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Pharmacogenetics in metabolic diseases: The impact of cytochrome P450 variants on drug response

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ABSTRACT

Pharmacogenetics is a field of medicine that combines genetics and pharmacology, primarily focusing on the identification of genetic variants to help predict drug response and possible adverse reactions. As both response rates and the occurrence of side effects vary between patients, genetic testing can help explain the reason for these differences. Pharmacogenetic testing helps personalize treatment with the objective of enhancing drug efficacy, safety, and outcomes. In this review, we focused on the impact of cytochrome P450 variants on treating hypercholesterolemia and type 2 diabetes. Optimizing cholesterol management and diabetes treatment can lower cardiovascular risk and mortality, which poses a huge threat to today's world due to the increasing popularity of a sedentary lifestyle and the growing incidence of these metabolic diseases.

1. INTRODUCTION

Pharmacogenetics is a field linked to genetics and pharmacology, identifying genetic variants that can help with predicting the body's response to specific drugs [1]. Both response rate and occurrence of adverse drug reactions (ADRs) range widely among patients. The purpose of Pharmacogenetic (PGx) testing is to use genomic information to individualize drug therapy by tailoring the treatment to the patient's predicted response with the objective of increasing drug efficiency, ensuring greater safety, and improving treatment outcomes [2]. Nowadays, PGx testing is used in the diagnosis and personalization of treatment within a vast number of diseases, such as cardiovascular diseases, diabetes, autoimmune diseases, mental disorders, and cancer. The aim of this article is to examine different effects of cytochrome P450 genetic variants on the treatment of metabolic diseases—hypercholesterolemia and diabetes.

Effective cholesterol management and the implementation of improved strategies for the prevention and treatment of type 2 diabetes can significantly reduce the risk of cardiovascular events and overall mortality [3–5]. Given the complex aetiology and pathophysiological processes of metabolic diseases, understanding the role of cytochrome P450 enzymes is crucial for optimizing therapy.

2. MATERIALS AND METHODS

This review examines the pharmacokinetics of cytochromes in relation to selected antidiabetic and antihyperlipidemic drugs, with a focus on the impact of genetic polymorphisms on drug efficacy and metabolism in human populations.

The PubMed and Scopus databases were used as the source for the analysis. Publishing platforms such as Springers, Frontiers, Elsevier, and Multidisciplinary Digital Publishing Institute were additionally searched to increase the completeness of this review.

The following MeSH terms were used „Statins", „Atorvastatin", „Fluvastatin", „SAMS", „ADRs", „Pharmacogenetics", „Pharmacogenomics", „CYP enzymes", „Sulfonylureas", „Glibenclamide", „Glinides", „Repaglinide", „Nateglinide", „Glitazones", „Rosiglitazone", „Hypercholesterolemia", and „Diabetes".

This research retrieved 63 articles published over the past 25 years, with a particular focus on the last 8 years. Studies

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published from 2000 to the present were included because we did not strictly enforce a chronological limit, but rather to guarantee thorough coverage, because we aimed to ensure a thorough and most comprehensive review of the available literature while including relevant studies from past years.

Original studies, review articles, and books written in English and Polish were considered. One study was excluded because it was available exclusively in Italian. Studies conducted on animal models or those focusing on other cytochromes not involved in the metabolism of the drugs discussed in this article were also excluded.

Initially, 80 publications were identified, but after excluding certain studies, only 63 were retained.

2.1. Identification

Records identified via PubMed, Scopus, and publishing platforms (Springer, Frontiers, Elsevier, and MDPI) (n = 80).

2.2. Screening

Records after excluding nonrelevant cytochromes, animal studies, and nonEnglish/Polish texts (n = 63).

2.3. Excluded

1 article (language barrier—Italian only), 16 articles (animal models or unrelated cytochromes).

2.4. Eligibility

Full-text articles assessed (n = 63).

2.5. Included

Final studies analyzed (n = 63).

2.6. Breakdown

Focused on cytochrome pharmacokinetics and genetic polymorphisms, included statins (Atorvastatin, Fluvastatin), included sulfonylureas (Glibenclamide), glinides (Repaglinide, Nateglinide), and glitazones (Rosiglitazone). Addressed pharmacogenetics, ADRs, and metabolic outcomes in human studies.

The studies were selected through a systematic, multistep procedure in accordance with a structured framework based on PRISMA methodology (Fig. 1).

3. HYPERCHOLESTEROLEMIA

Hypercholesterolemia is a key modifiable risk factor in atherosclerosis and cardiovascular diseases, which remains the leading cause of deaths and hospitalizations in Europe [5]. Over 4 million Europeans lose their lives annually to cardiovascular diseases (CVD), with the majority of these deaths resulting from coronary heart disease and stroke [6].

3.1. Statins

The 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (statins) are amongst the most frequently used hypolipidemic drugs across the globe. Statins mode of action relies on reducing the production of cholesterol, thereby

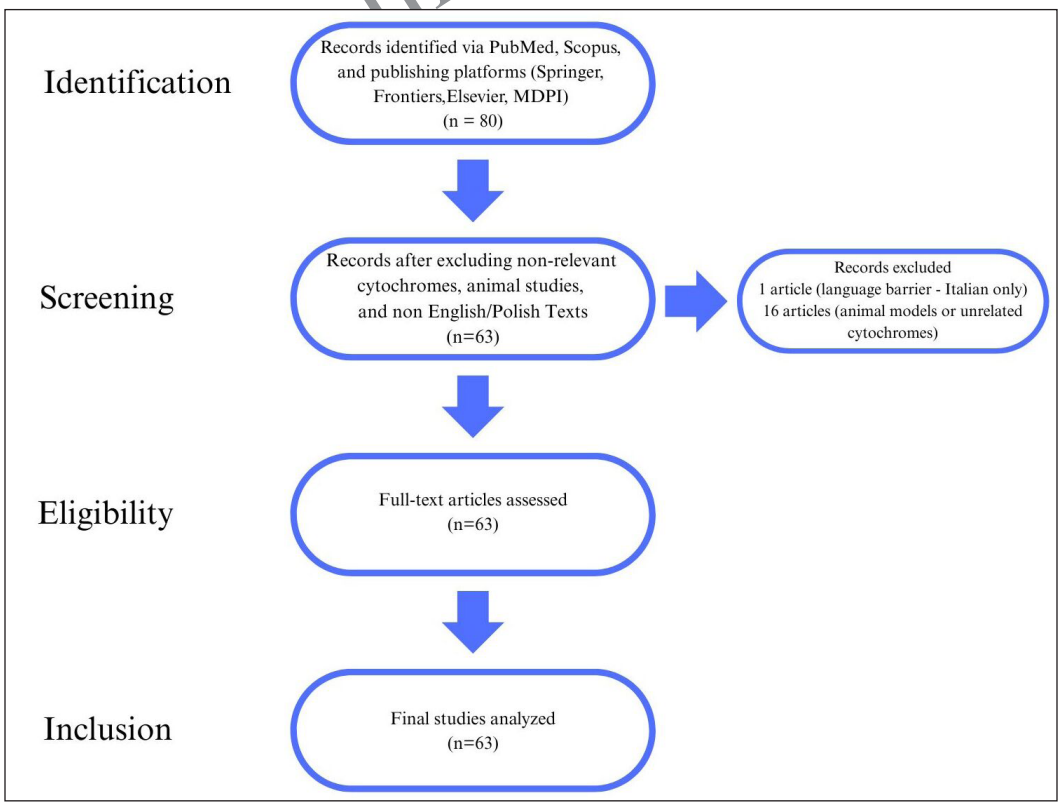

Figure 1. Prisma flowchart.

lowering the levels of LDL cholesterol and triglycerides in the bloodstream [7].

Research trials have confirmed the effectiveness of statins in preventing coronary heart disease, both initially and after its onset. In addition to their lipid-lowering effects, statins have shown pleiotropic benefits, such as promoting vascular relaxation and inhibiting platelet aggregation. They also help to reduce vascular smooth muscle proliferation, limit endothelial–leukocyte interactions, improve endothelial function, and exhibit antioxidant properties [8].

Despite their proven benefits, statin therapy, like other drugs, continues to face challenges related to adverse side effects and suboptimal effectiveness. Statins-associated muscle symptoms (SAMSs) are the most commonly reported side effects, which often lead to poor adherence and eventually to discontinuation of therapy. This, in turn, results in elevated LDL cholesterol levels and greater susceptibility to CVD. Thus, identifying possible key gene variants involved in statin metabolism and understanding their effects on patients can improve the effectiveness of statin therapy and help minimize side effects. This knowledge could serve as a valuable tool for clinicians in managing and monitoring patients receiving statin treatment [9].

Statins can be classified as either hydrophilic or lipophilic, based on their solubility in water or in lipid-based environments. Lipophilic statins, such as simvastatin, fluvastatin, atorvastatin, lovastatin, and pitavastatin, easily penetrate cell membranes, while hydrophilic statins, like rosuvastatin and pravastatin, exhibit greater liver selectivity. The action of lipophilic statins relies primarily on passive diffusion for cellular entry, and these medications undergo metabolism via cytochrome P450 enzymes, and thereafter are excreted through the biliary system (Fig. 2). Most lipophilic statins are processed

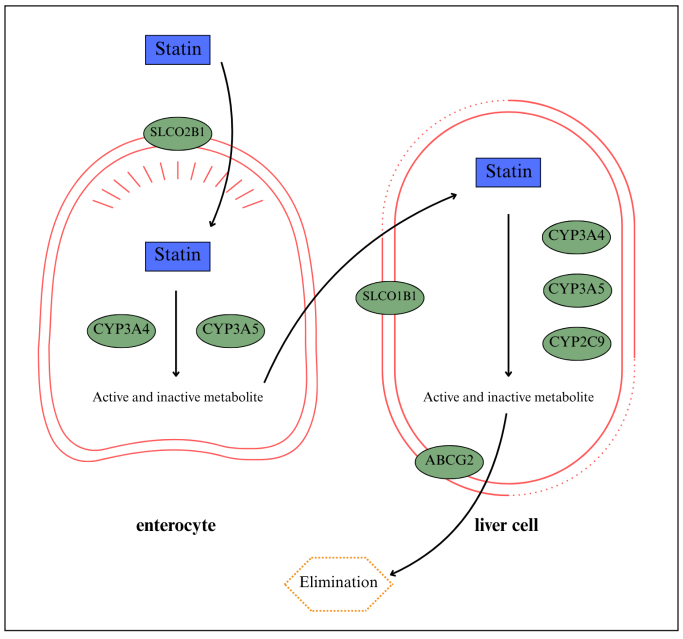

Figure 2. Schematic representation of statin metabolism and cytochrome enzymes involvement.

by the CYP3A4 enzyme, with the exception of fluvastatin, which is metabolized by CYP2C9. In contrast, hydrophilic statins are not extensively metabolized by CYP450 enzymes, but their mode of action relies on active transport in the liver and elimination through both hepatic and renal pathways. For instance, rosuvastatin is predominantly excreted unchanged. Hydrophilic statins are less likely to cause muscle-related side effects because they have limited passive diffusion into muscle tissue. This liver-selective distribution reduces their exposure to skeletal muscle, lowering the risk of SAMS [9,10].

The "2022 Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines" highlighted the role of pharmacogenetics in influencing the statin response, including pharmacokinetics, hepatotoxicity, SAMS, lipid-lowering effects, and overall clinical efficacy. These guidelines assessed a range of genes and were based on key studies and expert consensus. The genes with the strongest evidence linking them to ADRs include *CYP2C9* (for fluvastatin), *SLCO1B1* (for all statins), and *ABCG2* (for rosuvastatin). Consequently, the guidelines offer recommendations aimed at reducing the SAMS risk. While other aspects, such as how lipid-lowering performance is affected, are mentioned in various reviews, the guidelines specifically focus on recommendations that are related to ADRs. Although some studies according genes such as *HMGCR*, *CYP3A4*, and *CYP3A5*, are still in progress, there is currently insufficient evidence to justify any clinical implementation. As our review primarily focuses on cytochrome P450 (CYP) enzymes, a detailed discussion of *SLCO1B1* and *ABCG2* is omitted, being beyond its scope [9,11].

In February 2023, the Ubiquitous Pharmacogenomics Consortium published findings from "The Pre-emptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions (PREPARE)" study. This implementation study examined drug–gene variant combinations that were known to have a significant genetic impact on drug response. The study investigated the potential advantages of pre-emptive pharmacogenetic testing across several European countries, involving thousands of patients who were assessed using a "genetic passport" panel that included *CYP2C9* and *SLCO1B1* genotypes. Atorvastatin emerged as the most frequently analyzed medication, and when dosing was adjusted based on guidance from the Dutch Pharmacogenetics Working Group, a notable reduction, around 30%, in clinically significant ADRs was observed, highlighting the value of incorporating genetic information into prescribing practices [9,12].

3.1.1. CYP2C9 polymorphism in statins metabolism

CYP2C9 is one of the principal enzymes within the cytochrome P450 family, contributing to roughly 20% of total P450 content in hepatic microsomes [13]. Of all the statins, fluvastatin is uniquely and predominantly metabolized by CYP2C9. To date, approximately 75 allelic variants of this gene have been characterized. The Genetic Effects on STATins (GEOSTAT-1) study highlighted three key alleles: **1* (wild type), **2* (rs1799853), and **3* (rs1057910). The **1* allele encodes an enzyme with full metabolic capacity, while **2* and **3* variants are associated with reduced enzymatic activity by approximately 88% and 95%, respectively, when

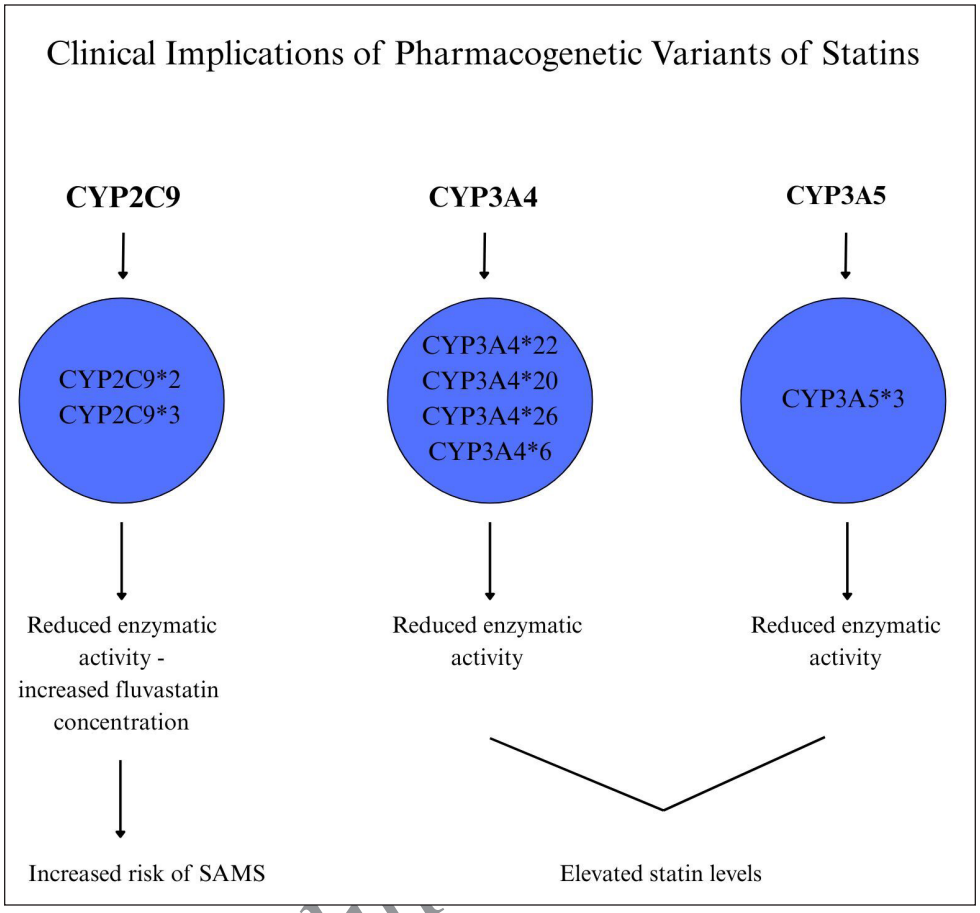

Figure 3. Clinical implications of pharmacogenetic variants of statins.

contrasted with the wild-type variant [14,15] Figure 3. The allele frequencies in European populations are estimated at 0.13 for **2* and 0.07 for **3* [11].

Metabolizer status is typically classified based on genotype. Individuals with two normal-function alleles (**1/*1*) are considered normal metabolizers. Those carrying one normal-function and one reduced- or nonfunction allele (**1/*2* or **1/*3*), or two reduced-function alleles (**2/*2*), are categorized as intermediate metabolizers. Carriers of two nonfunctional alleles (**3/*3*) or one reduced- and one nonfunctional allele (**2/*3*) are classified as poor metabolizers. These categories can also be quantified by an activity score: 2 for normal metabolizers, 1–1.5 for intermediate metabolizers, and 0–0.5 for poor metabolizers [11].

Individuals harboring *CYP2C9* variants that impair enzymatic activity may be predisposed to higher systemic concentrations of fluvastatin. This elevation increases the risk of SAMS, thereby necessitating either dose adjustments or substitution with an alternative statin. Corroborating this result, one study demonstrated that individuals who were homozygous or heterozygous for the **2* or **3* alleles had a 2.5-fold higher likelihood of experiencing adverse drug reactions compared to noncarriers. Notably, patients who carried at least one variant allele and were concurrently treated with CYP2C9 inhibitors exhibited over six-fold increased odds of adverse outcomes [16].

In contrast, another investigation noted a nonsignificant trend toward higher risk of fluvastatin intolerance among individuals carrying risk alleles. However, this result may have been underpowered due to limited sample size [17].

3.1.2. CYP3A4 polymorphism in statins metabolism

CYP3A4, a key member of the CYP3A subfamily, is the most prevalent cytochrome P450 enzyme and plays a major role in the metabolism of a wide range of medications, including many statins, estimated to be involved in the biotransformation of nearly half of all prescribed drugs [18]. Among the statins, atorvastatin, lovastatin, and simvastatin are primarily metabolized through CYP3A4-dependent pathways [19].

Several *CYP3A4* gene polymorphisms that affect enzyme activity have been identified. One such variant, *CYP3A4*22* (rs35599367), is a reduced-function allele found predominantly in individuals of European descent, with an allele frequency around 5%. This variant has been associated with lower expression levels of CYP3A4, potentially affecting the pharmacokinetics of drugs such as simvastatin, atorvastatin, and lovastatin. Reduced CYP3A4 activity may result in higher systemic exposure to these statins, which could increase the

likelihood of concentration-dependent adverse effects [18–20]. Other identified variants, including **26* (rs13806538), **20* (rs67666821), and **6* (rs4646438), are considered to have minimal or no enzymatic function, although most are exceedingly rare, with the exception of *CYP3A4*20* [20,21]. As a result of their impact on enzyme activity, these alleles may lead to elevated systemic statin concentrations. However, the current body of evidence does not consistently demonstrate a clear connection between these variants and clinical outcomes of statin therapy due to inconsistent findings across studies [15]. In one clinical investigation, no significant association was observed between *CYP3A4* genetic variants and atorvastatin plasma concentrations [22]. In contrast, another study reported that individuals carrying the *CYP3A4*1/*22* genotype exhibited approximately 58% higher plasma levels of simvastatin at 12 hours post-dose compared to those with the *CYP3A4*1/*1* genotype, indicating a potential influence of this variant on drug exposure [23].

Consequently, routine genetic testing for *CYP3A4* variants is not currently recommended in clinical practice. Nevertheless, the significant role of CYP3A4 in metabolizing certain statins underscores the need for further research to better understand the clinical implications of these polymorphisms, especially in populations where variant alleles may be more prevalent [19].

3.1.3. CYP3A5 polymorphism in statins metabolism

By the common convention, the *CYP3A5*1* allele has been denoted as a normal-function (reference) allele. Notably, the **1* polymorphism is more commonly found in individuals of African descent (50%), while its frequency is lower among Caucasian and Asian populations (10%–30%) [24].

Among *CYP3A5* variants, the loss-of-function *CYP3A5*3* (rs776746) allele is the most widely studied and frequently occurring [25]. Findings from various studies indicate that individuals with certain genetic variations in the *CYP3A5* gene show differing responses to statin treatments. Statin concentrations are significantly elevated in those who are either heterozygous or homozygous for the *CYP3A5*3* variant compared to wild-type individuals [26,27]. One study demonstrated that individuals with the CYP3A5*3/*3 genotype experienced a more pronounced reduction in total cholesterol (37.5%) even at half the typical simvastatin dose, in contrast to a 35.2% reduction observed in those with at least one functional *CYP3A5* allele treated with standard dose [27]. Supporting these findings, *CYP3A5* expression status was shown to influence simvastatin pharmacokinetics in African–American individuals, where those with the *CYP3A5*3/*3* genotype had 33% higher simvastatin concentrations compared to individuals with the *CYP3A5*1/*3* genotype [28]. Furthermore, another study documented that carriers of the *CYP3A5*1* allele treated with simvastatin exhibited a 24% greater level in serum LDL concentration than those possessing the *CYP3A5*3* allele treated with the same drug [29]. Given that the *CYP3A5*3* allele is linked to reduced metabolic activity, it may contribute to the development of SAMS, as suggested by a meta-analysis conducted by Yee et al. [30].

4. DIABETES

There is a persistent increase in the occurrence of type 2 diabetes, affecting a growing number of people. According to the International Diabetes Federation, 61 million people in Europe suffer from type 2 diabetes, with the highest occurrence in countries such as Bulgaria (7.4%), Serbia (9.1%), and Spain (10.3%) [31]. In 2021, this disease was associated with as many as half a million premature deaths in the European region.

Diabetes treatment requires the use of various types of therapies, including oral medications, change of dietary habits, and weight loss promotion [32]. Genetic factors play an essential role in the efficacy of drugs and their metabolism. Differences in enzyme activity can have a considerable impact on treatment efficacy and may elevate the risk of unexpected adverse effects, such as hypoglycaemia, weight gain, and nausea [33,34].

Multiple classes of medications for type 2 diabetes may not be uniformly effective for all patients, and they can also exhibit diverse side effects that restrict their application. Several factors, including gender, age, and genetic predispositions, contribute to differences in individual responses to treatment [35].

4.1. Sulfonylureas

Sulfonylureas (SFUs) lower blood glucose by triggering insulin production from the pancreatic beta cells. By interacting with K-ATP channels in pancreatic β-cells, SFUs promote calcium entry into the cells and trigger membrane depolarization. This sequence of events ultimately results in the secretion of insulin [36].

They are among the first medications employed in the management of type 2 diabetes. SFUs are classified into two generations. The first generation includes tolbutamide and chlorpropamide, and the second one includes glibenclamide, glipizide, glimepiride, and gliclazide [37].

One of the most important elements influencing the pharmacokinetics and pharmacodynamics of sulfonylureas is the cytochrome P450 enzyme family, in particular the CYP2C9 isoenzyme.

4.1.1. CYP2C9 polymorphism in sulfonylureas metabolism

It has been found that genetic polymorphisms in the *CYP2C9* gene can cause variability in the effects of sulfonylureas, which may require adjustment of drug doses according to the patient's individual metabolic profile [38,39].

As stated before in the article, the *CYP2C9* gene exhibits significant variations, with the most common polymorphisms as *CYP2C9*3* (rs1057910) and *CYP2C9*2* (rs1799853) [40]. Research has shown that individuals with these CYP variants exhibit reduced drug elimination and increased plasma accumulation, impacting the safety and effectiveness of the treatment. Individuals with CYP2C9*2 or *CYP2C9*3 variants have an elevated risk of developing hypoglycemia, particularly when treated with glibenclamide, a sulfonylurea known for its prolonged duration of action [41] Figure 4. Consequently, these patients would require lower doses of these medications to achieve optimal glycaemic control in comparison to patients being homozygous for *CYP2C9*1* (thus exhibiting full

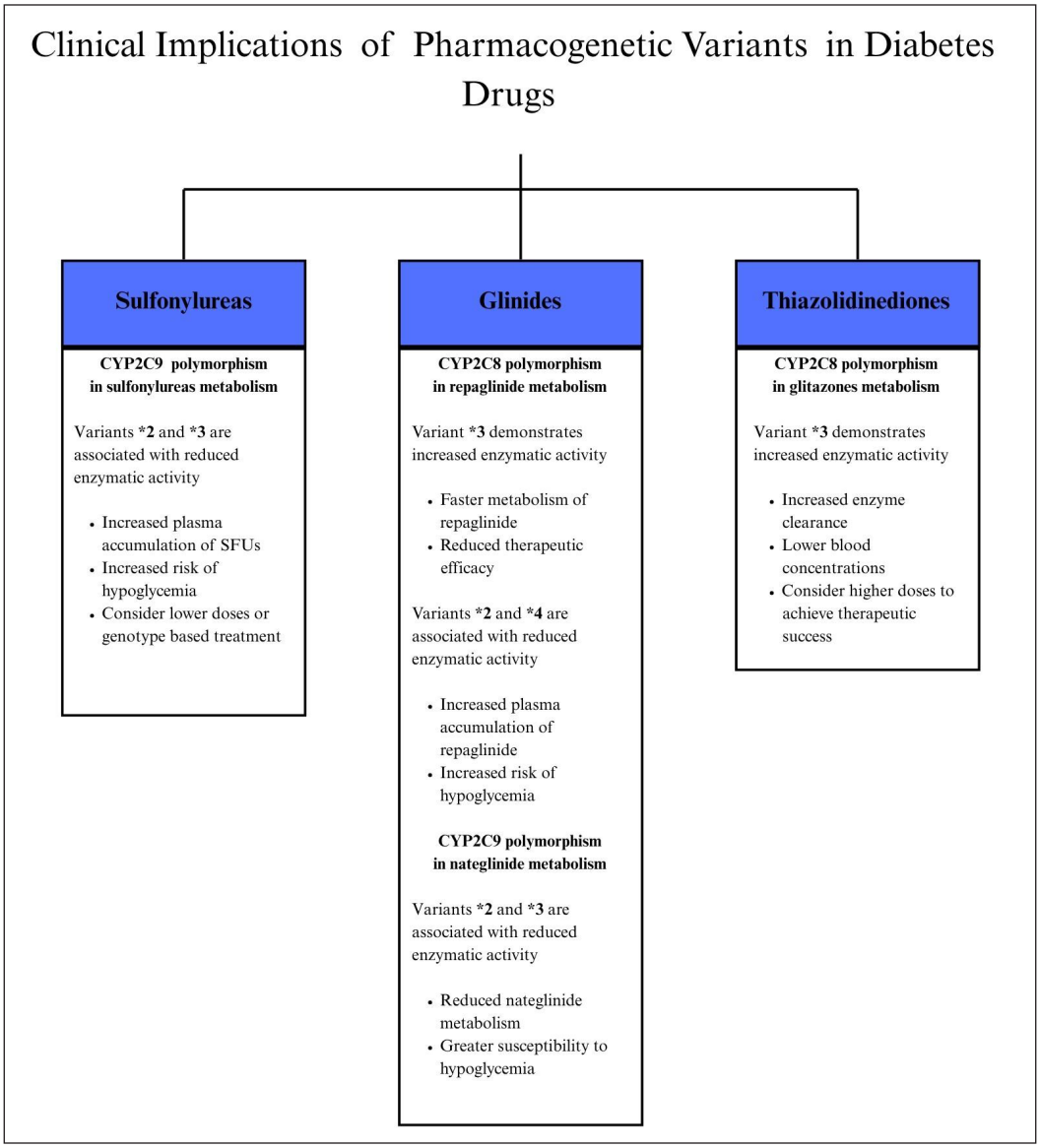

Figure 4. Clinical implications of pharmacogenetic variants in diabetes drugs.

enzymatic activity). This finding supports the implementation of genotype-based individualized treatment strategies [41,42].

The *CYP2C9*2* and *CYP2C9*3* polymorphisms have been associated with an enhanced treatment response and greater reduction (by 0,5%) in glycated haemoglobin (HbA1c) level in a study conducted in the United Kingdom [43]. However, a subsequent research performed in the Netherlands did not confirm these associations [44].

4.2. Glinides

Glinides are carbamoylmethylbenzoic acid derivatives, a class of diabetic drugs which work in a similar way to sulfonylureas, but interact with the receptor in a different manner. Their effect is primarily based on promoting insulin release from beta cells by inhibiting ATP-sensitive potassium channels. They stimulate insulin release for a short time, making these drugs useful for lowering the postprandial hyperglycemia seen in type 2 diabetes. Therefore, patients should administer them immediately before a meal [45]. This group of drugs includes, among others, repaglinide and nateglinide [46]. Genetic polymorphisms in genes involved in the metabolism of these drugs, such as *CYP2C9*, *CYP2C8*, and *CYP3A4*, may influence both the efficacy and the incidence of adverse effects [47,48].

4.2.1. CYP2C8 polymorphism in glinides metabolism

Orally administered repaglinide is quickly absorbed and shows a rapid onset of action (0.8 hours) [49]. Swiftly removed from the bloodstream, repaglinide is metabolized by CYP2C8, and by CYP3A4, however, to a minor extent. Individuals possessing the *CYP2C8*3* polymorphism (rs11572080 and rs10509681) demonstrated increased enzyme activity, leading to accelerated metabolism of repaglinide and inferior therapeutic efficacy [34].

According to a study performed in Finland, healthy patients who ingested a designated dose of repaglinide exhibited a maximum plasma drug concentration that was nearly 40% lower in *CYP2C8*3* genotype carriers in comparison with individuals possessing the wild-type *CYP2C8*1* alleles, thereby characterized by normal enzymatic activity.

In individuals with the *CYP2C8*2* (rs11572103) and *CYP2C8*4* variants (rs1058930), the cytochrome enzymes exhibit significantly reduced activity, potentially leading to the accumulation of repaglinide in the bloodstream. This, subsequently, increases the risk of side effects such as hypoglycaemia. The *CYP2C8*3* variant is more frequently observed in Caucasians with an occurrence rate of between 13% and 15%, compared to individuals of African descent, where the frequency is 2% [50].

Ultimately, screening for the *CYP2C8*3* variants may allow healthcare providers to identify patients who may require dose adjustments of repaglinide to achieve optimal therapeutic efficacy. This test may play an important role in personalizing treatment to enhance drug effectiveness in managing type 2 diabetes [50].

4.2.2. CYP2C9 polymorphism in glinides metabolism

Nateglinide is quickly absorbed when taken by mouth, with peak plasma levels typically occurring within 1 hour. Due to its short elimination half-life of around 30 minutes, it is commonly administered prior to meals to manage postprandial blood glucose elevations [51–53]. The enzyme CYP2C9 is a key contributor to the drug's metabolic processing.

Individuals carrying *CYP2C9*3* genetic variant demonstrate reduced metabolism of nateglinide. The enzymatic activity observed in patients carrying the *CYP2C9*2* variant did not show significant clinical differences when compared to that observed in individuals with the wild-type allele. On the other hand, altered nateglinide metabolism due to *CYP2C9* polymorphisms could be associated with a mildly increased susceptibility to hypoglycemia [51].

4.3. Thiazolidinediones—glitazones

Thiazolidinediones are pharmacological agents that act as agonists of the peroxisome proliferator-activated receptor gamma (PPAR-γ), a member of the nuclear transcription factor superfamily. It is known that activation of PPAR-γ induces the transcription of genes associated with adipocyte differentiation and metabolic regulation. In patients, it contributes to better insulin responsiveness in peripheral sites, including adipose tissue and skeletal muscles by enhancing insulin signalling pathways, increasing cellular glucose uptake, and by reducing insulin resistance in the liver and peripheral tissues [54]. Adipocytes, intestinal cells, and macrophages show the highest levels of receptor expression [55]. Three isoforms of PPAR-γ have been identified: γ1, γ2, and γ3, while γ2 is the most prevalent one in adipose tissue. These isoforms play a key role in transcription regulation of genes involved in glucose metabolism [54].

This class of medications, frequently employed in combination regimens for managing type 2 diabetes, includes rosiglitazone, troglitazone, and pioglitazone. However, troglitazone was withdrawn from clinical use due to severe hepatotoxicity observed, while rosiglitazone has been linked to an increased cardiovascular risk [56,57].

Both troglitazone and pioglitazone are eliminated predominantly by the cytochrome P450 enzymes CYP2C8 and CYP3A4 [58,59].

The metabolism of rosiglitazone is facilitated by CYP2C8, with CYP2C9 playing a minor role. Approximately 60% of rosiglitazone undergoes biotransformation into two primary metabolites with reduced activity: para-hydroxy rosiglitazone and N-desmethyl rosiglitazone. According to a study published in 2017, CYP3A4 and CYP2E1 have also been identified as having a small influence on rosiglitazone's metabolic pathway [60].

4.3.1. CYP2C8 polymorphism in glitazones metabolism

A pharmacogenetic study was conducted among Scottish patients with type 2 diabetes receiving treatment with either rosiglitazone or pioglitazone. Through genotyping, researchers identified variants of key metabolic enzymes, enabling an analysis of treatment outcomes in relation to the patients' *CYP2C8* genotype. The most common variant observed was the *CYP2C8*3*. People with the *CYP2C8*3* allele who received rosiglitazone had worse results than those of patients with the wild-type *CYP2C8*1* variant. This resulted from the faster metabolism of rosiglitazone, resulting in lower plasma concentration of this drug, which made it necessary to increase the dose to achieve therapeutic success. People with the wild-type allele more often experienced greater weight gain and higher HbA1c levels than those with the *CYP2C8*3* polymorphism [61].

Similar findings were obtained during studies on pioglitazone, where the presence of the *CYP2C8*3* was associated with a 52% increase in apparent clearance (CL/F), leading to a faster removal of pioglitazone from plasma. Consequently, individuals with the *CYP2C8*3* allele have reduced blood concentrations of pioglitazone compared to those carrying the wild-type *CYP2C8*1* allele [59,62].

5. DISCUSSION

Metabolic diseases are one of the greatest challenges of modern medicine. With the growing popularity of a sedentary lifestyle, the incidence of obesity is continuously increasing, which in turn, contributes to the growing number of patients suffering from hypertension, hyperlipidemia, coronary heart disease, and type 2 diabetes.

Hyperlipidaemia and type 2 diabetes have a proven connection with the occurrence of cardiovascular incidents. Both of these diseases can be effectively managed, but selecting an appropriate therapy often poses a challenge for specialists and exhibits the risk of adverse side effects. This, in turn, can result in discontinuation of treatment in some patients. In such cases, a new line of research for solutions is pharmacogenetics, which examines the impact of specific gene variants on the body's response to a given drug. Although pharmacogenetics remains a relatively unexplored area, significant research in this field is still ongoing. Due to the key role of cytochrome P450 enzymes in the metabolism of drugs used to treat metabolic

diseases, research on the impact of possessing a specific variant of a given gene and its influence on pharmacotherapy could have a profound effect on changing treatment regimens and expanding the concept of a more personalized approach to patient care.

In particular, for sulfonylureas, *CYP2C9*2* and *CYP2C9*3* polymorphisms necessitate dose adjustments to mitigate the risk of hypoglycemia, especially with glibenclamide. For glinides, genetic testing for *CYP2C8* polymorphisms could be beneficial in optimizing repaglinide therapy, ensuring appropriate dosing to avoid undertreatment or excessive drug accumulation. In the case of thiazolidinediones, the *CYP2C8*3* polymorphism plays a crucial role in drug clearance, necessitating dose modifications for rosiglitazone and pioglitazone. Individuals carrying loss-of-function or reduced-activity variants of *CYP2C9*, *CYP34*, and *CYP3A5* may experience higher plasma statin levels, increasing the risk of ADRs, and may need statin dose adjustment. These associations have been summarised in Figures 3 and 4.

Extensive, randomized controlled studies are required to validate the clinical relevance of these polymorphisms in everyday medical practice. However, there is still a lack of high-quality research involving large populations that confirms the impact of all aforementioned polymorphisms on the lipid-lowering effect of statins and the blood–glucose-lowering effect of antidiabetic drugs. The results of clinical trials published to date do not provide clear evidence of their clinical usefulness, with the exception of the CYP2C9 polymorphism and its association with the incidence of SAMS, which is highlighted by CPIC.

Implementation of pharmacogenetic testing in the healthcare system, especially at the primary care level, is progressing slowly. While there is a strong evidence base verifying the clinical utility of preemptive PGx testing of singular genes, there is a lack of unambiguous guidelines concerning the testing for metabolic diseases. This slow progress can be attributed to several barriers, including high implementation costs, insufficient infrastructure, and a lack of clinician education and training in pharmacogenomics [63].

6. CONCLUSION

Pharmacogenetics offers promising opportunities to optimize treatment for metabolic diseases by tailoring drug therapy based on individual genetic profiles. Specific polymorphisms, particularly in CYP450 enzymes, can significantly influence drug metabolism and the risk of adverse reactions. Despite growing evidence supporting their clinical relevance, widespread implementation remains limited due to insufficient large-scale studies and systemic barriers. Advancing personalized medicine requires continued research and the development of more precise clinical guidelines.

7. LIST OF ABBREVIATIONS

ADRs, Adverse drug reactions; CPIC, Clinical Pharmacogenetics Implementation Consortium; CVD, Cardiovascular diseases; PGx, Pharmacogenetic; PPAR-γ; Peroxisome proliferator-activated receptor gamma ; SAMS, Statin-associated muscle symptoms; SFUs, Sulfonylureas

8. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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10. CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

11. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

12. DATA AVAILABILITY

All the data is available with the authors and shall be provided upon request.

13. PUBLISHER'S NOTE

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14. USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declare that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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