



Pharmacogenomics in Diabetes Mellitus: Pathway to Personalized Medicine

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Abstract:

Diabetes, growing global health burden is a Multifactorial, heterogeneous group of disorders characterized by deficiency or failure in maintaining normal glucose homeostasis. The prevalence of Diabetes is rising across the globe at an alarming rate with India and china facing the greatest challenges with worsening trend affecting younger age groups. Diabetes and its complications not only increase morbidity and mortality rates but also have impact on the nation's economy and an urgent need for prevention and control of diabetes. Even though many drugs are available to maintain the normal glycaemic levels, many individuals are seen who does not respond to the therapy. In this scenario, personalized medicine for diabetes (PMFD) has come into light which makes the use of information about the genetic makeup of a person with diabetes to modify strategies for preventing, detecting, treating, or monitoring their diabetes. Many genetic variants (monogenic / polygenic) were identified which are determinants of Type 1(polygenic) / Type 2 Diabetes mellitus (HNF4A, HNF1A,IRS1 etc.) / other specific types of diabetes (MODY, Neonatal (KCNJ11, ABCC8)) and genetic variants which are responsible for the sensitivity / failure (TCF7L2, NOS1AP, AMPK, SLC22A1,SLC22A2,SLC47A1 etc.) of the Anti Diabetic drug therapy. Understanding the basis of this heterogeneity helps in personalizing the methodology of prevention and treatment strategies according to individual patient clinical and molecular characteristics. By the implication of pharmacogenomics in Diabetes mellitus we can identify the individuals at risk and suggest suitable anti diabetic therapy thereby reducing the social and economic burden on the society.

Keywords:

Diabetes Mellitus, Pharmacogenomics, Neonatal Diabetes, MODY, Anti Diabetic Drugs.

Introduction:

1.1: Diabetes mellitus: Diabetes is a growing global health burden, which is a Multifactorial, heterogeneous group of disorder characterized by a deficiency or failure in maintaining normal glucose homeostasis. An International expert committee under the sponsorship of American Diabetes Association (ADA) has classified diabetes mellitus into 4 types, i.e., Type1 (β -cell destruction). Type2 (may range from

predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance), Gestational Diabetes and other Specific Types (Genetic / Diseases of Pancreas / Endocrinopathies/Drug or Chemical Induced / Infections / Immune Mediated).

1.2: Epidemiology: The reason behind the concern about the Diabetes is because of its rising prevalence and the social / economic burden on the society. According to J.E. Shaw et al^[1], the world prevalence of diabetes among adults (aged 20–79 years) will be 6.4% in 2010 and which will increase to 7.7% by 2030 with higher rise in developing countries (69%) than the developed (20%). As per WHO's 'The World health statistics 2012 report', one in 10 is diabetic, one in six adults is obese and one in three have raised blood pressure. Type 2 diabetes mellitus (T2DM), its macro and micro vascular complications like cardiovascular diseases, blindness, amputation and kidney failure are accounting for much of the social and financial burden of the disease spending up to 13% of the world's health care budget and nearly 40% of their budget in high prevalence countries. The prediction that diabetes incidence will double by 2025 indicates a parallel rise in cardiovascular-related illness and death, with an inevitable and profound impact on global healthcare systems^[2]

1.3: Treatment of Diabetes mellitus: Current therapies in the management of diabetes include modification of lifestyle (exercise, diet) and pharmacotherapy with oral / injected hypoglycaemic agents. Ultimately, the goal of all treatment strategies is to maintain the near-normal glycaemic levels which have shown to decrease the risk for development and progression of disease complications. Not every patient with diabetes responds in the same way to a given treatment, some may respond or may not respond and some may have adverse reactions. There may be a number of reasons for the variation in response to the given treatment, in that genetic composition is one of the important factors. Here comes the concept of personalized medicine, which involves determining specific information about a particular patient and then prescribing a treatment that is specific for that patient^[3].

2.0: Pharmacogenomics and Diabetes Mellitus: The term pharmacogenetics was coined by Friedrich Vogel

in 1959 and was used for many years in reference to genetic differences in pharmacokinetic factors, particularly metabolic enzymes. Not until the 1990s did the term pharmacogenomics enter the scientific literature, with emergence of the Human Genome Project and the development of the genome sciences.

2.1: Personalized medicine: Personalized medicine for diabetes (PMFD) is the use of genetic information of a person with diabetes to tailor strategies for preventing, detecting, treating, or monitoring their diabetes. It represents an approach for defining disease subtypes and defining biomarkers that can identify patients who are most likely to respond /not respond / experience adverse effects from a specific treatment.

2.2: Genes involved in Diabetes mellitus: Different pathogenic mechanisms are involved in the development of various forms of diabetes, including genetic and environmentally determined alterations in the action of insulin, the development, survival of islet β-cells and the secretion of insulin. The differences in therapeutic approach to patients with type 1, type 2 diabetes, with or without coincident morbid obesity, represent a step towards personalized medicine. In this work up, we have obtained the data and enumerated the various types of genes involved in pathogenesis of Diabetes mellitus and its complications and the genes influencing the pharmacokinetic / pharmacodynamic properties of various anti diabetic drugs.

2.2.1: Monogenic Diabetes: Monogenic diabetes has been classified under specific types of Diabetes. There are now at least 27 known subtypes of diabetes secondary to single-gene mutations. Some subtypes of monogenic diabetes are permanent / temporary neonatal diabetes (PNDM/TNDM), maturity-onset diabetes of the young (MODY), maternally inherited diabetes and deafness (MIDD) and syndromes like Wolcott-Rallison, Wolfram, Werner’s etc. Although diabetes in the majority of patients is not caused by a single gene mutation, the evidence for improved efficacy of specific therapies in these monogenic disorders provides a model for personalized medicine.

2.2.1.1: Neonatal Diabetes mellitus (NDM): Till now forty four different genes were identified responsible for NDM (Table 1). For e.g. Heterozygous potassium inwardly rectifying channel subfamily J member 11(KCNJ11) mutations which encodes the Kir 6.2 subunit of the pancreatic β-cell K_{ATP} channel, present in approximately half of patients who develop diabetes within the first 6 months after birth. These patients respond better with the Sulfonylureas^[5] rather than insulin with good glycaemic control^[6] and hence this gene is readily selected for genetic screening.

Table 1: Genes identified in NDM

Gene	Locus	Function
KCNJ11 (30% of NDM)	11p15.1	β-Cell K _{ATP} channel closure
ABCC8 (20%)	11p15.1	β-Cell K _{ATP} channel modulator, sulfonylurea response
IDDM2(20%)	11p15.5	Insulin production
PTF1A	10p12.31	Pancreatic development
FOXP3	Xp11.23	Immune response control

2.2.1.2: Maturity-onset diabetes of the young (MODY): MODY was defined as a familial autosomal dominant form of early-onset type 2 diabetes, which usually develops in childhood, adolescence, or young adulthood and associated with primary defects of insulin secretion. The prevalence of MODY is estimated to be less than 5% of T2DM patients in most populations studied^[7]. There are 12 genetic subgroups of MODY identified as of now

Table 2: Genes involved in MODY

Gene	Incidence association & with other diseases	Therapy
HNF4A-MODY1	Familial common	most Respond well with SU
GCK-MODY2	2 nd most common	Mild hyperglycaemia, does not need any Rx
HNF1A-MODY3	most common	Respond well with SU & DPP-IV inhibitors
IPF1-MODY4	Very rare	Therapy not clear and need insulin.
HNF1B-MODY5	Cause Diabetes / developmental problems in kidneys/ abnormal reproductive organs	
NEUROD1-MODY6	Very rare	
KLF11-MODY7	Very rare	
CEL-MODY8	Pancreas are small, also lead to exocrine pancreatic insufficiency	
PAX4-MODY9	Very rare	
INS-MODY10	Cause NDM /Antibody negative T1DM/ MODY	
BLK-MODY11	Very rare	
ABCC8-MODY12	Frequently cause neonatal diabetes and rarely MODY	

Patients with MODY 1 and MODY 3 can have markedly increased blood glucose levels along with onset of Diabetes < 25 years of age and often misdiagnosed with T1DM. These patients respond

well with Sulfonylureas in contrast to patient's with T1DM [8]. Several case reports have suggested that dipeptidyl peptidase-IV inhibitors may further improve blood glucose control when used in combination with sulfonylureas in MODY 3 patients [9]. Studies done by V.Radha and V. Mohan on the MODY genes have shown that prevalence is high among the South Indians and the mutations in HNF1A were different when compared to the western population [10]. They also found that Ala98Val polymorphism of HNF1-a gene is associated with MODY and with onset of T2DM at an early age.

Prevalence of MODY genes: MODY 1, 2, and 3 in aggregate account for an estimated 0.5% to 1% of diabetes in US and western European populations. However, it is estimated that 20% of MODY patients currently are identified [11]. The diagnosis and management of MODY [12] thus represents a potential area of personalized diabetes management that needs to be more effectively implemented.

2.2.1.3: Genes involved in other monogenic diabetes (Table 3):For e.g., in patients with lipotrophic diabetes secondary to a mutation in the lamin A/C (LMNA) gene responded well with the thiazolidinediones by its effect on adipocyte function via PPARγ than with Metformin [13].

Table 3: Genes involved in monogenic diabetes

Syndrome /Disease condition	Gene ^a	Gene function	
Wolcott Rallison syndrome	EIF2AK3	Endoplasmic reticulum stress control	
Wolfram syndrome	WFS1, CISD2	Cellular homeostasis Ca ²⁺	
Werner syndrome	WRN	DNA-helicase activity	
Friedreich's ataxia	FXN	Mitochondrial iron, transport/ respiration	
Hemochromatosis	HFE	Regulation of iron absorption	
Thiamine-responsive anaemia	SLC19A 2	Thiamine transporter protein	
IR	Generalized lipodystrophy	AGPAT2	Phospholipid biosynthesis
		BSCL2	Fat storage
		CAV1	Cell growth/differentiation
		LMNA	Nuclear stability, chromatin structure
	Partial lipodystrophy	LMNB2	Nuclear stability, chromatin structure
		ZMPSTE 24	LMNA processing
		PPARG	Cellular signalling/fat differentiation
		AKT2	Cellular signalling

2.2.2: Type 1 Diabetes mellitus (T1DM): Multiple genetic factors have been associated with type 1 diabetes. Genome wide association studies (GWAS) identified 40 genetic loci associated with T1DM [14]. Many of the identified genes at these loci are linked to autoimmunity, whereas others appear to be functionally related to β-cell survival [15]. Some of the

genes are HLA DR/DQ, INS, PTPN 22, SUMO4, LPP5, ENSA, CTLA-4 etc. Knowledge of these specific genes and loci does not yet have practical application in individualizing therapy of T1DM.

2.2.2: Type 2 Diabetes mellitus (T2DM): Type 2 diabetes accounts for 90% of diabetic cases, typically characterized by combination of both decreased insulin secretion and development of insulin resistance (IR) along with gradual loss of β-cell secretory capacity. It is associated with obesity, sedentary lifestyle, family history and ethnicity.

TABLE 4: Genes identified in the pathogenesis of T2DM

	β-cell dysfunction	↓ β-cell mass	IR	IR & ↓ insulin secretion	Altered BMI	Unknown
Reg ion / Genes	KCNJ 11 TCF7 L2 SLC30 A8 IGF2B P2 JAZF1 CDC1 23 /CAM K1D KCNQ 1 MTNR 1B	HHE X CDK N2A /CDK N2B NOT CH2	PPARG THAD A ADAM TS9 ENPPI	CA PN1 0	FTO	TSPAN 8/LGR 5
	CDKAL1 HNF1B WFS1 HNF4A HNF1A					

Although the current worldwide epidemic of T2D is greatly driven by lifestyle and dietary changes, a combination of the environmental factors and susceptible genetic determinants contributes to the development of T2DM. GWAS have identified at least 23 genes with sequence variations associated with type 2 diabetes across multiple populations [16] (Table 4) and many additional genes identified in smaller single population studies. The contribution to disease risk by any one of these genetic factors is small (Typically 1.5 - fold increased risk). Polymorphisms in the transcription factor 7-like 2 (T-cell- specific, HMG-box) (TCF7L2) gene correlate with an approximately 1.4-fold increased risk of type 2 diabetes in multiple populations [17]. A study by Dhanasekaran et al, found that the rs5435 (C→T) polymorphism of the GLUT4 gene is associated with type 2 diabetes in the south Indian population [18].

2.2.2.1: Genes influencing the Oral Anti Diabetic

Therapy: Pharmacologically, T2DM is treated with nine major classes of approved drugs, including insulin and its analogues, Sulfonylureas, Biguanides, Thiazolidinediones (TZD), Meglitinides, Glycosidase inhibitors, Amylin Analogues, Incretin Hormone mimetics and Dipeptidyl Peptidase 4 (DPP4) inhibitors. In a study of long-term glycaemic control in T2DM, Kahn et al^[19] found a cumulative incidence of monotherapy failure at 5 years of 15% with Rosiglitazone (a TZD), 21% with Metformin (a biguanide), and 34% with glyburide (a sulfonylurea). Various genes were identified influencing the drug response (Table 5) and those altering the pharmacokinetic properties (Table 6). Here we have discussed pharmacogenetic variation of some of the oral anti diabetic drugs.

Table 5: Genes involved in response with Oral Anti diabetic Drugs

Oral Anti diabetic Drugs	Genes identified for drug response	Genes/polymorphism identified in non responders
Sulfonylureas	KCNJ11 HNF1a ABCC8Ser1369Ala	KVNJ11Glu23Lys IRS-1Gly972Arg TCF7L2rs12255372G/T TCF7L2 rs7903146 T/C
Metformin	IRS-1Gly972Arg	STK11rs74165
TZD	PPAGPro12Ala PGC1αGly482Gly	APM1T45G APM1T276G LPLSer447X
αGlucosidase Inhibitors	PGC1αGly482Ser	APM1T276G
DPP4 Inhibitors	TCF7L2	MTNR1Brs1387153 GLP1R T149M

Sulfonylureas: Sulfonylureas (SU) are one of the most widely used oral hypoglycemic agents. The common SU agents are gliclazide, glibenclamide, and glimepiride. Most individuals respond well to these drugs, but efficacy is variable. For example, 10-20% of treated individuals do not achieve adequate glycemic control using even the highest recommended dose (“primary sulfonylurea failure”) and 5-10% of patients with T2D who initially respond to sulfonylurea treatment will subsequently lose the ability to maintain near-normal glycaemic levels (“secondary sulfonylurea failure”)^[20]. Although failure to respond, or deterioration of, response to sulfonylurea 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, the strongest predictor of failure is deterioration of β-cell function. In series of studies done by Pearson et al, patients with HNF1A, KCNJ11, ABCC8 mutations have shown good response with SU’s compared to Metformin^[21,22]. Genes influencing Metabolism : Most studies have found that individuals carrying at

least one *2 or *3 allele exhibit reduced CYP2C9^[23] activity, while those with either the *2/*3 or *3/*3 genotype show reduced drug metabolizing activities, with a lower dose requirement, compared with individuals having the wild type Arg144/Ile359 (CYP2C9*1) allele^[24].

Meglitinides^[25]: This group of drugs having similar mechanism of action as Sulfonylureas but binds at a different site on the sulfonylurea receptor. These are metabolised by CYP2C9, CYP2C8 hence the genes affecting these variants increase or decrease the clearance. The other gene affecting the pharmacokinetics of Meglitinides is SLCO1B1 which encodes the organic anion transporter.

Metformin: Uptake of Metformin into hepatocytes by organic cation transporter 1 (OCT1) encoded by gene SLC22A1 is a critical step for achieving its hypoglycaemic effects. Variants in SLC22A1 may be expected to contribute to differential glycaemic response to the drug. Shu et al^[26], were the first to address this possibility by investigating 4 non-synonymous SLC22A1 variants (i.e. R61C, G410S, 420del, and G465R: all of which are associated with reduced OCT1 function) in 21 healthy volunteers given Metformin. A study done by Umamaheshwaran et al in South Indian Population found that the frequency of *OCT1* gene polymorphism was similar to the frequencies observed in African-Americans and other Asian populations but different from those in Caucasians^[27]. Studies done by Song et al, Chen et al found interethnic differences in the genotype and allele frequencies of *OCT1* gene polymorphism when compared with other major populations. Single observational study has reported a significant association of TCF7L2 polymorphisms with sulfonylurea failure but not with Metformin failure^[28].

Thiazolidinediones (TZD): TZD are a class of insulin-sensitizing drugs that are agonists for the nuclear receptor peroxisome proliferator-activated receptor-γ (PPARG). An obvious genetic target to assess pharmacogenetics of TZD therapy is PPARG, the target of TZDs. A specific common variant in PPARG (rs1801282; Pro12Ala) was initially shown to be associated with T2D and insulin sensitivity by Deeb et al^[29], later Wolford et al have shown the association of eight single nucleotide polymorphism (SNP) of PPARG with TZD action^[30]. The other genes involved are APM1 (ACDC) for adiponectin, LPL for lipoprotein lipase, PGC1 and PLIN encoding perilipin.

Alpha Glucosidase Inhibitors: In individuals carrying Gly482Ser polymorphism of PGC1 gene, Acarbose prevented the development of Diabetes mellitus. Acarbose increased the risk of T2DM in patients with TT genotype of +276G/T polymorphism of Adiponectin gene.

Table 6: Genes identified influencing the pharmacokinetic properties

Oral Anti diabetic Drugs	Gene involved	Gene function
Sulfonylureas	Cyp2C9*2 Cyp2C9*3	poor metabolizers
	Cyp2C19*2 Cyp2C19*3	poor metabolizers
Metformin	SLC22A1	Transports Metformin into hepatocytes by OCT1 ^a
	SLC22A2	Transports Metformin into renal epithelium for excretion by OCT2 ^b Variants with T allele - ↓ clearance
	SLC47A1	Excretion of Metformin from cells into bile/urine by MATE1 ^c
	SLC47A2	Excretion of Metformin in urine
Meglitinides	Cyp2C9*3Ile359 Ile	↓ clearance
	Cyp2C8*3Arg13 9Lys	↑ clearance
	SLCO1B1 521 T/C	Changes in pharmacokinetic parameters
	IGF2BP2	
Thiozolidinediones	CYP2C8*1/*3 or *3/*3	↑ clearance

^aOCT1: Organic cation transporter 1; ^bOCT2: Organic cation transporter2; ^cMATE1: Multidrug and toxic extrusion protein

2.3: PGx and Complications of Diabetes: Much of the mortality comes from the microvascular (Nephropathy, Neuropathy, Retinopathy) and macrovascular (ischemic heart disease, peripheral vascular diseases, cerebrovascular diseases) complications arising from DM which correlates with the inadequate glycaemic control. Here we have discussed only few complications and their associated genes.

Diabetic Retinopathy: A study done by Suganthakshmi et al, have shown significant association of gene RAGE rs2070600 polymorphism with Diabetic retinopathy in Indian population ^[31].

Diabetic nephropathy: Multiple studies support association of the ACE II genotype with a lower incidence of diabetic nephropathy and the I/D or DD genotypes with higher incidence ^[32]. In more advanced nephropathy, genetic variants of the protein kinase C-B1 (PRKCB1) gene recently were found to associate with end-stage renal disease in T2DM and by identifying the patients with this gene can benefitted by intensive overall efforts at reducing diabetic nephropathy risk (e.g., intensive control of glycaemia, blood pressure, and dyslipidaemia) ^[33]. The efficacy of any pharmacologic therapy is due to a balance between drug action (pharmacodynamics) and clearance (pharmacokinetics), coupled with a minimal

adverse effect profile. Driven by the recent advances in genetic and other molecular technologies, there is a strong interest in more personalized approaches to diabetes management. Numerous genes that influence pharmacogenetics of oral antidiabetics have been discovered to date. Even though studies suggesting that India will become world Diabetes Capital by 2030, pharmacogenomic studies in India were limited, indicating the need of research in this field. With the concept of personalized medicine we can not only identify the individuals at risk but also can give the right drug for the right individual with lesser adverse reactions. Thus by bringing the probability of “personalized medicine” to realization, this can reduce the disease morbidity, mortality and improve quality of life for individuals with T2DM.

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