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Chapter

From Pharmacogenetics to Gene Expression: Implications for Precision Medicine in Diabetes

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Abstract

Approximately 25–60% of patients show specific pharmacological responses to a particular drug. We call this interindividual variability (IV) response to drugs affecting their efficacy and the appearance of side effects in individuals. This IV may be due to multifactorial components such as genetic factors (single nucleotide polymorphisms, SNPs; and copy number variations, CNV), environmental stimuli, epigenetic modulation, disease/health conditions, or drug interactions, among others. Therefore, these factors can influence the response to the drug by modifying absorption, metabolism, pharmacokinetics (PK), and pharmacodynamics (PD), causing the loss of treatment efficacy or leading to adverse drug reactions with negative consequences for patients. The knowledge in pharmacogenetics (study of pharmacological consequences of single gene mutations) and pharmacogenomics (study of the influence of many gene or gene patterns in the reponse to drugs), disciplines that seek to predict how a specific individual responds to the administration of a particular drug, has advanced by leaps and bounds thanks to "omics" technologies. Nonetheless, despite, the development of next-generation sequencing platforms and the mapping of the human genome have transformed the field of pharmacogenetics, the translational into clinical practice has been slow. Therefore, identification of SNPs that could affect the expression of pharmacogenes in order to make associations with PK and PD will improve our understanding of genetic effects on drug efficacy and transfer it to the clinic. Type 2 diabetes (T2D) represents a national public health problem, not only because of the high frequency of the disease reported worldwide, but also because of the poor adherence to therapeutic management, whose causes have not yet been clarified. One of the challenges in the management of diseases to reach optimal treatment is the complex genetic background. Hence, the integration of multiple levels of pharmacological information, including variation in gene sequence, impact in drug response, and function of drug targets, could help us to predict sources of interpatient variability in drug effects, laying the basis for precision therapy. Thus, the present chapter aims to collect all the available data about genetic variations in pharmacogenes affecting drug response in T2D and integrate it with their effect on gene expression to elucidate their impact in pharmacological efficacy.

Keywords: diabetes, pharmacogenetics, pharmacogenes, expression

1. Introduction

Although there is no consensus in the contribution of genetic component to drug response, many studies from the 1970s have estimated that could be between 20 and 95% of the variability in drug disposition and effects [1]. The difficulty in reaching a consensus is because the contribution of environmental and genetic components to pharmacogenetics cannot be evaluated, through only one approach, that is, analyzing only one drug or group of drugs, or only a SNP or a group of SNPs; we have to talk about PK, PD and related outcomes. In this context, there are a variety of studies focused on PK, or PD, but the convergence of all these concepts has been difficult, so the translation to the clinical practice has been challenging. Along with these barriers are additional factors, such as gene–environment interactions and gene–gene interactions [2]. Moreover, the different responses among ethnicities are another factor to add to this complex phenomenon.

The knowledge on which the participation of genetics in response to the action of drugs in an individual or group of individuals has been generated through various studies, applying different strategies such as those described below. In this regard, in past decades, different laboratories in four countries carried out twin studies with different drugs to determine the contribution of genetic and environmental factors to interindividual variations. The results from all studies converged in that PK variation were similar between monozygotic twins and was preserved within dizygotic twins, and even as similar as the monozygotic twins [3]. Researchers from these laboratories conclude that genetic factors primarily controlled interindividual variations in the metabolism of a wide range of drugs [3–8]. In the field of heritability of antidiabetics drug response, the studies are scarce, but one classic example is tolbutamide. In this context, an intravenous administration to 42 nondiabetic subjects, eight of their relatives, and to five sets of twins, the authors observed a monogenic control of tolbutamide revealed by a heritability value of 0.995 (this value means that considering a trait with 1.0 heritability, such as a Mendelian trait, the genetic factors have a great or complete influence in phenotype; in contrast, a trait with 0.0 heritability will not be influenced by genetic factors) [9]. In a more recent study by Gjesing et al., they found high heritabilities estimations for acute insulin secretion subsequent to glucose stimulation (0.88 ± 0.14), for insulin sensitivity (0.26 ± 0.12), disposition index (0.56 ± 0.14) and disposition index after tolbutamide administration (0.49 ± 0.14) in 284 non diabetic family members of patients with T2D after an intravenous injection of tolbutamide [10]. In another study of genome-wide complex trait analysis in patients in the Genetics of Diabetes Audit and Research in Tayside Scotland (GoDARTS) study, the heritability of glycaemic response to metformin varied by response phenotype, with a heritability of 34% (p = 0·022) for the absolute reduction in HbA_{1c} in 2085 individuals in treatment with metformin [11]. Hence, these studies clearly show that the response to different types or classes of drugs is modulated by the individual's genetics and can be passed on to their descendants showing a clearly genetic component.

2. Variability in drug response in T2D

Diabetes has become a health problem (by 2030, the number of individuals with diabetes is estimated to rise to 578 million and 700 million by 2045) [12]. Approximately, 90–95% of cases of diabetes correspond to T2D. T2D is a chronic metabolic disease characterized by hyperglycemia, resulting from insulin resistance and

reduced insulin secretion, which leads to impaired glucose utilization, dyslipidemia and hyperinsulinemia [13].

The great prevalence of T2D impacts both direct and indirect costs. In 2019, the International Diabetes Federation estimated that total diabetes-related health spending reached $ 760 billion. By the years 2030 and 2045, spending is forecast to reach $ 825 billion and $ 845 billion, respectively [12]. Moreover, approximately the 32% of annual costs per diabetic patient is destined to treatment [14]. Furthermore, approximately 50% of T2D patients have good glycemic control considering HbA1c < 7%, which means that ~50% have poor glycemic control [15]. Besides, as consequence of adverse drug reactions (approximately 20–30%) there is a high prevalence of treatment abandonment [16–18] All these facts denote the need for new drugs or strategies to improve glycemic control. Current treatment to control diabetes is aimed at specific key targets in glucose metabolism such as: adipose and muscle tissue to reduce insulin resistance, or act on the liver to inhibit glucose production, as well as stimulate the pancreas to release insulin. However, it is necessary to go beyond lowering glucose levels. In clinical practice it is often observed that T2D patients who receive identical antidiabetic regimens have significant variability in drug response, hence interindividual variation may be caused by numerous factors, such as genetic factors, physical inactivity, hypertension, age, gender and others [19]. Particularly, the genetic variability of therapy response was recently shown in several independent studies for the common drugs used for T2D treatment. Therefore, identification of genetic variants and their impact in drug response may improve our knowledge in the field, in order to be able of translate it into clinical practice. This could help in decision making on the therapeutic approach, reducing the rates of side effects and improving the adherence to treatment. Thus, the present chapter aims to collect all the available data about genetic variations in pharmacogenes affecting drug response in T2D and integrate them with their effect on gene expression, and to elucidate their impact on pharmacological efficacy.

In order to cover the objective, we compile all the available information about pharmacogenetics and epigenetics in T2D. We carried out a literature search using PubMed and Google Scholar. For this purpose, search words used were the following: diabetes + pharmacogenetics (826 studies); type 2 diabetes + pharmacogenetics (421 studies), diabetes + pharmacogenomics (1,184 studies); type 2 diabetes + pharmacogenomics (456 studies). When we added the words "drug response" the result was 338 and 267 papers, for pharmacogenomics and pharmacogenetics, respectively; or when we added the words "personalized medicine" in the search, we retrieved 152 and 114 papers, for pharmacogenomics and pharmacogenetics, respectively. **Table 1** shows all the studies considered significantly associated with antidiabetics drug response. Regarding the Epigenetics section, this was covered with a literature search using the words diabetes + drug response + epigenetics. **Table 2** shows the reports of epigenetics variations that influence drug response in T2D treatment. All the studies were chosen taking into account glycemic control and significance.

2.1 Single nucleotide polymorphisms

SNPs, are modifications in the DNA sequence, that implies changes in single nucleotides, which are the most common variations and the main source of interindividual diversity [99]. Interindividual variability could be explained in part by SNPs in genes encoding drug-metabolizing enzymes, transporters, receptors and molecules involved in drug metabolism. In this context, many SNPs related with the metabolism of antidiabetic drugs have been described. In the following section we

Drug group	Gene (Encoded protein)	dbSNP ID	Aminoacid change	Population	Effect	References
Biguanides (Metformin)	*SLC22A1* (OCT1)	rs12208357	Arg61Cys	European	Association with metformin intolerance	[20–22]
		rs72552763	Met420del			
		rs34059508	Gly465Arg			
		rs34130495	Gly401Ser		Lower decrease in HbA1c	
		rs1867351	Ser52Ser	Asian	Reductions in PPG and ΔHbA1c	[23]
		rs622342	Intron A > C	South Indian	Less response to metformin	[24]
				European	Decreased reduction in HbA1c levels	[25]
				Mexican	High ΔHbA1c values	[26]
		rs36056065	Indel GTAAGTTG	European	Association with metformin side effects	[27]
		rs628031	Val408Met	Mexican	High ΔHbA1c values	[26]
				Chinese	Reduction in ΔHbA1c and ΔFPG	[23]
				European	Association with metformin side effects	[27]
		rs594709	597 A > G	Mexican	Increase in HbA1c values	[26]
				Chinese	Increase in FINS decrease in HOMA-IS and in QUICKI	[28]
		rs145450955	Thr201Met	Iranian	High HbA1c values	[29]
	SLC22A2 (OCT2)	rs316019	Ala270Ser	Chinese	Higher incidence of hyperlactacidemia	[30–32]
				South Indian	Better response	
		rs3119309	Intergenic	European	Association with metformin inefficiency	[33]
		rs7757336				
		rs2481030				

Drug group	Gene (Encoded protein)	dbSNP ID	Aminoacid change	Population	Effect	References
	SLC47A1 (MATE1)	rs2252281	g. − 66 T → C	European African American	Enhanced response	[34]
		rs2289669	g. − 130G → A	European	Association with reduction in HbA1c levels	[35]
	SLC47A2 (MATE2)	rs12943590	Gly211Val		Reduced response	[34]
				South Indian	Better response	[31]
		rs34399035	Gly393Arg	European	Lower decrease in HbA1c	[22]
	SLC2A2 (GLUT2)	rs8192675	Intron C > T	European American African American Asian American Latino	Reduction in HbA1c values	[36, 37]
					Reduction in blood glucose	
	C11orf65 (MFI)	rs11212617	Intron C > A	European	Association with treatment success	[38]
	CPA6 (CBPA6)	rs2162145	UTR variant T > A / C/G	European African American	Better response	[39]
	PRPF31 (PRP31)	rs254271	Intron T > A /C/G		Worse response	
	STK11	rs2075604	Intron G > T	Chinese	Better therapeutic efficacy	[32]
	CAPN10 (CAN10)	rs3792269	Arg197Gly	European African American	Association with less treatment success and with smaller reduction in HbA1c	[40]
	SP1	rs784892	Intron G > A	European American African American Asian American	Association with decreased efficacy	[41]

Drug group	Gene (Encoded protein)	dbSNP ID	Aminoacid change	Population	Effect	References
	FMO5	rs7541245	Intron C > A	Not provided	Association with decreased glycemic response (decrease response to metformin)	[42]
	SLC22A3 (OCT3)	rs2076828	C > G	European African American	Association with reduced response	[43]
Sulfonylureas	*CYP2C9*	rs1799853 (*2)	Arg144Cys	European	Greater response to sulfonylureas	[44, 45]
		rs105791o (*3)	Ile359Leu	Mexican	Association with good glycemic control	
	ABCC8	rs757110	Ser1369Ala	Chinese	Association with FPG, 2 h plasma glucose and HbA1c decrease	[46, 47]
					Association with therapeutic efficacy	
		rs1799854	Intron C > T	European	Lower HbA1c concentration	[48]
		rs1799859	Arg1273Arg			
		rs1801261	Thr759Thr	Chinese	Less reduction in FPG and HbA1c levels	[49]
	KCNJ11 (KCJ11)	rs5219	Glu23Lys	European Chinese	Better response	[50, 51]
				Mexican	Lower response	[52]
		rs5210	UTR G > A	Chinese	Association with FPG decrease	[46]
	KCNQ1	rs163184	C > G	European	Lower FPG response	[53]
		rs2237892	Intron C > T	Chinese	Association with treatment success	[54]
		rs2237895	Intron A > C, T		Association with treatment success	
	TCF7L2 (TF7L2)	rs7903146	Intron C > T	European	Lower effect of gliclazide	[55]
		rs12255372	Intron G > T		Association with therapeutic failure	[56, 57]
	NOS1AP (CAPON)	rs10494366	Intron G > C/T		Less effectiveness of treatment	[58]

Drug group	Gene (Encoded protein)	dbSNP ID	Aminoacid change	Population	Effect	References
	IRS1	rs1801278	Gly972Arg	African	Association with increased risk for secondary failure	[59, 60]
				European		
	ABCA1	rs9282541	Arg230Cys	Mexican	Association with decreased response to treatment	[61]
Thiazolidinediones	*PPARG2* (PPARγ2)	rs1801282	Pro12Ala	Chinese	Association with better response	[62, 63]
					Higher ΔFPG	
		rs880663	Intron A > G	Mexican American	Association with response to troglitazone	[64]
		rs4135263	Intron T > C			
		rs1152003	G > C			
		rs6806708	G > T			
		rs13065455	C > A/G			
		rs13088205	T > G			
		rs13088214	T > C			
		rs13073869	Intron G > A/C			
	PPARGC1A (PGC-1α)	rs8192678	Gly482Ser	Chinese	Reduced ΔFPG and ΔFINS	[65]
		rs2970847	Thr394Thr		Reduced ΔPINS	
	UCP2	rs659366	−866 G/A	Chinese	Smaller attenuated PINS and greater attenuated HbA1c	[66]
	CYP2C8	rs10509681 (*3)	Lys399Arg	European	Association with reduced glycemic response	[67]
	SLCO1B1	rs4149056	Val174Ala	European	Association with enhanced glycemic response	[67]

Drug group	Gene (Encoded protein)	dbSNP ID	Aminoacid change	Population	Effect	References
	KCNQ1	rs2237892	Intron C > T	Chinese	Larger augmentation in Δ2h glucose	[54]
		rs2237895	Intron A > C/T		Greater decrement in ΔHbA1c	
	ADIPOQ (ADPN)	rs266729	−11377 C > G		Attenuated rosiglitazone effect	[68]
		rs2241766	GLy15Gly		Attenuated ΔFINS	
					Greater decrease in HbA1c and association with pioglitazone treatment	[69]
		rs1501299	SNP + 276 G > T	Korean	Smaller reductions in FPG and HbA1c	[70]
		rs182052	−10068 G > A	Chinese	Increased reduction in HbA1c	[71]
	RETN	rs1862513	−420 C > G	Japanese	Correlation with reduction of HbA1c	[72]
	LEP	rs7799039	G-2548A	Chinese	High differential values of FINS and PINS	[73]
	TNFA	rs1800629	G-308A		Lower values of FINS	
	PTPRD	rs17584499	Intron C > T		Higher ΔPPG	[63]
DPP-4 inhibitors	*TCF7L2* (TF7L2)	rs7903146	Intron C > T	European African Asian	Lower reduction of HbA1c	[74]
	KCNJ11 (KCJ11)	rs2285676	UTR A > G/T	Asian	Association with better response	[75]
	CTRB1/2	rs7202877	T > C/G	European	Smaller decrease of HbA1c	[76]
	KCNQ1	rs163184	Intron T > C/G		Association with a reduced glycemic response	[77]
	GLP1R	rs3765467	Arg131Gln	Korean	Association with HbA1c reduction	[78–80]
		rs6923761	Gly168Ser	European		
	DPP4	rs2909451	Intron C > T	Not Provided	Association with DPP-4 activity	[81]
		rs759717	Intron G > C			
		rs6733162	Intron G > C/A			

Drug group	Gene (Encoded protein)	dbSNP ID	Aminoacid change	Population	Effect	References
	PRKD1	rs57803087	Intron A > G	Taiwanese	Association with DPP-4 inhibitor response	[82]
	ABCB1 (MDR1)	rs1128503	Gly412Gly	Asian	Association with response to therapy	[83]
	CDKAL1	rs7754840	Intron C > G	Japanese	Association with HbA1c reduction	[84]
		rs7756992	Intron A > G			
GLP-1 receptor agonists	GLP1R	rs10305420	Pro7Leu	Chinese		[85]
	TCF7L2 (TF7L2)	rs7903146	Intron C > T	Brazilian	Association with PINS	[86]
		rs761386	Intron C > G/T	Taiwanese	Association with changes in the standard deviation of plasma glucose	[87]
	SORCS1 (SORC1)	rs1416406	A > G/T	Chinese	Association with FINS	[88]
	CNR1	rs1049353	Thr453Thr	European	Association with improvement of insulin resistance	[89]
SGLT2 inhibitors	*UGT1A9*	rs72551330	Met33Thr	Not Provided	Higher AUC (26%)	[90, 91]
	SLC5A2 (SGLT2)	rs9934336	Intron G > A	European	Association with reduced 30-min plasma glucose	[92]

OR: Odd ratio; BG: Blood glucose; FINS: Fasting serum insulin; PINS: Postprandial serum insulin; PPG: Postprandial plasma glucose; HOMA-IS: Insulin sensitivity by homeostasis model assessment; HOMA-IR: Insulin resistance by homeostasis model assessment; HOMA-BCF: homeostatic index of percentage of β-cell function; FBG: fasting blood glucose; FG: fasting glucose; AUC: Area under the curve. The gray cells indicate a haplotype associated with metformin intolerance in the study of Dujic et al. in 2015 [21].

Table 1.
Changes in DNA sequence that influence T2D treatment.

Drug Metabolism

Drug group	Gene /miRNA (Encoded protein)	CpG site	Effect	References
Biguanides (Metformin)	CFAP58 (CFA58)	cg03529510	Association with glycemic metformin response	[93]
	OR4S1	cg05402062		
	GPHA2	cg16704073		
	SAP130 (SP130)	cg16240962		
	SEPT11 (SEP11)	cg01070242		
	LRRN2	cg05151280		
	CSTT	cg07511259		
	SCYL1	cg27553780	Association with metformin intolerance	
	FOXA2 (HNF-3B)	cg12356107		
	PGM1	cg02994863		
	FAM107A (F107A)	cg08148545		
	SLC22A1 (OCT1)	cg24864413	Lower DNA methylation and lower glucose levels	[94]
	SLC22A3 (S22A3)	cg06295784		
		cg07883823		
	SLC47A1 (MATE1)	cg01530032		
		cg07829432		
		cg12550399		
	miR-192	N. A.	Decreased fasting glucose and HbA1c	[95, 96]
	miR-140-5p			
	miR-222			
Sulfonyulureas	KCNJ11 (KCJ11)	N.R..	26.2% vs. 27.2%	[97]
	ABCC8		0% vs. 7.2%	
SGLT2 inhibitors	miR30e-5p	N. A.	Upregulated	[98]
	miR199a3p		Downregulated	

N.R. Not reported.

Table 2.
Epigenetics variations that influence T2D treatment.

described the most significant SNPs associated with drug response, specifically glycemic control, with antidiabetics treatment.

2.1.1 Biguanides (Metformin)

First-line drugs in T2D therapy are biguanides, however, when the patient is not obese, the sulfonylureas group is usually prescribed and the response to treatment will be evaluated after 3 months [100]. Guidelines from the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommend early initiation of metformin as a first-line drug for monotherapy and combination therapy for patients with T2D [101]. Approximately 30% of patients with T2D do not respond to metformin and about 20 to 30% experience intolerable side effects [102]. There is considerable variability in the glycemic response and PK characteristics of metformin. In terms of PK, metformin

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is not metabolized, and is excreted unchanged in the urine, with a half-life of roughly 5 h. In particular, mean plasma concentrations of metformin fluctuate between 0.4 and 1.3 mg/L at a dose of 1,000 mg twice daily [103].

The disposition of metformin includes elimination and tissue distribution, which in turn involves organic transporters (OCTs) and multidrug and toxin extrusion proteins (MATEs); both may contribute to the wide variation in metformin PK. Metformin response variability is important, in fact >30% of patients receiving metformin are classified as poor responders [102]. This drug is a polar molecule largely eliminated by the kidney without undergoing hepatic metabolization. The processes of uptake and secretion of metformin are highly dependent on membrane transporters, among which are solute carrier family 22A members 1 and 2 (SLC22A1/OCT1 and SLC22A2/OCT2, respectively), multidrug and toxin extrusion proteins MATE1 (SLC47A1) and MATE2 (SLC47A2) and the plasma membrane monoamine transporter PMAT (SLC29A4/hENT4). Therefore, impacting variants in any of these transporters may have an influence in metformin efficacy and adverse effects (**Table 1**). In this context, the most studied genes are SLC22A1/OCT1, SLC22A2/OCT2, SLC47A1/MATE1 and SLC47A2/MATE2. Genetic variants in SLC22A1/OCT1 are responsible for the adverse gastrointestinal effects experienced by many patients with T2D diabetes who use metformin. Dujic et al. found that 47% of participants with T2D, incident users of metformin, experienced gastrointestinal adverse effects. In the study the number of SLC22A1/OCT1 reduced-function alleles was highly correlated with over two-fold risk of gastrointestinal side effect development [20]. Consequently, the gastrointestinal adverse effects and in some cases intolerance to metformin could lead to treatment abandonment. In this same gene other variants associated to metformin response have been reported. As it can be seen in **Table 1**, most of the reported variants are related to a decrease in the effect of metformin, reflected in the less reduction in HbA1c levels (high concentration of HbA1c). In contrast variant rs316019 in SLC22A2/OCT2 is associated with lactic acidosis and better response to metformin, due to the evidence that this variant is related to a reduced level of metformin clearance [30, 104]. Therefore, patients with these variants may benefit receiving alternative therapy instead metformin.

The studies that evaluated the role of SLC47A1/MATE1 and SLC47A2/MATE2 SNPs in PK and PD in patients receiving metformin revealed that promoter variants in MATE1 (g.-66 T → C, rs2252281; g.-130G → A, rs2289669) are associated with a greater response to the drug in T2D patients [34, 35]. Interestingly, it is also reported that the MATE1 variant affects the PD but not the PK of metformin, a very important finding that reveals that the distribution of drugs occurs in response to the organ-specific location of the various transporters [34]. Most studies have associated variants in SLC47A2/MATE2 with contradictory effects. Concerning rs12943590, it was related to a reduced response in European populations and a better metformin response in South Indian populations; whilst rs34399035 was associated with a reduced response to metformin in European populations [31, 34]. It is important to mention that the studies were carried out in different populations, and that investigations in other ethnicities had not found associations between these variants and metformin response [105, 106]. In a recent meta-analysis by Dujic et al. there was no association between rs12943590 and glycemic response [107]. Nonetheless, it is important to note that SNP-drug interactions and SNP-SNP interactions cannot be ruled out, since the presence of other SNPs also modulate the response to drugs and are different in each individual, thus, genotyping of these SNPs should be considered if it is desired apply personalized medicine in diseases such as T2D [34].

Other SNPs in candidate genes such as SLC2A2/GLUT2 (solute carrier family 2/Glucose transporter 2) have been associated with reduction in HbA1c or treatment success, together with rs11212617 in *C11orf65* (MFI, inhibitor of mitochondrial

fission), in rs2162145 CPA6 (encoded protein CBPA6, this peptidase may convert inactive angiotensin I into the biologically active angiotensin II) and rs2162145 in STK11 (serine/threonine-protein kinase involved in cell metabolism) [36–39]. In contrast, variants in genes *PRPF31* (PRP31), CAPN10 (CAN10), SP1, FMO5 and *SLC22A3* (OCT3) are related to reduced response to metformin. Nonetheless, these associations have not been replicated in other studies or populations.

2.1.2 Sulfonylureas

Sulfonylureas are a class of oral antidiabetic agents widely used for the management of T2D [108]. They are chosen in the first line of treatment if the patient does not present with obesity or with insulin resistance or if there is intolerance or contraindication to metformin. Also, they are used in the second line in combination with other oral hypoglycemic agents, such as metformin [109]. According to the 2003–2016 National Health and Nutrition Examination Survey (NHANES), sulfonylurea monotherapy decreased from 33–8%, nonetheless, the combination with insulin or metformin was used in 50% of patients in the mentioned period [110]. Patients with a short duration of diabetes with residual beta cell function (high C-peptide levels) are likely to be most responsive to sulfonylurea therapy [111]. The mechanism of action of sulfonylureas consists of promoting insulin secretion via binding to sulfonylurea receptor 1 (SUR1), an element of the ATP-sensitive K+ (KATP) channel. The link between sulfonylurea and SUR1 inhibits the K-ATP channel, depolarizing the β cells, increasing intracellular Ca^{2+}, and consequently insulin granule exocytosis [112]. The rise of insulin levels regulates postprandial glycemia, stimulating peripheral glucose utilization [113]. Despite, sulfonylureas have a relatively short half-lifes (3 to 5 hours); they can cause hypoglycemia, which affects the quality of life and adherence to therapy in patients with T2D [114]. Two studies have reported hypoglycemia had occurred in 16–39% of patients treated with sulfonylureas [115, 116]. As a consequence, it has been estimated that 10–20% of individuals treated with sulfonylureas do not attain adequate glycemic control and 5–10% initially responding to sulfonylurea subsequently lose the ability to maintain normal glycemic level [117].

The most commonly used sulfonylureas, including the second-generation: glyburide, glipizide, and glimepiride are mainly metabolized through the cytochrome P450 (CYP) 2C9 enzyme. CYP2C9 belongs to the cytochrome P450 gene family and is the enzyme most abundantly expressed in liver. Indeed, CYP2C9 accounts for approximately 20% of total hepatic P450 protein, based on mass spectrometry quantitation [118]. It contributes to the metabolism of approximately 15% of all drugs that are subject to P450-catalyzed biotransformation, and it is responsible for >25% of metabolic clearance of oral hypoglycemic agents, such as chlorpropamide, glibenclamide, gliclazide, glimepiride, nateglinide and tolbutamide [119, 120]. Although CYP2C9 is highly polymorphic, however, only two polymorphisms have shown impact in enzyme expression and function, both allelic variants CYP2C9*2 (Arg144Cys, rs1799853) and CYP2C9*3 (Ile359Leu, rs1057910), encode proteins with less enzymatic activity for the metabolism of several substrates compared with the wild-type allele CYP2C9*1 (Arg144/Ile359). CYP2C9*2 and CYP2C9*3 are generally associated with more than 80% reduction in CYP2C9-mediated intrinsic clearance, while the effect of CYP2C9*2 is generally slightly smaller and varies considerably, depending on the substrate [120]. In both cases patients present more drug event reactions. Some studies have shown that CYP2C9 loss-of function alleles CYP2C9*2/*3 are associated with higher sulfonylurea levels and greater response to sulfonylureas. In the Go-DARTS study, patients with two copies of a loss-of-function allele were 3.4 times more probable to reach good glycemic control compared with patients with two wild-type CYP2C9 alleles,

corresponding with a 0.5% greater reduction in HbA1c [44, 45]. In several pharmacokinetic studies the two variants rs1799853 and rs1057910 in CYP2C9 have been associated with hypoglycemic events, suggesting identification of these variants as a tool to predict adverse effects of these drugs in the patients with T2D [121].

Polymorphisms in KCNJ11, ABCC8, NOS1AP, TCF7L2, CYP2C8, KCNQ1, and IRS1 genes have been associated with altered therapeutic response to sulfonylureas, which will be described below [122]. ABCC8 and KCNJ11 encode K-ATP channel proteins SUR1 and Kir6.2, respectively, both form the K-ATP channel, which controls glucose-dependent insulin secretion in pancreatic β-cells [123, 124]. It has been reported that 50% of cases of neonatal diabetes are caused by mutations in KNJ11 or ABCC8 (SUR1) [125]. Therefore, genetic variants in ABCC8 and KCNJ11 genes could influence K-ATP channel function of beta cells, leading to changes in depolarization of the cell membrane and impact insulin secretion. Most studied SNPs in the ABCC8 gene include rs757110 (Ser1369Ala), rs1799854 (intronic variant) and rs1799859 (Arg1273Arg). Feng et al. demonstrated the association of the Ser1369Ala variant in the ABCC8 gene with fasting plasma glucose test (FPG) and two-hour plasma glucose after oral glucose tolerance test decreases after 8 weeks of gliclazide therapy. Additionally, the authors found a nominal association of the variant with levels of HbA1c, suggesting a role of this SNP on antidiabetic efficacy of gliclazides [46]. Several authors have attempted to associate this variant with insulin secretion; however, the findings have been contradictory. A study in the Diabetes Prevention Program population that includes Caucasian, African Americans, Hispanic Americans, American Indians and Asian Americans, found an association with a significantly lower insulin index, nevertheless, other studies failed to replicate this association [126–128]. Despite these data, it is interesting to mention that variant Ser1369Ala has been related with progression to diabetes [126]. Nikolac et al., found that rs1799854 and rs1799859 in the ABCC8 gene were associated with sulfonylurea efficacy in Caucasians, evidenced by significantly lower HbA1c concentrations in carriers compared with noncarriers [48].

As mentioned above, the KCNJ11 gene encodes the Kir6.2 subunit; four pore forming subunits assemble with four regulatory subunits of SUR1 to form the K-ATP channel of the β-cell [129]. Two SNPs have been associated with sulfonylureas response, rs5219 and rs5210. The rs5219 (Lys23Glu, p.E23K) A allele plays an important role in insulin secretion through reduction of ATP sensitivity of the K-ATP channel and suppression of insulin secretion. Previous studies, have demonstrated that carriers of a common variant, E23K, with normal glucose tolerance showed up to 40% reduction in glucose-stimulated insulin secretion [130, 131]. However, the mechanism of action of this locus in the insulin secretion pathway is still not completely understood. Although early observations have reported that E23K carriers exhibit higher predisposition to secondary failure when treated with sulfonylureas, other investigations have associated this variant with a better response to sulfonylureas [50, 51, 132, 133]. Additionally, some studies have suggested that the presence of the E23K variant is related to the severity of hypoglycemia in patients with sulfonylureas therapy or with lower response [52, 133]. Regarding rs5210, it has been reported that the G allele acts as a potential target for miR-1910, which is implicated in T2D; however, the mechanism of action of this miRNA in the development of T2D is unknown [134]. Moreover, variant rs5210, has been associated with gliclazide response, revealed by decreased levels of FPG test in carriers of this SNP [46].

The KCNQ1 gene belongs to a large family of voltage-gated K+ channels [135]. Although KCNQ1 is mainly expressed in the tissues or cells in the heart, it is also expressed in other tissues or organs such as pancreas islets [136]. Blockading the channels with KCNQ1 inhibitors, might stimulate secretion of insulin in pancreas, suggesting the association of KCNQ1 with the regulation of insulin secretion,

specifically with reduced insulin secretion [137]. The intronic SNPs rs2237892 and rs2237895 were shown to increase gliclazide efficacy, whereas the intronic variant rs163184, was reported to lower-sulfonylureas effects on FPG levels [53, 54].

The transcription-factor-7-like-2 (TCF7L2) gene encodes the transcription factor 7 like-2 [138]. TCF7L2 can act through GLP-1 protein (Glucagon Like Peptide 1), which plays a central role in glucose homeostasis and is involved in the regulation of insulin secretion [139]. Several studies have suggested that TCF7L2 stimulates the proliferation of β-cells in the pancreas and facilitate the production of GLP-1 in intestinal cells. In this context, it is postulated that the SNP rs7903146 could decrease the expression levels of TCF7L2 in the pancreas and lead to lower secretion of insulin due to the decreased levels of GLP1. However, the association between TCF7L2 and T2D is more complex and is not limited to the decrease in GLP1, but also to alterations in other processes regulated by TCF7L2 such as the differentiation of pancreatic beta cells, in the normal metabolism of cholesterol and in the production of other incretins [140]. Pearson et al. determined the association of two genetic variants rs1225372 and rs7903146 in TCF7L2 with the treatment success of sulfonylurea therapy in T2D patients. It was shown that 12% of the diabetic population are homozygous carriers of SNP rs1225372 and were twice as unlikely to achieve good glycemic control within 1 year of treatment initiation compared to 42% of the population with wild type [56]. These findings were replicated in Indian and European populations among others [57, 141]. Therefore, carriers of these variants are at high risk of therapy failure with sulfonylureas.

The rest of SNPs that were associated with decreased response to sulfonylurea treatment and are found in the following genes: nitric oxide synthase 1 adaptor protein (NOS1AP), insulin receptor substrate 1 (IRS-1) and ATP binding cassette subfamily A member 1 (ABCA1). NOS1AP binds to neuronal nitric oxide synthase (nNOS). This enzyme plays a role in the electrical current of the heart and in insulin release from pancreatic β cells [142, 143]. Some polymorphisms in the NOS1AP gene have been described as predictive markers of cardiovascular mortality in diabetics treated with sulfonylureas. In patients with the rs10494366 TG/GG genotypes, glibenclamide is less effective in reducing glucose levels and mortality rates compared with the wild type TT genotype. By contrast, mortality risk was lower in tolbutamide and glimepiride users who carried a G allele compared with the T/T genotype [58]. Of note, no genotype differences in mortality were observed in metformin or insulin users. The mechanisms through which this polymorphism influenced mortality risk and the reason why this association differed based on the type of sulfonylurea used are unclear. Moreover, it was shown that in users of glibenclamide the TG and GG genotypes were associated with an increased risk of mortality; in tolbutamide and glimepiride users, the TG or GG genotypes were associated with a reduced risk of mortality [144]. Conversely, in a Korean study no significance was found between rs10494366 in the NOS1AP gene and response on glimepiride treatment [145].

Regarding rs1801278 in the ISR-1 gene, this variant has been associated with increased risk for secondary failure in African an European populations [59, 60]. In case of rs9282541, T2D patients carriers of variant needed a higher dose of glyburide in order to achieve the same glucose lowering effect that persons with the wild type variant [61].

2.1.3 Thiazolidinediones

Thiazolidinediones (TZDs) are pharmacologic agents that specifically treat insulin resistance. TZDs are effective at lowering HbA1c by ∼1–1.25% on average [146]. Despite durability in action, TZDs show weight gain which has limited their clinical utility [147, 148]. For every 1% reduction in HbA1c, an estimated 2–3%

weight gain is reported [149]. TZDs are transported into the liver by OATP1B1 (encoded by *SLCO1B1* gene*)* and metabolized by CYP450 2C8 enzyme (encoded by *CYP2C8* gene) [150, 151]. The most studied variant allele in the CYP2C8 gene is CYP2C8*3, which comprises two linked polymorphisms at codon 139 and codon 399 (Arg139Lys; Lys399Arg) [152].

TZDs decrease insulin resistance directly through activation of peroxisome proliferator-activated receptors-γ (PPARγ) receptors, which facilitate differentiation of mesenchymal stem cells into adipocytes, promote lipogenesis in peripheral adipocytes, decrease hepatic and peripheral triglycerides, decrease activity of visceral adipocytes, and increase adiponectin. These primary effects of TZDs markedly ameliorate insulin resistance and decrease insulin requirements [153, 154]. Individuals differ in drug response, and $\sim$ 20–30% of diabetic patients fail to respond to thiazolidinediones [155]. To date, numerous case–control studies have been conducted to identify the possible relationship between PPARG gene polymorphisms with the risk of T2D in various ethnic populations [156]. The most common variant is located at exon-2 of PPARG, rs1801282, and consists of a non-synonym change Pro12Ala. This substitution leads to a change in the structure of PPARγ protein, which in turn decreases the binding effect of target genes, and reducing transcriptional activity [157]. PPARγ is also the target of antidiabetic TZD drugs, which have a unique and powerful insulin-sensitizing effect [158].

2.1.4 DPP-4 inhibitors/GLP-1 receptor agonists

Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) are enzyme inhibitors that inhibit the enzyme dipeptidyl peptidase-4 (DPP-4). Inhibition of the DPP-4 enzyme prolongs and enhances the activity of incretins which play an important role in insulin secretion and blood glucose regulation [159]. DPP-4 is a 766 amino acid transmembrane glycoprotein, which is also known as adenosine deaminase or CD26, is a ubiquitously expressed glycoprotein of 110 kDa, which was first characterized by Hopsu-Havu and Glenner [160].

The DPP4 gene encodes a serine aminopeptidase enzyme, which inactivates GLP-1, GIP and other proteins via dipeptide cleavage of the N-terminal amino acid. Other DPP-4 substrates include peptides containing proline or alanine, such as growth factors, chemokines, neuropeptides, and vasoactive peptides [161].

Inhibitors of DPP-4 reversibly inhibit the hydrolysis of endogenous incretins, which increases plasma levels of GIP and GLP- 1, producing an increase in insulin response and a decrease in glucagon secretion. Therefore, the increase in the concentration of GLP-1 in plasma is the pharmacological effect of DPP-4 inhibitors, which increases insulin synthesis in β cells of the pancreas, stimulates the growth of these cells and prevents apoptosis [162]. Hence, DPP4 inhibition leads to greater exposure to incretins and therefore prolongs the half-life of insulin action. Because of this, DPP4 became a major target for the treatment of T2D [163].

However, it has recently been reported that some patients taking DPP-4 inhibitors are at increased risk of heart failure. It has been suggested that DPP-4 polymorphisms could potentially lead to a change in gene expression in renal cells in patients with T2D; these changes would be related to the renin-angiotensin-aldosterone system causing cardio-renal damage or myocardial hypertrophy, however further studies are needed to clarified the impact of these polymorphisms in DPP-4 inhibitors response [164].

2.1.5 SGLT-2 inhibitors

Sodium-glucose cotransporter inhibitors are adjunctive medications in the treatment of T2D. These drugs decrease HbA1c concentrations in diabetic patients,

with few adverse effects seen to date. In a healthy adult, the kidneys filter approximately 180 g of glucose per day, this is almost entirely reabsorbed into the circulation and less than 1% of glucose is excreted in the urine filtered. This reabsorption is possible thanks to the action of a family of transmembrane proteins called sodium-glucose cotransporters (SGLT, sodium glucose co-transporter) [165]. So far, seven types of sodium-glucose transporters have been identified. Particularly, type 2 (SGLT2) is responsible for glucose renal reabsorption; and is mainly found in the epithelial cells of the proximal convoluted tubule.

Glycosuria, which was initially observed as an etiopathogenic component of some renal and urinary complications in patients with T2D, has been proposed as a means to lower glucose concentrations through the pharmacological use of SGLT2 inhibitors [166]. Some SGLT-2 inhibitors can be glucuronidated by UGT enzymes (UDP-glucuronosyltransferase), thereby polymorphisms like UGT1A9*3 allele (rs72551330), in the genes encoding these drug-metabolizing enzymes could potentially influence its response. Despite, higher values of area under the curve (AUC) of canaglifozina in carriers if UGT1A9*3, the studies have not found clinical implications [90, 91]. Recently Zimdahl et al. found that common genetic variants in the SLC5A2 gene do not affect diabetes-related metabolic traits and they do not have a clinically relevant impact on response to treatment with the SGLT2 inhibitor empagliflozin [167]. Nonetheless, a study in a Caucasian population showed that rs9934336 carriers presented increased 30-min glucose concentrations after oral glucose tolerance test [92]. Studies on these drugs are few, because SGLT2 inhibitors are relatively recent. Thus, the efficacy and safety evaluation of these drugs in various clinical settings has not yet been fully established.

2.2 Epigenetics

Despite, the major contribution in drug response can be attributed to genetic components, common genetic polymorphisms explain only less than half of this genetically encoded variability, thus it is important to address other factors of drug response, such as pharmacoepigenomics [168].

Pharmacoepigenomics combines the analysis of genetic variations and epigenetic modifications in an effort to advance personalized medicine [169]. Epigenetic modification refers to processes that modify DNA or chromatin structure in a manner that alters the level of expression of genes but not the DNA sequence itself. Chemical processes that fall into the realm of epigenetics include DNA methylation and post-translational modifications of histones such as the addition of methyl, phosphate, and acetyl groups. These modifications influence the overall chromatin structure and the availability of gene regulatory regions to transcription machinery [170].

On the other hand, regulatory processes involve molecules such as miRNAs. Although miRNAs do not directly interact with DNA, they inhibit mRNA translation, therefore it is considered as having epigenetic effects [158].

Specific genes can be expressed or silenced depending on specific stimulators, such as hormone levels, dietary components or drug exposure, and can also accommodate gene-expression changes in response to gene–environment interactions [171]. Although, the cellular machinery responsible for the secretion of miRNA is not fully understood yet, it is recognized that miRNAs are packaged into microvesicles, exosomes, lipid drops and apoptotic bodies by a broad range of cell types and can be found in various types of body fluids, such as serum, plasma, and urine [172]. The miRNAs participate as negative regulators in post-transcriptional processes inhibiting mRNA translation or degrading the mRNA via the seed sequence region at the 5′ end of the miRNA, which allows the binding to its

3-´untranslated region (3 -UTR) of mRNA. miRNAs are estimated to affect approximately 30% of the process of protein coding genes [173]. A single miRNA is responsible for the expression of hundreds of proteins, and a protein-coding gene can be modulated by more than one miRNA, this is therefore a highly complex mechanism, but its results largely contribute to inter-individual variability in response to drugs. Although the study of miRNAs has focused on their involvement in the genesis of some complex diseases [174, 175] there is some evidence about their participation in the response to treatment in T2D. Interestingly the treatment with dapagliflozin (an inhibitor of sodium-glucose co-transporter 2, SGLT2), but not with hydrochlorothiazide (useful in treating high blood pressure), significantly up-regulated miR30e-5p and downregulated miR199a-3p ($P < 0.05$). These miRNAs are involved in the pathophysiology of heart failure and suggest a cardioprotective effect of SGLT2 inhibitor response [165].

Metformin can also interfere with the levels of miRNAs in the blood, which results in a change in the expression of the genes that are controlled by these. Ortega et al. have shown that increasing the dose of metformin modifies the levels of circulating miRNAs (started at a 425 mg/day and increased progressively during the first week to reach 1,700 mg/day), increased miR-192 (49.5%; $P = 0.022$) and decreased miR-140-5p (-15.8%; $P = 0.004$), and miR-222 (-47.2%; $P = 0.03$), in parallel to decreased fasting glucose and HbA1c. Revealing the response of circulating miRNAs to metformin therapy [95].

The information generated on miRNAs and their molecular actions place these molecules as innovative applications in the industry. Among the most promising prospects is the use of miRNA in medical therapy. Future studies of miRNAs that allow the generation of knowledge about their probable role in the modulation of pharmacogene expression will undoubtedly contribute to personalizing the treatment of T2D. miRNA-based therapies offer advantages over other nucleic acid therapies, because miRNAs are efficient silencers and, in contrast to plasmid DNA or synthetic oligonucleotides, miRNAs are naturally found in the bloodstream. As they target multiple mRNAs, the resulting synergistic effects could be positive for therapy, however, there are still multiple aspects that must be addressed before application to clinical trials in various human pathologies, among them, to identify the best miRNA candidates of miRNA targets for each disease type, the design of more efficient vehicles for the targeted delivery of oligonucleotides to specific organs, as well as avoiding potential toxicities and off-target effects. Low toxicity and good tolerance in patients treated with antagomiR a 15-nucleotide locked nucleic acid–modified antisense oligonucleotide whose action is sequestering mature miR-122 in a highly stable heteroduplex, thereby inhibiting its function avoiding the stability and propagation of hepatitis C virus (HCV), supporting the beneficial role of miRNAs in therapy [176]. miRNAs are naturally endogenous regulators of cell processes that are often dysregulated in diabetes restoration of any given miRNA function to normal levels will be the ultimate therapeutic goal. Several miRNAs appear to affect the function of the differentiated state of the pancreatic β-cell, while miRNAs in skeletal muscle, the liver, and adipose tissue constitute sets of different miRNAs, which is why the choice of the best molecules to treat this disease becomes very complex. Several challenges will need to be overcome in the field of pharmacotherapy with miRNA in the control of diabetes, but they will undoubtedly contribute to personalizing the treatment of this disease.

It has been suggested that epigenomics may act synergistically with pharmaco-genomics towards optimization of drug therapy [177]. In addition, epigenomic somatic alterations represent an emerging class of biomarkers that hold promise for personalized therapy particularly to overcome drug resistance [178].

Regarding methylation, García-Calzón et al. evaluated the potential blood epigenetic markers associated with metformin glycemic and intolerance response. They analyzed DNA methylation in blood from newly diagnosed patients with T2D after 1.5 years of metformin treatment. According to the authors, the methylation risk scores explain 68–73% of the variation in glycemic response to metformin. In addition, the methylation risk scores explain 50–51% of the variation in metformin tolerance. In the same study, the researchers also assessed whether any of 26 SNPs previously associated with metformin response were associated with DNA methylation of any of the identified epigenetic markers. They identified one significant association between a SNP in SCL22A1 (rs628031) and DNA methylation of cg05151280 (P = 0.001, q = 0.028). The A/A genotype carriers had lower methylation (83.6 ± 2.3%) compared to carriers of the G/G (85.3 ± 1.9%, P = 0.002) and G/A (85 ± 1.8%, P = 0.006) genotypes in 132 participants from the discovery and replication cohorts. Lower methylation of this CpG site was associated with a better glycemic response to metformin (**Table 2**) [93]. In previous work from the same group, they assessed the DNA methylation in OCT1 encoded by *SLC22A1*, OCT3 encoded by *SLC22A3*, and MATE1 encoded by *SLC47A1* liver biopsies from gastric bypass surgery. Lower promoter DNA methylation of *SLC22A1*, *SLC22A3*, and *SLC47A1* were found in diabetic subjects receiving metformin. These findings suggest that metformin decreases DNA methylation of metformin transporter genes in the human liver, in contrast with the higher methylation levels in these genes associated with hyperglycemia and obesity. These findings show how a drug is capable of modulating gene expression however, the presence of genetic variants in these genes would be interfering with the methylation process with unexpected results [94].

Methylation in KCNJ11 and ABCC8 gene promoters in T2D patients receiving sulfonylurea therapy have been assessed by Karaglani et al., their results show that epigenetic changes such as methylation influence interindividual variability in treatment with sulfonylureas. They considered hypoglycemia as an outcome of the treatment. KCNJ11 methylation was detected in 21.6% of hypoglycemic individuals and in 27.7% of non-hypoglycemic patients (P = 0.353) in this study, while ABCC8 methylation in 7.2% of non-hypoglycemic and none of the hypoglycemic patients (P = 0.012). These findings suggest that ABCC8 methylation is associated with hypoglycemic events in sulfonylurea-treated T2D patients [97].

3. Conclusions

The interindividual variability in the response to a drug is the consequence of various factors, including pharmacokinetic causes: absorption, distribution, metabolization and excretion of the drug that affects the intensity and duration of the response, or to pharmacodynamic causes in drug-receptor interaction. Each of these PK and PD factors is different in each individual due to genetic, environmental or pathological determinants, and also depends on the severity or intensity of the disease to be treated.

One of the main obstacles to transferring findings from pharmacogenetics to the clinic is the impact of ethnicity on genetic variation. The highly significant associations between SNPs and the response modulated by pharmacogenetics can differ considerably between populations, which has a direct impact on drug use and dosage decisions. It is necessary then that the studies to evaluate pharmacological efficacy and pharmacogenetics, have uniformity in research designs, dosage regimens, study populations, and analytical methods.

The epidemic of T2D has forced the use of drugs that aim at glycemic control and avoid secondary complications that cause very high medical costs and decrease the quality of life of patients. However, it has been observed that even though many patients carefully follow medical guidelines, the glycemic control so desired is not achieved. Thus, with the advent of pharmacogenomics, various studies are carried out to achieve personalized medicine in this field having an impact on a better quality of life and also reducing the costs of treatment of this disease by the Health services.

In this review, the main drugs used for the treatment of T2D were analyzed and the implications that the various SNPs have on their target genes, which will affect their pharmacological response. All this opens the way for us to apply these genomic findings in daily clinical practice, in search of personalized medicine that impacts adequate glycemic control in patients with T2D in search of a better quality of life.

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