β cells. Decreased insulin sensitivity occurs due to disturbances in various cellular pathway responses of muscle, liver and adipose peripheral tissue to insulin. In addition, the function of pancreatic β cells decreases, resulting in insulin secretion deficiency which results in hyperglycemia.[4] Impaired insulin secretion and insulin resistance to some extent contribute to the development of pathophysiological conditions. Impaired insulin secretion is a decrease in glucose response. Disorders of insulin secretion are generally progressive, and their development involves glucose toxicity and lipotoxicity. If untreated, this disease can cause a decrease in pancreatic cell mass.[5]

The development of impaired pancreatic cell function greatly affects long-term blood glucose control.[5,6] Insulin resistance develops and extends before the onset of the disease.[7] Polymorphisms of the insulin receptor and insulin receptor substrate (IRS)-1 which play a role in insulin signaling, or polymorphisms of the adrenergic receptor gene and the release protein gene which influence visceral obesity and insulin resistance also play a role in the incidence of type 2 DM.[6]

In addition to hyperglycemia and hyperlipidemia, the presence of inflammatory mediators can influence the mechanisms of impaired insulin secretion and insulin signaling. Certain processes such as inflammation, reticulum stress, and mitochondrial dysfunction are the main mechanisms currently identified that are associated with the development of insulin resistance.[6,7,8] Estrogen levels in post-menopausal women are inversely related to inflammatory conditions that trigger hyperglycemia. Postmenopausal women tend to have higher lymphocyte and monocyte counts, proinflammatory cytokine expression, and senescent inflammatory cells than premenopausal women.[9]

Clinically, patients are categorized as type 2 DM if there are classic symptoms including polyuria, polydipsia, polyphagia which can be accompanied by unexplained weight loss. Sometimes there are also other complaints such as body weakness, tingling, itching, blurred vision, erectile dysfunction in men or vulvar pruritus in women. Type 2 DM category based on laboratory examination if there is an increase in blood glucose levels through enzymatic glucose examination via venous plasma blood but therapeutic monitoring is carried out through capillary blood glucose examination.[10]

The principle of managing DM patients is how to improve their quality of life by reducing or even eliminating DM complaints so as to reduce the risk of acute complications. The uncontrolled

blood glucose in long term period can be manifested in microangiopathy complication including retinopathy and neuropathy. The macroangiopathy complications are nephropathy diabetic and cardiovascular disease.[11] One pharmacotherapy option that is widely used and still one of the first-line therapy for treating type 2 DM is Metformin. The pharmacodynamic effects of metformin occur through several mechanisms, including changing insulin signaling pathway mediators, acting as an AMP-activated protein kinase (AMPK) activator, epigenetic modifications, and increasing glucose expression and translocation transporter 4 (GLUT4) to the plasma membrane.[12]

METHODS

This narrative review article was prepared by reviewing several articles through a search from the PubMed database, google scholar by entering the keywords diabetes mellitus type 2, metformin, mutation, PRKAA2, SLC22A3. The article only include studies focusing on PRKAA2 and SLC22A3 gene mutation which directly influence the effect of metformin. This reviews only include articles that are available in English during year 2014 to 2024.

DISCUSSION

Pharmacology of Metformin as first-line therapy for Type 2 Diabetes Mellitus

Metformin has several advantages, apart from being proven to be effective in reducing the risk of cardiovascular events and death, this drug is relatively cheap and widely available. Metformin preparations include conventional tablets (immediate release tablets/capsules) which is given twice a day or in extended release form which can be given once daily. From existing research, for use as first-line treatment, metformin can reduce HbA1c levels better than sulfonylureas, with minimal side effects, does not cause hypoglycemia and weight gain.[13] Metformin enters hepatocytes, so that increase glycogen synthesis and decrease gluconeogenesis.[13] This drug also act on the intestine to increase glucose and GLP-1 utilization, as well as alter the microbiome.[14] Metformin is excreted unchanged in the urine. Its concentrations in humans are usually in the low micromolar range. Metformin elimination through renal filtration by active tubular secretion.[14]

The dose of metformin is 500 mg twice a day, a maximum of 2,550 mg/day or around 35 mg/kg/day. After oral administration, the immediate-release dosage form of metformin is rapidly absorbed from the small intestine. The absolute oral bioavailability of this drug reaches 40-60%, gastrointestinal absorption occurs within 6 hours. Metformin's distribution is fast, and it is not bound to plasma proteins. The concentration of metformin in the liver is 3-5 times higher than in the portal vein. The half-life is around 5 hours with an average renal clearance (CLr) of 510 ± 120 ml/minute. Several drugs interact significantly with metformin.[15]

Metformin concentrations were high in the intestine, liver, kidney and bladder after oral administration but the opposite was true in muscle. There are other mechanisms associated with potential cardiovascular benefits, as well as cancer prevention and aging.[14] Side effects that often occur due to administration of metformin are gastrointestinal intolerance and lactic acidosis if levels are very high in plasma. This can be minimized by gradually dose titration and/or use of extended-release formulations. Metformin is considered safe for use in people with an estimated glomerular filtration rate ≥30 mL/min/1.73 m2.[13]

At the molecular level, metformin inhibits the mitochondrial respiratory chain in the liver, activating AMPK directly and indirectly, ultimately increasing insulin sensitivity (through effects on

fat metabolism) and decreasing cAMP. This will reduce the expression of gluconeogenic enzymes. Type 2 DM patients treated with metformin showed a significant reduction in the expression of interleukin 6 (IL-6), TNF-a, and IL-1b.[16] In vitro studies showed that metformin reduces replicative senescence and cell death. Metformin can also delay and reduce functional disorders of mesenchymal stromal cells.[17]

AMPK Activation and Signaling

The pharmacodynamic effects of metformin are determined by the genes encoding AMPK and organic cation transport for metformin absorption. The two genes are PRKAA2 for AMPK and the gene for OCT3. AMP-activated protein kinase (AMPK) is the main regulator of cellular energy homeostasis which is able to maintain cardiac function by preventing cardiac hypertrophy and heart failure. Apart from that, AMPK can also influence the autophagy. thus inhibition of AMPK can lead to reduced autophagy. Phosphorylation of PRKAA/AMPKα (AMP alpha-activated protein kinase catalytic subunit) in the Thr172 segment is important in autophagy process.[18]

AMPK has three types of subunits: a, b, and g which are expressed differently and specifically in each tissue. The formation of each subunit is coded by different genes. AMPKa and b by two genes, and the g subunit by three genes.[19] Glucose metabolism affects the expression of the gene encoding AMPK acutely or chronically. Activation of AMPK increases expression and cell surface translocation of the glucose transporter GLUT4 via the TF MEF2. in addition, glycolysis increases along with increased expression of glucose transporters and cell surface translocation.[20]

Most AMPK activators activate AMPK indirectly through the following 3 categories.[21,22] First, inhibit ATP synthase thereby increasing the intracellular CAMP:ATP and ADP:ATP ratio. These include biguanides, metformin and its more potent analogue phenformin activate AMPK through inhibition of Complex I in the respiratory chain. Several plants such as resveratrol, berberine, galegine can activate AMPK by first inhibiting various components of the respiratory chain. Therefore, these compounds cause cellular accumulation of AMP, which binds to the g subunit and activates AMPK. AMP levels can also increase through ATP dependent glycolysis which is inhibited by the glycolytic inhibitor 2-deoxyglucose, a glycolysis inhibitor.[21,22]

The second group of AMPK activators is known as AMP mimetics. This group is a pro-drug, which undergoes metabolism to become an AMP analogue. An example of this group is 5-aminoimidazole-4-carboxamide-1-β ribofuranoside (AICAR). AICAR will be recruited by adenosine transporters into cells and then converted to ZMP, which mimics the effect of AMP on AMPK. Another AMPK activator is the compound 5-(5-hydroxyl-isoxazol-3-yl)-furan-2-phosphonic acid 2 (C2) which is given as a pro-drug C13. C2 is more potent, but can only activate AMPK complexes containing AMPKα1.[21]

The third group, for example Salicylate, a breakdown product of aspirin, is a molecule that directly binds and activates AMPK through phosphorylation of the AMPKβ1 CBM domain at the Ser108 segment.[21,22]

The Role of AMPK in Disease

Impaired AMPK function can result in genetic disturbances in the processes of autophagy, glucose and lipid metabolism, and mitochondrial biogenesis which can contribute to the development of pathological conditions.[23]

Inhibition of apoptosis is considered promising in the treatment of inflammatory bowel disease. In NAFLD, upregulation of AMPK may prevents apoptosis through downregulation of

caspase-6. Activation of AMPK signaling prevents the formation of inflammatory factors that play a role in reducing inflammation. AMPK overexpression prevents lipogenesis and p38 phosphorylation thereby leading to prevention of hepatic inflammation in liver diseases.[22] The function of AMPK in cancer is not yet known with certainty, eventhough studies have shown a role for AMPK overexpression in cervical lesions and lymph node metastases. AMPK signaling influences the process through NF-κB mediators, increasing AMPK regulation is able to prevent glucose uptake and induce cessation of the growth cycle of breast tumor cells.[23]

AMPK is a target for the treatment of various non-infectious chronic diseases such as obesity, inflammation, diabetes, and especially cancer because of AMPK's ability to maintain cell and organ homeostasis. AMPK activators, whether they activate AMPK directly or indirectly, are able to form components that resemble AMP or even activate AMPK at the ADaM site so that the complexity of the regulatory model for the combination of different AMPK subunit isoforms in each tissue still poses a challenge.[24]

Hyperglycemia due to insulin resistance causes impaired mitochondrial function which can reduce p-AMPK and Akt levels (AMPK/Akt axis). Mitochondrial dysfunction that occurs before AMPK downregulation plays a role in the emergence of diabetic neuropathy.[23]

AMPK subunits are expressed in substrate and tissue specific ways. The prognosis of liver hepatocellular carcinoma (LIHC) is also determined by the expression of PRKAA2 in LIHC tissue, PRKAA2 overexpression significantly increases LIHC immune escape.[25] This compound also inhibits ribosomal 6 kinase (RSK) family proteins. BAY-3827 showed good anti-proliferative effects against androgen-dependent prostate cancer cells by blocking HMGCR, fatty acid synthase (FASN) and PFKFB2. AMPK is an important molecular target for chemoprevention and chemosensitization for cancer therapy.[26] Activation of AMPK reduces increased neural network activity in neurons of all patients with BD and sodium currents in LNR neurons.[27]

Role of Organic Cation Transporter 3

Organic Cation Transporter 3 (OCT3) is expressed in many organs, including the small intestine, liver, kidney, brain, heart, adipose tissue, skeletal muscle, lymphocytes, and monocytes.[28] Metformin is an organic cation transporter (OCT) substrate in the SLC22A family. The OCT group plays a role in cellular absorption and transport of metformin in various organs. Metformin is a substrate of OCT3.[29] OCT3 helps the entry of organic cations from the lumen into enterocytes and/or hepatocytes, so can influences metformin uptake in hepatocytes.[29]

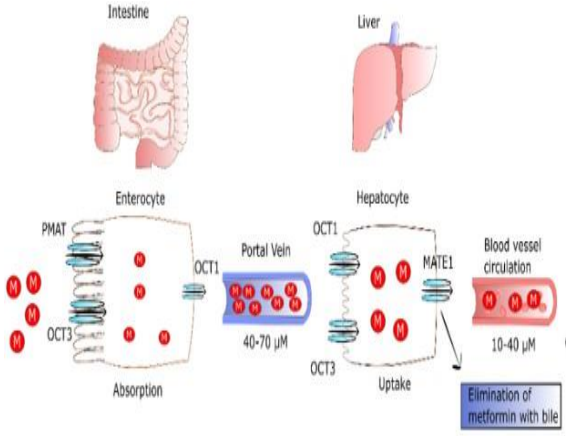

Figure 1 : localization of OCT3 and how the its role in the transport molecule in intestine and liver (Source : Szymczak-Pajor, 2022)

In the body, OCT3 plays a role in facilitating the distribution and expression of metformin in the fetus during pregnancy. gestational age characteristics, genetic polymorphisms, or differences in pharmacological inhibitors also modulate the expression or activity of OCT3 in the placenta so that it can change the expression and response of the fetus to metformin.[30] Both OCT3 and PMAT appear to be important for the development of sensitization to the locomotor stimulant effects of amphetamine in women, and PMAT in men.[31]

AMPK Coding Gene Mutations

Several mutations have been found in the gene that encodes AMPK. Point mutations in PRKAG2 cause differences in the glycogen storage process and the pathomechanism of cardiac hypertrophy. 32 Several mechanisms mediated by this point mutation are: (1) increased insulin sensitivity through activation of Akt which stimulates cardiomyocyte proliferation; (2) downregulation of FoxO signaling and (3) activation of mTOR in the heart which triggers cardiac hypertrophy. This elucidates an important mechanism underlying PRKAG2 cardiomyopathy, and furthermore, reveals a new function of γ2-AMPK that is critical for the use of AMPK as a therapeutic target.[32]

The implications of excessive glycogen reserves due to PRKAG2 mutations can affect cardiac cell growth, manifesting as a tetrad of cardiac syndrome consisting of familial ventricular preexcitation, conduction system disease, and HCM cardiac hypertrophy, as well as atrial tachyarrhythmia. Research conducted on 885 subjects with HCM found that 12 subjects had PRKAG2 mutations (1.4%).[33] Nearly half (47%) of PRKAA2 gene mutations are found in skin cancer and melanoma. Missense mutations in the PRKAA2 gene expressed in HEK-293 cells cause partial or complete loss of AMPK activity.[31] AMPK-α2 mutations become specific isoforms in skin cancer and melanoma.[34]

The PRKAA2 gene encoding the α2 subunit of AMPK is mutated in ∼9% of skin melanomas, and these mutations tend to co-occur with NF1 mutations. AMPKα2 knockout promotes tumor growth and metastasis of NF1-mutated melanoma due to growth of NF1-mutant melanoma cells. Additionally, loss of AMPKα2 accelerates the growth of NF1 mutant melanoma tumors and increases brain metastasis in immunodeficient mice. PRKAA2 mutations occur simultaneously with NF1 mutations in melanoma. Of the two catalytic subunits of AMPK, only α2 is frequently mutated and lost in melanoma.[35]

SLC22A3 Gene Mutation

SLC22A3 is a gene that is associated with various chronic diseases including cancer, cardiovascular disease and metabolic disease. Carriers who have the SLC22A3 genes rs555754 and rs3123636 are susceptible to type 2 DM. Two variants, namely rs2292334 and rs3088442, are related to the effectiveness of metformin in different populations.[36] Loss of OCT function induces TGF 1 expression. Mutations in Oct3 will trigger fibrogenesis resulting in fibrosis through a TGF1-mediated homeostasis mechanism.[36]

Mutations in the SLC22A gene that codes for OCT can cause loss of OCT function as a transporter resulting in an increase in TGF1 which determines the development of fibrosis and increases fibrogenesis.[37] OCT3 directly and together with environmental factors and carcinogens also influences the mechanism of tumor development. In HepG2 cells, SLC22A3 mutation affects OCT3 expression and may lead to increased proliferation or hepatocarcinogenesis. These mutations

often occur after exposure to polycyclic aromatic hydrocarbons (PAH), which are known carcinogens.[38]

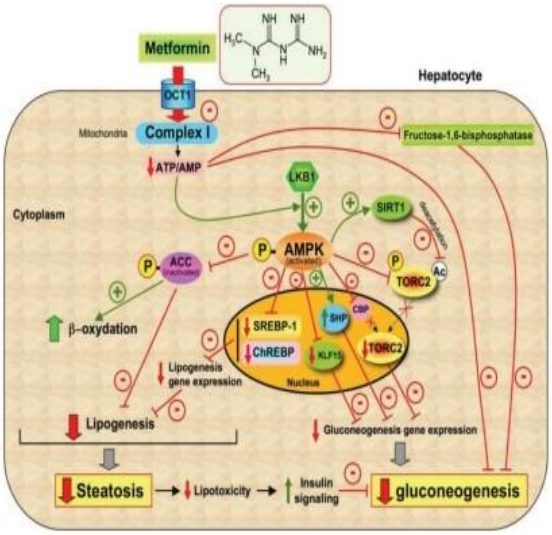

Figure 2 : Role of OCT, AMPK in metformin action in hepatocyte (Source : Szymczak-Pajor, 2022)

Correlation between PRKAA2 gene mutations and metformin pharmacodynamics

Cross-sectional study by Virginia et al to analyze the relationship of rs857148 A>C as a 3'UTR variant to several cardiometabolic parameters including blood pressure, HbA1c levels and lipid levels in type 2 DM patients receiving metformin. HbA1c levels tended to increase in the group of subjects with the CC genotype and C allele. Meanwhile, a decrease in HbA1c levels was more common in subjects with the AA genotype compared to the AC+CC genotype. compared with the AA genotype, the AC genotype was significantly associated with total cholesterol levels. The rs87148 polymorphism, CC genotype and C allele, were significantly associated with HbA1c and total cholesterol compared with AA genotype.[39]

Virginia et al found that there was no significant difference between the genotype and allele frequency of the PRKAA2 gene variation and the efficacy of metformin.[40] Only the AG PRKAA2 rs2796498 genotype was closely associated with metformin response in T2DM patients who received metformin as monotherapy, after adjusting for BMI, WC, pressure blood, eGFR, and lipid profile. The effect of PRKAA2 gene variations rs9803799 and rs2746342 on the efficacy of metformin has not been fully proven in the Indonesian population.[40]

A case-control study involving 107 participants to evaluate the correlation prediction between PRKAA2 genetic variations and 10-year ASCVD risk among newly diagnosed T2DM patients on metformin monotherapy showed that in a total of 91 participants, there was a significant difference in age ($p < 0.01$), HbA1c levels, gender, and smoking status between low risk and high risk groups. The GT rs9803799 genotype had higher risk to develop a 10-year high risk of ASCVD than the TT genotype. The rs9803799 dominant model also showed that GT+GG had higher risk to experience 10-year ASCVD risk compared to TT genotype. But other results showed that the G allele of rs980377 has lower risk to experience a 10-year high risk of ASCVD than the T allele.[41]

Systematic review and meta-analysis to analyze the association between PRKAA2 variations and the succeptibility to T2DM. This meta-analysis uses five different genotype models to estimate the effect of PRKAA2 variations and T2DM risk, including (1) Allele contrast model (G versus T allele); (2) Additive model (GG versus TT); (3) Additive model (GG versus TG); (4) Dominant model (TG + GG versus TT) and (5) Recessive model (GG versus TT + TG).[42] However, only two SNPs, rs10789038 and

rs2746342, are susceptible to developing type 2 DM. Patients with the G allele have a greater risk of suffering from type 2 DM than patients with the T allele.[42] Patients with the GG genotype are also more susceptible to experience type 2 DM than patients with the TT genotype. Subjects with PRKAA2 variations at rs2746342 in the G allele model, additive, dominant, and recessive, are more at risk of developing type 2 DM. The G allele is the factor that plays the most role in susceptibility to type 2 DM.[42]

Correlation between SLC22A3 Gene Mutations and Metformin Pharmacodynamics

Mutations in SLC22A3 gene encoded OCT3 can cause changes in the pharmacokinetics of metformin, namely in the transport and uptake processes of metformin, thereby affecting the effectiveness of metformin in type 2 DM patients. The major organic cation transporter transporter group consisting of OCT1, OCT2, and OCT3 is involved in the transfer of amino compounds. OCT is encoded by the transporter family gene SLC22A.[39] Response to antidiabetic drugs is likely influenced primarily by genetic variants in the OCT2 (SLC22A) gene. OCT3, as a master transporter, also contributes to the overall regulation of neurotransmission and maintenance of homeostasis in the central nervous system. The OCT3 rs2292334 gene polymorphism is one of the genetic risk factors for the development of T2DM among male subjects of Malaysian Indian ethnicity.[43] Chen et al found that the volume of distribution, clearance and bioavailability of metformin decreased up to 2 times normal in experimental animals with the SLC22A3 mutation.[44]

The OCT3-1233G>A (rs2292334) has an association with response to metformin. The HbA1c and BMI parameters in the responder group with GA + AA genotype and GG genotype are significantly lower compared to the non-responder group after 3 months of metformin therapy. The mean decrease in HbA1c levels after 3 months was higher in patients with HbA1c allele A compared with homozygous G allele. The GA + AA genotype has greater average decrease compared to the GG genotype, in HbA1c values from baseline (0.34% in respondents and 0.14% in non-respondents).[45]

Ghaffari-Cherati et al found the frequency of the SLC22A3 genotype found in the Iranian population is greater in GG genotype compared to other genotype (51.3% GG, 36% AG, and 12.7% AA). The frequencies of the major allele (G) also greater than minor allele (A) in the OCT3-564G>A variant (0.69 vs 0.31), respectively. The GG genotype and GA + AA groups have lower fasting glucose, HbA1c level, body mass index, and lipid profiles after 3 months of metformin therapy. But HbA1c and fasting glucose levels were lower in patients with the GA + AA genotype compared to patients with the GG genotype variants in both responders and nonresponders, but the differences were not statistically significant.[46]

A study evaluating the correlation among twenty-one single nucleotide polymorphisms (SNPs) in the SLC22A1, SLC22A2, and SLC22A3 genes and their influence on metformin pharmacogenetics in Jordanian patients diagnosed with type 2 diabetes mellitus. The average HbA1c level was lower in the SLC22A3 rs12194182 gene variant, especially in the CC genotype. Genotype variants in the SLC22A1, SLC22A2, and SLC22A3 genes, body mass index (BMI), and age at diagnosis were significantly associated with glycemic control.[47]

The field of pharmacogenomics shows good prospects for improving patient care by optimizing drug choice and dosage, reducing the risk of side effects, and implementing personalized medicine. Although the field of pharmacogenomics is still hampered by several factors, the mastery of pharmacogenomics in cases of chronic diseases such as type 2 DM is still only starting to develop with the large number of studies related to genomics. Genetic and transcriptome profiles of drug-

naïve T2DM patients receiving metformin can be used to identify drug-genetic variations and interactions in non-responsive and responsive patients so that patient management can be tailored.

FUTURE DIRECTION

The large variety functions of AMPK encoded by PRKAA2 gene on pharmacodynamics and OCT3 encoded by SLC22A3 gene on pharmacokinetics, toxicity of antidiabetic still need more investigation as well as the interaction of many drugs with OCT3 substrate or AMPK activator. The single nucleotide variations in PRKAA2 genes and SLC22A3 have been identified, but how these mutations affect the chronic disease in different ethnic, different population with multiple co-morbidities and or advance age still remain unclear and challenging.

CONCLUSION

PRKAA2 gene mutations are directly related to metformin pharmacodynamics through effects on AMPK, while SLC22A3 gene mutations affect metformin pharmacokinetics which in turn will affect the effectiveness of metformin in type 2 DM patients. Further research with diverse subject populations is needed to confirm the relationship of PRKAA2 genetic variations and SLC22A3 with clinical outcomes in type 2 DM patients. PRKAA2 and SLC22A3 gene mutations may contribute to individual variability in response to metformin. Knowledge of the effect of PRKAA2 and SLC22A3 genetic mutations on metformin pharmacodynamics can provide information on a genetic profile-oriented type 2 DM treatment database for the application of personalized medicine.

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Conflict of Interest
The authors declare no competing interest

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