ISSN: 2357-0547 (Print)
ISSN: 2357-0539 (Online)

Review Article / JAPR / Sec. D
Naesa and Joujeh., 2024, 8 (2), 93-106

Journal of Advanced Pharmacy Research

Section D: Clinical Pharmacy & Pharmacology

The Glucoregulatory Mechanisms, Pharmacokinetics and Pharmacogenetics of Metformin in Type 2 Diabetes Mellitus

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Submitted on: 01-03-2024; Revised on: 03-04-2024; Accepted on: 06-04-2024

To cite this article: Naesa, H.; Joujeh D. The Glucoregulatory Mechanisms, Pharmacokinetics and Pharmacogenetics of Metformin in Type 2 Diabetes Mellitus. *J. Adv. Pharm. Res.* **2024**, *8* (2), 93-106. DOI: 10.21608/aprh.2024.273831.1257

ABSTRACT

Background and Objective: Type 2 diabetes (T2D) is a common chronic disease affecting more than 420 million people worldwide. Metformin, a biguanide drug that lowers blood glucose remains the first-choice drug for T2D. In this review, we mainly discusse the available data on the mechanism of action, pharmacokinetics and pharmacogenetics of metformin and review the evidence for an association between genetic variation and metformin response in T2D patients. **Methods:** This review was created by searching Pubmed and Google Scholar, using the following keywords to find research published in English in PubMed, and google scholar: “Type 2 diabetes”, “metformin”, “pharmacokinetics”, “pharmacogenetics”, “precision medicine”, “genetic variation”, “mechanism of action”, “drug response”. **Key Content and Findings:** Several mechanisms have been proposed to explain the metformin action in T2D patients, including activation of AMPK, suppression of hepatic glucose production, inhibition of mitochondrial complex 1, stimulation of insulin-stimulated glucose uptake into skeletal muscle, reducing the intestinal glucose absorption, modulation of the gut microbiota and increasing insulin sensitivity. However, metformin does not work the same way for everyone. It is well established that interindividual differences in the human genome influence individual responses to the same drug therapy. Pharmacogenetic studies mainly focused on single nucleotide polymorphism based variations and demonstrated that there is association between several SNPs in metformin pharmacokinetic genes and some pharmacodynamic genes, and metformin responsiveness in T2D. **Conclusions:** Although great progress has been made in understanding the pharmacogenetics of metformin response, there are still significant gaps in that need to be filled before implementation in clinical practice. Therefore, further research is needed. We hope that this review will help facilitate more effective use of the drug to treat T2D.

***Keywords**: Type 2 diabetes, metformin, pharmacokinetics, pharmacogenetics, genetic variation.*

INTRODUCTION

Diabetes mellitus is a metabolic disorder occurs due to decreased insulin secretion and/or insulin activity[1]. There are several types of diabetes, including type 1 diabetes (T1D), type 2 diabetes (T2D), gestational diabetes (GD), and diabetes due to other causes (such as monogenic diabetes). Most cases of diabetes are type 2

(90-95%) or type 1 (5-10%) [2]. T2D is a common chronic disease affecting more than 420 million people worldwide [3]. Over the past decade, the prevalence of this disease (particularly T2D) has increased by 30% globally [4]. According to the International Diabetes Federation, there will be about 784 million people with diabetes by 2045, about 90% of whom will have T2D [5]. As the burden of diabetes on health care will continue to rise [4], at an alarming rate, there is an urgent need to understand the mechanism of disease development, and to provide optimal treatment for patients. Effective control of disease symptoms through appropriate medications can help reduce the risk of complications and mortality.

Professional guidelines developed by experts recommend starting diabetes treatment with metformin, a biguanide drug that lowers blood glucose through a variety of insulin-independent mechanisms. It has been proven to be an effective, safe and inexpensive drug [6]. The effect of metformin in treating type 2 diabetes in humans was proven by the French doctor Jean Sterne more than half a century ago [7]. It is derived from Galligin, a natural product of the *Galiga officinalis*, which was used which was used in the Middle Ages in herbal medicine in Europe [8]. In 1922, metformin was synthesized for the first time, and in 1929 the first report was published on the use of metformin in lowering blood glucose levels in rabbits [9]. It was first used to treat T2D in the late 1950s. In 2022, metformin remains the first-choice drug used by about 150 million people daily [10]. However, metformin does not work the same way for everyone [11].

It is well established that interindividual differences in the human genome influence individual responses to the same drug therapy [12]. Numerous studies have demonstrated the association between genetic variations in metformin transporters and its therapeutic outcomes [11].

In this review, we discuss the available data on the mechanism of action and the pharmacokinetics of metformin. We also reviewed several pharmacogenetic research conducted to detect the association between genetic variations and metformin response or efficacy in T2D patients. We hope that this review will help facilitate more effective use of the drug to treat T2D.
We present this article in accordance with the Narrative Review reporting checklist.

METHODS

The review was created by searching Pubmed and Google Scholar, over the period October 2023 to January 2024. We used the following keywords to find research published in English in PubMed, and google scholar: “Type 2 diabetes”, “metformin”, “pharmacokinetics”, “pharmacogenetics”, “precision medicine”, “genetic variation”, “mechanism of action”, “drug response”. All authors independently selected articles in the context of the central idea of the study, evaluated the quality, presentation, and interpretation of the data, and then compiled the final reference list.

Pharmacodynamics of Metformin: Glucoregulatory mechanisms in T2D

Although metformin has been used clinically for decades, its mechanism of action is still not fully understood [13].

It is clear that metformin's primary action is to suppress hepatic glucose production, but its secondary mechanism is a subject of debate [7]. Rather than having a uniform mechanism of action on a single organ, it acts on multiple tissues through different underlying mechanisms rather than on a single organ via a unifying mode of action [14]. Here, we discuss the main proposed mechanisms of metformin action in T2DM.

Activation of AMPK

One of the most widely studied mechanisms of metformin is activation of the signalling kinase AMPK[15].

Metformin affects energy metabolism by activating AMP-activated protein kinase (AMPK) through a decrease in energy position within the liver, thereby decreasing of gluconeogenic genes [16]. AMPK is a three-dimensional complex consisting of catalytic alpha subunit, a scaffold protein beta subunit, and a non-catalytic regulatory γ subunit [17]. Previous study showed that AMPK alpha1 or alpha 2 plays a role in the inhibition of hepatic glucose production by metformin and that AMPKα1 is the main subunit for this inhibition. The study also showed that AMPK activation by metformin increases the phosphorylation of CREB-binding protein (CBP) at S436, resulting in disassembly of the cAMP response element-binding protein (CREB)-CBP/CRTC2 complex and inhibition of gluconeogenic gene expression and hepatic glucose production [18].

Nutrient-sensing serine/threonine kinases are activated when cellular energy levels are low (i.e., when the ratio of intracellular adenosine monophosphate (AMP): adenosine triphosphate ATP is high). Once activated, AMPK normally acts through downstream substrates by stimulating processes that generate ATP (such as fatty acid oxidation) and inhibiting processes that use ATP (such as triglyceride and protein synthesis). Overall, the activation of AMPK can improve glucose homeostasis and insulin sensitivity, making it an attractive target for type 2 diabetes [19].

Suppression of hepatic glucose production

It is clear that the main effect of metformin is to suppress glucose production in the liver[7]. Metformin has been shown to noncompetitively inhibit shuttle mitochondrial glycerophosphate dehydrogenase. This alters the redox status in hepatocytes, reduces the

conversion of lactate and glycerol to glucose, and decreases hepatic gluconeogenesis [20]. Additionally, metformin can inhibit the hepatic gluconeogenesis through AMPK dependent regulation of the orphan nuclear receptor the small heterodimeric partner (SHP; NR0B2) [21].

Inhibition of mitochondrial complex 1

Metformin also inhibits mitochondrial complex I, resulting in increased cellular levels of AMP, ultimately leading to activation of AMPK [22]. Therefore, the inhibition of this complex prevents gluconeogenesis through AMPK activation, as well as suppression of glucagon signaling through inactivation of adenylate cyclase. This alteration results in improved glucose metabolism and decreased insulin resistance in the liver, ultimately leading to improved blood sugar control [23].

3.4. Stimulation of Insulin-stimulated glucose uptake into skeletal muscle:

In addition to inhibiting hepatic gluconeogenesis, metformin also acts on skeletal muscle, increasing insulin-stimulated glucose uptake [24]. Both muscle cells and adipocytes express OCT3. Therefore, they are also able to uptake metformin [25]. Glucose uptake in skeletal muscle cells and adipocytes is induced by insulin and involves glucose transporters (GLUTs). The inhibition of SH2-containing inositol 5'-phosphatase (SHIP2) is the molecular mechanism by which metformin can increase the glucose uptake in muscle cells. SHIP2 dephosphorylates phosphatidylinositol 3,4,5-trisphosphate to phosphatidylinositol 4,5-diphosphate, thereby suppressing insulin signaling. While Metformin block the activity of SHIP2, it decreases GLUT4 endocytosis and increases glucose uptake in skeletal muscle cells [25].

Reducing the intestinal glucose absorption

Accumulating information have suggested that metformin's metabolic benefits may be due to its effects in the gut [14]. Metformin accumulates in the small and the large intestine at very high concentrations (30–300 times higher than the concentration in the circulation) [18]. This suggests that the gastrointestinal tract is likely to be an important site of metformin action for the management of T2D [14]. Metformin may inhibit the intestinal absorption of dietary glucose in patients with T2D [9]. Glucose transporters of enterocytes including sodium glucose-linked transporter-1, glucose transporter-2 and insulin-sensitive channels are involved in this effect [26]. Recently, it was found that a single dose of metformin can reduce the apical density of Sodium-Glucose transporter 1 (SGLT1) in cultured enterocytes, and acutely decreased the intestinal absorption of intraluminal glucose [27]. Results from a previous study also confirmed that the inhibition of intestinal transepithelial glucose transport is responsible for lowering the level of blood glucose during the initial response to oral metformin administration [28]. However, the effects of metformin on intestinal glucose transport remain highly controversial.

On the other hand, numerous studies suggested that the intestine also contributes in metformin's hypoglycemic effects [28]. The gastrointestinal tract regulates the recycling of bile acids and increases the secretion of glucagon-like peptide 1, the glucose-lowering gut incretin hormone [14].

Modulation of the Gut Microbiota

The gut microbiota has gained interest as an important factor in the treatment of T2D [29]. Recently, the clinical benefits of metformin have been shown to be associated with changes in the composition of the gut microbiome [24].

Metformin exerts some of its hypoglycemic effects by altering the gut microbiota in a way that maintains intestinal barrier integrity, increases short-chain fatty acids production, modulates bile acid metabolism [30], improves the gut permeability, modulates immune response and regulates glucose homeostasis [29].

It has also been indicated that metformin can increase the level of glycocursodeoxycholic acid by modulating the gut microbiota (e.g., by inhibiting the growth of *Bacteroides fragilis*), thus inhibiting the farnesoid X receptor (FXR) signaling pathway, reducing the blood glucose and maintain the blood glucose homeostasis [31]. However, it is still unclear how metformin regulates glucose homeostasis via the gut microbiome [29].

Increasing insulin sensitivity

By using various measurements of insulin sensitivity in humans, many studies have shown that metformin improves insulin sensitivity throughout the body. This effect may be related to multiple mechanisms, such as increasing the glycogen synthesis, the insulin receptor tyrosine kinase activity, and the GLUT4 recruitment and activity [32]. Previous study showed that transgenic mice engineered to express the human *GLUT4* gene and promoter maintain increased insulin sensitivity on a high-fat diet compared to non-transgenic mice [33].

Pharmacokinetics of metformin

When immediate-release metformin is administered orally to humans, approximately 70% of the dose is absorbed from the small intestine, with the remainder entering the colon and excreted in the feces. Metformin is excreted unchanged in the urine, without metabolites [8].

At physiological pH, it is hydrophilic. Thus, it does not diffuse efficiently across the biological membrane and needs carrier-mediated transport [34].

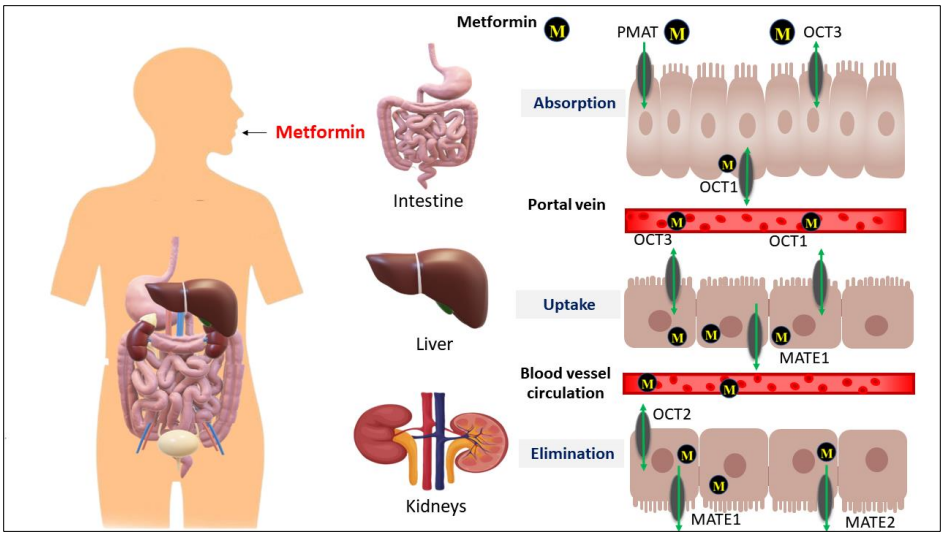

Figure 1. Pharmacokinetics of metformin

The metformin pharmacokinetics (PK) is mainly determined by membrane transporters, including the plasma membrane monoamine transporter (PMAT), the organic cation transporters (OCTs) [35], which include three subtypes (OCT1; OCT2; and OCT3), widely distributed in the human intestine, liver, kidney, and other organs [5], and the multidrug and toxin extrusion (MATE) transporters [17]. Additionally, it has been shown that metformin is a substrate for the thiamine transporter 2 (THTR-2), which may play a role in its intestinal absorption and renal reabsorption [35].

After oral administration, metformin is taken up by enterocytes by PMAT [36]. OCT3 located on the apical membrane of enterocytes is involved in the absorption of metformin [25]. Additionally, SERT (Serotonin transporter) and THTR-2 may also contribute to the intestinal absorption [37].

OCT1 is expressed on the basement membrane of enterocytes, and bidirectional transport of OCT allows OCT1 to transport metformin from enterocytes to the portal vein [18].

Metformin is then delivered to the liver and absorbed by OCT1/OCT3, which are expressed on the basement membrane of hepatocytes, and secreted from the liver into the circulation by MATE1. Eventually, metformin is absorbed into the circulation [17].

It enters the cells of renal proximal tubule from the blood via OCT-2, s specific cationic transporter located in the basement membrane of the proximal tubule [38].

Meanwhile, metformin is eliminated from the kidney by both MATE1 and MATE2 [39] on the apical membrane of renal proximal tubule cells **(Figure 1)** [17].

Table 1 displays a summary of various genes involved in pharmacokinetics or pharmacodynamics of metformin with tissue expression, encoded protein and its function.

Pharmacogenetics (PG) of Metformin

Pharmacogenomics studies the influence of genetics on drug response. It aims to give patients the right dose of the right medication at the right time. Almost all patients have one or more genetic variants that can alter a patient's response to a drug [59]. This variation can increase or reduce the activity of the drug in the body. Therefore, studies of these variations should be strongly considered to achieve the desired response in a patient [37].

Currently, treatment guidelines for T2DM use a one-size-fits-all approach without considering inter-individual variation in drug response [60]. Diabetes patients do not equally respond to glucose lowering therapies [61]. Recent literature suggests that approximately 50% of T2D patients fail to achieve glycemic goals after treatment with metformin [60]. Therefore, using genetics to guide the pharmaceutical treatment of diabetes is an important step toward precision treatment [61].

Genetic Variations and Metformin Response in T2DM patients

Metformin response is influenced by non-genetic factors such as sex, age and physiological state, and genetic factors which also play an important role in the drug bioavailability [5].

Several pharmacogenetic studies have shown that variations in genes related to metformin PK are associated with different levels of efficacy and toxicity[62].

Table 1. A summary of various genes involved in pharmacokinetics or pharmacodynamics of metformin with tissue expression, encoded protein, and its function.

Gene	Location/ Exon count	Tissue expression	Protein encoded by gene	Function of protein	Reference
SLC22A1	6q25.3 (12 exons)	sinusoidal membrane of hepatocytes	OCT1	OCT1 plays a role in the hepatic uptake of metformin	(40,41)
SLC22A2	6q26 (11 exons)	basolateral membrane of the renal epithelium	OCT2	OCT2 is a major facilitator of renal epithelial cells uptake of metformin	(42,43,41)
SLC22A4	5q31.1 (11 exons)	apical membranes of small intestine	OCTN1	OCTN1 is involved in the intestinal absorption of metformin	(25,44,41)
SLC22A3	6q25.3 (15 exons)	apical membrane of enterocytes, and in multiple tissues such as liver, kidney, heart, skeletal muscle and brain	OCT3	OCT3 appears to be related to metformin absorption into muscle	(45,25,41)
SLC29A4	7p22.1 (12 exons)	human intestine and at the periphery of the mucosal epithelial layer	PMAT	PMAT plays a role in the intestinal absorption of metformin	(46,34,41)
SLC47A1	17p11.2 (17 exons)	hepatocytes and kidney cells	MATE1	MATE1 transports metformin from hepatocytes to bile and metformin is excreted via the kidneys	(47,39,41)
SLC47A2	17p11.2 (22 exons)	renal proximal tubules	MATE2	It regulates metformin excretion in the kidney	(45,41)
PRKAA1	p13.15 (12 exons)	many tissues including the kidney, liver, lung, heart, and brain	AMPK alpha 1	AMPKα1 is the main catalytic subunit involved in the inhibition of hepatic glucose production	(48,18,41)
PRKAA2	p32.21 (10 exons)	heart, kidney and other tissues	AMPK alpha 2	It plays a role in the inhibition of hepatic glucose production	(18,41)
SLC19A3	2q36.3 (9 exons)	intestine and other tissues including the brain	THTR-2	It plays a role in the intestinal absorption of metformin	(49,37,41)
SLC6A4	17q11.2 (15 exons)	gastrointestinal tract, female tissues, and lung	SERT	It is involved in intestinal absorption of metformin	(50,51,41)
SLC2A2	3q26.2 (12 exons)	liver, pancreatic islet beta cells, intestine, central nervous system and the kidney	GLUT2	It is responsible for the bi-directional transportation of glucose from and into cells. It is also responsible for the release of liver glucose	(52,53,41)
TCF7L2	10q25.2-q25.3 (20 exons)	pancreatic islets, adipose tissue, and the liver	TCF7L2 / TCF-4	TCF7L2 has a crucial role in glucose metabolism, and plays a significant role in controlling the biosynthesis and secretion of insulin	(54,55,56,41)
ATM	3(77)	many tissues, including the brain, skin, and endothelial cells	ATM	It regulates the enzymes involved in the response to metformin. It is also involved in metformin's activation of AMPK	(57,58,41)

Genetic variants may affect gene expression, mRNA stability, or protein function in a variety of ways, all of which are likely to influence gene function and human phenotype [11]. Pharmacogenetic studies mainly focused on single nucleotide polymorphism (SNP)-based variations in candidate genes [12], particularly the genes involved in the PK of metformin, and their effects on metformin response.

OCTs, which belong to the *SLC22* gene family, play an important role in the PK of metformin. PG

researchers speculate that genetic variants may alter the structure and function of OCTs, leading to inter-individual differences in response to metformin [5]. Various SNPs in the OCT genes have been shown to affect the metformin PK and pharmacodynamics (PD), and thus the patient response to the drug [43]. It has been reported that rs622342 polymorphism does not change the sequence of amino acid, but it may affect the gene expression of OCT1 [5]. OCT2 is responsible for about 80% of total metformin clearance. Therefore, the loss-of-function variant of OCT2 may influence the PK and PD properties of metformin. OCT2-T201M (602C>T) is one of the variants that has a functional impact on OCT2 [63]. OCT3 genetic variants may also influence the clinical response to metformin. Previous studies showed that several different variants of OCT3 such as rs3088442, rs543159, rs1317652, rs2292334 and rs1219418, affect metformin response (64,11,65,43).

Some studies have shown that polymorphisms in the *SLC47A1* gene affect pharmacokinetic variation and glycemic response [47]. Changes in MATE-1 activity can affect drug disposition, and lead to drug accumulation in proximal tubular cells, and thus provoking nephrotoxicity and lactic acidosis [38].

The rs12943590 is one of the most relevant clinical variants in the gene *SLC47A2* (MATE2). It affects metformin depuration [66]. There is inconsistency between previous studies regarding the effect of the SNP rs12943590 on metformin response. A previous study indicated that This SNP played a role in the inter-individual variability of metformin efficacy [66], but another study showed no effect [67].

The transcription factor 7-like 2 gene (*TCF7L2*) is closely associated with T2D through impaired glucose control and insulin production [37]. The common *TCF7L2* variant (rs7903146) is a very strong genetic risk factor **associated** with T2D to date. Most studies suggested that the rs7903146 variant affects β-cells and insulin secretion. Since metformin primarily acts by improving insulin action, the pharmacogenetic effect of this variant on metformin response in T2D was explored [68]. However, the influence of *TCF7L2* SNP (rs7903146) on metformin treatment remains controversial, and more studies are needed to reach a consensus about this association.

The ataxia telangiectasia mutated gene *(ATM)* belongs to the family of phosphatidylinositol 3-kinase-related kinase. A genome-wide association study (GWAS) suggested that ATM SNP (rs11212617) is related to metformin response [69]. Metformin has been shown to act through both AMPK-dependent and AMPK-independent mechanisms [17]. AMPK is a heterodimeric complex consisting of a catalytic subunit (alpha α, encoded by PRKAA1 and PRKAA2 genes) and two regulatory subunits (beta β and gamma γ) [70].

Polymorphisms in the PRKAA1 (encoding α1), and PRKAA2 (encoding α2) were found to influence the hypoglycemic effect of metformin [71].

On the other hand, a large meta-analysis was conducted on approximately 8,000 T2D patients, and demonstrated that the polymorphisms in genes that encode transporters involved in the PK of metformin (OCT1, OCT2, OCTN1, MATE1, and MATE2) does not affect the glycemic response to the drug. According to the analysis' results, these polymorphisms may modulate the PK of metformin, but they do not seem to be critical to the PD of metformin in diabetic patients [72]. However, this analysis included T2DM patients with European ancestry only.

Regarding PD, a GWAS suggested that GLUT2, has a significant effect on metformin response. One of the main effects of metformin is the inhibition of hepatic gluconeogenesis. It is possible that metformin targets GLUT2 (*SLC2A2*), which is responsible for the last step (glucose release) of the gluconeogenesis pathway. That is, metformin may decrease the function or expression of GLUT2, and thus reduce hepatic glucose production. People with reduced function variants of *SLC2A2* gene may be sensitive to this effect and respond better [35]. Previous studies have reported that the rs8192675 variant in the *SLC2A2* gene is associated with a better response to metformin [45],[52],[73].

Statistically significant interactions between metformin and genetic variants were also reported for genes encoding additional proteins related to AMP-activated protein kinase–dependent gluconeogenesis inhibition [*PPARGC1A, PCK1, STK11, PRKAB2*, and *PPARA*], insulin secretion [*HNF1B, ABCC8, HNF4A, CDKN2A/B*, and *KCNJ11*]; and insulin sensitivity [*GCK, CAPN10, ENPP1* and *ADIPOR2*]. [74]

Multiple variations in the *STAT, CPA6*, and *PRPF31* genes have also had GWAS. These differences represent a small proportion of variable responses to metformin treatment [60]. However, other genes contributing to these anomalies may remain unexplored. In **(Table 2),** we compiled several studies conducted to detect the association between the SNPs in metformin pharmacokinetic genes and selected pharmacodynamic genes, and metformin responsiveness in T2D. It is clear that previous results regarding the effects of genetic variation on metformin response have been inconsistent, likely due due to differences in dose form, dose size, sample size, study design and analytic methods [35]. In addition, clinical response to metformin is associated with gender and BMI [69]. It also differed between different ethnic groups, with African Americans having a greater response to metformin than European Americans [61]. Therefore, a comprehensive analyse is needed to characterize the role of genetic variation on clinical response and intolerance to metformin [5].

Table 2. List of the known metformin pharmacokinetic genes and selected pharmacodynamic genes for which there are associations with a clinical response of metformin

Gene	Protein	SNP	RS number	Patients	Age	Sex	Duration of treatment	Population	Outcome	Ref
SLC22A1	OCT1	A>C	rs622342	63	44–66 years	37M/26F	6 months	Lebanese	This SNP was associated with decrease in FBS (Fasting blood sugar) levels and HbA1c (Hemoglobin A1c), and may be associated with metformin pharmacokinetics	(75)
SLC22A1	OCT1	A>C	rs622342	122	49.57 ± 9.88	47M/75F	12 weeks	Indians	There was a significant association between this SNP and metformin response	(76)
SLC22A1	OCT1	M420del	rs72552763	102	52.24 ± 10.746	54M/48F	3 months	Iraqis	There was a significant association between this SNP and metformin response	(77)
SLC22A1	OCT1	G/A	rs628031	478	25–60 years	-	12 weeks	Indians	Individuals carrying the 'GG' genotype or 'G' allele for *SLC22A1* gene variant rs628031 G/A are better responders for Metformin	(12)
SLC22A1	OCT1	C/T	rs1208357	299	60.92 ± 13.00	93M/206F	6 months	Russia	There was a significant association between this SNP and metformin response	(78)
		G/A	rs1867351							
		C/T	rs2282143							
		T/C	rs2297374							
SLC22A1	OCT1	G/A	rs461473	212	56.64 ± 9.4	82M/130F	At least 6 months	Jordanians	There was no significant association between these SNPs and glycemic outcomes	(43)
		G/T	rs4646272							
		G/C	rs683369							
		C/A	rs622342							
SLC22A1/ SLC47A1	OCT1 / MATE1	A/G	rs594709/ rs2289669	267	49.82 ± 10.11	143M/124F	3 months	Chinese	These polymorphisms may affect the metformin effectiveness together	(79)
SLC22A2	OCT2-T201M	C/T	rs145450955	40	52.35 ± 11.86	13M/27F	–	Iranians	This variant contributes to changes in insulin resistance and beta cell activity in T2D patients	(63)
		T/C	rs10755577							
SLC22A2	OCT1	C/T	rs17588242	212	56.64 ± 9.4 years	82M/130F	At least 6 months	Jordanians	There was no significant association between *SLC22A2* SNPs and glycemic control.	(43)
		C/G	rs17589858							
		A/G	rs2928035							

		C/T	rs3127573							
		A/G	rs316024							
		G/A	rs316025							
		C/T	rs316026							
		T/C	rs533452							
		C/T	rs662301							
SLC22A3	OCT3	G/A	rs3088442	150	52.7 ± 10.7	-	3 months	Iranians	Metformin had an impact in glycemic control, and this effect is regardless of OCT3-564G>A variant	(64)
SLC22A3	OCT3	C/A	rs543159	200	55.84 ± 4.8 (responders) 56.99 ± 4.8 (non responders)	95M/105F	25 weeks	Iranians	This variant was associated with better response to metform	(11)
SLC22A3	OCT3	C/T	rs1317652	200	55.84 ± 4.8 (responders) 56.99 ± 4.8 (non responders)	95M/105F	25 weeks	Iranians	This variant was associated with better response to metform	(11)
SLC22A3	OCT3	A/G	rs2292334	177	49.64 ± 10.12 (responders), 50.66 ± 10.73 (nonresponders)	53M/50F	3 months	Indian	There was a significant association between the SNP rs2292334 in the gene *SLC22A3* and the response to metformin treatment	(65)
SLC22A3	OCT3	C/T	rs2292334	212	56.64 ± 9.4 years	82M/130F	At least 6 months	jordanian	This SNP is linked to lower mean HbA1c levels	(43)
SLC22A3	OCT3	C/T G/A	rs12194182 rs2504927	212	56.64 ± 9.4 years	82M/130F	At least 6 months	jordanian	The SNP rs12194182 is associated with lower mean HbA1c level	(43)

		C/T	Rs3123634							
SLC47A1	MATE1	G/A	rs2289669	116	76.8 ± 6.7	47M/69F	30 days	Caucasians	The SNP was linked to the A1C-lowering effect of metformin	(42)
SLC47A1	MATE1	G/A	rs2289669	71	55.1 ± 11.4	-	6 Months	iranians	The SNP was significantly associated with the response to metformin	(80)
SLC47A1	MATE1	G/A	rs2289669	105	35-65	51M/54F	3 months	Indians	The SNP was not associated with metformin response	(67)
SLC47A2	MATE2	G/A	rs 12943590	105	35-65	51M/54F	3 months	Indians	The SNP was not associated with metformin response	(67)
SLC47A2	MATE2	A/G	rs 12943590	82	49.80 ± 12.18	38M/44F	2 months	Chinese	The SNP played a role in the inter-individual variability of metformin effectiveness	(66)
SLC2A2	GLUT-2	C/T	rs8192675	110	58.2 ± 14	50M/ 47F	90 days	Chinese	Patients with this SNP (CC type) are sensitive to metformin and have better hypoglycemic effect	(52)
SLC2A2	GLUT-2	C/T	rs8192675	227	53 ± 10 years	M65% F35%	1 year	Germans	This variant is associated with an improved glucose response to metformin	(73)
ATM	ATM	A/C	rs11212617	104	AC+AA 56.42 ± 10. 40 CC 57.92 ± 9.7 3	_	6 months	Chinese	There was no difference in the effect of this SNP on metformin glycemic response	(69)
TCF7L2	TCF-4	C>T	rs7903146	61	47.63 ± 9.58	42M/19F	12 weeks	Iraqis	There was a significant association between the SNP and metformin response	(68)

Precision Medicine in Diabetes

The term "precision medicine (PM)" was coined as the omics era is embracesed in the medical field, with big data providing new insights into pathophysiology and disease progression. PM aims to ensure that all patients receive optimal treatment [81].

PM is part of the logical evolution of modern evidence-based medicine that aims to reduce errors and improve outcomes in medical decision and health recommendations [82].

PM in diabetes treatment focuses on designing diagnoses or treatments for subgroups of the population that share similar characteristics. It aims to optimize treatment decisions for individual patients, thereby minimizing the risk of severe complications of diabetes, including retinopathy, neuropathy, cardiovascular outcomes and overall mortality, while maximizing effectiveness [83].

The promise of precision pharmaceutical medicine for T2D remains largely unfulfilled, reflecting in part the highly heterogeneous nature of T2D, and the fact that pharmacological treatments are typically chosen based on costs, side effects, or comorbidities rather than on a specific basis [81]. Therefore, stratification of diabetic patients based on genetic background and pathophysiological mechanism may be considered when implementing PM in diabetes [61].

While the ideal PM for diabetes treatment will likely ultimately include metabolomic panels, imaging results, and etc., the use of genetic information and its inclusion in a patient's health record is a practical and a convincing first step forward [58].

CONCLUSION

This review mainly discusses the mechanism of action, PK and PG of metformin and reviews the evidence for an association between genetic variation and metformin response in T2D patients. Although great progress has been made in understanding the PG of metformin response, there are still significant gaps that need to be filled before implementation in clinical practice. Therefore, further research on large cohorts of previously examined patients from different genetic, ethnic, and cultural backgrounds are needed to improve understanding. We hope that this review will help facilitate more effective use of metformin to treat T2D.

Funding Acknowledgments

None.

Conflict of interest

The author declares that there isn't any conflict of interest regarding the publication of this paper.

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