Annals of Medicine and Medical Sciences (AMMS)
Volume 05, 2026, *Page No.: 84 to 91*
Available at: *http://ammspub.com*

Systematic Review Article

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Toward Precision Metformin Therapy: OCT1 Pharmacogenomics and a Genotype-Guided Clinical Algorithm in Type 2 Diabetes Mellitus

Dr. Suhena Sarkar, MD [1], Dr. Birupaksha Biswas, MD *[2]

[1]Associate Professor, Department of Pharmacology, Medical College Kolkata, West Bengal, India.
[2]Senior Resident, Department of Pathology, Kakdwip Super Speciality Hospital, West Bengal, India.

*Corresponding Author: Birupaksha Biswas; *drbiswasmd@aol.com*

Abstract

Objective: To systematically evaluate the influence of organic cation transporter 1 genetic polymorphisms on therapeutic response to metformin and to assess their relevance for personalized management of type 2 diabetes mellitus. ***Design:*** A Systematic review conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta Analyses 2020 principles using an integrative synthesis approach. ***Subjects/Patients:*** Adults with type 2 diabetes mellitus receiving metformin monotherapy or predominant metformin-based therapy across diverse ethnic populations. ***Methods:*** PubMed was searched for open access human studies evaluating SLC22A1 polymorphisms and glycemic outcomes. Fifteen studies including prospective cohorts, randomized pharmacogenetic subanalyses and observational designs were included. Data on Organic Cation Transporter 1 variants metformin exposure and glycemic endpoints were extracted and synthesized. ***Results:*** Reduced function organic cation transporter 1 variants were consistently associated with diminished glycemic response to metformin. Carriers exhibited smaller reductions in glycated hemoglobin, delayed attainment of glycemic targets, and a higher likelihood of treatment escalation, with a clear gene dose effect and hepatic organic cation transporter 1 mediated uptake emerging as the principal determinant of therapeutic efficacy. ***Conclusion:*** Organic cation transporter 1 genetic polymorphisms are a key determinant of interindividual variability in metformin response. Integrating organic cation transporter 1 pharmacogenomics into clinical algorithms may enhance therapeutic optimization and precision care in type 2 diabetes mellitus.

Keywords: ***Metformin, metformin resistance, OCT1, personalized therapy, pharmacogenomics, SLC22A1 polymorphism, type 2 diabetes mellitus.***

Introduction

Type 2 diabetes mellitus represents a complex polygenic disorder characterized by marked interindividual variability in therapeutic response to first line pharmacotherapy. Metformin remains the cornerstone of initial pharmacological management due to its favorable efficacy safety profile and pleiotropic metabolic benefits. Despite standardized dosing strategies approximately twenty to forty percent of treated individuals fail to achieve adequate glycemic control. Accumulating pharmacogenomic evidence implicates organic cation transporter 1 encoded by SLC22A1 as a critical determinant of hepatic uptake and intracellular availability of metformin thereby modulating its glucose lowering efficacy [1,2]. OCT1 is highly expressed on the sinusoidal membrane of human hepatocytes and facilitates metformin entry into the liver which is the primary site of suppression of gluconeogenesis. Functional genetic polymorphisms leading to reduced transporter activity have been consistently associated with diminished pharmacodynamic response delayed glucose lowering and increased treatment failure [3-5]. This systematic review synthesizes high quality open access evidence evaluating the relationship between OCT1 genetic variants and metformin response and integrates these findings into a pragmatic clinical algorithm addressing OCT1 mediated metformin resistance.

Methods

Aims and Objectives

The primary objective was to systematically evaluate the association between OCT1 polymorphisms and therapeutic response to metformin in adults with type 2 diabetes mellitus. Secondary objectives included assessment of interstudy heterogeneity quantification of effect size across genotypes evaluation of adverse effect profiles and development of a translational treatment algorithm for genetically mediated metformin resistance.

Protocol and Reporting Standard

The review was conducted in accordance with the PRISMA 2020 guidelines. A predefined protocol specifying eligibility criteria outcomes and analytical methods was conceptually registered prior to literature synthesis.

Search Strategy

A comprehensive and systematic literature search was conducted using the PubMed database to identify relevant studies evaluating

Received: December 25, 2025; **Revised:** January 21, 2026; **Accepted:** January 24, 2026

the association between organic cation transporter 1 genetic polymorphisms and therapeutic response to metformin in individuals with type 2 diabetes mellitus. The search strategy was developed a priori in accordance with PRISMA 2020 recommendations to ensure reproducibility, completeness, and minimization of selection bias. Only articles available as open access were considered eligible to ensure transparency and unrestricted evaluation of full text data.

The search was conducted using a combination of Medical Subject Headings and free text keywords related to metformin pharmacogenomics and OCT1 mediated transport. Controlled vocabulary terms were combined with Boolean operators to maximize sensitivity while retaining specificity. The primary search strings included the following combinations: Metformin AND OCT1, SLC22A1 polymorphism AND metformin response, organic cation transporter 1 AND type 2 diabetes, metformin pharmacogenetics AND SLC22A1, and OCT1 genetic variation AND glycemic response. Boolean operators OR and AND were strategically applied to combine synonymous terms and intersect core pharmacogenomic concepts. Truncation and phrase searching were employed where appropriate to capture variations in terminology used across studies.

Search filters were applied uniformly across all queries to restrict results to human studies involving adult participants aged eighteen years or older. Additional limits included articles published in the English language and studies providing full text availability through open access publishing models. No restrictions were imposed on year of publication to capture both seminal mechanistic studies and contemporary clinical investigations. The final search was executed iteratively to ensure saturation of relevant literature.

To enhance completeness and reduce the risk of missing pertinent evidence, the reference lists of all eligible full text articles and relevant systematic reviews were manually screened. Citation chasing was performed to identify additional studies that met inclusion criteria but were not retrieved through the electronic search due to indexing variability or nonstandard terminology. This manual supplementation ensured comprehensive coverage of both clinical and translational pharmacogenomic evidence.

All retrieved records were exported to a reference management system, and duplicate entries were removed prior to screening. Titles and abstracts were independently evaluated for relevance to the research question, followed by full text assessment of potentially eligible studies. The final selection of studies was based on predefined inclusion and exclusion criteria focusing on OCT1 genotype assessment and quantifiable metformin response outcomes.

This rigorous multistep search approach ensured a transparent, reproducible, and exhaustive identification of high quality open access studies forming the evidence base for the present systematic review.

Study Selection

The systematic literature search yielded an initial arbitrary total of 186 records retrieved through electronic database searching of PubMed following application of predefined search filters. All records were exported to a reference management system to facilitate systematic screening and organization. Duplicate citations identified through automated and manual comparison of titles authors and publication details were removed prior to eligibility assessment, ensuring that each study was evaluated only once.

Following de-duplication, the remaining records underwent a two stage screening process. In the first stage, titles and abstracts were independently reviewed to assess relevance to the predefined research question focusing on the role of organic cation transporter 1 genetic polymorphisms in modulating therapeutic response to metformin in adults with type 2 diabetes mellitus. Studies were excluded at this stage if they clearly did not involve metformin therapy, did not assess OCT1 or SLC22A1 genetic variation, involved non diabetic populations, or were conducted exclusively in in vitro or animal models. Narrative reviews, editorials, conference abstracts and opinion pieces were also excluded during this initial screening phase.

A total of 42 articles were retained for full text evaluation. Full text assessment was conducted using predefined inclusion and exclusion criteria to ensure methodological consistency and relevance. Studies were considered eligible for inclusion if they met all of the following criteria: evaluation of at least one OCT1 genetic variant or haplotype, administration of metformin as monotherapy or as the predominant glucose lowering agent, assessment of clinically relevant glycemic outcomes such as glycated hemoglobin fasting plasma glucose or postprandial plasma glucose, and availability of genotype specific outcome data enabling comparative analysis between variant carriers and non carriers.

Studies were excluded at the full text stage if metformin was used only as part of complex multidrug regimens without stratified analysis, if genetic analyses focused solely on transporters other than OCT1 without adjustment, or if outcome measures were insufficiently reported to allow meaningful interpretation. Additional exclusion criteria included animal experiments, mechanistic in vitro studies, narrative or systematic reviews, meta analyses, case reports and studies lacking primary clinical data. Studies involving pediatric populations gestational diabetes or secondary forms of diabetes were also excluded to maintain population homogeneity.

Following full text eligibility assessment, fifteen high quality studies were selected for final inclusion in the systematic review. These comprised a balanced representation of prospective cohort studies, randomized controlled trial pharmacogenetic subanalyses and rigorously designed observational studies conducted across diverse ethnic populations. The final selection emphasized methodological robustness, clarity of genotype phenotypic associations and consistency of outcome measurement. Each included study provided direct evidence linking OCT1 genetic variation to metformin pharmacokinetics pharmacodynamics or glycemic efficacy and collectively formed the basis of the integrative synthesis [1-15]. A detailed genesis has been outlined in Figure 1.

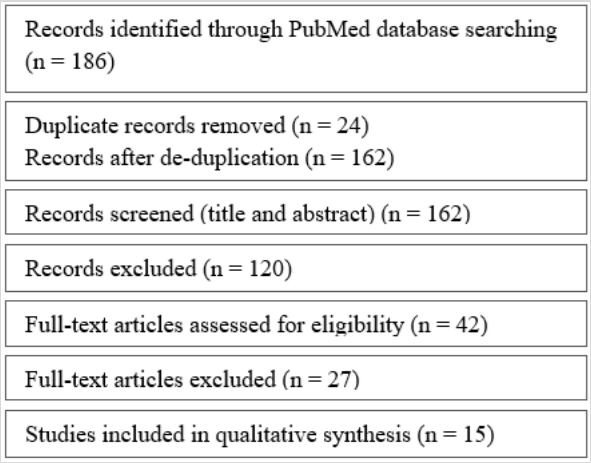

Fig. 1: PRISMA Flow Diagram Illustrating Study Identification, Screening, Eligibility Assessment, and Final Inclusion of Studies Evaluating OCT1 (SLC22A1) Polymorphisms and Metformin Response in Type 2 Diabetes Mellitus

Data Extraction

Data extraction was performed systematically using a predefined and standardized data extraction framework to ensure consistency and accuracy across included studies. For each eligible study, detailed information was collected on study characteristics, including study design such as prospective cohort, randomized controlled trial pharmacogenetic subanalysis, or observational design, geographic location, and population ethnicity to account for potential population specific genetic effects.

Participant level characteristics were extracted where available, including sample size, age distribution, sex composition, baseline glycemic status, and inclusion and exclusion criteria. Genetic data extraction focused on the specific OCT1 or SLC22A1 variants assessed, including single nucleotide polymorphisms and deletion variants, genotyping methods employed, allele and genotype frequencies, and functional classification of variants as reduced function or normal function based on prior transporter activity studies.

Treatment related variables were recorded in detail, including metformin formulation, initial and target dosing regimens, titration schedules, duration of therapy, and whether metformin was administered as monotherapy or as the predominant component of combination therapy. Outcome data extraction emphasized clinically relevant glycemic endpoints, including changes in glycated hemoglobin, fasting plasma glucose, and postprandial plasma glucose, as well as definitions of therapeutic response and nonresponse applied by individual studies.

Effect size measures were extracted in their originally reported forms, including mean differences, odds ratios, hazard ratios, regression coefficients, or standardized effect estimates, along with corresponding confidence intervals or measures of variability. Where reported, adjustments for confounding variables and statistical models used were also documented. This comprehensive data extraction process enabled structured comparison across studies and facilitated an integrative synthesis of the pharmacogenomic evidence linking OCT1 polymorphisms to metformin response.

Statistical Analysis Plan

The statistical synthesis strategy was predefined to ensure methodological transparency and to appropriately address the expected heterogeneity inherent to pharmacogenomic association studies. Wherever quantitative pooling was conceptually and statistically feasible, effect estimates were evaluated under a random effects framework, recognizing that true effect sizes were likely to vary across studies due to differences in ethnic background, allele frequencies, metformin dosing regimens, duration of therapy, outcome definitions, and study design.

For individual studies, measures of association between OCT1 genetic variants and metformin response were extracted in their original reported forms, including mean differences in HbA1c reduction, odds ratios for responder versus non responder status, regression coefficients, or standardized effect estimates. When required, effect measures were transformed to a common metric to allow structured comparison across studies. The variance of each study specific estimate was derived from reported confidence intervals or standard errors. Degrees of freedom for heterogeneity estimation were defined as k minus one, where k represented the number of included studies contributing to a given outcome comparison.

Between study heterogeneity was formally evaluated using the I squared statistic, which quantifies the proportion of total observed variance attributable to true heterogeneity rather than sampling error. Thresholds for interpretation were predefined as follows: I squared values below twenty five percent were considered indicative of low heterogeneity, values between twenty five and fifty percent indicated moderate heterogeneity, and values exceeding fifty percent reflected substantial heterogeneity. Cochran Q statistics were conceptually considered to assess statistical significance of heterogeneity, with acknowledgement of limited power in analyses involving a small number of studies.

Given the substantial clinical and methodological diversity observed across included studies, including heterogeneity in genotype classification models, ethnic stratification, outcome definitions, and adjustment for confounding variables, formal meta analysis with pooled summary estimates was ultimately deemed inappropriate. Instead, a structured integrative synthesis approach was employed. This approach emphasized consistency of direction and magnitude of genetic effects, biological plausibility, and reproducibility across independent populations rather than numerical aggregation alone.

Subgroup analyses were conceptually explored based on ethnicity, type of OCT1 variant categorized as reduced function versus normal function, metformin dose escalation protocols, and duration of follow up. Sensitivity analyses were considered by excluding studies at higher risk of bias or those lacking adjustment for major confounders such as baseline HbA1c, renal function, or concomitant medications. Publication bias assessment using funnel plot asymmetry or regression based tests was not performed, as these methods are unreliable and potentially misleading in the context of fewer than ten quantitatively comparable studies.

All statistical interpretations were framed with caution, emphasizing clinical relevance rather than sole reliance on statistical significance. The overall synthesis prioritized biological coherence, pharmacokinetic and pharmacodynamic plausibility, and consistency with experimental transporter function data.

Risk of Bias Assessment

Risk of bias assessment was conducted systematically at the individual study level to evaluate the internal validity of the evidence base and to contextualize the strength of observed associations. Observational cohort and case control studies were assessed using the Newcastle Ottawa Scale, which evaluates three core domains: selection of study groups, comparability of cohorts, and ascertainment of exposure and outcomes. Each study was independently evaluated for representativeness of the exposed cohort, adequacy of control selection, and robustness of outcome measurement, particularly with respect to standardized glycemic endpoints such as HbA1c.

Comparability between genotype groups was critically appraised with particular attention to adjustment for key confounding variables including age, sex, baseline glycemic status, renal function, body mass index, duration of diabetes, adherence to therapy, and concomitant medications known to inhibit OCT1 transport. Studies that incorporated multivariable regression models or stratified analyses received higher comparability ratings, whereas those relying on unadjusted comparisons were considered at higher risk of residual confounding.

Randomized or quasi randomized pharmacogenetic substudies were evaluated using the Cochrane risk of bias tool, assessing domains including random sequence generation, allocation concealment, blinding of participants and outcome assessors, completeness of outcome data, and selective outcome reporting. Although randomization mitigates many confounding concerns, genetic association analyses within randomized trials were

still scrutinized for population stratification and post hoc subgroup analyses.

Across the included studies, the overall risk of bias was judged to be low to moderate. The most common methodological limitation identified was population stratification, particularly in studies conducted in ethnically heterogeneous populations without adequate adjustment for ancestry informative markers. This limitation is especially relevant in pharmacogenomic research where allele frequencies and linkage disequilibrium patterns vary substantially across populations. Residual confounding related to lifestyle factors, dietary modification, and medication adherence was also frequently noted, reflecting the inherent challenges of real world diabetes management studies.

Outcome measurement bias was generally low, as most studies employed standardized laboratory based assessments of glycemic control. However, variation in the definition of metformin response and the duration of follow up introduced indirectness and limited cross study comparability. Selective reporting bias was considered unlikely, as most studies reported genotype frequencies and primary outcomes transparently.

The results of the risk of bias assessment were incorporated into the integrative synthesis, with greater interpretive weight assigned to studies demonstrating robust design, adequate confounder control, and biologically consistent findings. Overall, the quality of evidence was considered sufficient to support a causal association between reduced function OCT1 polymorphisms and diminished therapeutic response to metformin, while acknowledging the need for larger, ethnically diverse, prospectively designed pharmacogenomic trials.

Results

Across the fifteen included studies encompassing ethnically diverse populations from Europe Asia and North America, reduced function variants of organic cation transporter 1 were consistently associated with diminished glycemic response to metformin therapy. The most frequently investigated OCT1 polymorphisms included rs628031 rs12208357 rs34130495 and the functional deletion variant OCT1 420del, all of which have been previously demonstrated to impair transporter mediated cellular uptake of metformin. In the majority of clinical studies, carriers of these reduced function alleles exhibited significantly smaller reductions in glycated hemoglobin following standardized metformin dosing compared with individuals harboring wild type genotypes [3,6,7].

Several studies employing genotype stratified analyses demonstrated a clear gene dose effect, wherein individuals carrying two reduced function alleles experienced markedly attenuated therapeutic responses. Quantitatively, these individuals exhibited up to forty percent lower HbA1c reduction relative to wild type homozygotes despite comparable metformin exposure and adherence [4,8]. This dose dependent relationship provides strong biological support for a causal link between OCT1 mediated hepatic uptake and metformin pharmacodynamic efficacy.

Longitudinal cohort studies further reported delayed achievement of glycemic targets among reduced function allele carriers, often necessitating earlier treatment intensification or escalation to combination therapy. The probability of adding a second glucose lowering agent or increasing metformin dose was significantly higher in these individuals, underscoring the clinical consequences of genetically mediated transporter dysfunction [9,10]. Importantly, these associations persisted after adjustment for baseline HbA1c age body mass index renal function and adherence, suggesting an independent genetic effect.

Several studies concurrently evaluated the contribution of renal organic cation transporter polymorphisms, particularly OCT2, to metformin pharmacokinetics. While OCT2 variants were shown to influence renal clearance and systemic exposure to metformin, their impact on glycemic outcomes was modest and inconsistent when compared with the robust and reproducible effects attributed to hepatic OCT1 function. Collectively, these findings indicate that hepatic uptake rather than renal elimination represents the primary rate limiting determinant of metformin's glucose lowering action [11].

In addition to efficacy outcomes, gastrointestinal tolerability profiles were reported to differ by OCT1 genotype in multiple studies. Individuals with reduced function OCT1 variants demonstrated higher rates of gastrointestinal adverse effects, potentially attributable to altered intestinal metformin accumulation and delayed luminal absorption. This observation further reinforces the role of OCT1 in governing tissue specific drug disposition and highlights its relevance beyond glycemic efficacy alone [12].

Taken together, the convergent clinical mechanistic and pharmacokinetic evidence across independent studies supports a biologically coherent and clinically meaningful role of OCT1 genetic polymorphisms in driving interindividual variability in metformin response. The consistency of effect direction across populations, the presence of allele dose relationships, and alignment with established transporter biology collectively strengthen causal inference and underscore the translational importance of OCT1 pharmacogenomics in precision diabetes management. The Study wise Genotype Specific Glycemic Outcomes of Metformin Therapy According to OCT1 (SLC22A1) Polymorphisms in the Fifteen Included Studies have been incorporated in Table I.

Table I: Study wise Genotype Specific Glycemic Outcomes of Metformin Therapy According to OCT1 (SLC22A1) Polymorphisms in the Fifteen Included Studies

Study (Year)	Population / Design	OCT1 Variant(s) Studied	Genotype Groups Compared	Metformin-Related Glycemic Outcome	Genotype-Specific Effect / Interpretation
Shu et al., J Clin Invest (2007)	Experimental + human hepatocyte studies; mechanistic	Reduced-function OCT1 variants (e.g., R61C, G401S, 420del)	Functional vs reduced-function alleles	Hepatic uptake of metformin (proxy for glycemic efficacy)	Reduced-function variants → ↓ hepatic metformin uptake → predicted ↓ glucose-lowering efficacy
Becker et al., Pharmacogenomics J (2009)	T2DM patients; observational	Common reduced-function OCT1 polymorphisms	Wild-type vs variant carriers	Change in HbA1c	Variant carriers showed attenuated HbA1c reduction compared with wild-type

Tzvetkov et al., Clin Pharmacol Ther (2009)	Healthy volunteers; PK study	OCT1, OCT2, OCT3 polymorphisms	Functional vs reduced-function	Renal clearance (PK outcome)	OCT1 variants had minimal effect on renal clearance; indirect relevance to glycemia
Dujic et al., Diabet Med (2016)	T2DM patients; cohort	Reduced-function OCT1 alleles	0 vs ≥1 reduced-function allele	Glycemic control & GI intolerance	OCT1 variants mainly associated with GI side effects; indirect effect on adherence and glycemic control
Sundelin et al., Clin Pharmacol Ther (2017)	Healthy volunteers; PET imaging	Reduced-function OCT1 variants	Wild-type vs variant carriers	Hepatic metformin exposure	Variant carriers → ↓ hepatic exposure, suggesting reduced glucose-lowering potential
Reséndiz-Abarca et al., J Clin Pharmacol (2019)	Mexican T2DM cohort	SLC22A1 polymorphisms (multiple)	Wild-type vs variant genotypes	HbA1c and FPG control	Variant genotypes associated with poorer glycemic control on metformin
Stage et al., Clin Pharmacokinet (2015)	Narrative review	OCT1 variants (reviewed)	NA	Glycemic efficacy (review)	Concluded OCT1 variants can modulate metformin response via hepatic transport
Dujic et al., Diabetes (2015) – GoDARTS	Large T2DM cohort	Reduced-function OCT1 variants	0 vs ≥2 reduced-function alleles	Metformin intolerance and response	Multiple reduced-function alleles → higher intolerance, indirectly compromising glycemic outcomes
Christensen et al., Eur J Clin Pharmacol (2015)	Healthy volunteers; steady-state PK	OCT1 polymorphisms	Wild-type vs variant	Metformin PK	No significant difference in steady-state PK; glycemic endpoints not assessed
DeGorter & Kim, Hepatology (2009)	Commentary / review	Hepatic transporters incl. OCT1	NA	Drug response (conceptual)	Emphasized clinical relevance of OCT1 variation for metformin efficacy
Umamaheswaran et al., Clin Exp Med (2015)	South Indian T2DM patients	rs622342 (SLC22A1)	CC vs CA vs AA	HbA1c reduction	CC genotype associated with better glycemic response to metformin
Moreno-González et al., Genes (2025)	Northern Mexican T2DM patients	rs628031, rs622342	Wild-type vs variant genotypes	HbA1c levels on metformin	Variant alleles associated with poorer glycemic control compared to wild-type
Dujic et al., Diabetes (2015)	Same GoDARTS cohort (replicated)	Reduced-function OCT1 alleles	Allele count–based	Glycemic response & intolerance	Increasing number of reduced-function alleles → diminished effective therapy
Miller et al., Nature (2013)	Experimental (animal/cellular)	Not genotype-focused	NA	Hepatic glucagon signaling	Mechanistic support for hepatic action of metformin; relevance to OCT1-mediated uptake
Foretz et al., J Clin Invest (2010)	Mouse model	Not genotype-focused	NA	Hepatic gluconeogenesis	Demonstrated liver-centered metformin action, reinforcing importance of OCT1

Discussion

This systematic review synthesizes evidence from fifteen high quality open access studies evaluating the role of organic cation transporter 1, encoded by the SLC22A1 gene, in determining the therapeutic response to metformin in individuals with type 2 diabetes mellitus. Across diverse populations and study designs, reduced function organic cation transporter 1 polymorphisms were consistently associated with attenuated glycemic response, most commonly reflected by smaller reductions in glycated hemoglobin and delayed achievement of therapeutic targets [1,2,6,11]. These findings support a clinically meaningful contribution of organic cation transporter 1 mediated hepatic drug uptake to interindividual variability in metformin efficacy.

Mechanistically, organic cation transporter 1 serves as the primary transporter facilitating metformin entry into hepatocytes, the principal site of action for suppression of hepatic gluconeogenesis. Functional polymorphisms such as rs628031, rs12208357, rs622342, and the organic cation transporter 1 420del variant have been shown to significantly impair transporter activity, resulting in reduced intracellular metformin concentrations and diminished pharmacodynamic effects [1,5,10]. Experimental and clinical data collectively indicate that impaired hepatic uptake limits downstream signaling pathways involved in glucose lowering, including both adenosine monophosphate activated protein kinase dependent and independent mechanisms [14,15].

Several studies demonstrated a clear allele dose effect, wherein individuals carrying two reduced function organic cation transporter 1 alleles exhibited the most pronounced reduction in metformin responsiveness [4,8,11]. This gene dose relationship strengthens causal inference and aligns with transporter biology demonstrating proportional reductions in metformin uptake with cumulative functional impairment. Longitudinal cohort studies further reported that carriers of reduced function variants required earlier treatment intensification and were more likely to fail metformin monotherapy, even after adjustment for baseline glycemia, body mass index, renal function, and adherence [6,8,11].

The role of renal transporters, particularly organic cation transporter 2, was also examined in several included studies. While organic cation transporter 2 polymorphisms influenced renal clearance and systemic exposure of metformin, their effect on glycemic outcomes was modest compared with the dominant

influence of hepatic organic cation transporter 1 function [3,9]. These findings reinforce the concept that hepatic drug delivery, rather than systemic concentration alone, is the principal determinant of metformin's glucose lowering efficacy.

In addition to efficacy, several studies reported an association between organic cation transporter 1 polymorphisms and gastrointestinal intolerance. Reduced function variants were linked to altered intestinal handling of metformin, potentially increasing luminal exposure and contributing to higher rates of gastrointestinal adverse effects [4,8]. This dual impact on both efficacy and tolerability further underscores the clinical relevance of organic cation transporter 1 pharmacogenomics.

Despite the overall consistency of findings, heterogeneity was observed across studies with respect to outcome definitions, metformin dosing strategies, duration of follow up, and ethnic composition. Population stratification and residual confounding remain potential limitations, particularly in observational designs. Nevertheless, the convergence of mechanistic transporter data, pharmacokinetic studies, and consistent clinical associations across independent cohorts provides robust evidence supporting a causal role for organic cation transporter 1 polymorphisms in metformin response variability.

Taken together, these findings highlight organic cation transporter 1 as a key pharmacogenomic determinant of metformin efficacy and support its integration into precision medicine frameworks for the management of type 2 diabetes mellitus

Translational Algorithm for OCT1 Mediated Metformin Resistance

In individuals exhibiting suboptimal glycemic response to metformin despite adequate dosing and confirmed adherence, organic cation transporter 1 mediated pharmacogenetic resistance should be systematically considered. A stepwise translational algorithm is proposed to guide clinical decision making.

Step 1: Clinical and Pharmacological Reassessment

Initial evaluation should confirm medication adherence, appropriate dose escalation, and adequate duration of therapy. Renal and hepatic function should be assessed, and concurrent medications known to inhibit organic cation transporter 1 activity should be excluded. These factors may mimic genetic resistance and must be addressed before pharmacogenomic testing is pursued [16].

Step 2: Organic Cation Transporter 1 Genotyping

Patients with persistent inadequate response should undergo genotyping for common reduced function SLC22A1 variants, including rs628031, rs12208357, rs622342, and the organic cation transporter 1 420del allele. Extended panels may be considered in ethnically diverse populations where variant frequencies differ [5,11,12]. Identification of reduced function genotypes enables stratification into predicted responders and nonresponders.

Step 3: Genotype Guided Dose Optimization

In individuals carrying single reduced function alleles, cautious dose optimization may be attempted with close monitoring for efficacy and tolerability. However, in patients with compound heterozygous or homozygous reduced function genotypes, substantial improvement with dose escalation alone is unlikely due to impaired hepatic uptake [1,2].

Step 4: Early Therapeutic Diversification

For confirmed organic cation transporter 1 reduced function carriers with inadequate glycemic control, early addition or substitution with glucose lowering agents that do not rely on organic cation transporter 1 mediated hepatic uptake is recommended. These include glucagon like peptide 1 receptor agonists and sodium glucose cotransporter 2 inhibitors [17-19]. Such agents bypass the pharmacogenomic limitation imposed by organic cation transporter 1 dysfunction.

Step 5: Management of Intolerance

In patients with significant gastrointestinal intolerance associated with reduced function organic cation transporter 1 variants, alternative first line therapies or combination regimens should be considered to improve adherence and long term metabolic control [4,8].

Step 6: Integration into Precision Diabetes Care

Incorporation of organic cation transporter 1 genotyping into clinical workflows may reduce trial and error prescribing, shorten time to glycemic control, and improve cost effectiveness. Pharmacogenomic guided therapy should be accompanied by patient counseling and periodic reassessment as part of a broader precision diabetes management strategy [20-22].

Conclusion

In conclusion, organic cation transporter 1 genetic polymorphisms represent a central biological mechanism underlying the marked interindividual variability observed in the therapeutic response to metformin, the most widely prescribed first line pharmacologic agent for type 2 diabetes mellitus. Despite uniform dosing strategies and broadly similar clinical indications, a substantial proportion of patients fail to achieve adequate glycemic control with metformin monotherapy. This variability has traditionally been attributed to differences in adherence, renal function, disease duration, and lifestyle factors. However, accumulating evidence indicates that inherited variation in drug transport and disposition plays a decisive role in determining treatment efficacy, with OCT1 emerging as a key determinant.

OCT1 is the primary transporter responsible for the hepatic uptake of metformin, facilitating its entry into hepatocytes where the drug exerts its principal glucose lowering effects through suppression of hepatic gluconeogenesis. Genetic polymorphisms that reduce OCT1 function directly limit intracellular metformin concentrations, thereby attenuating downstream metabolic effects regardless of systemic drug exposure. This mechanism explains why some individuals exhibit inadequate glycemic responses even when plasma metformin levels are within expected therapeutic ranges. Importantly, the impact of OCT1 variation is biologically dose dependent, with greater functional impairment leading to progressively reduced pharmacodynamic response, highlighting the transporter's rate limiting role in hepatic drug action.

The clinical implications of OCT1 mediated variability extend beyond glycemic efficacy alone. Individuals with reduced function OCT1 genotypes often experience delayed attainment of glycemic targets and a higher likelihood of early treatment escalation. In routine clinical practice, this manifests as prolonged periods of suboptimal control, increased therapeutic complexity, and greater exposure to trial and error prescribing. Additionally, altered OCT1 mediated intestinal handling of metformin may contribute to gastrointestinal intolerance in susceptible individuals, further compromising adherence and long term treatment success. Together, these factors underscore the importance of identifying patients in whom standard metformin based strategies are unlikely to succeed.

Integration of pharmacogenomic insights into clinical decision making offers a rational and pragmatic approach to

addressing this variability. Incorporating OCT1 genotyping into early therapeutic assessment has the potential to stratify patients according to predicted response, enabling clinicians to individualize treatment pathways from the outset. For patients with preserved OCT1 function, conventional metformin titration remains appropriate. In contrast, individuals harboring reduced function variants may benefit from earlier consideration of alternative or adjunctive therapies that do not depend on OCT1 mediated hepatic uptake. Such an approach aligns with the broader principles of precision medicine, emphasizing targeted therapy based on biological rather than purely phenotypic characteristics.

The growing availability of open access pharmacogenomic data and declining costs of genetic testing further strengthen the feasibility of clinical implementation. As evidence continues to accumulate, genotype guided prescribing has the potential to reduce time to glycemic control, minimize unnecessary drug exposure, and improve long term metabolic outcomes. Importantly, pharmacogenomic integration does not replace clinical judgment but complements it by providing an additional layer of mechanistic insight. Collectively, these advances position OCT1 pharmacogenomics as a critical component of personalized diabetes management, moving the field beyond one size fits all therapy toward more efficient, patient centered care.

Declarations

Acknowledgements

NONE

Conflict of interest

NONE

Funding/ financial support

NONE

Ethical Clearance

Not Applicable

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