Indonesian Journal of Pharmaceutical and Clinical Research
Journal homepage: https://idjpcr.usu.ac.id

The Role of *SLC22A1* Polymorphisms in Metformin Therapeutic Response: A Bioinformatics Based Literature Review

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ARTICLE INFO

Article history:
Received 16 December 2025
Revised 25 June 2026
Accepted 27 June 2026
Published 30 June 2026

E-ISSN: 2620-3731
P-ISSN: 2615-6199

How to cite:
Amukti D.P., Irham L.M., Estiningsih D., Kusumawardani N., Purwanto B.D., Pratami R.I., Marpaung M.P., (2026). The Role of *SLC22A1* Polymorphisms in Metformin Therapeutic Response: A Bioinformatics Based Literature Review. Indonesian Journal of Pharmaceutical and Clinical Research 09 (01), 034-042.

http://doi.org/10.26594/register.v6i1.idarticle

ABSTRACT

Metformin is the most common first-line therapy used in the management of type 2 diabetes mellitus (T2DM). However, therapeutic response to metformin varies between individuals, which is largely influenced by genetic factors, especially polymorphisms in the *SLC22A1* gene. This gene encodes the organic cation transporter 1 (OCT1), which plays a role in the transport of metformin into hepatocytes. This literature review used a bioinformatics approach to explore the impact of *SLC22A1* polymorphisms on the efficacy of metformin. Genetic and pharmacogenomic data were collected from two major databases, namely PharmGKB and GTEx Portal. Relevant polymorphic variants were identified based on data that were associated with drug response. Tissue expression analysis of *SLC22A1* in GTEx was used to evaluate the biological relevance of gene expression in metformin target organs. The results showed that *SLC22A1* gene expression was significantly highest in liver tissue, which plays a key role in the efficacy of metformin in T2DM patients. *SLC22A1* functions as a major transporter in transporting metformin into hepatocytes, where its pharmacological action occurs. Genetic variations such as rs622342, rs594709, and rs628031 can significantly affect the expression and function of these transporters, which ultimately have a direct impact on the efficacy of metformin therapy. This study emphasizes the importance of pharmacogenomic approaches in personalized medicine for T2DM patients.

Keyword:

ABSTRAK

Metformin merupakan terapi lini pertama yang paling umum digunakan dalam penatalaksanaan diabetes melitus tipe 2 (DMT2). Namun, respons terapeutik terhadap metformin bervariasi antar individu, yang sebagian besar dipengaruhi oleh faktor genetik, terutama polimorfisme pada gen SLC22A1. Gen ini mengkode transporter kation organik 1 (OCT1), yang berperan dalam transpor metformin ke dalam hepatosit. Tinjauan pustaka ini menggunakan pendekatan bioinformatika untuk mengeksplorasi dampak polimorfisme SLC22A1 terhadap efikasi metformin. Data genetik dan farmakogenomik dikumpulkan dari dua basis data utama, yaitu PharmGKB dan GTEx Portal. Varian polimorfik yang relevan diidentifikasi berdasarkan data yang terkait dengan respons obat. Analisis ekspresi jaringan *SLC22A1* pada GTEx digunakan untuk mengevaluasi relevansi biologis ekspresi gen pada organ target metformin. Hasil penelitian menunjukkan bahwa ekspresi gen SLC22A1 secara signifikan tertinggi di jaringan hati, yang memainkan peran kunci dalam efikasi metformin pada pasien T2DM. SLC22A1 berfungsi sebagai transporter utama dalam mengangkut metformin ke dalam hepatosit, tempat aksi farmakologisnya terjadi. Variasi genetik seperti rs622342, rs594709, dan rs628031 dapat secara signifikan memengaruhi ekspresi dan fungsi transporter ini, yang pada akhirnya berdampak langsung pada efikasi terapi metformin. Polimorfisme rs622342, rs594709, dan rs628031 pada gen SLC22A1 memengaruhi respons terhadap efikasi terapi metformin. Studi ini menekankan

pentingnya pendekatan farmakogenomik dalam pengobatan personalisasi untuk pasien T2DM.
Keyword: *Metformin, SLC22A, rs622342, rs594709, rs628031*

1. Introduction

Type 2 diabetes mellitus (T2DM) is a complex metabolic disease characterized by insulin resistance, pancreatic beta cell dysfunction, and impaired glucose metabolism (1,2). This condition continues to increase globally and is one of the major health problems with a significant impact on morbidity and mortality (2). Controlling blood glucose levels is the goal of T2DM treatment in order to avoid long-term consequences such cardiovascular disease, nephropathy, and neuropathy.The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend metformin as the first-line therapy for T2DM (3,4). Metformin works by reducing glucose production in the liver through inhibition of complex I of the mitochondrial electron transport chain, leading to an increase in the AMP/ATP ratio in hepatocytes (5,6). This increase in the ratio activates AMP-*activated protein kinase* (AMPK), which plays a role in reducing the expression of gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), thereby inhibiting glucose production by the liver. The effectiveness of metformin is highly dependent on its transport into hepatocytes, which is mediated by the organic cation transporter OCT1 (Organic Cation Transporter 1) (7). This transporter is encoded by the *SLC22A1* gene, which is expressed primarily in the liver and plays a key role in regulating the distribution of metformin within cells (8,9).

However, patient response to metformin is highly variable, with some patients showing resistance to metformin, requiring higher doses or combinations with other drugs to achieve optimal glycemic control (10). This variation is influenced not only by environmental factors such as diet and physical activity, but also by genetic factors, particularly polymorphisms in the *SLC22A1* gene (10). Several studies have identified that certain genetic variants in *SLC22A1* can reduce the activity or expression of OCT1, thereby inhibiting metformin transport into hepatocytes and reducing its hypoglycemic effect. Several pharmacogenetic studies have shown that *SLC22A1* gene polymorphisms are associated with decreased OCT1 function, leading to decreased hepatic uptake of metformin (11,12). As a result, patients with these variants tend to have a lower therapeutic response than individuals with normal *SLC22A1* function. Furthermore, these polymorphisms have different distributions across populations, emphasizing the importance of population-based analyses in understanding the efficacy of metformin more specifically (13,14).

With the advancement of technology, bioinformatics approaches are increasingly playing a role in understanding the relationship between genetic variation and drug response, including the efficacy of metformin (15,16). Various bioinformatics databases have been developed to integrate gene expression data, polymorphism frequencies, and gene-protein interactions in metabolic pathways. Some databases that are often used in pharmacogenetic analysis include GTEx (Genotype-Tissue Expression), PharmGKB which allow in-depth exploration of *SLC22A1* gene expression, polymorphism distribution in various populations, and the relationship between genetic variation and pharmacological response to metformin(17,18). Through the integration of bioinformatics databases, this study aims to explore the effect of *SLC22A1* polymorphisms on metformin efficacy by analyzing genetic expression, protein interactions, and the distribution of genetic variation in certain populations (19). This approach is expected to provide deeper insight into the molecular mechanisms underlying metformin response variations and support the development of precision medicine therapy for T2DM patients. By understanding the role of *SLC22A1* polymorphisms, more personalized treatment strategies can be applied, so that the efficacy of metformin therapy can be improved based on individual genetic profiles.

2. Methods

This study is a bioinformatics study that aims to analyze the effect of *SLC22A1* polymorphism on the effectiveness of metformin by integrating data from various bioinformatics databases (20,21). The analysis was carried out using an in silico approach using publicly available bioinformatics resources, including PharmGKB, GTEx, dbSNP, Ensembl, and The Human Protein Atlas. The search for *SLC22A1* polymorphism data was carried out through PharmGKB (https://www.pharmgkb.org/) which was accessed on April 3, 2025, which is a pharmacogenetic database that provides information on the relationship between genetic variants and drug response. The search was carried out by entering the keywords "*SLC22A1*" AND

"Metformin" in the Gene-Drug Association feature in PharmGKB. The information collected includes genetic variants (Single Nucleotide Polymorphisms/SNPs), pharmacogenetic annotation status (Level of Evidence/LOE), and their impact on the effectiveness of metformin. SNPs with high LOE (1A/1B) were further analyzed to evaluate their effects on metformin transport into hepatocytes. To understand the expression of SLC22A1 in liver tissue, data were extracted from the Genotype-Tissue Expression (GTEx) Portal (https://gtexportal.org/). Gene expression was analyzed based on TPM (Transcripts Per Million) and RPKM (Reads Per Kilobase per Million Mapped Reads) values to obtain a quantitative picture of *SLC22A1* expression in various tissues, with a primary focus on the liver as the target organ of metformin.

3. Results and Discussion

Data analysis from PharmGKB showed that *SLC22A1* polymorphisms affect the effectiveness of metformin. From various studies conducted in different biogeographic groups, it was found that some variants showed significant associations with the response to metformin, while others did not show statistical significance. Table 1 summarizes the associations between SLC22A1 polymorphisms and metformin efficacy across different biogeographic populations based on evidence curated in PharmGKB. The results of the analysis include genetic variants in different populations, with some variants showing significant associations and others not significant. rs622342 (European) showed mixed results among studies in European populations. In some studies, this variant did not show a significant association with metformin efficacy ($p = 0.07$, $p = 0.39$, $p = 0.05$, and $p = 0.26$), while in other studies, rs622342 was found to have a significant association ($p = 0.005$, $p = 0.0013$). The significant results indicate that rs622342 may play a role in modulating metformin transport, but its efficacy varies among individuals with different genetic backgrounds in European populations. For rs622342 (East Asian), this variant showed a significant association with metformin efficacy in East Asian population ($p < 0.05$, $n = 71$). This indicates that rs622342 may have a stronger impact on metformin response in individuals with East Asian genetic background. In Central/South Asian group, rs622342 also showed high significance ($p = 0.0009$, $n = 122$), indicating that this variant may have an important influence in modulating metformin efficacy in South Asian population, where drug transport may be more affected by this polymorphism compared to European population.

In rs594709 (East Asian) showed a significant association with metformin efficacy in East Asian population ($p < 0.05$, $n = 53$), although the sample size is relatively small. This variant suggests that in individuals with East Asian genetic background, rs594709 may play a role in modulating the response to metformin. rs628031 (East Asian) also showed significant results in East Asian group ($p = 0.05$, $n = 9$). Despite the limited sample size, these findings suggest that rs628031 has the potential to influence metformin response in East Asian individuals, although further studies with larger sample sizes are needed to confirm these findings. Meanwhile, for rs72552763 (European) and rs12208357 (European), these two variants did not show significant association with metformin efficacy in European population, with p-value of 0.85 and 0.47, respectively, indicating that these variants may not play a role in modulating metformin transport in European individuals. Overall, these findings suggest that there is variation in response to metformin based on *SLC22A1* genetic polymorphisms, which is influenced by geographical and ethnic factors. Some variants, such as rs622342, showed significant association with metformin efficacy in East Asian and Central/South Asian populations, while in European the results were more heterogeneous. This emphasizes the importance of population-based pharmacogenetic approaches in improving the efficacy of metformin therapy in individuals with different genetic backgrounds.

Table 1. *List of Polymorphisms in the SLC22A1 Gene Associated with Metformin Response Based on the PharmGKB Database*

PharmGKB ID	Variants	Gene	Significance	P-Value	of Cases	Biogeographical Groups
769169370	rs622342	*SLC22A1*	no	0.07	98	European
769169373	rs622342	*SLC22A1*	yes	0.005	98	European
769169367	rs622342	*SLC22A1*	no	0.39	98	European
1451934880	rs622342	*SLC22A1*	yes	< 0.05	71	East Asian
608178461	rs622342	*SLC22A1*	no	0.05	102	European
1448631754	rs622342	*SLC22A1*	no	0.26	5434	European
1448631748	rs72552763	*SLC22A1*	no	0.85	4423	European
1452828220	rs622342	*SLC22A1*	yes	0.0013	292	European
1444935134	rs622342	*SLC22A1*	yes	0.0009	122	Central/South

						Asian
1447980951	rs594709	*SLC22A1*	yes	0.001	53	East Asian
827826357	rs628031	*SLC22A1*	yes	0.05	9	East Asian
1448631741	rs12208357	*SLC22A1*	no	0.47	4557	European
1448998582	rs72552763	*SLC22A1*	no	0.05	40	European

Table 2 details the relationship between SLC22A1 genetic variants and metformin medication response in people with PCOS and Type 2 Diabetes Mellitus (Type 2 DM). Based on the individual's genotype or allele, a number of genetic variants have been examined, including rs622342, rs72552763, rs594709, rs628031, and rs12208357, which are linked to the efficacy of metformin. The AC and CC genotypes were linked to a better response to metformin in those with the genetic variant at rs2289669 in the rs622342 variant, but there was no significant correlation with the AA genotype. The rs622342 variant Carriers of the C allele exhibited a smaller reduction in HbA1c levels following metformin treatment than carriers of the A allele, indicating a reduced glycemic response (22). In terms of rs72552763 polymorphism, the del allele did not show any significant association with metformin response in T2DM patients when compared to the GAT allele, while for rs594709, the AA and AG genotypes were associated with increased response to metformin in individuals with T2DM when compared to the GG genotype (23,24). The rs628031 polymorphism showed that the A allele was associated with a lower response to metformin in T2DM patients compared to the G allele, while rs12208357 showed that the T allele had no significant effect on metformin response when compared to the C allele. Finally, in the population of women with PCOS, the del allele at rs72552763 did not show any significant association with metformin response when compared to the GAT allele. These findings illustrate the complexity of the pharmacogenetic response to metformin, where certain genetic variants may affect the efficacy of therapy differently in different patient groups (23,25).

Table 2. The Relationship of Genetic Polymorphisms with Metformin Effectiveness Based on Genotype and Allele Types in Type 2 Diabetes Mellitus Patients

PharmGKB ID	Variants	Association	Phenotype Categories
769169370	rs622342	People with genetic variant at rs2289669 who have genotype AC respond to metformin.	Efficacy
769169373	rs622342	In those having genetic polymorphism at rs2289669, genotype CC is linked to metformin responsiveness.	Efficacy
769169367	rs622342	In individuals with genetic polymorphism at rs2289669, genotype AA is not linked to metformin response.	Efficacy
1451934880	rs622342	In individuals with Type 2 Diabetes, genotype AC is linked to a greater response to metformin than genotypes AA + CC.	Efficacy
608178461	rs622342	When metformin is used to treat diabetes mellitus, allele C is linked to a lower drop in HbA1c levels.	Efficacy
1448631754	rs622342	Compared to allele A, allele C is not linked to metformin response in individuals with Type 2 Diabetes.	Efficacy
1448631748	rs72552763	Compared to the GAT allele, the del allele is not linked to the responsiveness to metformin in individuals with Type 2 Diabetes.	Efficacy
1452828220	rs622342	In individuals with diabetes mellitus, allele A is linked to a greater response to metformin than allele C.	Efficacy
1444935134	rs622342	In individuals with Type 2 Diabetes, genotypes AC + CC are linked to a worse response to metformin than genotype AA.	Efficacy
1447980951	rs594709	When compared to genotype GG, individuals with Type 2 Diabetes who have genotypes AA + AG respond more to metformin.	Efficacy
827826357	rs628031	Compared to allele G, allele A is linked to a worse response to metformin in individuals with Type 2 Diabetes.	Efficacy
1448631741	rs12208357	Compared to allele C, allele T is not linked to metformin response in individuals with Type 2 Diabetes.	Efficacy
1448998582	rs72552763	In women with Polycystic Ovary Syndrome, the GAT allele is not linked to metformin response, in contrast to the del allele.	Efficacy

The expression of the *SLC22A1* gene in the liver is related to the activity of transporter proteins involved in the transport of various organic compounds, including cations such as drugs and endogenous metabolites (26). This gene encodes *OCT1*, which plays an important role in the metabolism and elimination of chemical compounds in the body. In the liver, *SLC22A1* plays a key role in transporting drugs from the blood into hepatocytes, allowing drug metabolism and regulating the concentration of certain compounds in the body (27). The expression of the *SLC22A1* gene in the liver can vary depending on individual genetic factors, the environment, and certain physiological conditions, which can affect the response to drugs, especially drugs metabolized by *OCT1* such as metformin (28).

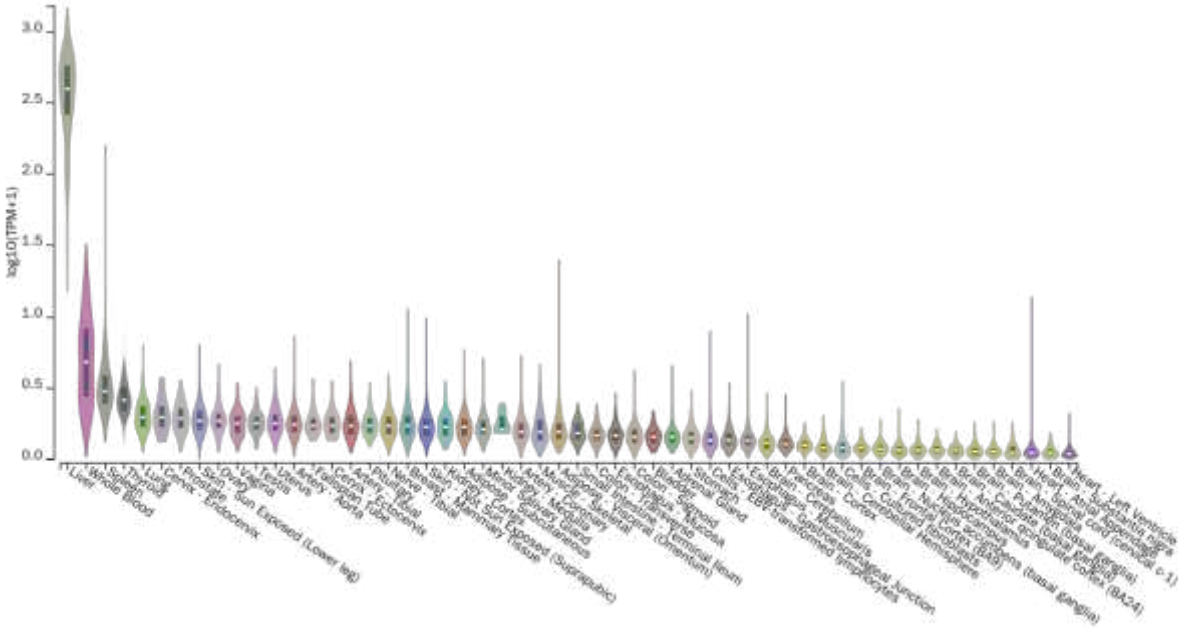

Figure 1. Bulk tissue gene expression for *SLC22A1* (ENSG00000175003.15)

The *SLC22A1* gene that encodes the *OCT1* protein plays a key role in the transport of organic compounds, including drugs, into liver cells. *OCT1* functions to transport organic cations such as metformin, used in the treatment of type 2 diabetes, as well as other drugs that are metabolized via the hepatic pathway (29,30). In the liver, *OCT1* helps transport these drugs into hepatocytes, where they are then metabolized by liver enzymes for excretion (31). Variations in the expression or mutations of the *SLC22A1* gene can affect the efficiency of transport of these drugs, which in turn can affect drug concentrations in the body and, ultimately, the effectiveness of treatment (32). The relationship between genetic variation in *SLC22A1* and treatment effectiveness is particularly evident in an individual's response to drugs that are metabolized by *OCT1(30).* Genetic variations that affect *OCT1* activity can lead to reduced or increased drug transport into hepatocytes, which in turn alters the pharmacokinetics and pharmacodynamics of the drug. Individuals with mutations or genetic variations that reduce *OCT1* function may exhibit resistance to drugs such as metformin, which may lead to inadequate glucose control. Conversely, increased *OCT1* expression may increase hepatic drug uptake, enhance drug metabolism, and affect the dose required to achieve the desired therapeutic effect (33).

Genetic variants associated with response to metformin treatment, particularly in individuals with Type 2 Diabetes Mellitus and other related conditions, such as *Polycystic Ovary Syndrome* (PCOS). Metformin is a drug commonly used to control blood glucose levels in patients with diabetes, but its effectiveness can vary between individuals (25). Certain genetic variations, such as those seen in rs622342, may affect how the body responds to metformin. Below is a detailed explanation of the association of gene variants with metformin effectiveness based on the data provided. genetic variation. The rs622342 variant is associated with a decreased response to metformin in individuals with the rs2289669 More specifically, the AC genotype often has a decreased response to metformin when compared to the AA genotype (34). This decreased response may reflect the influence of other genetic variations that affect the body's ability to access or metabolize the drug, which in turn decreases its effectiveness in controlling blood glucose levels. On the other hand, individuals with the A allele at rs622342 tend to show a better response to metformin, meaning the treatment is more effective in lowering blood glucose levels and achieving therapeutic goals (35).

HbA1c Level Impact The rs622342 mutation shows that when people with Type 2 Diabetes Mellitus take metformin, the C allele is linked to a lower drop in HbA1c levels. The efficacy of diabetes treatment is shown by a drop in HbA1c levels, which is a metric used to assess long-term blood glucose management. People who carry the C allele in this variant might not respond as well to metformin, which would result in a less than ideal drop in their HbA1c levels (36). This indicates that they may require additional therapy or more careful dose regulation to achieve the same therapeutic outcome as individuals with the A allele. In the rs72552763 variant, the del allele (deletion) did not show any association with the response to metformin compared to the GAT allele in individuals with Type 2 Diabetes Mellitus (37). This suggests that this genetic variation does not contribute significantly to differences in response to metformin treatment in the context of diabetes. However, these findings also suggest that not all genetic variants have a major impact on the response to metformin, and some variants may not need to be considered in routine treatment for diabetic patients. In the rs594709 variant, the AA and AG genotypes were associated with a better response to metformin in individuals with Type 2 Diabetes Mellitus, compared with the GG genotype. This suggests that genetic variation in rs594709 may affect the effectiveness of metformin in lowering blood glucose levels (36). People with the AA and AG genotypes might respond better to metformin, which would make it simpler for them to control their blood sugar levels with recommended dosages. In the rs628031 variation, people with Type 2 Diabetes Mellitus who had the A allele had a worse response to metformin than those who had the G allele. This implies that metformin treatment may not result in the best blood glucose reduction for people with the A allele, and that they may need to take different drugs or dose changes to achieve adequate glucose control. The rs12208357 T allele variant did not show a significant association with metformin response when compared to the C allele in individuals with Type 2 diabetes mellitus (38,39). This suggests that this variant may not have a major impact on the effectiveness of metformin in controlling blood glucose levels although in some populations, this variant may be relevant in considering more personalized therapy (38).

In women with *Polycystic Ovary Syndrome* (PCOS), the GAT allele at the rs72552763 variant was not associated with a higher response to metformin compared to the del allele. This suggests that other factors, in addition to this variant, may play a role in determining the response to metformin in women with PCOS(40). These findings also suggest that metformin therapy in PCOS patients may be more influenced by other clinical conditions, such as insulin resistance, than by a single genetic variant (37). Overall, this study highlights the importance of genetic variation in influencing the effectiveness of metformin in individuals with Type 2 diabetes mellitus and other related conditions. Understanding the relationship between genetic variants and response to treatment may help in designing more personalized and targeted treatment approaches, thereby increasing the effectiveness of therapy, reducing side effects and helping patients achieve optimal blood glucose control.

4. Conclusion

The results showed that the highest expression of the *SLC22A1* gene was found significantly in liver tissue, which plays a key role in the effectiveness of metformin in T2DM patients. *SLC22A1* functions as a major transporter in transporting metformin into hepatocytes, where its pharmacological action occurs. Genetic variations such as rs622342, rs594709, and rs628031 can significantly affect the expression and function of these transporters, which ultimately have a direct impact on the effectiveness of metformin therapy.

Acknowledgements :
The authors have no support to report.

Funding

The authors have no funding to report.

Competing Interests

The authors have declared that no competing interests exist.

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