Pharmacogenomics of Type 2 Diabetes Mellitus; A Step Toward Personalized Medicine

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ABSTRACT

Type 2 diabetes is a complex multifactorial disease characterized by insufficient insulin secretion and insulin resistance. Global prevalence of diabetes is increasing day by day making diabetes a global epidemic. Various factors increase risk of diabetes and genetic predisposition is one of very important factor. Many anti-diabetic treatments are available to control blood glucose level in diabetic patients now-a-days. Initially, oral anti-diabetic treatment is successful but it fails later on and requires insulin administration and there are large numbers of non-responders also. Even patients that do respond show variability in drug response and tolerance. Pharmacogenomics is the study to determine the inter-individual differences that contribute toward drug response. Many studies have shown positive contribution of different polymorphism in alteration of drug response in various ethnicities. But still data related to pharmacogenomics of Asian population is limited. In this review, we have tried to summarize the genetic variations and their effect on three major classes of oral anti-diabetic medication that include thiazolidinediones, metformin and sulfonylureas.

Key words: T2D, pharmacogenomics, anti-diabetic, sulfonylurea, thiazolidinediones, metformin

1. INTRODUCTION

Type 2 diabetes (T2D) is a common chronic disease that is characterized by hyperglycemia and insulin resistance. It is associated with various co-morbidities like hypertension, obesity, hyperlipidemia, nonalcoholic fatty liver disease and resulting microvascular and macrovascular complications (neuropathy, retinopathy, atherosclerosis, nephropathy, and cardiovascular disease — . Prevalence of diabetes is increasing globally and recent studies show that underdeveloped countries in continent like Asia and Africa are more affected than developed countries like United States. It is estimated that about 371 million people suffered from diabetes in 2012 and it will increase to 552 million people till 2030 . T2D is also a disease of development and lifestyle changes. The known risk factors for diabetes include modifiable (overweight and obesity, dietary factors, sedentary lifestyle) and non-modifiable risk factors (age, ethnicity, sex, history of gestational diabetes and family history) (Chen et al., 2012).

It has been known for more than five decades that genetic differences among people contribute toward differences in response to drugs. Pharmacogenomics is the term used for studying inter-individual genetic differences that influence the drug response. It is a relatively new field of study that involves identification of genes and inter- and intra-individual variations that not only affect response to drug but also help to design and predict new drugs. Similarly like other diseases, the genetic variability among individuals also influences anti-diabetic treatment that contributes toward metabolism, absorption and distribution of drugs. These genetic variations might also affect the drug target making some individual drug resistant. Identification of such variations related to drug response can help physicians in making drug selection decisions, better disease management, avoiding adverse drug reactions (Hu, 2012).

Along with the various known environmental factors that increase the risk of type 2 diabetes, multiple genetic factors also contribute toward its pathogenesis through interaction with detrimental environmental factors . Recently using the candidate gene studies and genome-wide association studies more than 40 loci have been associated with T2D among common variants in European genome . T2D is a complex disease so these genetic associations do not identify the exact causal variant and culprit gene for pathogenesis of T2D (Ostbye et al., 1989; Zeggini et al., 2008; Billings and Florez, 2010; Dupuis et al., 2010; Voight, Scott et al., 2010; Herder and Roden, 2011; Saxena et al., 2013). These genetic variations contribute toward the pharmacodynamics and pharmacokinetics of drugs because various genes encode proteins that are involved in drug absorption and metabolism (Huang and Florez, 2011). Primary management of T2D involves lifestyle modifications, but these may not be enough. As the disease progresses T2D management likely will require medication. Previously only two oral medicines were available, but recent advances in therapeutics have provided physicians with an opportunity to choose from various medicines with different modes of action including sulfonylurea, biguanides, a-glucosidase inhibitor, thiazolidinediones, glinides, DPP-IV and SGLT2 inhibitors, and non-insulin injectable (Goldfine, 2001; Gadsby, 2002). Their mechanism of action includes increasing insulin secretion (sulphonylureas and meglitinides), reduction of carbohydrate uptake from gastrointestinal tract and decreasing level of glucose release from liver (Metformin, thiazoledinediones, and alpha glucosidase inhibitors),

however the biological mechanisms of some anti-diabetic medication are not well understood (Goldfine, 2001; Huang and Florez, 2011).

1.1. Thiazolidinediones

Thiazolidinediones are a class of drugs that increase insulin sensitivity in the liver, muscle, and fat tissues. These agents increase lipolysis and suppress glucose release from liver through increased binding of the peroxisome proliferator-activated receptor γ (PPARG) to its target (DNA response element), thereby decreasing the glycemic load on the pancreatic beta cell (Hofmann et al., 1992; Saltiel and Olefsky, 1996; Altshuler et al., 2000). Initial studies on pharmacogenetics were focused on a common polymorphism of PPARG (functional missense mutation P12A). This mutation has been reported to be associated with protective effect against T2D (Altshuler et al., 2000).

One study showed a significant decrease in glucose levels in people carrying this P12A polymorphism in response to rosiglitazone administration (Bozkurt et al., 2007), but two other studies (Bluher et al. 2003; Snitker et al., 2004) showed that percentage of responders does not differ between alanine carriers and proline homozygotes. In one of these studies, the TRIPOD study (Troglitazone in prevention of diabetes), one third of the cases did not show an increase in insulin sensitivity in response to troglitazone. Snitker et al. continued their studies by genotyping the 131 common variants of PPARG and found association of eight different polymorphisms in response to troglitazone administration. Conversely, Kang et al. showed that patients with P12A polymorphism showed better response to rosiglitazone treatment. Another study failed to show an association of P12A along with five other polymorphisms with troglitazone (Bluher et al., 2003; Snitker et al., 2004; Kang et al., 2005; Wolford et al., 2005; Florez et al., 2007). One possibility for these variable results might be presence of other novel variants in PPARG or other T2D associated genes influencing response to thiazolidinediones. Environmental and epigenetic factors can also influence drug response. However, the use of troglitazone was withdrawn from market due to its hepatotoxic effects (Fowler, 2007).

In contrast carriers of P12A show an increase in glucose levels, resulting in higher conversion to diabetes in response to acarbose. This effect has also been shown in carriers of a polymorphism in adiponectin gene (ADIPOQ) (Bozkurt et al., 2007). A polymorphism in CYP2C8 gene was found to be associated with changed clearance rate of rosiglitazone (Kirchheiner et al., 2006). All of these results need to be verified through extensive experiments and research.

1.2. Biguanide

Metformin is a safe and effective medicine that primarily increases glucose uptake in muscle and fat tissues and reduce gluconeogenesis output from liver thus increasing insulin sensitivity similar to thiazolidinedione's (Montanari et al., 1992; Bell and Hadden, 1997). It is the first line biguanide agent in treatment of T2D (Stumvoll et al., 1995). The absorption of metformin from intestine involves two steps. The first step involves active uptake process that is mediated by broad-specificity transporters OCT1 and OCT2 that belong to highly polymorphic solute carrier family 22 (SLC22A1 and SLC22A2) to hepatocytes and renal tubular cells, respectively. The second step involves the MATE1 protein (multidrug and toxin extrusion protein) that helps excretion of un-metabolized metformin into bile and urine. OCT 2 has more affinity than OCT1 for metformin. A study in Chinese and Japanese population found that nonsynoymous polymorphisms in SLC22A1 were associated with different plasma concentration of metformin (Koepsell, 1998; Jonker and Schinkel, 2004; Kimura et al., 2005; Koepsell et al., 2007; Shu et al., 2008; Chen et al., 2010).

Metformin stimulates AMP-activated protein kinase (AMPK), a key regulator of glucose metabolism. Metformin induces AMPK activation or its adenosine analogue suppresses SREBP-1 expression (which is an important transcription factor of lipogenesis). Research has shown that activated AMPK is required for inhibitory effect of metformin on glucose production by hepatocytes (Zhou et al., 2001). A GWAS in Scottish patients in response to metformin treatment showed an association of rs11212617 SNP in ATM gene with metformin treatment success. Variation in ATM gene upstream of AMPK modifies response to metformin. This indicates that ATM and AMPK both genes enhance metformin response (Zhou et al., 2011). Association of this SNP has been replicated in Netherland and UK (van Leeuwen et al., 2012). Another study showed that ATM gene does not directly affect AMPK activation in response to metformin. Instead KU-55933 reduces AMPK activity independent of ATM (Woods et al., 2012). Another study also showed role of KU-55933 in metformin response (Yee et al., 2012).

Different SLC22A1 variants cause increase or decrease in uptake of metformin. Studies have shown that variants of SLC22A1 including Gly220Val, Ser189Leu, Ser14Phe, Met420del, Arg61Cys, Gly401Ser, and Gly465Arg increase uptake and variants Arg61-Cys, Ser189Leu, Gly220Val, Gly401Ser, Met420del, Gly465Arg decrease uptake in vitro (Shu et al., 2008). Polymorphisms Arg61Cys, Gly401Ser, Met420-del, and Gly465Arg with synonymous variant Ser52Ser were found to be associated with renal clearance of metformin by reduction in OCT1 expression/activity (Chen et al., 2010). A European cohort study suggested association in reduction of HbA1c in diabetic patients with non-coding SNP rs622342C/A in response to metformin treatment, but this study was not replicated in American-European population (Becker et al., 2009; Jablonski et al., 2010).

SLC22A2 variants Thr201Met and Ala270Ser were identified in a small Japanese group of non-responders to metformin treatment, and a new variant Thr199Ile was identified in Korean population. These variants influence clearance and tubular excretion of metformin and thus increase plasma concentration of metformin (Kang et al., 2007; Shikata et al., 2007; Song et al., 2008; Wang et al., 2008; Chen et al., 2009). However, association and genotype-phenotype correlation for these variants could not be replicated in Asian populations (Sakata et al., 2004; Kirchheiner et al., 2006; Kim et al., 2007; Shu et al., 2008; Jablonski et al., 2010; Huang and Florez, 2011).

1.3. Sulfonylureas

Sulfonylureas is a class of T2D medication that binds to the sulfonylurea receptor SUR1 in the plasma membrane of the beta cells that is coupled to the KATP-channel. KATP-channel consists of two subunits Kir6.2 and SUR1 and triggers glucose dependent stimulation of insulin secretion (Panten et al., 1996; Gloyn et al., 2004). These subunits are encoded by potassium inwardly-rectifying channel, subfamily J, member 11 (KCNJ11) gene and ATP-binding cassette, sub-family C (CFTR/MRP), member 8 (ABCC8) gene, respectively (Flanagan et al., 2009). Studies have shown gain of function and loss of function mutations in these genes cause neonatal diabetes mellitus. These mutations generate permanent opening or closure of KATP channels causing insulin deficiency or hypersecretion of insulin, respectively (Gloyn and Ellard, 2006; Murphy et al., 2008; Sattiraju et al., 2008). These mutations' effects suggest that these could be potential target to study drug responses.

Sesti et al. showed that patients with lysine 23 (K23) variant of the KCNJ11 glutamic acid (E) 23K polymorphism had a relative risk of secondary failure (loss of effective anti-diabetic response after years of treatment) 1.45 as compared with homozygotes of E23E (Sesti et al., 2006). This study is in contrast to UK Prospective Diabetes Study (UKPDS) in which significant association of 23K was not found in response to sulfonylurea treatment (UK Prospective Diabetes Study Group 1998). Later, various meta analysis studies showed strong association of E23K polymorphism of KCNJ11's association with response to sulfonylurea treatment (Florez et al., 2004; Holstein et al., 2009). These studies in Caucasian populations did not show any association with higher risk of secondary sulfonylurea failure in patients (Gloyn et al., 2003;Sesti et al., 2006; Holstein et al., 2009). Also a decreased sulfonylurea response was observed in isolated human pancreatic islets from diabetic donors carrying KCNJ11 E23K variant (Sesti et al., 2006). Two other studies in Asian populations showed better response to sulfonylurea therapy in patients having risk allele of both KCNJ11 and ABCC8 (Zhang et al., 2007; Feng et al., 2008). Despite previous studies saying what, a 2012 study showed strong association of E23K variant of KCNJ11 in response to sulfonylurea treatment for first time in caucasions (Javorsky et al., 2012).

KCNJ11 and ABCC8 genes are located on chromosome 11 and separated by a region of only 5kb, which is why many variants within these genes are strongly correlated (Florez et al., 2004). A missense mutation Ala1369Ser (A1369S) in ABCC8 is strongly associated with KCNJ11 E23K in all populations studied (Inoue et al. 1997; Florez et al. 2004). Hamming et al., showed that K23/A1369 variant increases the risk of T2D, sunsequently associating the A allele in ABCC8 with increased risk of T2D and enhanced reponse to gliclazide in vitro (Hamming et al., 2009). Various studies have showed strong association of variants of ABCC8 in the UK, Denmark, Neitherland, France, Mexican, and Caucasian cohorts from Utah in the USA, Chinese and American populations (Inoue et al., 1996; Hani et al., 1997; Goksel et al., 1998; Hansen et al., 1998; Hart et al., 1999; Elbein et al., 2001; Meirhaeghe et al., 2001; Barroso et al., 2003). Meta analysis of ABCC8 gene variants rs1799854C/T and Thr759Thr (T759T) showed no association in caucasian poulation (Gloyn et al., 2003). The variants in ABCC8 and KCNJ11 were not associated with response to glimepride treatment in Korean population. This contradiction in reported study results suggests the hypothesis that the risk haplotype of KCNJ11 and ABCC8 gene causes a conformatonal change in the sulfonylurea binding domain recognized by some sulfonyurea molecules (Cho et al., 2011; Lang et al., 2012).

The strongest association of any gene reported to be associated with T2D to date is for TCF7L2. This association has been reported in a substantial number of ethnicities. Although the exact mechanism of how TCF7L2 contributes toward pathogenesis of T2D is still not clear, it possibly causes a defect in GLP-1 metabolism (Damcott et al., 2006; Florez et al. 2006; Chandak et al., 2007; Loos et al., 2007; Wang et al., 2007). Various replication studies also confirmed its association with decreased sulfonylurea treatment response (Cauchi et al., 2006; Florez et al., 2006; Grant et al., 2006; Humphries et al., 2006; Pearson et al., 2007). Go-DARTS study of UK population showed that T allele variant of TCF7L2 is associated with therapeutic failure in T2D patients (Kimber et al., 2007). Another study carried out by the same group showed that patients with risk allele failed treatment with sulfonylurea, but had no effect on metformin treatment (Pearson et al., 2007). This association was confirmed by a study conducted in German population which also showed increased rate of sulfonylurea tretment failure in patients having T allele in TCF7L2 gene at rs7903146 (Holstein, Hahn et al., 2011). In Chinese population another intronic variant rs290487C/T was reported that influence eficacy of reaglinide in patients with T2D (Yu et al., 2010).

These studies suggest that genetic variations play an importanct role not only in the pathogenesis of complex diseases like T2D but also influence the drug metabolism and action. Ethnic variations also play an important role in disease susceptibility and it is important to study genetic variations associated with diseases in multiple ethnicities and compare the differences and the effect of these variations on ethnicities as well.

2. CONCLUSION

Common oral anti-diabetic therapies include anti-hyperglycemic drugs that are administered immediately after diagnosis. These oral anti-diabetic drugs include thiazolidinediones, metformin, sulfonylureas, dipeptidyl peptidase-IV (DPP-IV) inhibitors and GLP1 mimetics. It is clear from clinical data that initially diabetic patient's glycemic control is well managed by anti-diabetic treatment but with the passage of time combination therapy may be required. Ultimately anti-diabetic treatments fail to control diabetes and thus require insulin administration as well. There is also variable response to oral anti-diabetic treatment due to inter-individual variability. Reserchers are struggling to identify underlying genetic variance that modify drug reponse but to date very limited informations is available and only few genes and polymorphisms have been verified to be associated with anti-diabetic therapy. These findings are also not consistent among ethnicities and even less data is available for

Asian populations. Due to complex nature of disease it is not possible to infer complete mechanism of modified drug reponse by one SNP. For this purpose new techniques like next generation sequencing should be employed to sequence all genes that are associated with T2D to find their role and effect in drug metabolim. Specially additional research is needed in Asian countries to generate comprehensive data. Despite all the efforts and positive results we cannot apply pharmacogenetics in clinical practice unless accurate interpretation of genetic factors of anti-diabetic therapeutic response has been achieved.

Conflict of Interest

The authors declare no conflict of interests

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