VIA MEDICA
REVIEW ARTICLE
ISSN 2450–7458
e-ISSN 2450–8187

Shambo Samrat Samajdar[1], Anuj Maheshwari[2], Ajoy Tiwari[2], Shatavisa Mukherjee[3], Kaushik Biswas[4], Banshi Saboo[5], Anup Kumar Rawool[6], Shashank R. Joshi[7]

[1]Diabetes and Allergy-Asthma Therapeutics Specialty Clinic, Kolkata, India
[2]Hind Institute of Medical Sciences, Lucknow, India
[3]School of Tropical Medicine, Kolkata, India
[4]Medica Superspecialty Hospital, Kolkata, India
[5]DiaCare, Ahmedabad, India
[6]Medgenome, Bangalore, India
[7]Joshi Clinic, Mumbai, India

Decoding the Genetic Blueprint: Advancing Personalized Medicine in Type 2 Diabetes through Pharmacogenomics

ABSTRACT

Objective: The escalation of type 2 diabetes (T2D) as a global health crisis necessitates a shift towards personalized medicine to optimize treatment efficacy and minimize adverse drug reactions (ADRs). This review article underscores the significant role of pharmacogenomics in refining T2D management. We explore the influence of genetic variations on the pharmacokinetics and pharmacodynamics of commonly used antidiabetic drugs, including metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, and SGLT2 inhibitors.

Materials and methods: A systematic review of existing literature was carried out, concentrating on studies exploring personalized medicine in T2D through pharmacogenomics. The literature search encompassed databases such as Medline, Scopus, Web of Science (WOS), and PubMed. Key insights regarding the role of pharmacogenomics in managing T2D were compiled and analyzed.

Results and conclusions: The review highlights how genetic polymorphisms in drug transporters, metabolizing enzymes, and drug targets correlate with variations in drug response and tolerance. We advocate for preemptive genotyping and integration of genetic data into clinical decision-making, which could revolutionize patient care in T2D. The future of diabetes treatment lies in harnessing pharmacogenomic insights to tailor therapeutic regimens, thereby transitioning from a one-size-fits-all approach to a more nuanced, individualized treatment strategy. With advancements in genomic technologies and a reduction in genotyping costs, the implementation of genetic testing in routine clinical practice is becoming increasingly viable, signaling a new era in the personalized management of T2D.

Keywords: type 2 diabetes, pharmacogenomics, personalized medicine, antidiabetic drugs, genotyping

Address for correspondence:
Shatavisa Mukherjee
School of Tropical Medicine, Kolkata, India
E-mail: shatavisa100@gmail.com
Clinical Diabetology 2024
DOI: 10.5603/cd.102035
Received: 11.08.2024 Accepted: 15.09.2024
Early publication date: 22.10.2024

Introduction

Type 2 diabetes (T2D) remains a global epidemic, characterized by significant variability in individual responses to pharmacotherapy, complicating effective management and control. With the increasing prevalence of T2D worldwide, there is a pressing need for personalized treatment strategies that not only enhance therapeutic efficacy but also minimize adverse effects. In this context, pharmacogenomics (PGx) — the study of how genes affect a person's response to drugs — emerges as a transformative approach to diabetes management. This review article delves into the potential of pharmacogenomics to tailor treatments based on genetic profiles, thus revolutionizing the paradigm of T2D management.

Pharmacogenomics combines the disciplines of pharmacology and genomics to predict how individuals might respond to specific drugs based on their genetic makeup. It holds the promise of optimizing drug therapy by customizing medications in a way that maximizes efficacy and minimizes risk, thereby embodying the principles of personalized medicine. By analyzing the interplay between genetic variants and drug responses, pharmacogenomics aims to identify the most suitable drug and dosage for each patient, reducing the trial-and-error approach that is often prevalent in diabetes treatment.

The field of pharmacogenomics distinguishes itself from pharmacogenetics, although the terms are often used interchangeably. Pharmacogenetics focuses on the influence of single gene variants on drug response, traditionally examining monogenic effects, where variations in one gene can significantly impact how a patient metabolizes or responds to a drug. Common examples include variations in genes encoding drug-metabolizing enzymes like the CYP450 family, which significantly influence the metabolism of various antidiabetic drugs[1].

Conversely, pharmacogenomics embraces a broader scope, examining the effects of multiple genes (polygenic influences) and how they interact with environmental and lifestyle factors to affect drug response. This comprehensive approach is particularly vital in T2D, where the disease mechanism and drug reactions are influenced by a complex network of genetic, environmental, and lifestyle factors. Pharmacogenomics, therefore, seeks to understand these complex interactions on a genome-wide scale using advanced technologies such as genome-wide association studies (GWAS) [1].

However, the application of pharmacogenomics in clinical practice faces significant challenges, including the need for large-scale studies to validate genetic markers of drug response and the integration of complex genetic data into practical treatment decisions. Moreover, the variability in drug response genes across different populations highlights the necessity for diverse and inclusive research that ensures the global applicability of pharmacogenomic discoveries.

This review aims to explore the current landscape of pharmacogenomics research in T2D, highlighting key genetic determinants of drug response, the integration of pharmacogenomic data into clinical practice, and future directions in this field. By advancing our understanding of genetic influences on drug efficacy and safety in T2D, pharmacogenomics not only promises to enhance individual patient care but also to facilitate broader advancements in the field of personalized medicine.

Types of genetic variation influencing drug response

In the context of T2D treatment, the impact of genetic variation on drug response is a critical consideration for tailoring effective therapies. Genetic variations, or pharmacogenetic traits, influence drug efficacy and safety, dictating personalized treatment approaches. These variations can be broadly categorized based on their frequency in the population, the number of base pairs involved, their location within the gene, and the effects on the encoded protein. In a groundbreaking study involving approximately 150,000 individuals from 5 diverse ancestry groups, researchers have discovered 12 rare protein-truncating variants in the SLC30A8 gene, which is responsible for encoding the islet zinc transporter ZnT8. This gene was already known for a common variant that impacts T2D susceptibility and influences glucose and proinsulin levels. Notably, individuals carrying these truncating variants exhibited a significant 65% reduction in the risk of developing T2D, highlighting a novel protective genetic mechanism. Specifically, Icelandic carriers of a frameshift variant (p.Lys34Serfs*50) showed notably lower glucose levels, underscoring the potential of targeting ZnT8 for T2D prevention. This discovery provides robust human evidence that contradicts previous animal models, suggesting that inhibiting ZnT8 could be a viable therapeutic strategy for reducing T2D risk [2]. This insight not only advances our understanding of genetic influences on diabetes but also opens new avenues for therapeutic intervention. This section discusses how these genetic factors affect drug response and highlights the relevance of understanding these variations in the management of T2D.

Frequency and commonality of pharmacogenetic variants

Pharmacogenetic variants differ greatly in their frequency within populations, which can significantly influence the selection pressure on these genes. For instance, variants involved in drug metabolism often have no noticeable impact until a drug is administered, leading to a lack of natural selection against potentially deleterious alleles. As a result, certain pharmacogenetic variants are remarkably common compared to those associated with severe genetic disorders. An example relevant to diabetes treatment is the variability in the CYP3A5 gene, where most individuals of European descent carry non-functional alleles, whereas many from African descent have one or more functional alleles. This difference can affect the metabolism of drugs commonly used in diabetes management, such as sulfonylureas, which are metabolized by CYP enzymes [1].

Size and nature of genetic variations

Genetic variations influencing drug response include single-nucleotide variants (SNVs), which are alterations of a single base pair, and copy number variants (CNVs), which involve larger segments of DNA and can include whole genes. For example, the number of functional CYP2D6 enzyme variants a person has can vary widely, influenced by over 100 possible SNVs and CNVs that might delete or duplicate the gene. Such variability can affect the metabolism of many drugs used in diabetes care, altering their effectiveness and risk of adverse effects [1].

Impact on protein function and expression

Variations can also directly alter the amino acid sequence of proteins, potentially leading to gains or losses of function. For instance, the UGT1A1*28 variant, which features an additional TA repeat in the promoter region, is associated with reduced expression of the enzyme in the liver [3]. This variant not only influences drug metabolism but is also linked to Gilbert's syndrome, a condition that may complicate drug therapy in diabetes due to elevated bilirubin levels. Understanding these genetic variations is crucial for anticipating drug responses in diabetic patients.

Pharmacogenomic haplotypes and their clinical implications

The complexity of pharmacogenomic effects is often encapsulated in haplotypes — a series of linked genetic variants that tend to be inherited together. Haplotypes can be more predictive of drug response than individual SNVs due to the combined effects of multiple linked variants. The "star allele" nomenclature is used to describe these haplotypes concisely, with "1" typically indicating a functional allele. For example, the CYP3A51 allele indicates normal enzyme activity, crucial for the metabolism of certain diabetes medications, while CYP3A5*3, common in Europeans, indicates a loss of function, which can alter drug processing and efficacy [4].

Implications for diabetes management

The identification and characterization of these genetic variants through association studies and genome-wide association studies (GWAS) provide critical insights into patient-specific drug metabolism profiles. However, these studies must be followed by functional characterizations to confirm the causative links between genetic variants and drug responses [1, 4]. Moreover, the variations in linkage disequilibrium patterns across populations highlight the need for population-specific studies to ensure the generalizability of pharmacogenomic applications in diabetes treatment.

By integrating pharmacogenomic data into the clinical management of diabetes, healthcare providers can better predict patient responses to various therapeutic agents, optimizing treatment plans to achieve better glycemic control while minimizing adverse effects. This approach not only enhances individual patient care but also moves the field toward a more nuanced and effective management strategy for T2D.

The role of pharmacogenes in drug response

Pharmacogenes play a pivotal role in the body's response to medications by determining drug effects and concentrations. These genes encode for enzymes, transporters, and drug targets that are integral to pharmacokinetics — the movement of drugs through the body — and pharmacodynamics, which concerns the effects drugs have on the body. For instance, variations in the CYP2C9 gene affect the metabolism of Warfarin, a widely used anticoagulant, which can lead to differences in drug efficacy and safety profiles among individuals. Likewise, genetic differences in SLCO1B1 can alter the transport and hence the impact of simvastatin, which is used to control hyperlipidemia. These pharmacogenomic variations also extend to the drug targets themselves, such as VKORC1 with warfarin, where genetic differences can influence the drug's anticoagulant effect. The intricacies of these interactions become even more pronounced when considering adverse drug reactions, which can be categorized as immune-mediated or non-immune. For example, genetic variants in HLA-B5701 are associated with hy-

persensitivity to abacavir, while variants in HLA-B5801 are linked to severe skin reactions with allopurinol [5]. Such knowledge is instrumental in anticipating individual responses to pharmacotherapy, emphasizing the need for genetic screening prior to prescribing certain medications.

Genetic variability and drug metabolism

The genetic blueprint of an individual significantly influences their capacity to metabolize drugs. This process is highly heritable, and certain genetic phenotypes are associated with varying degrees of metabolism efficiency, categorized as poor, intermediate, or normal metabolizers. A classic example is the CYP2C19 gene, where different haplotypes, referred to as "star alleles," can profoundly affect the enzyme's functionality. The CYP2C191 allele is associated with normal function, whereas the CYP2C192 and 3 alleles result in no enzyme activity. Conversely, the CYP2C1917 allele leads to increased enzyme expression and potentially ultra-rapid drug metabolism. These genetic variations can have significant implications for the efficacy and safety of drugs metabolized by CYP2C19, such as certain anticonvulsants and antiplatelet agents [1]. Large-scale studies, including twin studies, have underlined the genetic underpinnings of these metabolic traits, which has substantial ramifications for personalized medicine, especially in the context of diabetes, where pharmacotherapy is a cornerstone of disease management.

A framework for evaluating PGx in type 2 diabetes

To harness the full potential of pharmacogenomics in the context of T2D, a structured approach to evaluate its impact on drug therapy is essential. The provided framework delineates the variation in pharmacokinetic and pharmacodynamic responses, as well as genetic predisposition to diabetes itself. For example, the genetic makeup affecting drug transport and metabolism can lead to variations in treatment efficacy, such as the intolerance seen in some patients to metformin, a first-line T2D medication. Similarly, the genetic factors contributing to the disease's etiology, such as those influencing the risk of developing diabetes, have been linked to disparate pharmacogenomic effects in monogenic versus polygenic forms of diabetes. Large PGx effects are observed in monogenic diabetes due to the direct association with single-gene defects, while smaller PGx effects are seen with polygenic T2D. Additionally, the genetic determinants of drug targets and downstream action can inform the selection of therapies, such as sodium-glucose cotransporter-2 (SGLT2) inhibitors, where moderate PGx effects are possible [6]. This framework underscores the complexity of evaluating PGx in T2D and the necessity for a comprehensive understanding of genetic influences to optimize pharmacotherapy for individual patients.

Together, these insights underscore the intricate connections between genetic variation and drug response in T2D management. They provide a blueprint for integrating pharmacogenomic data into clinical practice, paving the way for more personalized, effective, and safe treatment strategies.

Genetic variability and its impact on metformin efficacy in type 2 diabetes

Metformin operates through complex pharmacokinetic processes influenced significantly by genetic polymorphisms in transporter genes. The absorption and distribution of metformin are mediated by various organic cation transporters (OCTs) and multidrug and toxin extrusion proteins (MATEs), which are encoded by the SLC22 and SLC47 gene families, respectively [7]. Notably, the SLC22A1 gene, encoding OCT1, plays a pivotal role in metformin's hepatic uptake, with polymorphisms such as rs622342 significantly affecting therapeutic efficacy in different ethnic groups. For instance, this polymorphism has been associated with varied responses in South Indian and Chinese patients with T2D, indicating a differential impact on metformin's glucose-lowering effect [8, 9].

Furthermore, the impact of genetic variations extends to other transporter genes like SLC22A2 and SLC22A3, which encode OCT2 and OCT3, respectively. These transporters facilitate the renal and hepatic uptake of metformin. Studies have shown that polymorphisms in these genes can alter the pharmacokinetics of metformin, influencing its clearance from the bloodstream and consequently its efficacy in lowering blood glucose levels. For example, the SLC22A2 808G>T variant has been observed to enhance the glucose-lowering efficiency of metformin in Chinese patients by delaying its renal transport [10].

Moreover, the SLC47A1 and SLC47A2 genes, encoding MATE1 and MATE2, are crucial for the excretion of metformin into urine and bile. Polymorphisms in these genes, such as SLC47A1 rs2289669, have been linked to significant differences in metformin response, with some variants associated with improved glycemic control through delayed renal elimination or increased basal glucagon-like peptide-1 (GLP-1) levels [11, 12]. Understanding these genetic influences is essential for tailoring metformin therapy to individual patients, potentially enhancing therapeutic outcomes and minimizing side effects.

Table 1. The Impact of Genetic Polymorphisms on Metformin Pharmacokinetics and Therapeutic Response

Gene	Protein	Function in Metformin transport	Polymorphism	Impact on metformin response	Notable ethnic variation
SLC22A1	OCT1	Hepatic uptake of metformin	rs622342	Affects therapeutic efficacy; linked to varied glucose-lowering effects	Significant in South Indian, Chinese
SLC22A2	OCT2	Renal uptake of metformin	808G>T	Enhances glucose-lowering efficiency by delaying renal transport	Notable in Chinese
SLC22A3	OCT3	Uptake in intestine and liver	Various	Influence on therapeutic efficacy varies with specific polymorphisms	Varies by ethnicity
SLC47A1	MATE1	Excretion into urine and bile	rs2289669	May improve glycemic control through delayed renal elimination	Varied responses in different populations
SLC47A2	MATE2	Renal excretion of metformin	Various	Linked to changes in HbA1c levels and treatment failure rates	Significant in diverse populations
SLC29A4	PMAT	Intestinal absorption of metformin	Various	Associated with gastrointestinal intolerance and renal clearance	Significant in Korean

Table 1 provides an overview of how different polymorphisms in key transporter genes can influence the effectiveness of metformin in managing T2D across various ethnic groups, highlighting the importance of personalized medicine.

Genetic influences on sulfonylurea efficacy and metabolism in type 2 diabetes management

Sulfonylureas are a critical class of medications used in the management of T2D by enhancing insulin secretion. This class of drugs operates by targeting and closing the ATP-sensitive potassium channels (KATP channels) located on the membranes of pancreatic beta cells. These channels are composed of 2 main subunits: sulfonylurea receptor 1 (SUR1), which is encoded by the ABCC8 gene, and the inward-rectifier potassium ion channel (Kir6.2), encoded by the KCNJ11 gene. The closure of these channels leads to cellular depolarization and subsequent insulin release via calcium channel activation [13].

Significant genetic variations in these target genes, such as the ABCC8 gene, can markedly influence the response to sulfonylurea drugs. For instance, the Ser1369Ala polymorphism in the ABCC8 gene has been associated with differential therapeutic efficacy in various ethnic populations [14]. Research has demonstrated that this specific variant can impact the effectiveness of gliclazide, a common sulfonylurea, with notable associations found in Chinese patients, suggesting a significant modulation of drug response based on genetic makeup [15, 16]. However, other studies have provided conflicting results, indicating that the same polymorphism might not universally affect the response to sulfonylurea treatment across different populations [13].

In addition to the SUR1 gene, the KCNJ11 gene encoding Kir6.2 also exhibits polymorphisms that affect sulfonylurea efficacy. The E23K variant of KCNJ11 is particularly noteworthy; studies have shown it can influence both the risk of hypoglycemia and overall therapeutic response to sulfonylureas. For example, this polymorphism was associated with higher HbA1c reduction following gliclazide treatment in Caucasian populations and varied responses in treatment efficacy and hypoglycemia risk among different ethnic groups [15, 17].

Furthermore, the metabolism of sulfonylureas is predominantly facilitated by the cytochrome P450 enzymes, specifically CYP2C9, in the liver. Polymorphisms in the CYP2C9 gene, such as the *2 and *3 variants, have been found to significantly alter the pharmacokinetics of sulfonylureas. These genetic variants can lead to higher drug concentrations and prolonged drug activity, thereby modifying the risk of therapy failure and potentially enhancing glycemic control in patients treated with these drugs [18].

These insights underscore the crucial role of genetic profiling in optimizing the management of T2D with sulfonylureas. Understanding individual genetic differences in the ABCC8, KCNJ11, and CYP2C9 genes provides a foundational basis for personalized medicine approaches, aiming to tailor treatments according to patient-specific genetic backgrounds to maximize therapeutic efficacy and minimize adverse effects.

Table 2. Pharmacogenomic Variants and Their Clinical Impact on Thiazolidinedione Therapy in Type 2 Diabetes [29]

Gene	SNP	Alleles	Clinical significance of variant	Adverse effect
CYP2C8	rs10509681	C/T	Influences pharmacokinetics of TZDs, related to edema	Edema
	rs78637571	C/A	Affects rosiglitazone pharmacokinetics, associated with hypoglycemia	Hypoglycemia
	rs11572103	A/T	Modulates pioglitazone pharmacokinetics	—
	rs11572080	A/G	Alters rosiglitazone response and risk of edema	Edema
PPARG	rs1801282	C/G	Associated with TZD response, impacts FPG, HbA1c, TG	—
PPARGC1A	rs8192678	A/G	Influences response to rosiglitazone	—
	rs2970847	C/T	Related to rosiglitazone response	—
ADIPOQ	rs266729	C/G	Related to improved TZD response, affects FPG, HbA1c	—
	rs2241766	A/C	Associated with rosiglitazone response, impacts FPG, HbA1c	—
	rs1501299	G/T	Linked to changes in fasting glucose and HbA1c post-rosiglitazone therapy	—

FPG — fasting plasma glucose; HbA1C — glycated hemoglobin; SNP — single nucleotide polymorphisms; TG — triglycerides; TZDs — thiazolidinediones

Genetic variability and glinide response in diabetes treatment

Glinides, notably repaglinide, are medications used to stimulate insulin release in diabetic patients by targeting the ATP-sensitive potassium (KATP) channels on pancreatic β-cell membranes. These channels consist of SUR1 and Kir6.2 subunits, encoded by the ABCC8 and KCNJ11 genes, respectively. Detailed pharmacogenomic research indicates that specific genetic variants in these genes markedly influence the therapeutic response to glinides. Specifically, the ABCC8 rs1801261 single nucleotide polymorphism (SNP) exhibits variable effects based on its alleles; patients with the CT genotype show significant reductions in fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) levels compared to those with the more common CC genotype [19, 20]. Additionally, the CC genotype of the ABCC8 rs1799854 SNP is linked to improved insulin sensitivity, as shown by lower values in the homeostasis model assessment of insulin resistance (HOMA-IR). Similarly, for the KCNJ11 E23K variant (rs5219), individuals carrying the K allele (either E/K or K/K genotypes) have significantly reduced HbA1c and postprandial glucose levels, indicating a more favorable pharmacological response to repaglinide [21, 22]. These findings emphasize the necessity of integrating genetic testing into the treatment planning for diabetes, as they confirm that genetic polymorphisms can substantially alter drug efficacy and patient outcomes. This tailored approach to diabetes management could lead to more precise and effective treatment strategies, enhancing therapeutic success rates and patient quality of life.

Pharmacogenomic insights into thiazolidinediones

The pharmacogenomics of thiazolidinediones (TZDs), which encompasses pioglitazone and rosiglitazone, has garnered attention due to its impact on the therapeutic outcomes in T2D management. These drugs, functioning as insulin sensitizers, are metabolized primarily by cytochrome P450 enzymes, particularly CYP2C8. Notably, the CYP2C83 haplotype, characterized by rs11572080 and rs10509681 polymorphisms, is associated with a decreased rosiglitazone area under the curve (AUC) and an altered risk of edema, while the CYP2C811 variant, marked by the rs78637571 stop-gain mutation, heightens rosiglitazone bioavailability. The rs11572103 variant, indicative of CYP2C8*2, also influences pioglitazone pharmacokinetics, particularly in African Americans [23, 24]. PPARG, the target receptor for TZDs, harbors the Pro12Ala polymorphism (rs1801282), consistently linked with a lower T2D risk and improved responses to pioglitazone, as shown by enhancements in fasting glucose, HbA1c, and triglycerides, although some studies contest this association. PPARGC1A variants such as Thr394Thr (rs2970847) and Gly482Ser (rs8192678) have been shown to have an influence on rosiglitazone response in Chinese T2D patients, but with no significant effect noted with pioglitazone [25, 26]. In the adiponectin encoding gene ADIPOQ, the rs266729 variant upstream of the gene correlates with better pioglitazone response, and the synonymous T45G polymorphism (rs2241766) is associated with pioglitazone response in Southern Chinese T2D patients. The intronic SNP rs1501299 also associates with fasting glucose and HbA1c reductions

Table 3. Genetic Variants Influencing Response to DPP-4 Inhibitors and GLP-1 Receptor Agonist Therapies in Type 2 Diabetes [29]

Gene	SNP	Alleles	Chromosomal region	Molecular function	Clinical impact on therapy
GIPR	rs13306399	C/G	19q13.32	Missense Cys46Ser	Alters GIP binding, affects GIP sensitivity
GIPR	rs13306403	G/T	19q13.32	Missense Arg316Leu	Decreases GIP sensitivity
GIPR	rs1800437	C/G	19q13.32	Missense Glu354Gln	Reduces GIPR signaling, linked to CVD
GLP1R	rs10305420	C/T	6p21.2	Missense Pro7Leu	Modulates response to liraglutide
GLP1R	rs6923761	A/G	6p21.2	Missense Gly168Ser	Influences DPP-4i efficacy, alters liraglutide response
KCNQ1	rs163184	C/A	11p15.4	–	Affects HbA1c reduction from DPP-4i treatment
TCF7L2	rs7903146	C/T	10q25.2	–	May reduce GLP-1 action on beta cells, influences response to linagliptin

CVD — cardiovascular disease; DPP-4i — dipeptidyl peptidase 4 inhibitor; GIP — gastric inhibitory polypeptide; GIPR — gastric inhibitory polypeptide receptor; GLP-1 — glucagon-like peptide-1; SNP — single nucleotide polymorphisms

post-rosiglitazone therapy [27, 28]. These genetic findings inform the pharmacogenomic landscape of TZD responsiveness, indicating the potential of personalized medicine in enhancing the management of T2D by tailoring treatments based on individual genetic profiles.

Table 2 is simplified for clarity and focuses on the clinical implications of the genetic variants on the efficacy and side effects of TZD therapy in patients. The term "—" is used where there is no direct adverse effect mentioned or the effect is not clearly defined.

Genetic determinants of response to DPP-4 inhibitors and GLP-1 receptor agonists

In the treatment landscape of T2D, dipeptidyl peptidase 4 (DPP-4) inhibitors and GLP-1 receptor agonists have emerged as effective modalities, known for their low hypoglycemia risk and beneficial impact on patients' quality of life. These agents exploit the incretin pathway: DPP-4 inhibitors prolong the activity of incretins like GLP-1 and gastric inhibitory polypeptide (GIP) by preventing their rapid degradation, while GLP-1 receptor agonists directly stimulate the GLP-1 receptor, enhancing glucose-mediated insulin secretion.

Polymorphisms within the genes encoding the GIP receptor (GIPR) have been identified, such as rs13306399 (Cys46Ser), which alters GIP binding, and rs13306403 (Arg316Leu), which reduces GIP sensitivity in beta cells [30]. The rs1800437 polymorphism is linked to cardiovascular disease incidence and affects the receptor's signaling dynamics, with implications for incretin-based therapies [31]. Additionally, the intronic variant rs10423928 in the GIPR gene may influence the receptor's function and has been associated with changes in glucose levels and body composition markers in response to incretin effects [32].

For the GLP-1 receptor, the rs367543060 (Thr149Met) variant is noteworthy for its functional impact in vitro and on insulin response to GLP-1 in vivo [33]. The rs6923761 (Gly168Ser) SNP presents a complex picture: it is associated with a reduced insulin response to GLP-1, but it predicts greater efficacy of liraglutide treatment and favorable changes in weight and metabolic profiles. The haplotype including rs6923761 and rs10305420 (Pro7Leu) further illustrates the nuanced genetic impact on treatment efficacy with liraglutide [34]. Other variants such as rs3765467 (Arg131Gln) and rs10305492 (Ala316Thr) have been linked to beta-cell responsiveness and fasting glucose levels, respectively.

KCNQ1 gene polymorphisms also exhibit associations with GLP-1 and GIP release and responses to DPP-4 inhibitor treatment, as exemplified by the rs163184 G allele's association with lower HbA1c reduction. This reflects findings across different ethnicities and underscores the gene's role in both incretin release and insulin secretion.

Notably, TCF7L2, which may influence GLP-1 synthesis, harbors variants such as rs7903146 and rs12255372 that could attenuate GLP-1 action on beta cells [35], as shown by differential responses to the DPP-4 inhibitor linagliptin. This finding, however, is not uniformly supported across studies.

These genetic insights accentuate the importance of personalized medicine in T2D. By understanding the genetic determinants that modulate the response to DPP-4 inhibitors and GLP-1 receptor agonists, clinicians can better tailor treatments, improving efficacy and minimizing adverse effects, thereby advancing the paradigm of individualized therapy in diabetes care.

Table 3 encapsulates genetic variations that have been identified as influencing the efficacy and response to DPP-4 inhibitor therapy and GLP-1 receptor agonists. The GIPR gene's SNPs have been associated

Table 4. Pharmacogenomic Influences on SGLT2 Inhibitor Efficacy and Metabolism [43]

Gene	SNP (rs number)	Clinical impact of genetic variation	Drug association	Notes on drug efficacy or metabolism
WFS1	rs10010131	Carriers of the A allele exhibit a decrease in body weight	Dapagliflozin	Weight reduction more pronounced in individuals with two A alleles
PNPLA3	rs738409	Associated with variations in liver fat content. CG/GG genotype linked with higher reduction in liver PDFF with combined therapy	Dapagliflozin + omega-3-carboxylic acids	Lower reduction in liver PDFF with dapagliflozin alone
UGT1A9	rs72551330	Higher dose-normalized steady-state AUC (AUC_ss) and lower M/P ratio for M5 metabolite	Canagliflozin	Indicates increased plasma exposure to canagliflozin in carriers
UGT2B4	rsNot provided	Higher dose-normalized AUC_ss and lower M/P ratio for both metabolites	Not specified	Suggests variation in metabolism efficiency
SLC5A2	rs3116650, rs3116149, rs11646054	Changes in systolic blood pressure and fasting postprandial glucose levels	Empagliflozin	Allelic variations correspond to changes in drug efficacy and metabolic response

AUC — area under curve; PDFF — proton density fat fraction; SNP — single nucleotide polymorphisms

with variations in the sensitivity and expression of GIP, which are essential for the incretin effect utilized by these therapeutic agents. Variants in the GLP1R gene, such as rs10305420 and rs6923761, show differential responses to liraglutide treatment and general DPP-4 inhibitor responses, influencing therapy outcomes. The KCNQ1 and TCF7L2 gene variants also play a role in treatment efficacy, indicating potential areas where personalized medicine can optimize T2D management by considering individual genetic backgrounds. Adverse effect like cardiovascular disease (CVD) is noted as a concern for the rs1800437 SNP in the GIPR gene.

SGLT2 inhibitors: a shift in diabetes management and pharmacogenomic insights

SGLT2 inhibitors represent a significant advancement in the management of T2D, providing a mechanism to lower glucose levels with a lower risk of hypoglycemia and improving life quality for patients. Initially discovered through phlorizin, a non-selective SGLT inhibitor derived from apple tree bark, the development of selective SGLT2 inhibitors like dapagliflozin, canagliflozin, empagliflozin, and ertugliflozin has revolutionized diabetes therapy. These modern drugs, structurally related to phlorizin, have minimal adverse effects and have proven to be highly effective in enhancing glycemic regulation and inducing weight loss through increased glucose elimination in urine.

Dapagliflozin stands out as a potent, orally active SGLT2 inhibitor that competes with glucose at the renal binding site, thereby blocking glucose reabsorption and promoting its excretion. This process is dose-dependent, leading to significant glucose excretion and serum uric acid reduction, with a noted oral bioavailability of 78% [36]. Despite its benefits, the use of dapagliflozin is carefully monitored due to possible side effects such as genital infections, vertigo, hypotension, and potential renal function deterioration. The drug's metabolism primarily involves oxidative reactions and glucuronidation, excluding the involvement of CYP isoenzymes, and its elimination is facilitated through both renal and biliary pathways.

Pharmacogenetic studies have delved into the interindividual variations in response to dapagliflozin. Notably, the WFS1 gene, coding for a transmembrane protein implicated in cellular homeostasis and calcium signaling, has been associated with weight loss in patients treated with dapagliflozin [37, 38]. Another gene, PNPLA3, related to lipid metabolism and NAFLD risk, has shown an interaction with the treatment's efficacy, especially regarding liver fat content [39].

Canagliflozin, another FDA-approved SGLT2 inhibitor, has been linked to a reduced risk of cardiovascular events and end-stage kidney disease. Its glucose-lowering action is dose-dependent, and its oral bioavailability is 65%. Metabolized into inactive O-glucuronide metabolites by UGT1A9 and UGT2B4, canagliflozin is also affected by genetic polymorphisms that influence the rate of glucuronidation and therapeutic responses. For instance, carriers of the UGT1A9*3 allele exhibit increased plasma exposure to the drug, suggesting a heightened sensitivity [40, 41].

Empagliflozin, known for its high selectivity for SGLT2, is notable for reducing cardiovascular mor-

tality in T2D patients. The drug demonstrates high oral bioavailability and is extensively metabolized by UGT isozymes, with its pharmacokinetic and dynamic profiles being affected by genetic variants within the SLC5A2 gene, which can alter patient responses, including blood pressure regulation and glucose levels [42].

In conclusion, the pharmacogenomics of SGLT2 inhibitors highlight the crucial role of genetic variations in dictating drug responses and potential adverse effects in T2D management. Personalized medicine approaches, therefore, necessitate an integration of genetic testing to tailor treatments, mitigate risks, and optimize clinical outcomes in diabetes care.

Table 4 captures the genetic variants across different genes that influence the pharmacodynamics and pharmacokinetics of various SGLT2 inhibitors. It highlights the impact of specific SNPs on clinical outcomes such as body weight, liver fat content, and metabolic changes such as glucose and uric acid levels. It is noted that while certain SNPs are directly linked to the metabolism of the drugs (UGT1A9 and UGT2B4), others (WFS1, PNPLA3, and SLC5A2) influence the response to the drugs, demonstrating the complex nature of pharmacogenomics in diabetes treatment.

Embracing genomic diversity in diabetes care

As we decode the genetic intricacies underlying T2D, it is imperative to harness the power of pharmacogenetics to steer clinical decision-making towards a more personalized approach. The therapeutic landscape of T2D is complex, as is its genetic underpinning, but significant strides have been made to elucidate how genetic variability can influence treatment outcomes.

Metformin: bridging genes and gastrointestinal tolerance

Metformin, the cornerstone of T2D management, presents a unique case where genetic variations in transporters like OCT1 (SLC22A1), PMAT (SLC29A4), and SERT (SLC6A4) significantly influence drug tolerance. Approximately 5–10% of patients experience gastrointestinal intolerance to metformin, which may stem from the high concentrations of the drug in the enterocytes, altered gut microbiota, or interference with bile acid reabsorption. Variants in the aforementioned transporters not only modulate the drug's absorption and distribution but also the risk of intolerance, underscoring the need for genetic considerations in metformin therapy.

Sulfonylureas and the KATP channel: a genetic conundrum

Sulfonylureas operate by stimulating insulin secretion via the KATP channel, but genetic variations like those in ABCC8/KCNJ11 and TCF7L2 influence their effectiveness and safety. The response to sulfonylureas is significantly better in individuals with slower CYP2C9 metabolism, exemplifying how genetic factors can inform drug dosing and efficacy. The challenge remains in leveraging these insights to mitigate adverse effects such as hypoglycemia while optimizing glycemic control.

Thiazolidinediones: navigating through genetic metabolism

For TZDs, the metabolic process governed by CYP2C8 and SLCO1B1 is critical. Genetic variants influencing these enzymes can modify the therapeutic effects and side effects of TZDs, as seen with rosiglitazone. This understanding could direct the choice of specific TZDs and predict weight gain responses in patients.

DPP-4 inhibitors: uncovering genotype--influenced efficacy

DPP-4 inhibitors have shown variability in HbA1c reduction due to genetic differences near the CTRB1/2 gene. This variance elucidates the potential for genotype-guided therapy for DPP-4 inhibitors, highlighting the nuanced interplay between genetic makeup and drug response.

Tailoring diabetes care by SGLT 2 inhibitors with genetic insights

Dapagliflozin, a SGLT2 inhibitor, offers an illustrative case of the potential for tailored medication based on genetic insights. The WFS1 gene, associated with the regulation of cellular homeostasis, when bearing the rs10010131 variant, can predict the degree of weight loss a patient might experience with dapagliflozin. Similarly, the PNPLA3 gene, with its rs738409 SNP, has been linked with changes in liver fat content, suggesting a nuanced interaction with dapagliflozin's efficacy, particularly when combined with omega-3 carboxylic acids in patients with specific genotypes like CG/GG. In the metabolism of canagliflozin, genetic variants like UGT1A93 (rs72551330) and UGT2B42 demonstrate their significance by modulating drug exposure and metabolism, highlighting the profound impact genetic variations have on therapeutic outcomes. Empagliflozin's response is similarly influenced by genotypic variations in SLC5A2, with SNPs like rs3116650, rs3116149,

and rs11646054 linked to modifications in blood pressure and glucose levels.

The dawn of preemptive genotyping

As the field progresses, the case strengthens for the implementation of preemptive genotyping, which could enable the embedding of genetic data within medical records. This advancement would transform clinical decision-making, providing healthcare professionals with valuable insights into genetic predispositions that may impact the choice and dosage of T2D medications. It underscores a shift towards a model in which genetic data informs the prescription process, aiming to enhance therapeutic benefits and reduce the risk of ADRs.

Conclusions

A new paradigm in type 2 diabetes management

The future of diabetes treatment pivots on the integration of pharmacogenetics into the standard of care, marrying genetic data with clinical judgment to provide tailored treatments. While the genetic architecture of T2D is complex, driven by multiple variants with small effects, the clinical relevance of pharmacogenetic interactions cannot be overlooked. The emergence of low-cost genotyping platforms has paved the way for preemptive genotyping, making it feasible to consider genetic factors in real-time prescribing decisions.

The successful adoption of this paradigm will require a concerted effort to standardize processes that facilitate the use of genetic information in clinical settings. With the incorporation of preemptive panel genotyping and clinical decision support tools that synthesize genetic and phenotypic data, a future in which personalized medicine is the norm for T2D management is within reach. The implications are profound: a redefined approach to diabetes care where therapy is finely tuned to the individual's genetic profile, fulfilling the promise of truly personalized medicine in the era of pharmacogenomics.

Article information

Author contributions

SSS, AM, AT, BS: study conceptualization, data acquisition, manuscript preparation; SM, KB, AKR: data acquisition, manuscript preparation; SJ: study supervision, manuscript preparation

Funding

None.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Roden DM, Van Driest SL. Pharmacogenetics and Pharmacogenomics. In: Brunton LL, Knollmann BC. eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14th Edition. McGraw-Hill Education; 2023. https://accessmedicine.mhmedical.com/content.aspx?bookid=3191§ionid=268215725 (12.04.2024).
2. Flannick J, Thorleifsson G, Beer NL, et al. Go-T2D Consortium, T2D-GENES Consortium. Loss-of-function mutations in SLC30A8 protect against type 2 diabetes. Nat Genet. 2014; 46(4): 357–363, doi: 10.1038/ng.2915, indexed in Pubmed: 24584071.
3. Marques SC, Ikediobi ON. The clinical application of UGT1A1 pharmacogenetic testing: gene-environment interactions. Hum Genomics. 2010; 4(4): 238–249, doi: 10.1186/1479-7364-4-4-238, indexed in Pubmed: 20511137.
4. Pulley JM, Shirey-Rice JK, Lavieri RR, et al. Accelerating Precision Drug Development and Drug Repurposing by Leveraging Human Genetics. Assay Drug Dev Technol. 2017; 15(3): 113–119, doi: 10.1089/adt.2016.772, indexed in Pubmed: 28379727.
5. Rollinson V, Turner R, Pirmohamed M. Pharmacogenomics for Primary Care: An Overview. Genes (Basel). 2020; 11(11), doi: 10.3390/genes11111337, indexed in Pubmed: 33198260.
6. Pearson ER. Diabetes: Is There a Future for Pharmacogenomics Guided Treatment? Clin Pharmacol Ther. 2019; 106(2): 329–337, doi: 10.1002/cpt.1484, indexed in Pubmed: 31012484.
7. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia. 2017; 60(9): 1577–1585, doi: 10.1007/s00125-017-4342-z, indexed in Pubmed: 28776086.
8. Umamaheswaran G, Praveen RG, Damodaran SE, et al. Influence of SLC22A1 rs622342 genetic polymorphism on metformin response in South Indian type 2 diabetes mellitus patients. Clin Exp Med. 2015; 15(4): 511–517, doi: 10.1007/s10238-014-0322-5, indexed in Pubmed: 25492374.
9. Xiao Di, Guo Yu, Li Xi, et al. The Impacts of SLC22A1 rs594709 and SLC47A1 rs2289669 Polymorphisms on Metformin Therapeutic Efficacy in Chinese Type 2 Diabetes Patients. Int J Endocrinol. 2016; 2016: 4350712, doi: 10.1155/2016/4350712, indexed in Pubmed: 26977146.
10. Zhou Y, Ye W, Wang Y, et al. Genetic variants of OCT1 influence glycemic response to metformin in Han Chinese patients with type-2 diabetes mellitus in Shanghai. Int J Clin Exp Pathol. 2015; 8(8): 9533–9542, indexed in Pubmed: 26464716.
11. Dujic T, Causevic A, Bego T, et al. Organic cation transporter 1 variants and gastrointestinal side effects of metformin in patients with Type 2 diabetes. Diabet Med. 2016; 33(4): 511–514, doi: 10.1111/dme.13040, indexed in Pubmed: 26605869.
12. Phani NM, Vohra M, Kakar A, et al. Implication of critical pharmacokinetic gene variants on therapeutic response to metformin in Type 2 diabetes. Pharmacogenomics. 2018; 19(11): 905–911, doi: 10.2217/pgs-2018-0041, indexed in Pubmed: 29914345.
13. Nikolac N, Simundic AM, Katalinic D, et al. Metabolic control in type 2 diabetes is associated with sulfonylurea receptor-1 (SUR-1) but not with KCNJ11 polymorphisms. Arch Med Res. 2009; 40(5): 387–392, doi: 10.1016/j.arcmed.2009.06.006, indexed in Pubmed: 19766903.
14. Klen J, Dolžan V, Janež A. CYP2C9, KCNJ11 and ABCC8 polymorphisms and the response to sulphonylurea treatment in type 2 diabetes patients. Eur J Clin Pharmacol. 2014; 70(4): 421–428, doi: 10.1007/s00228-014-1641-x, indexed in Pubmed: 24442125.
15. Li Q, Chen M, Zhang R, et al. KCNJ11 E23K variant is associated with the therapeutic effect of sulpho- nylureas in Chinese type 2 diabetic patients. Clin Exp Pharmacol Physiol. 2014;

41(10): 748–754, doi: 10.1111/1440-1681.12280, indexed in Pubmed: 25115353.
16. Li Q, Tang TT, Jiang F, et al. Polymorphisms of the KCNQ1 gene are associated with the therapeutic responses of sulfonylureas in Chinese patients with type 2 diabetes. Acta Pharmacol Sin. 2017; 38(1): 80–89, doi: 10.1038/aps.2016.103, indexed in Pubmed: 27694910.
17. Javorsky M, Klimcakova L, Schroner Z, et al. KCNJ11 gene E23K variant and therapeutic response to sulfonylureas. Eur J Intern Med. 2012; 23(3): 245–249, doi: 10.1016/j.ejim.2011.10.018, indexed in Pubmed: 22385882.
18. Zhou K, Donnelly L, Burch L, et al. Loss-of-function CYP2C9 variants improve therapeutic response to sulfonylureas in type 2 diabetes: a Go-DARTS study. Clin Pharmacol Ther. 2010; 87(1): 52–56, doi: 10.1038/clpt.2009.176, indexed in Pubmed: 19794412.
19. Niemi M, Backman JT, Kajosaari LI, et al. Polymorphic organic anion transporting polypeptide 1B1 is a major determinant of repaglinide pharmacokinetics. Clin Pharmacol Ther. 2005; 77(6): 468–478, doi: 10.1016/j.clpt.2005.01.018, indexed in Pubmed: 15961978.
20. Pei Qi, Liu JY, Yin JY, et al. Repaglinide-irbesartan drug interaction: effects of SLCO1B1 polymorphism on repaglinide pharmacokinetics and pharmacodynamics in Chinese population. Eur J Clin Pharmacol. 2018; 74(8): 1021–1028, doi: 10.1007/s00228-018-2477-6, indexed in Pubmed: 29748863.
21. Kalliokoski A, Backman J, Neuvonen PJ, et al. Effects of the SLCO1B1*1B haplotype on the pharmacokinetics and pharmacodynamics of repaglinide and nateglinide. Pharmacogenet Genomics. 2008; 18(11): 937–942, doi: 10.1097/FPC.0b013e32830d733e, indexed in Pubmed: 18854776.
22. Dai XP, Huang Q, Yin JY, et al. Polymorphisms of the KCNQ1 gene are associated with the therapeutic responses of sulfonylureas in Chinese patients with type 2 diabetes. Clin Exp Pharmacol Physiol. 2012; 39(5): 462–468, doi: 10.1111/j.1440-1681.2012.05701.x, indexed in Pubmed: 22414228.
23. Daily EB, Aquilante CL. Cytochrome P450 2C8 pharmacogenetics: a review of clinical studies. Pharmacogenomics. 2009; 10(9): 1489–1510, doi: 10.2217/pgs.09.82, indexed in Pubmed: 19761371.
24. Martis S, Peter I, Hulot JS, et al. Multi-ethnic distribution of clinically relevant CYP2C genotypes and haplotypes. Pharmacogenomics J. 2013; 13(4): 369–377, doi: 10.1038/tpj.2012.10, indexed in Pubmed: 22491019.
25. Stage TB, Christensen MMH, Feddersen S, et al. The role of genetic variants in CYP2C8, LPIN1, PPARGC1A and PPARγ on the trough steady-state plasma concentrations of rosiglitazone and on glycosylated haemoglobin A1c in type 2 diabetes. Pharmacogenet Genomics. 2013; 23(4): 219–227, doi: 10.1097/FPC.0b013e32835f91fc, indexed in Pubmed: 23426382.
26. Dawed AY, Donnelly L, Tavendale R, et al. CYP2C8 and SLCO1B1 Variants and Therapeutic Response to Thiazolidinediones in Patients With Type 2 Diabetes. Diabetes Care. 2016; 39(11): 1902–1908, doi: 10.2337/dc15-2464, indexed in Pubmed: 27271184.
27. Zhang KH, Huang Q, Dai XP, et al. Effects of the peroxisome proliferator activated receptor-γ coactivator-1α (PGC-1α) Thr394Thr and Gly482Ser polymorphisms on rosiglitazone response in Chinese patients with type 2 diabetes mellitus. J Clin Pharmacol. 2010; 50(9): 1022–1030, doi: 10.1177/0091270009355159, indexed in Pubmed: 20498286.
28. Li Z, Peng X, Wu Y, et al. The influence of adiponectin gene polymorphism on the pioglitazone response in the Chinese with type 2 diabetes. Diabetes Obes Metab. 2008; 10(9): 794–802, doi: 10.1111/j.1463-1326.2008.00905.x, indexed in Pubmed: 18494805.
29. Mannino GC, Andreozzi F, Sesti G. Pharmacogenetics of type 2 diabetes mellitus, the route toward tailored medicine. Diabetes Metab Res Rev. 2019; 35(3): e3109, doi: 10.1002/dmrr.3109, indexed in Pubmed: 30515958.
30. Fortin JP, Schroeder JC, Zhu Y, et al. Pharmacological characterization of human incretin receptor missense variants. J Pharmacol Exp Ther. 2010; 332(1): 274–280, doi: 10.1124/jpet.109.160531, indexed in Pubmed: 19841474.
31. Nitz I, Fisher E, Weikert C, et al. Association analyses of GIP and GIPR polymorphisms with traits of the metabolic syndrome. Mol Nutr Food Res. 2007; 51(8): 1046–1052, doi: 10.1002/mnfr.200700048, indexed in Pubmed: 17624916.
32. Mohammad S, Patel RT, Bruno J, et al. A naturally occurring GIP receptor variant undergoes enhanced agonist-induced desensitization, which impairs GIP control of adipose insulin sensitivity. Mol Cell Biol. 2014; 34(19): 3618–3629, doi: 10.1128/MCB.00256-14, indexed in Pubmed: 25047836.
33. Tokuyama Y, Matsui K, Egashira T, et al. Five missense mutations in glucagon-like peptide 1 receptor gene in Japanese population. Diabetes Res Clin Pract. 2004; 66(1): 63–69, doi: 10.1016/j.diabres.2004.02.004, indexed in Pubmed: 15364163.
34. Jensterle M, Pirš B, Goričar K, et al. Genetic variability in GLP-1 receptor is associated with inter-individual differences in weight lowering potential of liraglutide in obese women with PCOS: a pilot study. Eur J Clin Pharmacol. 2015; 71(7): 817–824, doi: 10.1007/s00228-015-1868-1, indexed in Pubmed: 25991051.
35. Gotthardová I, Javorský M, Klimčáková L, et al. KCNQ1 gene polymorphism is associated with glycaemic response to treatment with DPP-4 inhibitors. Diabetes Res Clin Pract. 2017; 130: 142–147, doi: 10.1016/j.diabres.2017.05.018, indexed in Pubmed: 28624668.
36. Boulton DW, Kasichayanula S, Keung CF, et al. Simultaneous oral therapeutic and intravenous ^{1} C-microdoses to determine the absolute oral bioavailability of saxagliptin and dapagliflozin. Br J Clin Pharmacol. 2013; 75(3): 763–768, doi: 10.1111/j.1365-2125.2012.04391.x, indexed in Pubmed: 22823746.
37. Fischer TT, Ehrlich BE. Wolfram Syndrome: a Monogenic Model to Study Diabetes Mellitus and Neurodegeneration. Curr Opin Physiol. 2020; 17: 115–123, doi: 10.1016/j.cophys.2020.07.009, indexed in Pubmed: 32864536.
38. Pereira MJ, Lundkvist P, Kamble PG, et al. A Randomized Controlled Trial of Dapagliflozin Plus Once-Weekly Exenatide Versus Placebo in Individuals with Obesity and Without Diabetes: Metabolic Effects and Markers Associated with Bodyweight Loss. Diabetes Ther. 2018; 9(4): 1511–1532, doi: 10.1007/s13300-018-0449-6, indexed in Pubmed: 29949016.
39. Machado CM, Leite NC, França PH, et al. PNPLA3 gene polymorphism in Brazilian patients with type 2 diabetes: A prognostic marker beyond liver disease? Nutr Metab Cardiovasc Dis. 2019; 29(9): 965–971, doi: 10.1016/j.numecd.2019.06.002, indexed in Pubmed: 31377187.
40. Francke S, Mamidi RN, Solanki B, et al. In vitro metabolism of canagliflozin in human liver, kidney, intestine microsomes, and recombinant uridine diphosphate glucuronosyltransferases (UGT) and the effect of genetic variability of UGT enzymes on the pharmacokinetics of canagliflozin in humans. J Clin Pharmacol. 2015; 55(9): 1061–1072, doi: 10.1002/jcph.506, indexed in Pubmed: 25827774.
41. Heo CUk, Choi CI. Current Progress in Pharmacogenetics of Second-Line Antidiabetic Medications: Towards Precision Medicine for Type 2 Diabetes. J Clin Med. 2019; 8(3): 393, doi: 10.3390/jcm8030393, indexed in Pubmed: 30901912.
42. Zimdahl H, Haupt A, Brendel M, et al. Influence of common polymorphisms in the SLC5A2 gene on metabolic traits in subjects at increased risk of diabetes and on response to empagliflozin treatment in patients with diabetes. Pharmacogenet Genomics. 2017; 27(4): 135–142, doi: 10.1097/FPC.0000000000000268, indexed in Pubmed: 28134748.
43. Kaur P, Behera BS, Singh S, et al. "The pharmacological profile of SGLT2 inhibitors: Focus on mechanistic aspects and pharmacogenomics". Eur J Pharmacol. 2021; 904: 174169, doi: 10.1016/j.ejphar.2021.174169, indexed in Pubmed: 33984301.