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Pharmacogenetics of Oral Antidiabetic Drugs: Potential Clinical Application

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Abstract

Oral antidiabetic drugs (OADs) are widely used to treat type 2 diabetes mellitus (T2DM). However, inherited difference is one of the major issues that affect OADs therapeutic efficacy. In the present paper, we performed a critical review on recent advances in genetic polymorphisms that influence OADs therapeutic efficacy and metabolism. Sulfonylureas (SUs), Meglitinides, Metformin and Thiazolidinediones (TZDs) will be discussed.

Keywords: Diabetes; Oral Antidiabetic Drugs (OADs); Sulfonylureas (SUs); Meglitinides; Metformin; Thiazolidinediones; Polymorphism

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most serious public health problems worldwide [1]. It is characterized by two major pathophysiological features: insulin resistance and pancreatic β-cell dysfunction [2]. Oral antidiabetic drugs (OADs) are widely used to treat T2DM. However, inherited difference is one of the major issues that affect OADs therapeutic efficacy. Present OADs can be classified into at least five groups: Sulfonylureas (SUs), Meglitinides, Metformin, Thiazolidinediones (TZDs) and α-glucosidase inhibitors. Polymorphisms in drug-metabolizing enzymes, transporters, receptors and other drug targets have been proved to be correlated with efficacy and toxicity of many medications [3,4]. Thus, genetic polymorphism involved in drug absorption, distribution, metabolism and excretion (ADME) play important role in OADs treatment [5]. In the present paper, we performed a critical review on recent advances in genetic polymorphisms that influence OADs therapeutic efficacy (Table 1).

Sulfonylureas (SUs)

SUs are the first developed OAD. They close ATP-sensitive potassium channels (KATP) by targeting pancreatic β-cell membrane, which lead to an enhanced insulin secretion in a glucose independent manner. Genetic polymorphisms are critical important for the individual different sensitivity to SUs. Cytochrome P450 (CYP) 2C9 is the main enzyme that catalyzes biotransformation of Sulfonylureas, thus its polymorphisms affect SUs therapeutic efficiency [6]. In addition, polymorphisms of potassium inwardly-rectifying channel, subfamily J, member 11 (KCNJ11) and transcription factor 7-like 2 (TCF7L2) also affect SUs medication [7], thus these genetic polymorphisms will be discussed in this section.

Polymorphisms of CYP2C9: Genotyping of CYP2C9 allelic variants is a relatively easy and inexpensive test, thus its polymorphisms were widely studied [8]. In a study of 20 T2DM patients with severe hypoglycemia during sulfonylurea treatment, the *3/*3 and *2/*3 genotype carriers were significantly higher than those in control subjects and T2DM patients without hypoglycemia [8]. However, another prospective study conducted by the same group showed that CYP2C9 slow metabolizer genotypes were not correlated with hypoglycemia [9]. This study included 102 T2DM patients with sulfonylurea-induced hypoglycemia and 101 control patients. There were no significant difference of CYP2C9 *2/*2, *2/*3 and *3/*3 genotype frequencies between case and control populations. Thus, the conclusion of correlation of CYP2C9 polymorphisms and sulfonylurea treatment efficacy needs further confirmation.

Polymorphisms of KCNJ11: KCNJ11 encodes Kir6.2, which is a subunit of KATP channel. KCNJ11 polymorphisms and sulfonylurea response in T2DM patients was widely studied. The most intensively investigated polymorphism is Glu23Lys (E23K) [10-12]. It was hypothesized that K23 allele may be associated with interindividual variability of sulfonylurea response. This hypothesis was tested in a group of newly diagnosed diabetes patients treated with Sulfonylureas [10]. However, in this study, the KCNJ11 E23K variant was not significantly associated with patients' response to sulfonylurea. In another study, Sesti et al. [13] showed that E23K variant was associated with an increased risk of secondary sulfonylurea failure in T2DM patients. Thus, the correlation between KCNJ11 E23K variant and sulfonylurea response in T2DM patients need more investigations.

Polymorphisms of TCF7L2: Among T2DM associated genes, TCF7L2 were widely studied. It correlated with an increased risk of T2DM in several populations [14]. It was reported that TCF7L2 polymorphisms influence the initial success treatment of sulfonylurea in T2DM patients. The most intensively studied polymorphisms are rs12255372 and rs7903146, which were associated with diabetes risk. In a study of large sample size T2DM patients, risk allele carriers of rs12255372 and rs7903146 were more sensitive to sulfonylurea. However, no association was detected for metformin [15].

Sulfonylurea therapy is safe and effective for a short term use in most patients and may successfully replace treatment with insulin injections [16]. It dramatically improves glycemic control and should be considered as the first line drug for patients with poor glycemic control on an appropriate diet [17]. However, polymorphisms of above mentioned genes need to be considered when using SUs.

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Drug Classification	Drugs	Related gene polymorphisms	rs number	Genotype/Observation	Ref
Sulfonylureas	Sulfonylureas	TCF7L2 G483+9017T	rs12255372	GG/More sensitive to sulfonylurea	[15]
	Glibenclamide	KCNJ11 G635A	rs5219	AA/Increased risk of secondary failure to sulfonylurea	[13]
		CYP2C9*2		CYP2C9 *2/*3/Increased risk of severe hypoglycaemia	[8]
		CYP2C9*3		CYP2C9 *3/*3/Increased risk of severe hypoglycaemia	[8]
Meglitinides	Repaglinide	KCNJ11 G635A	rs5219	GG/ Good drug efficacy	[20]
		SLC30A8 C826T	rs13266634	CC/ Poor drug efficacy.	[21]
		SLC30A8 G827A	rs168s89462	GG/ Poor drug efficacy	[21]
		NAMPT G-3186T	rs11977021	CT/ Poor drug efficacy	[22]
		IGF2BP2 C239+29254G	rs4402960	GG/ Good drug efficacy	[23]
		IGF2BP2 A239+11861C	rs1470579	AA/ Poor drug efficacy	[23]
		TCF7L2 T948-1026C	rs290487	TT/ Good drug efficacy	[20]
		KCNQ1 C1795-10451T	rs2237897	TT/ Good drug efficacy	[44]
		CYP2C8*1		CYP2C8*1/*3/ Lower AUC(0-infinity) and C_{max} of repaglinide	[25]
		CYP3A4*1		CYP3A4*1/*18/Reduced mean elimination rate constant and increased mean half-life	[26]
	Nateglinide	CYP2C9*3		CYP2C9*3/*3 / Increased risk of hypoglycaemia.	[27]
Metformin	Metformin	SRR T-4-2593C	rs391300	GG/ Poor drug efficacy	[58]
		SLC22A1 C181T SLC22A1 G1201A SLC22A1 G1393C SLC22A1 M420del	rs12208357 rs34130495 rs34059508	Defective variants /Poor drug efficacy Defective variants /Poor drug efficacy Defective variants /Poor drug efficacy Defective variants /Poor drug efficacy	[50,51] [50,51] [50,51] [50,51]
Thiazolidinediones	Rosiglitazone	PPARγ2 C34G	rs1805192	CG/ Good drug efficacy	[63]
		PGC-1α G1182A	rs2970847	GG/ Good drug efficacy	[73]
		PGC-1α G1444A	rs8192678	GG/ Good drug efficacy	[73]
		Adiponectin T45G	rs2241766	TT/ Good drug efficacy	[67]
		Adiponectin C-11377G		CC/ Good drug efficacy	[67]
		UCP2 G-866A		GG/ Good drug efficacy	[76]
		TNF-α G-308A		GG/ Poor drug efficacy	[79]

Table 1: Selected studies on pharmacogenomics of oral antidiabetic drugs.

Meglitinides

Meglitinides (repaglinide and nateglinide) are a new class of insulin secretagogues, which structurally unlike to sulfonylureas. They decrease blood glucose by stimulating release of insulin. Repaglinide, similar to sulfonylureas, closes the β cell KATP channel. Inhibition of the KATP channel depolarizes the cells and causes cell calcium channel open, as a result, the calcium influx induces insulin secretion [18]. Nateglinide is also a KATP channel inhibitor, but its selective enhancement of early-phase insulin secretion enables nateglinide to minimize post-meal hyperglycemia with minimal propensity for hypoglycemia [19]. A number of individual differences in the meglitinides therapeutic efficacy have been reported [6], our previous studies showed that genetic polymorphisms were one of the major contributors [20-23]. Thus, those studies will be discussed in this section.

Polymorphisms of CYP: One of the meglitinides, repaglinide is mainly metabolized by CYP3A4 and CYP2C8 [24]. CYP2C8*3 variant was related with reduced plasma concentrations of repaglinide [25]. Subjects with CYP2C8*1/*3 genotype showed lower AUC (0-infinity) and C_{max} of repaglinide compared with those with CYP2C8*1/*1 genotype (P<0.05). CYP3A4 metabolizes 66% repaglinide, it is reported that CYP3A4*18 affects repaglinide pharmacokinetics[26], carriers with CYP3A4*18 have reduced clearance. Nateglinide is mainly metabolized by CYP2C9. It is reported that moderate dose adjustment based on CYP2C9 genotypes help reduce interindividual variability of anti-hyperglycemic effects of nateglinide. Carriers of CYP2C9*3/*3 genotype have a slightly higher risk of hypoglycemia compared to carriers of CYP2C9*1, particularly when taking nateglinide doses above 120 mg [27]. Therefore, CYP genetic polymorphisms play an important role in the pharmacokinetics of meglitinides.

Polymorphisms of KCNJ11: KCNJ11 plays a crucial role in insulin secretion and glucose metabolism. Although it is not the target of meglitinides, its gene polymorphism influences the action of meglitinides by influencing KATP channel sensitivity to ATP [28]. Our study found that subjects with at least one A allele of KCNJ11 rs5219 polymorphism showed lower level of fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) (P<0.05), thus patients with A allele are more sensitive to repaglinide [20].

Polymorphisms of SLC30A8: SLC30A8 encodes ion channel zinc transporter protein member 8 (ZnT-8), which carries zinc from the cytoplasm into insulin secretory vesicles. It is a critical molecule during the insulin maturation and release process [29]. Nonsynonymous SNP rs13266634 (973C>T) [30] and missense mutation rs16889462 (974G>A) [31] have been found to be associated with T2DM onset and development. Our study showed that SLC30A8 rs13266634 (973C>T) and rs16889462 (974G>A) polymorphisms were associated with repaglinide therapeutic efficacy in Chinese T2DM patients [21]. T2DM patients with C allele of rs13266634 or an allele of rs16889462 have better repaglinide drug efficacy than TT or GG genotypes.

Polymorphisms of NAMPT: Nicotinamide adenine dinucleotide (NAD) is an essential coenzyme in many metabolic reactions [32]. Nicotinamide phosphoribosyl transferase (NAMPT), the rate-limiting enzyme during nicotinamide conversion into nicotinamide nucleotide (nicotinamide mononucleotide; NMN), is an NAD biosynthetic enzyme that plays precise role in the regulation of glucose metabolism by affecting the insulin secretion in β cells [33]. Thus, NAMPT may be involved in the repaglinide action. Despite contradictory results were reported about the correlation of NAMPT gene polymorphisms and T2DM susceptibility [34,35], our result showed that -948G>T and -3186C>T polymorphisms are not associated with T2DM susceptibility in Chinese population. However, -3186C>T polymorphism is

associated with plasma levels of postprandial insulin secretion (PINS) and cholesterol (CHO) in Chinese T2DM patients with repaglinide monotherapy [22].We also found that frequencies of -3186C> T polymorphism in Chinese Han population were different from those in Caucasian populations, thus, different dosages of repaglinide may be used among different populations.

Polymorphisms of insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2): IGF2BP2 participates in the insulin signaling pathway and insulin secretion by targeting insulin-like growth factor 2 (IGF-2), which is an important growth and insulin signaling molecule [36]. T2DM patients with different *IGF2BP2* genotypes showed various levels of insulin secretion [37]. It has also been confirmed that *IGF2BP2* gene polymorphisms were related with T2DM susceptibility, especially in Asia populations [31,38]. Our previous study indicated that *IGF2BP2* rs1470579 and rs4402960 polymorphisms increase T2DM risk in the Chinese population. In addition, rs1470579 and rs4402960 polymorphisms in the *IGF2BP2* gene showed reduced therapeutic efficacy of repaglinide treatment [23]. Patients with C allele of rs1470579 have reduced treatment on FPG ($P<0.05$) and PPG ($P<0.05$). Patients with T allele of rs4402960 exhibited enhanced effect of repaglinide treatment of PINS ($P<0.01$). These results provided basis for clinical dose adjustment in the future.

3.2.6) Polymorphisms of TCF7L2: As TCF7L2 plays an important role in insulin secretion, glucose metabolism and β-cells functional regulation, mutations of *TCF7L2* were reported to be associated with T2DM susceptibilities in different ethnic, including Chinese Han population [39]. We investigated whether *TCF7L2* gene polymorphisms were associated with repaglinide efficacy, the results showed that rs290487 (C>T) variants enhanced repaglinide effect in Chinese patients with T2DM [20]. Subjects with *TCF7L2* rs290487 TT genotype are more sensitive to repaglinide than those with CC or CT genotypes. So far, there were no other reports about the association between *TCF7L2* gene variant and repaglinide therapeutic effect, thus larger sample size is needed to confirm our results. The potential mechanism underlying the enhanced repaglinide efficacy in individuals with TT genotype for *TCF7L2* needs future detailed studies.

Polymorphisms of *KCNQ*: *KCNQ1* (potassium voltage-gated channel KQT-like subfamily, member 1) encodes the pore-forming subunit of a voltage-gated K^+ channel (KvLQT1). Early *KCNQ1* genetic polymorphism studies focused on cardiac diseases [40,41]. Later, it is reported that *KCNQ1* was also expressed in pancreatic islets and the cultured insulin-secreting INS-1 cells and may play a role in regulation of insulin secretion [42]. In Chinese Han population, KCNQ1 gene polymorphisms are associated with type 2 diabetes and impaired fasting glucose, suggesting that the KCNQ1 variants may play a role in the pathogenesis of type 2 diabetes through impaired insulin secretion of pancreatic β-cells [43]. Yu et al. [44] recently found that *KCNQ1* rs2237897 were associated with repaglinide efficacy and might also be associated with rosiglitazone response, in Chinese patients with type 2 diabetes. However, how *KCNQ1* polymorphisms affect outcome of these two drugs is still unknown and needs to be investigated in the future.

Metformin

Metformin's primary effect was to reduce hepatic glucose output by increasing insulin suppression of gluconeogenesis. At the molecular level, the effects of metformin are mediated via AMP activated protein kinase (AMPK) [45]. One possible mechanism is to inhibit mitochondrial respiratory chain and thus indirectly activate AMPK by altering cellular ATP/AMP ratios [46]. The European Association for the Study of Diabetes (EASD) guidelines recommended metformin as initial pharmacotherapy for T2DM [47]. Since the publication of results of the United Kingdom Prospective Diabetes Study (UKPDS) in 1998, metformin has become the most widely prescribed oral agent for the treatment of T2DM.

Polymorphisms of organic cation transporter 1 (OCT1): Metformin is a good substrate of human OCT1 (SLC22A1) which is primarily expressed in the liver [48]. Therefore, OCT1 is important for inhibition of hepatic gluconeogenesis, which is one of the major pharmacologic effects of metformin. Previous study showed that liver OCT1 knockout mice abolished hepatic lactate production, suggested that OCT1 is crucial for metformin transporting [49]. There were some recent works on the role of SLC22A1 variation on metformin response. Shu et al. [50] investigated four non-synonymous polymorphisms of SLC22A1; they found that these polymorphisms significantly decreased metformin transport in vitro. The same group reported in another study that SLC22A1 polymorphisms were correlated with pharmacokinetics of metformin in healthy volunteers [51]. Taken together, SLC22A1 polymorphisms contribute to interindividual variability of metformin efficacy.

Polymorphisms of serine racemase (SRR): SRR synthesizes D-serine, which exist mainly in brain and some peripheral organs, such as pancreas [52,53]. Both D-serine and the neurotransmitter glutamate bind to the N-methyl D-aspartate (NMDA) receptors and trigger excitatory neurotransmission in the brain [54,55]. Both D-serine and SRR present in the pancreas. Glutamate signaling has function in peripheral tissues, including the pancreas, positively modulates secretion of both glucagon and insulin in pancreatic islets [56,57]. Thus, dysfunction of D-serine could alter glutamate signaling and affect insulin or glucagon secretion in T2DM pathogenesis. Our previous study showed that SRR polymorphism rs391300 was associated with metformin therapeutic efficacy in Chinese T2DM patients. The mutant allele carriers showed better fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and plasma concentrations of CHO improvement that wild-type patients [58].

Thiazolidinediones (TZDs)

TZDs (pioglitazone, rosiglitazone) are selective PPARγ ligands that activate peroxisome proliferator-activated receptors (PPARs), which is a class of intracellular receptor. They modulate transcription of insulin-sensitive genes involved in the control of glucose and lipid metabolism in lipidic, muscular tissues and liver, thus stimulate muscle glucose uptake and suppress hepatic glucose output [59].

Polymorphisms of PPARG gene: Peroxisome proliferator-activated receptor γ (PPARγ), targets of TZDs, is encoded by PPARG. Peroxisome proliferator-activated receptor γ2 (PPARγ2), one isoform of PPAR γ [60], is a transcription factor involved in energy homeostasis, adipogenesis and insulin sensitivity. Deeb et al. [61] first reported that PPARγ2 Pro12Ala variant contributed to T2DM risk in the Japanese-Americans. Recently, a meta-analysis study based on forty-one studies in the last 10 years summarized that, Pro12Ala polymorphism in the PPARγ2 gene is associated with insulin sensitivity, the G allele carriers showed significantly lower risks of T2DM in Caucasians populations[62]. It is reported that carriers with PPARγ2 Pro12Ala genotype in the gene had a better therapeutic response to rosiglitazone than those with the Pro12Pro genotype[63]. The Pro12Ala variant of the PPARG gene is also associated with PPARγ agonist-induced fluid retention and edema [64]. However, there was no association between Pro12Ala variant and therapy efficacy of pioglitazone [65], Pro12Ala polymorphism also can't explain the primary pioglitazone

therapy failure [66], suggesting that the drug-treatment response is independent from pharmacogenetic effects of pioglitazone.

Polymorphisms of adiponectin: Adiponectin, one of the important adipocytokines secreted by adipocytes, plays a vital role in the regulation of insulin sensitivity and glucose homeostasis. We found that adiponectin polymorphisms 45T>G and 11377C>G are significantly associated with therapeutic efficacy of multiple-dose rosiglitazone treatment in Chinese patients with T2DM [67]. Namvaran et al. [68] recently demonstrated that adiponectin 45T>G was an important determinant of T2DM in the Iranian population, but adiponectin 45T>G and adiponectin receptor-2 795G>A polymorphisms were not significantly associated with the response of pioglitazone in Iranian population. Therefore, further functional studies and large scale studies are needed to explore the association between adiponectin gene and TZDs drug effect.

Polymorphisms of peroxisome proliferator activated receptor-g coactivator-1a (PGC-1α): PGC-1α, a transcriptional coactivator of PPAR γ, is involved in the glucose-lipid homeostasis [69]. An autosomal genomic scan study revealed that PGC-1α genomic region on 4p15.1 is associated with fasting serum insulin concentrations [70]. We studied 2 common polymorphisms, PGC-1α Thr394Thr and Gly482Ser, which were reported to be significantly associated with risks of T2DM in the previous investigation [71,72]. Our result suggested that PGC-1α Thr394Thr and Gly482Ser polymorphisms were associated with therapeutic efficacy of multiple-dose rosiglitazone treatment in Chinese patients with T2DM, carriers of A allele of Thr394Thr or Ser482 allele of Gly482Ser showed a poor therapeutic efficacy to rosiglitazone when compared with GG or Gly/Gly carriers [73].

Polymorphisms of uncoupling protein 2 (UCP2): UCP2 is a candidate gene of metabolic disorders; it negatively regulates glucose-stimulated insulin secretion. Tian et al. [74] found that UCP2 expression increase induced by chronic exposure of pancreatic islets to palmitate was prevented by rosiglitazone. -866 G>A variant, a prevalent polymorphism in the human UCP2 gene promoter, was found to have significant impact on its transcriptional activity and T2DM pathogenesis [75]. Our study showed that there was a strong association between rosiglitazone treatment success and UCP2-866 G>A polymorphism [76].

Polymorphisms of tumor necrosis factor-α (TNF-α): TNF-α is partly secreted by adipocyte, it causes insulin resistance through inhibiting lipogenesis, stimulating lipolysis, impairing insulin signal pathway and decreasing insulin-induced glucose uptake [77]. G-308A was one of the most common polymorphisms located in the promoter region of TNF-α gene. Some in vitro experiments demonstrated that G-308A variant increases transcriptional activation of TNF-α, because it is located in a consensus sequence of the transcription factor AP-2 [78]. Our clinical trial results showed that TNF-α G-308A polymorphism was not associated with T2DM susceptibility but with the therapeutic efficacy of rosiglitazone in T2DM patients [79]. But the frequency of TNF-α G-308A allele in Asian population was so low that we only found 4 mutant allele carriers in the study. Therefore, a larger sample size study is needed to confirm our conclusion in the future. TZDs are widely used antidiabetic drugs with proven efficacy on improve hyperglycemia, insulin sensitivity and cardio metabolic profile. However, they have several severe adverse effects. For example, troglitazone was withdrawn in 2000 due to increased risk of hepatotoxicity [80]. Rosiglitazone was also associated with an increase myocardial infarction incidence. Pioglitazone have common adverse effects of weight gain, pedal edema and bone loss [81]. Wolford et al. [82] demonstrated that differential response to troglitazone may due to sequence variation in PPARG. Thus, it is likely that genetic polymorphisms correlated with TZDs adverse effects. Future studies are needed to confirm whether gene polymorphisms can explain these drug adverse effects.

Conclusion

Numerous studies investigated the influence of pharmacogenetics to OADs. Some genetic polymorphisms were concluded to be associated with differential response to OADs. However, results of some polymorphisms were contradictory, thus these polymorphisms need to be studied in a larger and well-designed cohorts investigation. With the development of pharmacogenetics, more and more mechanisms of interindividual variability of OADs response will be unveiled. These studies will lead to personalized therapy of T2DM patients.

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