Egyptian Journal of Medical Human Genetics

REVIEW

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Genetic polymorphism of organic cation transporter 2 (OCT2) and its effects on the pharmacokinetics and pharmacodynamics of Metformin: a narrative review

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Abstract

Background Organic cation transporter 2 (OCT2) is a renal carrier transporter protein found in the basolateral membrane of proximal epithelial cells, which facilitates active secretion of Metformin. The genetic polymorphism of OCT2 influences the pharmacodynamic and pharmacokinetic effect of Metformin in type 2 diabetes mellitus (T2DM) patients. This is also mainly associated with frequencies of the associated risk allele in a particular population.

Objective The purpose of the study is to determine the impact of OCT2 genetic polymorphism on Metformin pharmacodynamics (PD) and pharmacokinetics (PK).

Method of study Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used for performing the research. Following databases were used to conduct the search: PubMed/MEDLINE, Google Scholar, and the Cochrane Library. Relevant studies were retrieved and literatures were appraised for methodology, demographic characteristics, relevant SNPs, genetic intervention trials, and outcomes.

Results Based on the data collected, 13 OCT2 Single nucleotide polymorphisms (SNPs) were identified across various ethnic groups. There were significant differences between the frequency distribution of shared alleles and impact of thirteen SNPs on Metformin. Among the thirteen OCT2 variants studied, rs316019 variant produced the most diverse responses in population by showing positive and negative impact on PK & PD of Metformin.

Discussion and conclusion Each population's OCT2 polymorphism had a distinct effect on Metformin responsiveness. The findings of this study could bring significant benefits to patients with OCT2 genetic polymorphism if individualised T2DM therapy is introduced. Patient-centered treatment would improve the Metformin efficacy leading to new research in personalised medicine.

Keywords Genetic polymorphism, OCT2, SLC22A2, Substrate drugs, Metformin, Type 2 diabetes mellitus (T2DM), Pharmacogenetics, Personalised medicine

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Introduction

Organic cation transporters (OCTs) remain a kind of transport proteins that secrete and uptake cationic substances. Knockout mice examination studies have demonstrated their involvement in a very functional manner.

It is the most common OCT on the proximal tubular epithelium's basolateral membrane. It is essential for the renal clearance of cationic drugs, including oxyanions, from the bloodstream onto the reticuloendothelial system [1]. Diabetes is a chronic metabolic disorder characterized by high glucose levels (hyperglycemia), which over time can severely injure the heart, blood vessels, eyes, kidneys, and nerves. It mainly develops from insufficient insulin synthesis, secretion and resistance, or from a combination of the three [2].

Metformin, an antihyperglycemic medicine, is regarded as a firstline treatment for Type 2 diabetes mellitus (T2DM) and is an effective and extensively used medication. Additionally, Metformin is also beneficial in reducing some macro and microvascular complications including weight loss [2–5]. Despite the fact that the thorough mechanism of action of Metformin is unknown or unverified, some researchers claim that it serves as a metabolic inhibitor.

Metformin influences whole-body and cellular energy metabolism by activating AMP-activated protein kinase (AMPK) via a decrease in hepatic energy position, i.e., increasing the concentration ratios of Adenosine monophosphate (AMP): Adenosine di-phosphate (ADP) and/or ADP/Adenosine triphosphate (ATP), hence lowering transcription of gluconeogenic genes. Additionally, it reduces hepatic glucose production and increases insulin sensitivity, making it easier for the body to absorb and use glucose [3]. Evidence-based studies have repeatedly shown that genetic polymorphism of OCT2 role in the interindividual heterogeneity of metformin response. As a result, suggestive data emphasize the importance of future research into the effect of genetic polymorphisms on Metformin efficacy [6]. Plasma Membrane Monoamine Transporter (PMAT) and organic cation transporter 3 (OCT3) and are involved in absorption of Metformin in the gastrointestinal tract. Organic cation transporter 1 then transports the drug into the bloodstream (OCT1). Metformin cannot enter the liver without these OCT1 and OCT3 transporter protein genes. OCT2-gene (SLC22A2), mostly expressed in the basolateral membrane of renal tubules, plays a key role in the Metformin uptake from circulation into renal epithelial cells. Multidrug and toxic compound extrusion 1 (MATE1) (SLC47A1) and Multidrug and toxic compound extrusion 2 (MATE2-K) are involved in the transport of Metformin from the tubule cell to the lumen during renal excretion (SLC47A2) The impact of OCT2 (gene SLC22A2) genetic polymorphisms on pharmacokinetics of Metformin has been investigated in healthy population. In comparison to the reference genotype, the pharmacokinetics of OCT2 [c.596C > T, c.602C > T, and c.808G > T (rs316019)] genetic variations varied, with an increase in Area under the Curve (AUC) and Peak concentration (Cmax) and a decrease in renal clearance (CLr) [7].

Metformin is primarily eliminated through the kidneys and its tubular secretion has been demonstrated to be exclusively mediated by OCT2. Many literatures has demonstrated the existence of OCT2 genetic polymorphism in humans. Metformin activity has been found to be altered by OCT2 genetic polymorphism strongly indicating the significance of these genes in determining Metformin response. Few studies have found an association between OCT2 genetic polymorphism and Metformin efficacy and clearance, whereas others have found no association. Research examining the relationship between the genetic polymorphism of OCT2 and Metformin in various ethnic groups has a wide range of results. In order to examine the impacts of multiple SNPs in relation to Metformin clearance and response, it is vital to compile all the information into one review, which is why this study is significant. Extensive research is needed to comprehend the interindividual variation with different OCT2 SNPs for individualising the dosage regimen for patients with T2DM. This study aims to gather all available data on the impact of the OCT2 Single nucleotide polymorphism on the pharmacodynamics and pharmacokinetics of Metformin in patients with T2DM. It also seeks to understand and describe the distribution of OCT2 genetic variations throughout populations and their impact with Metformin responsiveness.

Materials and method

Inclusion criteria

We included the studies that evaluated the influence of OCT2 genetic polymorphism or SNPs on the pharmacodynamics and pharmacokinetics of Metformin in T2DMpatients.

Exclusion criteria

Studies involving the influence of OCT2 gene polymorphisms on the effect of Metformin in conditions other than T2DM are excluded.

Literature survey strategy

Electronic search

An electronic literature search was done using search engines like Google Scholar, PubMed/MEDLINE and the Cochrane Library. We searched for articles that addressed the influence of OCT2 genetic polymorphism on the pharmacodynamics and pharmacokinetic of Metformin in treating T2DM.

Keywords

Relevant keywords were used to retrieve the studies based on inclusion and exclusion criteria. We have

selected this search strategy approach to find relevant articles in PubMed: ("SLC22A2"[All Fields] AND "OCT2"[All Fields]) AND "genetic variant"[All Fields] AND "genetic polymorphism"[All Fields] AND, along[All Fields] AND ("metformin"[All Fields] AND "diabetes mellitus"[All Fields]) AND "type 2 diabetes"[All Fields] AND ("pharmacokinetics"[Subheading] OR "pharmacokinetics"[All Fields] OR "pharmacokinetics"[MeSH Terms]) AND ("pharmacology"[Subheading] OR "pharmacology"[All Fields] OR "pharmacodynamics"[All Fields] OR "pharmacology"[MeSH Terms] OR "pharmacodynamics"[All Fields]). Searches in the other databases were also conducted in the same manner. In addition, a systematic search of all citations to published research in journals was done to identify any relevant publications.

Quality assessment

The accuracy and validity of the included studies were assessed by screening the title, description, and complete text of each article.

Measures of different outcomes

Primary outcome

Pharmacokinetics: AUC, Renal Clearance.
Pharmacodynamics: Glycated hemoglobin (HbA1c).

Secondary outcome

Pharmacokinetics: C max, Maximun Velocity (V max), The Michaelis constant (Km).
Pharmacodynamics: Fasting blood glucose, Postprandial blood glucose.

Data collection

Replicas were removed from the search engine results before they were imported into Zotero. Four authors examined individual articles, and any discrepancies were resolved with a fifth author. The total number of participants in the study, endpoints, minor allele frequencies (MAF) were used to assess Metformin effectiveness, and changes in the context of SNP were extricated from the seven studies analysed (Fig. 1).

Results

Study features

After a preliminary examination of multiple databases with the relevant keywords, we retrieved 182 articles. Amongst these, 151 articles were from PubMed, 27 from Google scholar, and four from Cochrane. Duplicates were removed, after the second screening. We excluded 123 articles based on the titles, abstracts,language selection

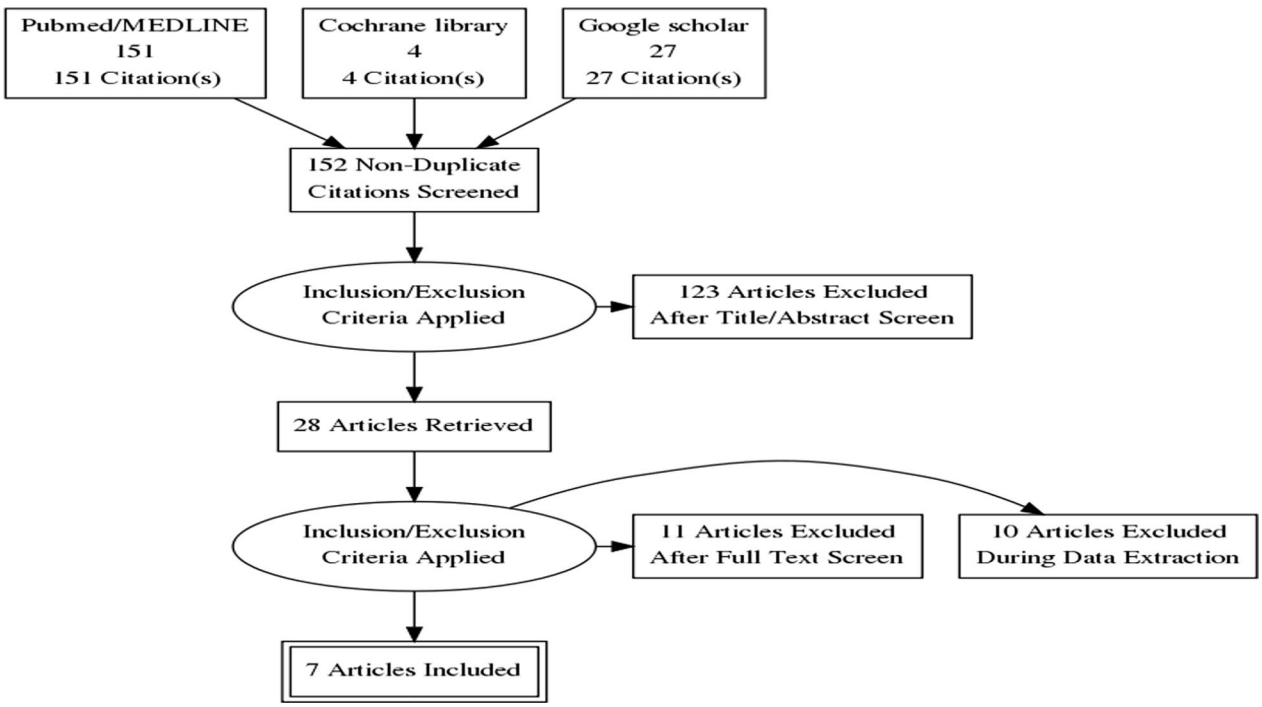

Fig. 1 Workflow procedure of literature search

and availability of full-text articles. Twenty-eight articles were found to be possibly eligible. Twenty one studies were excluded as they did not match the review's inclusion criteria with non relevance and unmatched end points. Finally seven studies are included based on the studies eligibility criteria.The majority of the research found to be done in Asian people. The duration of the research studies ranged from 24 h for single dosage studies on healthy volunteers to 6 months for patients who had been taking Metformin. The average participants age in the study ranged between 18 and 80 years.

The participants in the study were either healthy volunteers or diagnosed with T2DM on Metformin monotherapy. The Metformin's pharmacodynamic parameters were assessed through HbA1c, fasting blood glucose, postprandial blood glucose, or oral glucose tolerance test. Metformin's pharmacokinetics were evaluated by Peak Concentration (C max), Area Under the Curve (AUC), Maximum Time to achieve Cmax (Tmax), Elimination Rate Constant (K or kel), Metformin Uptake Extent and Half-Life (t1/2).

The genetic variants of the OCT2 polymorphism

A total of 13 SNPs were found from the included studies. The SNPs observed were *rs7757336, rs316019, rs201919876, rs17588242, rs10755577, rs17589858, rs3127573, rs2928035, rs316024, rs316026, rs316025, rs662301, rs533452.* The effects of the observed SNPs on metformin response were quite diverse and appeared to be either positive, negative, or both.

rs316019

Negative impact A study in a healthy volunteer Chinese population reported one SNP, 808G > T (Ala270Ser), with a Minor allele frequency of 13.3%. This study further substantiated the nonsynonymous SNP 808G > T polymorphism in the OCT2 gene with amino acid change: alanine to serine is linked with a decreased Metformin CL_r (renal clearance) and Metformin CL_r and Tubular Clearance (CL_t) were found to be significantly reduced in homozygous TT carriers (homozygous for 808G > T). Initially, the GT and TT groups seemed to have a higher total plasma concentration (AUC) of Metformin than the GG group, although this difference did not achieve statistical significance. However, it was discovered that there were significant differences in the CL_r and CL_t of Metformin between the three genotype groups ($P = 0.024$ and 0.037, one-way ANOVA). Additionally, the mean Metformin CL_r and CL_t values were 26.1% ($P = 0.022$) and 28.0% ($P = 0.036$) less in TT carriers than in GG carriers respectively [8].

Positive impact The SNP rs316019 (808G/T) was genotyped in European Americans (94) andAfrican Americans (66). The study was conducted only in healthy participants who are homozygous reference and heterozygous 808G/T gene as there were no homozygotes 808T/T found in the study. There is no significant difference in the mean Tmax and Cmax between the two genotype groups. The CL_R, Serum renal clearance ($SrCL_R$), and total clearance of Metformin were considerably higher in heterozygous variant allele (808G/T) of OCT2 compared to those reference allele (808G/G) homozygous. Statistically, significant difference was not found with the total clearance, presumably because of the diversity in the bioavailability of the subjects. The following variables (race, gender, OCT2 genotype, creatinine clearance (CL_{CR}) and age) were evaluated using multi-variant analysis as Metformin CL_R predictors. Merely, genotype and CL_{CR} were found to be good measures of Metformin CL_R among these variables. With genotype alone accounting for 28% versus 22% of the total variance in Metformin CL_R and CL_{CR}, respectively concluding OCT2 genotype as the only predictor of Metformin $SrCL_R$) which is significant [9].

A study included fifty healthy Caucasian volunteers and were genotyped for c.808G > T. Both peak plasma concentration (Cmax) and area under the curve of plasma concentration–time to infinity (AUC0-∞) were lesser in the homozygous variant group compared to homozygous and heterozygous and wild types. The apparent (CL/F = Dose/AUC0-∞)) total clearance, CL_{renal}, secretory clearance CL_{sec}, and volume of distribution (Apparent Vd/F) appeared to be higher in variant homozygous group compared to both the homozygous and heterozygous wild types. For all pharmacokinetic parameters, there were no statistically significant variations among the various c.808G > T genotype groups. On average, the GFR contributed for 22% of the variation in the CL_{renal}, and the addition of the OCT2 c.808 (G > T) genotype elevated this to 24% [10].

No impact The study involved 212 Denmark healthy population in total, and it determined that OCT2 c.808 (G > T) genotypes have no affect on the Cl_{renal} [11].

rs201919874

Positive impact The study established the frequencies of the SNP rs201919874 in Pakistani diabetes patients. The distributional properties of SNPs SLC22A2 rs201919874 in T2DM patients receiving Metformin monotherapy and in combination with sulfonylureas were compared to those of healthy individuals. There was a statistical differ-

ence between groups in terms of HbA1c, fasting, and random glucose levels. This study discovered an association between the SLC22A2 gene's allele A and the therapeutic effectiveness of Metformin. The Metformin response was associated with the heterozygous genotype GA of SLC22A2 rs201919874 in both patient groups ($p < 0.05$). As Group A patients failed to achieve normal levels of HbA1c as well as fasting and random blood glucose levels, GA and AA genotypes were associated with therapeutic efficacy of Metformin in these population ($p < 0.05$). Significant associations were observed in Metformin T2DM patients in terms of random blood glucose, fasting glucose, and HbA1c, however, no strong correlation were detected in combination T2DM patients. Patients treated with combination treatment versus metformin showed a significant variation in genotypes with regard to HbA1c levels [12].

rs7757336

Negative imapact The study was conducted in Latvia and Slovakia population and reported that the minor alleles of the SNP rs7757336 of OCT2 is strongly linked with Metformin inefficiency in newly diagnosed T2DM patients ($n = 233$). 25 healthy, non-diabetic volunteers participated in a pharmacokinetic study to understand the influence of the identified SNPs on Metformin. The findings of a pharmacokinetic study on 25 healthy volunteers supported the finding that SNP rs7757336 in the 5′ flanking regions of the genes coding for organic cation transporter 2 was associated with the absence of Metformin response and the minor alleles of rs775336 consistently related with lower concentrations of Metformin and AUC∞ of plasma. According to the results, allele probabilities for the major and minor alleles remained at 0.118 and 0.132, respectively. The study subjects were divided into a reference group ($n = 12$) and a risk group ($n = 13$) with at least one risk allele. Metformin's AUC∞ in plasma was considerably lower ($P = 0.009$) in the risk group (4.62 ± 1.29 μg/h/mL) compared with reference group (6.30 ± 1.51 μg/h/mL). In the reference group, there was indeed a significant rise in Cmax (0.84 ± 0.25 g/mL compared to 0.60 ± 0.18 g/mL, $P = 0.022$); meanwhile, the apparent clearance had grown significantly in the risk group (59.64 ± 18.11 g/h compared to 42.47 ± 9.50 g/h, $P = 0.01$). The genetic variant rs7757336 was strongly related to lower Metformin response [13].

rs17588242, rs2928035, rs316024, rs316026 rs662301, rs10755577, rs17589858, rs3127573, rs316025, rs533452

No impact A study by Al-Eitan et al., 212 Jordanians population were screened for 10 OCT2 polymorphisms, and they found nil significant association of glycemic control in T2DM patients on Metformin. The Study showed that there was no discernible correlation between renal Metformin clearance and these specific SLC22A2 SNPs (***rs2928035, rs17588242, rs316024, rs316026 rs662301, rs10755577, rs17589858, rs3127573, rs316025 and rs533452.***). Furthermore, no statistically significant evidence was found in the present investigation to support any of these examined SLC22A2 SNPs having effect on glycemic control. Polymorphisms found in this study had a *p* value greater than 0.05, indicating no statistical significance [14].

Discussion

OCTs, notably OCT2, are the kidney's Organic Cation Transporters. These proteins facilitate the metformin transport from blood stream to renal epithelial cells.. During the uptake of Metformin or other cationic medications from the blood to renal tubular epithelial compartments, OCT2 plays a critical role. Even though Metformin, the most commonly used drugs for the treatment of T2DM, there are reports which has shown treatment failure with Metformin at the right dose.. Multiple studies have suggested that the OCT2 genetic polymorphism stands as one of the reason for inter-individual disparity in the response of Metformin. Based on the information collected, with the present study, we reported 13 genetic polymorphisms (SNPs) of OCT2 from various ethnic groups which has shown association with metofromin Pharmacokinetics and Pharmacodynamics (Table 1).

When numerous ethnic groups were examined, there were variations in the frequency of the genetic polymorphisms. Out of all SNPs, the most commonly studied was found to be rs316019. Which showed diverse effects in different population with either positive, neagtive, no impact. The effects of rs316019 on the activity of metformin were statistically significant in the conducted studies of Chinese, European Americans, and African Americans. There were variations in Metformin CL_r and CL_t, AUC, and $t_{1/2}$ between genotype groups. Reduced renal and tubular Metformin clearance was a main component. In the Jordanian group, the genetic variant rs316019 demonstrated a favourable therapeutic impact (pharmacodynamic) of Metformin. The OCT2 genotypes in the Danish and Caucasian populations had no effect on CL_{renal}.

The rs7757336 allele was investigated in the Latvian population. The allele was substantially connected with Metformin inefficiency. rs775736 exhibited a diminished

Table 1 Organic cation transporter 2 (OCT2) and its effects on the pharmacokinetics and pharmacodynamics of Metformin

S. no.	Population	Author	Study design	Total sample	Age (mean/range), years	Duration of treatment	Polymorphism	MAF	Pharmacokinetic outcome	Pharmacodynamic outcome	Substrate drug	Overall effect
1	Chinese population	Wang et al. [8]	Open-label	112	21–32	2 weeks	rs316019	13.3	Significant variation in Metformin CLr and CLt, AUC, $t_{½}$ based on genotype	NIL	Metformin—500 mg	Negative impact
2	Latvian population-T2DMpatients	Zaharenko et al. [13]	Prospective cohort	131	22–37	3 years	rs7757336	0.132	The plasma AUC ∞ of Metformin throughout the risk category was dramatically lower than those in the reference category (6.30 ± 1.51 g/mL) ($P = 0.009$) A significant difference was seen between the reference group and the risk group in Cmax in plasma	NIL	Metformin—500 mg	Negative impact
3	94 Healthy—unrelated European Americans 66- unrelated African Americans population	Chen et al. [9]					rs316019	10	People with heterozygous mutant allele (808G/T) or homozygous conventional allele (808G/G) had remarkably different Metformin clearance (CLR) ($p < 0.005$) as well as gross secretion (SrCLR) than those who were homozygous for either allele	NIL	240 mL of water with 850 mg of metformin HCl tablet	Positive impact

Table 1 (continued)

S. no.	Population	Author	Study design	Total sample	Age (mean/range), years	Duration of treatment	Polymorphism	MAF	Pharmacokinetic outcome	Pharmacodynamic outcome	Substrate drug	Overall effect
4	Jordanian population-T2DMpatients	Al-Eitan et al. [14]		212	56.64 ± 9.4 year		rs10755577 rs17588242 rs17589858 rs2928035 rs3127573 rs316024 rs316025 rs316026 rs533452 rs662301	0.18 0.25 0.25 0.19 0.08 0.21 0.24 0.42 0.29 0.05		No significant association of glycemic control in T2DM patients taking Metformin was found	Metformin	No significant effect
5	Pakistani population-T2DMpatients	Moeez et al. [12]	Case–control study	1200	35–80 years	1 year	rs201919874	10.2	The heterozygous genotype Ga was associated with Metformin response ($p < 0.05$)	NIL	Group A-1500 mg Metformin q24hrs for six months Group B-1000 mg Metformin + 80 mg Sulfonylurea for one or more year	Positive impact
6	Caucasian population-healthy volunteers	Christensen et al. [10]	Cohort study	50	20–49 years		rs316019	13	No impact on Metformin renal clearance (CL_{renal}) as well as secretory clearance was seen with the c.808 (G > T) mutation (CL_{sec}). Participants having recessive alleles in c.808 had higher CL_{renal} and CL_{sec} levels	NIL	Metformin—500 mg	Positive impact
7	Denmark population-healthy inhabitants	Kuhlmann et al. [11]	Open-label, nonrandomised study	212	18–60 years		rs316019		GFRi were strongly linked to Metformin CL_{renal} & AUC 0 to 24 h The CL_{renal} is unaffected by OCT2 genotypes	NIL	Metformin—500 mg	No impact

Metformin response, as measured by a decreased AUC∞ of Metformin in plasma. rs201919874 was scrutinised to understand better Metformin's PK/PD effects in T2DM individuals from Pakistan. The polymorphism rs201919874 was strongly associated with a greater plasma concentration of Metformin and decreased renal clearance. An association between the SLC22A2 gene's allele A and the therapeutic effectiveness of Metformin is found. Many pharmacodynamic measures, including glycated haemoglobin, random, and fasting glucose levels, were significantly associated with genotypes.

The alleles rs10755577, rs17588242, rs17589858, rs2928035, rs3127573, rs316024, rs316025, rs316026, rs533452, rs662301 have no significant correlation with renal Metformin clearance but there was no statistically significant evidence found to support SLC22A2 SNPs effect on glycemic control. When we looked at how OCT2 polymorphisms affected Metformin's pharmacokinetic and pharmacodynamic profile, we noticed that ethnic groups exhibited considerably different outcomes and frequencies. Other confounding variables, such as age, the present status of the disease condition, and environmental circumstances, may substantially affect the result. Due to the data's inconsistency, the studies could not presume a genotype–phenotype link. The review's limitations include the scarcity of literature in this area of study.

Additionally, some studies reported a low sample size, implying that the study group may not wholly reflect the OCT2 variances. Consequently, a bigger sample size allows for establishing a more robust link between OCT2 genetic polymorphism and substrate drug reactions. The study's results might not have been as conclusive as they could be because of disparities in the types of participants and the methodology used to examine the influences of OCT2 genetic polymorphisms on Metformin response.

Conclusion

This narrative review examined the genetic influences of OCT2 polymorphisms upon the pharmacotherapeutic impacts of OCT2 as to its substrate drug, mainly Metformin. OCT2 polymorphisms were found to have positive and negative impacts, which were unique to the population. The findings of this study could bring significant benefits to patients with OCT2 genetic polymorphism if individualised T2DM therapy is introduced. Timely patient-centered treatment would improve the Metformin efficacy and disease prognosis. Presumably, resulting in decreased rates of macrovascular and microvascular T2DM consequences with better and more targeted treatment regimens.

Acknowledgements
The authors would like to thank our department staff for their constant support.

Author contributions
SSB, NRV, MAP and AKP was involved in the Conceptualization, Methodology, Drafting, Editing, Reviewing and Overall Supervision. SGK, RS, DP contributed in Literature Review, Drafting, Visualization, Investigation and Data Curation. All authors read and approved the final manuscript.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 28 June 2022 Accepted: 12 January 2023
Published online: 24 January 2023

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