Review
Sciences of Pharmacy

Effect of Gene Polymorphisms on Oral Antidiabetic Drug Response in Patients With Type 2 Diabetes Mellitus

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Abstract: Diabetes mellitus is currently one of the global health threats. The prevalence and incidence of this disease continue to increase, both in industrialised and developing countries, including Indonesia. There are different types of DM marker gene polymorphisms in each racial group. These genetic variations contribute to the response of oral antidiabetic drugs. This article aims to conduct a narrative review of the influence of gene polymorphisms on oral antidiabetic drug response in patients with type 2 diabetes mellitus. Article searches were conducted in PubMed, Scopus, Google Scholar, and Wiley published from 2014 to 2024. From the screening, 30 articles met the criteria. The articles reported various gene polymorphisms associated with the efficacy of oral antidiabetic therapy in patients with type 2 diabetes mellitus. In patients with type 2 diabetes mellitus with certain gene variations, there was no significant decrease in HbA1c values after taking medication. Gene polymorphisms may affect the pharmacokinetics of oral antidiabetics and therapeutic response in patients with type 2 diabetes.

Introduction

Diabetes Mellitus (DM) is a metabolic disease characterized by hyperglycemia that occurs due to abnormalities in insulin secretion, insulin action, or both (1). DM is currently one of the global health threats (2). Type 2 DM is the most common type of diabetes and accounts for more than 90% of all diabetes worldwide (3). Type 2 DM is a global health problem as the prevalence and incidence of the disease continue to increase, both in industrialized and developing countries, including Indonesia (4).

The Indonesian Health Survey Report 2023 by the Ministry of Health shows that the prevalence of DM in Indonesia has increased from 2.0% (2018) to 2.2% (2023) based on doctors' diagnoses in the population aged ≥ 15 years. The prevalence of diabetes based on blood sugar level examination in the population aged ≥ 15 years increased from 10.9% (2018) to 11.7% (2023) (5). WHO (World Health Organization) predicts an increase in the number of people with DM in Indonesia from 8.4 million in 2000 to around 21.3 million in 2030. This report indicates a 2-3-fold increase in people with DM by 2035 (6).

DM and its complications are complex, multifactorial conditions with both environmental and genetic components (7). Studies in Asia found that approximately 50-80% of the population had SNPs in the SLC22A1 rs628031 gene, while 20-50% had SNPs in the SLC47A1 rs2289669 gene. SLC22A1 gene polymorphism is associated with increased AUC, decreased VD of metformin, and increased renal discharge (8). NOS1AP rs12742393 polymorphism is associated with the effectiveness of repaglinide therapy in type 2 DM patients in China. The C risk allele of NOS1AP rs12742393 can cause poor therapeutic response after repaglinide administration (9).

The results of research obtained in DM patients with IL1B rs1143623 and EEF1A1P11-RPL7P9 rs10783050 polymorphisms affect the glucose-lowering efficacy of metformin in type 2 DM patients in China (10). Another study also showed that polymorphisms in the PPARD gene can affect the response to repaglinide in patients

with type 2 diabetes in China (11). Based on research in Korea, there is a significant relationship between glucose levels and rs7770619 gene polymorphism in individuals with normal fasting glucose, as well as the tendency of the relationship in individuals with impaired fasting glucose or type 2 DM (12). Research results in Cameroon showed that the TCF7L2 gene is associated with the risk of developing type 2 DM in the Cameroonian population (13). Research in China indicates that the MIR4532 rs60452575 variant affects KCNJ11 expression and sulfonylurea response (14).

Drug responses have great variability, both in terms of efficacy and toxicity. Drug efficacy and toxicity are determined by the balance of pharmacokinetics (the process of drug absorption, distribution, metabolism, and elimination) and pharmacodynamics (the drug's effect at the biological site of action). Genetic variations also contribute to drug response, as some genes code for proteins involved in drug pharmacokinetics and pharmacodynamics (15). Diabetes treatments are selected that are most effective, safe, and better tolerated by patients. Metformin is still the first choice of treatment for most patients. Alternative or second-line treatment options should be individualized depending on the characteristics of each patient (16).

Research on polymorphisms of various types of genes in patients with type 2 diabetes has been conducted in many countries. However, there are still limited narrative reviews in type 2 DM that look at the effect of gene polymorphisms on the response to antidiabetic drug therapy in patients with type 2 DM, so more in-depth information must be explored. This narrative review aims to look at gene polymorphisms on the response to oral antidiabetic drugs in patients with type 2 diabetes, so that it can be known which genes are more commonly found. The results of this narrative review can later become a source of information and reference for future research.

Data Collection and Analysis

Sample and Population

This research used a literature review design. This study used articles published in the last 10 years (2014-2024). In this review, the data used were articles that met the inclusion and exclusion criteria. The inclusion criteria in this study are articles in Indonesian and English, testing conducted in humans, related to the effect of gene polymorphisms on the response of oral antidiabetic drugs in type 2 DM patients, and articles published in the last 10 years (2014-2024). Exclusion criteria in this study are articles that cannot be accessed in full text, articles published in systematic reviews, review papers/articles, editorials, conference abstracts, case reports, and letters to the editor.

Data Collection

In the first stage, article searches were conducted by one person on online databases through PubMed, Scopus, Google Scholar, and Wiley using keywords related to “polymorphism”, “gene”, “oral antidiabetic”, and “type 2 diabetes mellitus”. The articles were retrieved from March to May 2024. The conjunction “AND” was used to connect the keywords. Articles related to polymorphism and drug response of type 2 diabetes mellitus will proceed to the next process. In the second stage, a screening was performed to check for duplication between articles from different online databases. In the third stage, the selection process was carried out by assessing the suitability of the title and abstract of the article with the research topic. In the fourth stage, the eligibility process was carried out by reading the article, including articles with titles and abstracts according to the research topic. At this stage of the screening, selection, and eligibility process, three people evaluated and complemented each other in making this article. The eligibility process aims to assess the suitability of the article content with the predetermined inclusion and exclusion criteria. The flow of the narrative review process is listed in the prism diagram (see **Figure 1**). The results of the narrative review obtained 30 articles that meet the requirements and are listed in **Supplementary Table 1**.

Data Analysis and Processing

The data collection method uses an Excel program to create a table containing data on article characteristics, including author and year of publication, title, research method, race type, type of gene, drug type, and the research results. The way to reduce duplicates in the collected articles is to use the Mendelay application in the tools section by using the check for duplicates option. In addition, we also use manual sorting in Excel. Data analysis was performed descriptively by comparing the research results between articles on the effect of gene polymorphisms on oral antidiabetic drug response in type 2 DM patients. The parameters compared included race type, gene type, drug type, the type of polymorphism that occurred, and significant changes in HbA1c values or fasting glucose levels in the samples used in the study.

A total of 979 articles were identified through database searches. After removing 4 duplicates, 975 articles were screened by title and abstract, excluding 651 for irrelevance. The remaining 324 underwent full-text review, with 294 excluded for not meeting inclusion criteria, mostly due to inaccessibility or being review articles. Ultimately, 30 articles were included in the analysis.

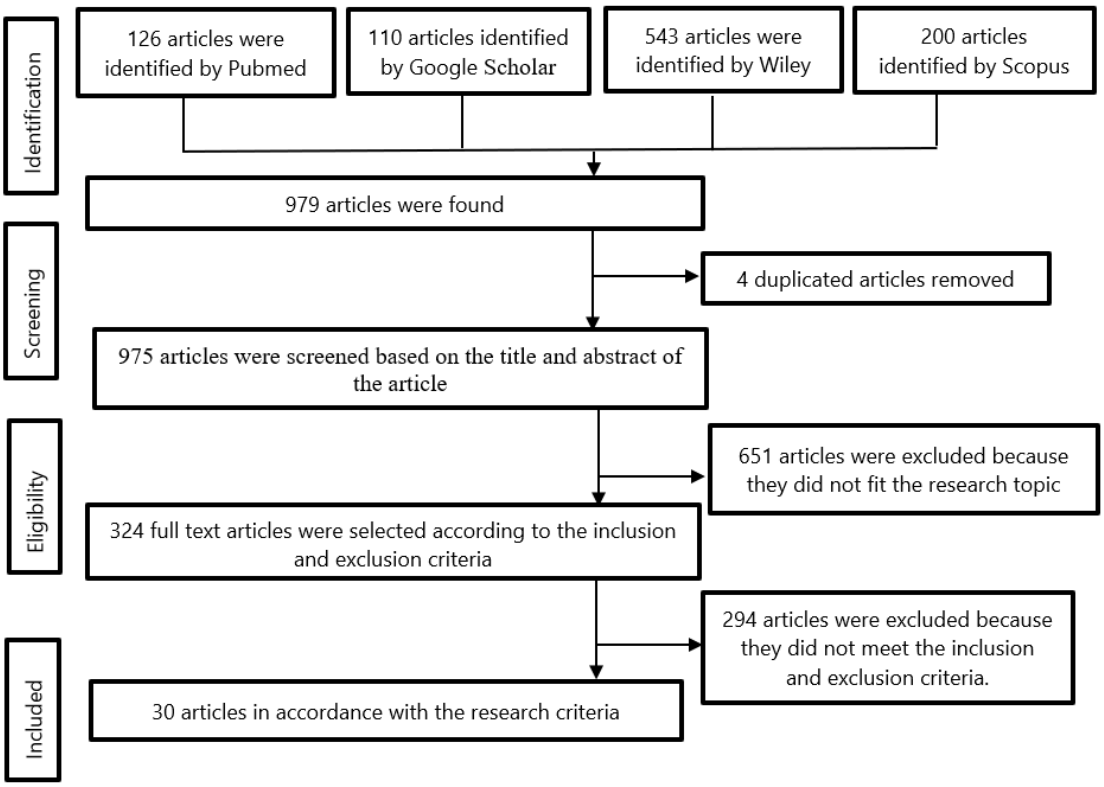

Figure 1. PRISMA flow chart diagram of the methodology.

Based on the articles found, the majority of studies were conducted in China (n=11), Iran (n=3), South India, USA, Lebanon, Mexico (n=2), and the rest came from Indonesia, Turkey, Italy, South Africa, UK, Italy, Russia, Slovakia, Sarajevo. The most widely used research methods are clinical research (n = 19), case control (n = 3), cohort study (n = 3), cross-sectional (n = 2), and the rest use the ongoing observation method, prospective clinical study, and prospective case-control study. The characteristics of type 2 DM patients can be seen in **Supplementary Table 1**.

Diabetes mellitus patients with uncontrolled blood glucose levels require comprehensive therapeutic management as an effort to prevent complications. The first-line drug of choice for most patients with type 2 diabetes is metformin (1). Based on the articles found, the majority of articles used biguanid (metformin) antidiabetic therapy (n= 12), a combination of biguanid (metformin) and sulfonylurea (n = 5), sulfonylurea group (glibenclamide, glimepiride, gliquidon or gliclazide) (n=4), thiazolidinediones (pioglitazone, rosiglitazone) (n=4), glinide (repaglinide) (n=4), combination of sulfonylurea and glinide (n=1).

Based on the results of research that has been done, the number of races studied is Mongoloid (n=16), Kaukasoid (n=11), Australoid (n=2), and Negroid (n=1). Genetic variations, including race, can influence an individual's response to medications as they can affect DM medications' metabolism, effectiveness, and side effects. With the distribution of genetic alleles differing between races, the response to DM drugs may differ between ethnic groups, and side effects or toxicity may also vary.

To achieve good metabolic control in diabetes, a combination of lifestyle changes and pharmacological treatment is required. There are various oral and injectable medications for type 2 DM. Treatment algorithms were developed to reduce the risk of DM complications and emphasize the importance of glycemic control. Metformin is still the first choice for most patients, but second-line treatments should be selected individually (16). The main effect of metformin is to decrease “hepatic glucose output” and lower fasting glucose levels. Monotherapy with metformin can reduce HbA1c by up to 1.5%. Metformin is generally well tolerated by patients. The most common unwanted effects are gastrointestinal complaints. Metformin monotherapy is rarely accompanied by hypoglycemia, and metformin can be used safely without causing hypoglycemia in prediabetes. An important non-glycemic effect of metformin is that it does not cause weight gain or cause slight weight loss (17).

The sulfonylurea group is the second most commonly used drug class in Indonesia and is an alternative monotherapy to metformin. The

sulfonylurea group works by increasing insulin secretion. The risk of hypoglycemia and weight gain requires that this group be given carefully (18). Combining sulfonylureas and metformin can reduce the risk of side effects from sulfonylureas and increase treatment effectiveness (19). Metformin with sulfonylurea is the most commonly used oral combination based on considerations of lower price, being widely available, and different mechanisms of action of the two drugs (20). This combination is an option in Africa, the Middle East, Southeast Asia, and Indonesia (21).

Pioglitazone is the only thiazolidinedione drug used in clinical practice to manage type 2 DM. Despite reports of side effects, pioglitazone remains an effective therapy due to its unique insulin-sensitizing action. The results showed that pioglitazone had equivalent effectiveness in reducing glycated hemoglobin (HbA1c) and was more effective in reducing fasting blood sugar (FBS) levels than other oral antidiabetic drugs. Pioglitazone is also effective in reducing insulin resistance and increasing high-density lipoprotein levels. However, there is an increase in blood pressure and triglyceride levels observed with pioglitazone use. Overall, pioglitazone is an effective therapeutic option for patients with type 2 DM, but it needs to be monitored for potential side effects (22).

The results of studies using repaglinide showed that no adverse effects were observed, and the minimal dose of repaglinide given twice daily had the same effectiveness and safety as the three times daily dose. This suggests that twice-daily repaglinide may be an alternative for patients who cannot take repaglinide three times a day (23).

Gene Polymorphism and Oral Antidiabetic Response in Type 2 DM

Type of Polymorphism

This review aims to determine the effect of gene polymorphism on oral antidiabetic drug response in patients with type 2 diabetes. Genetically, type 2 DM patients are affected by several genes that regulate energy metabolism in the body. Type 2 DM heirs have a 40% risk of developing type 2 DM if one of them has type 2 DM, while the risk will increase by 70% if both parents have type 2 DM (24). In Asian populations, genes that are susceptible to type 2 DM have been found, namely KCNQ1, TCF7F2, UBE2E2, C2CD4A-C2CD4B, CDKN2B, PPARG, FTO, and others (25). The results of the article review as listed in **Table 1** obtained several types of genes that experienced polymorphisms, namely SLC22A1 (n = 6), SLC47A1 (n = 4), ABCC8, TCF7L2 (n=3), CYP2C9, KCNQ1, NOS1AP, ADIPOQ (n=2), and IRS1, Visfatin, PPARD, SLC47A2, CYP2C8, SLCO1B1, STK11, GRK5, IGF2BP2, SLC22A2, CAPN10 (n=1).

Table 1. The types of genes, types of polymorphisms, and types of drugs.

Gene Type	Polymorphism Type	Drug Type
SLC47A1	Intronic	Biguanide
KCNQ1	Intronic	Sulfonylurea
TCF7L2	Intronic	Biguanide
PAX4	Intronic	Thiazolidinediones
NOS1AP	Intronic	Glinide
GRK5	Intronic	Glinide
IGF2BP2	Intronic	Thiazolidinedione
Visfatin	Intronic	Sulfonylurea, Glinide
CAPN10	Intronic	Biguanide
SLC47A2	Intronic	Biguanide
SLC22A1	Intronic	Biguanide
ABCC8	Missense	Sulfonylurea
IRS1	Missense	Biguanide
ADIPOQ	Missense	Biguanide, Thiazolidinedione
CYP2C8	Missense	Thiazolidinediones
SLCO1B1	Missense	Thiazolidinediones
KCNJ11	Missense	Sulfonylurea
CYP2C9	Missense	Biguanide, Sulfonylurea
STK11	Missense	Biguanide
PPARD	Missense	Glinide

The types of genes, types of polymorphisms, and types of drugs used in this article are listed in **Table 1**. Intronic gene polymorphisms occurred in the SLC47A1, KCNQ1, TCF7L2, PAX4, NOS1AP, GRK5, IGF2BP2, Visfatin, CAPN10, SLC47A2, and SLC22A1 genes. While the type of missense gene polymorphism occurs in the ABCC8, IRS1, ADIPOQ, CYP2C8, SLCO1B1, KCNJ11, CYP2C9, STK11, and PPARD genes. Genetic polymorphisms can affect the response of diabetes mellitus patients to treatment. The two types of polymorphisms in the articles we collected are intronic and missense polymorphisms. A missense polymorphism is a change of one nucleotide that causes a substitution of one amino acid in a protein, potentially altering the function of the protein. These missense mutations alter the function of ATP-sensitive ion channels in pancreatic β-cells, impairing insulin secretion and increasing the risk of type 2 diabetes (26). Missense polymorphisms can directly affect drug effectiveness by altering the drug's protein target. For example, the IRS1 G972R variant is associated with poor response to antidiabetic oral therapy (27). Intronic polymorphisms occur in the introns of genes, non-coding DNA segments that are not translated into

proteins. These intronic polymorphisms are associated with decreased insulin secretion and glucose sensitivity, increasing the risk of type 2 diabetes. Intronic polymorphisms can affect drug effectiveness by altering gene expression in glucose metabolism and insulin secretion (28).

Gene Class Relationship with Drug Response

Genetic variation can affect the effectiveness and tolerability of antidiabetic therapy, so understanding this relationship is important for more targeted treatment. In Indonesia, studies have also been conducted on the polymorphisms of these two genes in patients with type 2 DM. The frequency of SLC22A1 rs628031 G>A minor allele reached 60.47%, while the SLC47A1 rs2289669 minor allele was 61.05% (8). The polymorphisms that occurred in the CYP2C9 gene from the 2 articles were variants rs1799853 and rs1057910. Sulfonylurea class antidiabetic drugs, such as glibenclamide and gliclazide, are known to be metabolized by cytochrome P450, which is encoded by the CYP2C9 gene. Some studies have shown that in patients with variant alleles of CYP2C9*2 and CYP2C9*3, drug metabolism will be slower compared to the wild-type allele. Other reports have also shown that at least one CYP2C9 allele variant leads to a significant decrease in CYP2C9 activity, necessitating drug dose adjustments. Therefore, CYP2C9 gene polymorphisms are likely to affect metabolism and adverse drug reactions, such as ADRs in glibenclamide and gliclazide (29).

The mechanism of action of metformin is influenced by Organic Cation Transporter 1 (OCT1), which is encoded by the SLC22A1 gene. Variations or polymorphisms in the SLC22A1 gene affect the uptake of metformin in the liver, which is related to the effect of metformin in lowering blood glucose. Rs683369 is one of the polymorphisms of the SLC22A1 gene. The study results mentioned SLC22A1 rs683369 gene polymorphism with wild-type genotypes, homozygous variants, and heterozygous variants in patients with type 2 diabetes mellitus who take metformin (30). CAPN10 gene polymorphism can cause dysfunction of cell metabolism and signal transduction and increased fasting glucose levels (31). The results showed that the number of subjects with type 2 diabetes mellitus with SNP-19 CAPN10 2R/3R and 3R/3R genotypes was significantly higher than those with type 2 diabetes mellitus with 2R/2R genotypes. There is an association between SNP-19 CAPN10 and type 2 DM in Javanese ethnicity in Central Java (32).

Polymorphisms in the SLC47A2 gene may also impair protein function and transport activity. In addition, deleterious missense SNPs can also affect tissue distribution, renal clearance, and metformin toxicity. The results suggest that genetic variations in the SLC47A2 gene may affect an individual's response to metformin and should be considered in the treatment of type 2 diabetes through dose adjustments or the use of alternative drugs (33). The results of the study on SLCO1B1 gene polymorphisms found no significant association between SLCO1B1 rs4149056 and the risk of type 2 diabetes mellitus or glucose concentration, insulin sensitivity, or insulin secretion, confirming that this genetic variant has no direct effect on glucose metabolism (34).

In patients with type 2 diabetes, regardless of the presence or absence of comorbid obesity and chronic pancreatitis parameters, the glycemic profile was not significantly different between carriers of the C allele or A allele of the IRS1 (rs2943640) gene. The presence of the C allele of the IRS1 (rs2943640) gene may indicate a high risk of insulin resistance in patients with type 2 diabetes, regardless of the presence or absence of comorbid obesity and chronic pancreatitis, because it is a more important factor in the development of insulin resistance than obesity (35).

Polymorphisms that occur in the ABCC8 gene from 3 articles, namely variants rs1799854 and rs1801261. The ABCC8 gene is important in forming sulfonylurea receptor protein 1 (SUR1), part of the pancreatic beta cells' ATP-sensitive potassium (K-ATP) channel. These beta cells are responsible for secreting insulin that controls blood sugar levels. Insulin helps regulate the flow of glucose from the blood into cells to be used for energy. These K-ATP channels have a role in controlling insulin secretion and affect blood glucose levels. When the amount of glucose in the blood increases, these channels will close and stimulate insulin secretion by beta cells. The ABCC8 gene plays a role in determining the function of this channel and affects the achievement of blood glucose homeostasis (36).

Polymorphisms in the TCF7L2 gene from 3 articles are variants of rs7903146 and rs12255372. The TCF7L2 gene is the gene that signals the strongest susceptibility to type 2 diabetes mellitus (37). TCF7L2 is a locus strongly associated with type 2 diabetes risk and has been proven through genomic linkage studies. This gene is a transcription factor involved in the Wnt signaling pathway and has a highly conserved part that corresponds to the gene's function. The association between TCF7L2 and type 2 diabetes mellitus is one of the most genetically robust and has been reflected in various populations with different genetic backgrounds. Although the exact mechanism is still not understood, variants associated with type 2 diabetes in the TCF7L2 gene may affect the success of initial therapy with sulfonylurea oral hypoglycemic drugs. Therefore, further research is needed to address the role of other TCF7L2 gene variants in type 2 DM and their effect on drug response. Identifying these TCF7L2-related

variants will enable more precise treatment according to the patient's genotype (38). In Beloso's study, TCF7L2 gene mutations were found with SNP variants rs12255372 strongly associated with type 2 diabetes mellitus (39).

Polymorphisms that occur in patients with type 2 diabetes who use Sulfonylurea group drugs (glibenclamide, gliclazide, glimepiride, gliquidone) are ABCC8, KCNQ1, TCF7L2, SLC22A1, and KCNJ11. Polymorphisms in the KCNQ1 gene from 2 articles were the rs2237895 and rs2237892 variants. The KCNQ1 gene plays an important role in regulating the function of potassium channels in the body. These channels are mainly found in the inner ear, heart muscle, kidneys, lungs, stomach, and intestines. In the inner ear, these channels regulate the ion balance necessary for normal hearing. In the heart muscle, they are involved in recharging the heart muscle to maintain a regular rhythm. KCNQ1 proteins that interact with KCNE proteins, such as KCNE1, form potassium channels. These channels consist of four alpha subunits of the KCNQ1 protein and one beta subunit of the KCNE protein. This beta subunit binds to the channel and regulates its activity. Through these protein-protein interactions, potassium channels can function properly in regulating ion balance and delivering electrical signals in the body (40). One type of gene that is susceptible to type 2 diabetes mellitus in the Uyghur population, China, is KCNQ1 (OR = 0.79; 95% CI), and this gene regulates pancreatic cell secretion (41). Gao *et al*. (2017) also reported that the KCNQ1 gene is susceptible to type 2 diabetes mellitus in the Chinese Han population (42).

Polymorphisms that occur in patients with type 2 DM who use Thiazolidinediones (pioglitazone, rosiglitazone) are CYP2C8, SLCO1B1, PAX4, rs2241766, and IGF2BP2. The IGF2BP2 gene polymorphism study results showed that carriers of the TT genotype at rs4402960 have a higher risk of type 2 DM than carriers of the G genotype (TG + GG). In addition, carriers of the CC genotype at rs1470579 are also more susceptible to type 2 diabetes mellitus than carriers of the A genotype (CA + AA). IGF2BP2 polymorphisms are associated with the risk of type 2 diabetes mellitus in Asian populations (43).

Polymorphisms that occur in patients with type 2 DM who use Glinid group drugs (repaglinide) are NOS1AP, GRK5, ABCC8, and PPARD. The polymorphism in the NOS1AP gene from 2 articles is the rs12742393 variant. NOS1AP rs12742393 polymorphism is associated with the effectiveness of repaglinide therapy in T2DM patients in China. The C risk allele of NOS1AP rs12742393 may lead to poor therapeutic response after repaglinide administration (9).

The existing articles found that there was mostly an association between certain gene polymorphisms and the efficacy of oral antidiabetic therapy in patients with type 2 diabetes, where patients with specific gene variations did not significantly decrease HbA1c values. Gene polymorphisms may affect the pharmacokinetics of oral antidiabetics and therapeutic response in patients with type 2 diabetes.

Strengths and Limitations

The strengths of the articles selected as samples are: racial homogeneity of the study sample, the SNPs studied are varied, and the variety of genes studied is extensive. While the limitations of the articles selected as samples include: small sample size that may reduce statistical power, significantly affect the relevance of the associated SNP variants, and potentially result in failure to detect an association between the type of polymorphism and the response to drug therapy used by the patient; lack of information on patient compliance and lifestyle information, which may affect glycemic control and response to drugs used; no placebo group was enrolled in the current study, so the effect of lifestyle modification cannot be ignored; lack of existing data that can be used to analyze the impact of different variations in the same gene as well as the need for more than one measurement of blood glucose and HbA1c levels to obtain more accurate therapy outcome data. This is a preliminary article for further research, which will be conducted on patients with type 2 diabetes mellitus by looking at life behavior (patient compliance, diabetes distress), quality of life, gene polymorphisms, and therapy outcomes. The results of this article will be used as a basis for selecting genes to be studied in patients with diabetes mellitus.

Conclusion

There is an association between gene polymorphisms and the efficacy of oral antidiabetic therapy in patients with type 2 diabetes, where patients with certain gene variations do not significantly decrease HbA1c values. Gene polymorphisms may affect the pharmacokinetics of oral antidiabetics and therapeutic response in patients with type 2 diabetes. The results of this article will be used as a basis for selecting genes to be studied in studies of diabetes mellitus patients.

Abbreviations

HbA1c = Hemoglobin A1c, T2DM = Type 2 Diabetes Mellitus, VS = Volume Distribution, SNP = Single Nucleotide Polymorphism, PPARD = Peroxisome Proliferator Activated Receptor Delta, FTO = Fat Mass and Obesity-Associated.

Declarations

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Conflict of Interest
The authors declare no conflicting interest.

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Supplemental Material
Supplementary Table 1 is available at the following link:
https://etflin.com/file/document/202505030325011157885157.docx

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