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REVIEW ARTICLE

Effect of Oct3 Genetic Polymorphism on the Response of Metformin in Type 2 Diabetes Mellitus: Narrative Review

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Abstract: Context: Metformin, the first line therapy of Type 2 Diabetes Mellitus is known to be transported by OCT3 (Organic Cation Transporter 3). Polymorphisms in this gene may lead to inter individual differences in the response to metformin. Objective: This study aims to compile and summarise the effect of OCT3 polymorphism on effect of metformin. Methods: PubMed/MEDLINE, Research Gate, Google Scholar, Cochrane Library and Scopus were used for literature review. Cmax (Maximum concentration), T max (Time to reach maximum concentration), AUC (Area under the curve) and Kel (Elimination rate constant) were used to assess pharmacokinetics and HbA1c (Hemoglobin A1c), blood glucose levels for pharmacodynamics. Results: Data extraction showed that 19 OCT3 polymorphisms were analyzed in various ethnic communities with the plurality of Asians. The results of these genotype alleles were found to be favorable (9), negative (3) and have no impact (7) on the response of metformin. A positive effect on metformin response was expressed as higher Cmax (Maximum concentration), AUC (Area under the curve), lower Kel (Elimination rate constant) or reduced HbA1c (Hemoglobin A1c), FBG (Fasting blood glucose). Conclusion: Influence of OCT3 polymorphisms on metformin responses was unique to the population. This recommends new research requirement on association between OCT3 polymorphism and Metformin.

Keywords: *Genetic Polymorphism, Metformin, OCT3, SLC22A3, Type 2 Diabetes Mellitus.*

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Introduction

Diabetes mellitus (DM) is a metabolic disease characterized by chronic hyperglycemia resulting from inadequate insulin secretion and insulin action, or both. Type 1 DM is an autoimmune destruction of beta cells in pancreas whereas type 2 DM is a structural insulin resistance with relative insulin deficiency [1].

Metformin is the first line drug of choice and foundation therapy for Type 2 Diabetes and is considered to be efficacious and safe [2-8]. It can be used as monotherapy or in combination with other drugs [9]. It also reduces several macrovascular complications and is beneficial in diabetics with congestive heart failure and nephropathy. Metformin also aids in promoting weight loss [9-11]. Other indications of metformin include Polycystic Ovary Syndrome, Pre-diabetes and Gestational Diabetes [12]. Recent trials reported a protective effect on pancreatic cancer in long term use and studies are underway to demonstrate its value in the treatment of pancreatic cancer [13, 14]. Although rare, side effects of metformin include flatulence, vitamin B12 deficiency, lactic acidosis, asthenia, myalgia and hypoglycemia [15].

Metformin also acts by reducing the hepatic glucose production and increasing insulin sensitivity by promoting peripheral glucose uptake and its utilization [16-18]. Metformin reduces the rate of ATP (Adenosine Triphosphate) synthesis, resulting in higher AMP (Adenosine Monophosphate)/ATP ratios. Altered energy status of the cell leads to activation of AMP-activated protein kinase (AMPK), due to which metformin decreases the glucose output by liver [19-15]. Even though metformin is widely used, there is a

wide interindividual variation with metformin response and about 35% of patients taking metformin fail in achieving initial glycemic control with metformin monotherapy [2, 20-23]. Recent evidence indicates that genetic variation may contribute to variation in interindividual response to metformin therapy [24]. This necessitates the study of the role of genetic polymorphisms on the action of metformin [23]. Several transporters play an important role in absorption, distribution and elimination of metformin [25, 26].

Metformin is absorbed into the intestine with the help of OCT3 and PMAT (Plasma membrane monoamine transporter) genes. From the intestine, it enters the blood circulation using OCT1 protein. OCT1 and OCT3 are required for the uptake of metformin into the liver. Finally, OCT2, MATE1 (Multidrug and toxin extrusion protein 1) MATE2 (Multidrug and toxin extrusion protein 2) mediate renal excretion of metformin [27, 23, 28].

OCT3 gene is a member of the solute carrier family 22 and it is also called SLC22A3 which is located on chromosome 6 of the human genome. The gene is present in liver, kidney, intestine, salivary glands and other organs [29, 30, 31, 24, 28, 32]. A few drugs transported by OCT3 include metformin, cimetidine, procainamide, clonidine, varenicline, ranitidine etc [25]. SLC22A3 gene encodes for OCT3 protein which is a polyspecific, bi-directional, facilitative diffusional transporter [30]. OCT3 gene is responsible for the uptake of metformin, both in the liver and intestine, making it an important gene for the action of metformin [28].

OCT3 is known to increase the uptake of glucose in muscles and thereby reducing the blood glucose [33]. OCT3 is highly expressed in salivary glands and plays a role in metformin accumulation in salivary glands, which induces taste disturbances associated with metformin [28].

In spite of being present in the intestine and liver, OCT3 has received relatively less attention when compared to the other genes in the family [34]. However, studies showed that the action of metformin has been influenced by the genetic variations in OCT3 [14]. Further research in this area will be helpful in understanding the cause of interindividual variation in metformin therapy and designing patient specific dosage regimens. The aim of this review is to compile all the available data that has reported the effect of OCT3 genetic polymorphism on the pharmacokinetics and pharmacodynamics of metformin in treatment of Type 2 Diabetes Mellitus. To understand and summarise the distribution of OCT3 genetic polymorphisms in different populations and its effect on the response of metformin.

Materials and Methods

Inclusion Criteria

Studies that reported data on the effects of polymorphisms of OCT3 gene on the pharmacokinetics and pharmacodynamics of metformin when used to treat Type 2 Diabetes Mellitus.

Exclusion Criteria

We excluded Review articles, meta-analyses, case reports, editorials and comments from this review. Any articles assessing the effect of OCT3 gene on action of metformin when used for any condition other than Type 2 Diabetes were also excluded.

Outcome Measures

Primary endpoint: Pharmacodynamics: HbA1c

Pharmacokinetics: AUC

Secondary endpoint: Pharmacodynamics: Fasting blood glucose, Postprandial

Pharmacokinetics: C max, V max, Km

Literature Search Strategy

We conducted literature search in electronic databases like Pub Med/MEDLINE, Research Gate, Google Scholar, Cochrane Library and Scopus. Articles were taken from January 2001 to January 2020 to find studies which described the effect of OCT3 gene variations on the pharmacokinetic parameters and pharmacodynamics of metformin in treating Type 2 Diabetes Mellitus.

We searched using relevant keywords. The search strategy used in Pub Med was: (((((("slc22a3"[All Fields]) OR ("oct3"[All Fields])) OR ("organic cation transporter 3"[All Fields])) OR ("single nucleotide polymorphism"[All Fields])) OR ("genetic

variant" [All Fields])) OR ("genetic polymorphism"[All Fields])) AND (("metformin"[All Fields]) OR ("biguanide"[All Fields]))) AND ((("type 2 diabetes"[All Fields]) OR ("diabetes mellitus"[All Fields])) OR ("type 2 diabetes mellitus"[All Fields])). We used a similar strategy to conduct search in other databases. We identified articles sequentially; title, abstract and full text. In addition to this, we manually searched for all of the studies references quoted in the articles to retrieve any relevant articles.

Data collection

All of the studies obtained from search were exported to Zotero and duplicates were removed. Rests of the articles were evaluated manually by three individual authors and any discrepancies were fixed by a fourth author.

Vital information like sample size, minor allele frequencies, outcomes used to asses' metformin efficacy and the changes in the presence of SNP were extracted from the 8 included articles. (Insert Figure 1 here).

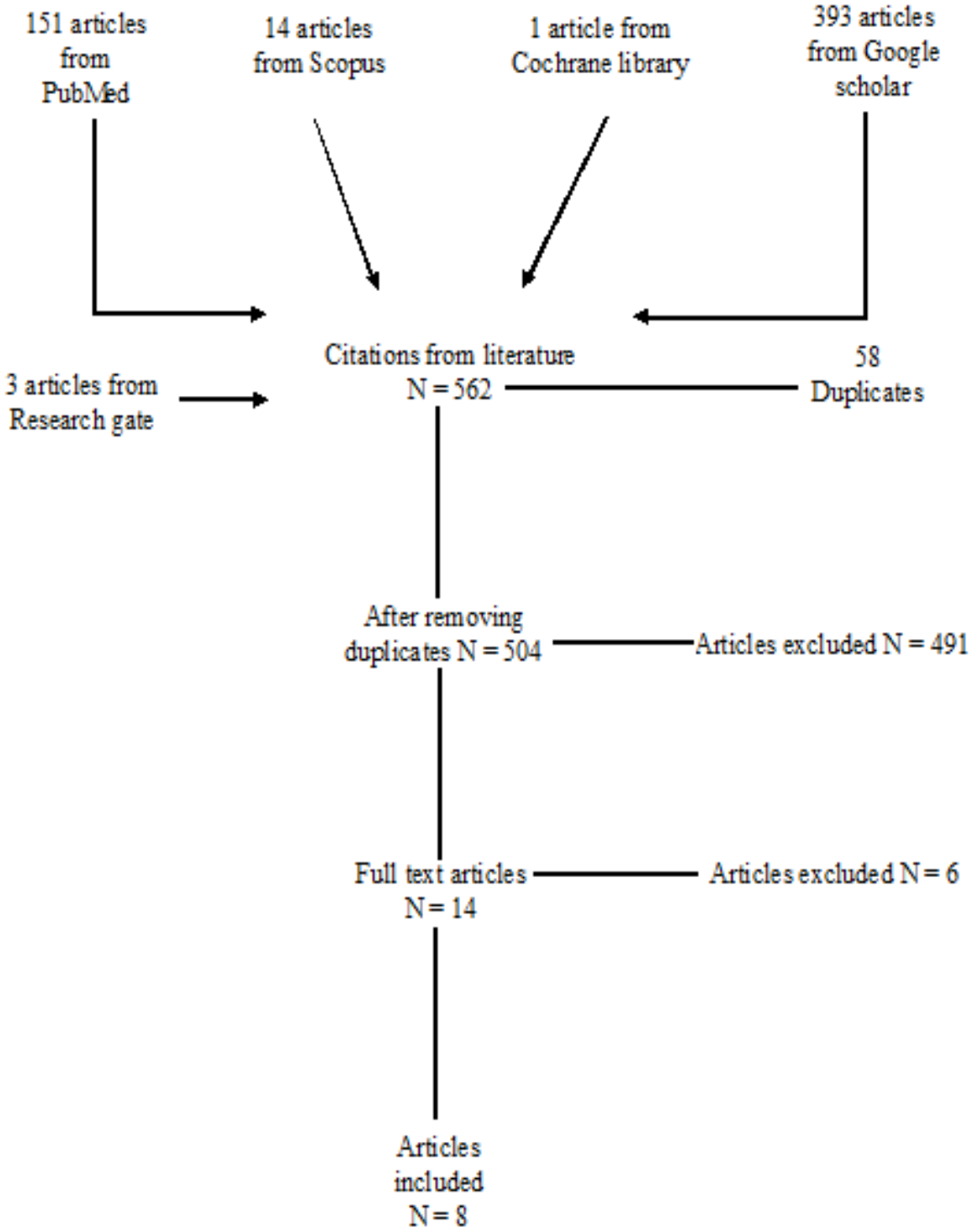

Fig. 1: Flow chart of article selection

Results

Study Characteristics

We identified 562 articles after the initial search in various databases. Among these, 151 articles were from Pub Med, 14 articles from Scopus, 393 from Google Scholar, 3 from Research Gate and 1 article from Cochrane Library. After screening of duplicates, titles and abstracts, 14 articles were found to be potentially eligible and full text articles were procured for further screening.

Of these, we excluded 6 as they did not meet the inclusion criteria and we included 8 articles for the review. Most of the studies were conducted on Asian population. One study was conducted in the USA on DNA samples from an ethnically diverse population. The number of participants in each study ranged from 48- 900 subjects. The study duration ranged from single dose studies on healthy volunteers for 24 hours to patients taking metformin from 6 months prior to the study. The subjects were categorised as responders or non-responders in case of diabetic patients and they were grouped based on their genotype in case of pharmacokinetic studies. The median age of study subjects ranged from 25 to 57 years among all the studies.

The action of metformin was assessed using HbA1c, fasting blood glucose, post prandial blood glucose and lipid profile or oral glucose tolerance test for pharmacodynamics. Pharmacokinetics were assessed using parameters such as Area Under the Curve (AUC), Peak Concentration (C max), Elimination Rate Constant (K or kel), Maximum Time to reach Cmax (Tmax), half-life ($t_{1/2}$) and extent of uptake of metformin. (Insert Table 1 here).

Table 1: Summary of study characteristics

Population	Author	Study design	Total sample	Duration of treatment	Polymorphism	MAF	Reported outcome	Metformin dose
Iranian	Ghaffari-Cherati, M et al., 2016[35]	observational study	150	3 months	564G>A rs3088442	0.31	Greater reduction of HbA1c and FBG GA/AA genotype. Not statistically significant.	1000mg twice a day.
Iranian	SR Hosseyni-Talei et al., 2017 [36]		150	3 months	1233G>A rs2292334	0.35	Higher decrease in HbA1c and FBG in polymorphed patients	100 mg/day
Arab Jordanians	Hakooz, N et al., 2017 [37]	Open label randomised study	116	24 hours	rs8187722 rs183669984 rs2292334	0.22 0 0.14	Higher C max and AUC in GA/GG population Polymorphism not detected Significantly high reduction in Cmax and AUC in variant	1000mg single dose

Population	Author	Study design	Total sample	Duration of treatment	polymorphism	MAF	Reported outcome	Metformin dose
Koreans	Kwon, E. Y et al., 2018 [38]		45	2 days	rs520685 rs520829 rs555754 -993C > G -423C > A	0.260 0.260 0.293 0.021 0.010	variant gene showed significantly higher AUC and C max of metformin - - -	1000mg, 750mg
Pakistan	Moeez, S et al., 2019 [39]	Case control study	900	6 months	rs3088442 G>A	59.6%	Variant population had better clinical response to metformin	-
Human	Chen, E. C et al., 2015 [19]		57		rs207688		No significant effect on pharmacokinetic parameters but there was reduced effect of metformin.	

Population	Author	Study design	Total sample	Duration of treatmen	Polymorphism	MAF	Reported outcome	Metformin dose
Jordanians	Al-Eitan, L. N et al., 2019 [40]		300		rs12194182 rs2292334 rs2504927 rs3123634	0.09 0.28 0.48 0.37	Lower HbA1c levels No statistically significant association between four *SLC22A3*	-
Ethnically diverse	Chen, L et al., 2010 [33]		247	-	rs68187715 rs8187725 rs8187716 rs668871 rs2292334 rs8187722 L423F A116S L186F V388M		Variants had higher metformin uptake and Vmax Decrease in metformin uptake and Vmax in variant allele - - - - No significant	-

HbA1c- Hemoglobin A1c; FBG- Fasting Blood Glucose; C max- Maximum Serum Concentration; AUC- Area Under the Curve; *SLC22*- Organic Cation Transporter 3; *SLC22A3* -Solute Carrier Family 22 member 3; SNPs-Single Nucleotide Polymorphisms.

Positive Impact

rs3088442

A study was conducted in 150 Iranian diabetic patients. They were classified into 2 groups 61 responders and 81 non-responders. They found that the genotypes frequencies

were 51.3% GG, 36% AG, and 12.7% AA. The Allele frequency of major allele (G) and minor allele (A) in *OCT3*- 564G>A variant was found to be 0.69 and 0.31, respectively. There was a significant reduction in fasting glucose, HbA1c, body mass index and lipid profile of all the patients after three months. However, HbA1c and fasting glucose levels were comparatively lower in the GA + AA genotype than the GG genotype but the differences were not significant statistically [35].

Another study was conducted in Pakistan among 900 individuals of whom 300 were metformin responders (only metformin), 300 metformin non-responders (metformin + sulfonylureas) and 300 healthy individuals. Moreover, it is a case control study. The minor allele frequency of *rs3088442* G>A variant in metformin responders, metformin non-responders and healthy individuals were 70%, 63% and 46.0% respectively.

The frequency of homozygous GG genotype was 36 out of 300 metformin-responders group, 26 out of 300 non-responders group and 114 out of 300 in healthy individuals was discerned as 12%, 9.0% and 38.0%.

Similarly, the frequency of heterozygous GA genotype was 106 from 300 in the metformin responders' group, 170 from 300 in the non-responders group and 98 from 300 in healthy individuals and 35%, 57%, and 33% respectively. And also, the frequency of homozygous AA genotype was 158 patients in 300, non-responders group of 104 patients in 300 and controls group of 88 individuals from 300, observed to be 53%, 34% and 29% respectively.

As change in the study variables after 6 months showed a significant protective effect of A allele in the clinical response to metformin with the responders than non-responders based on change in the parameters including HbA1c, weight, total cholesterol, postprandial and fasting glucose levels.

In addition to studying the frequency of the variant and its effect on metformin, they also analyzed the role of micro RNA 147 in the expression of *SLC22A3*. It was found that a significant increase in expression of micro RNA 147 *SLC22A3* in responders group compared to non-responders [39].

rs2292334

A study was conducted in 150 Iranian patients with newly type 2diabetes. The study was conducted to determine the genotype frequency of the variant *OCT3*-1233G>A (*rs2292334*). The patients were classified into two groups following three months of metformin therapy: responders (by more than 1% reduction in HbA1c from baseline) and non-responders (less than 1% reduction in HbA1c from baseline).

The frequency of the GG genotype was 41.4% while GA and AA genotypes was 48%, and 10.6% respectively. In this study the parameters such as HbA1c and BMI in both patients with GA + AA genotype and GG genotype decreased significantly following 3 months of metformin therapy compared with baseline.

The mean reduction in HbA1c levels following 3 months was higher in patients with the A allele (0.77% reduction from baseline) than in those with the homozygous G allele (0.54% reduction from baseline). The mean reduction of HbA1c in GA + AA genotypes when compared with GG genotypes was 0.34% in responders and 0.14% in non-responders [36].

Another study on the same genetic variant was conducted in healthy Arab Jordanian population with an open-label study design where genotyping studies were conducted in 116 healthy volunteers. The effect of polymorphism was studied in 26 individuals. Mutant allele frequency was found to be 0.14. There was a significantly higher C_{max}, AUC and lower K_{el} of metformin in heterozygous (GA) volunteers when compared to the wild population.

Homozygous variant population was not detected in this study however these genetic variants were not within Hardy-Weinberg equation resulting $\chi 2$, $p < 0.05$ [37]. Two volunteers had combined heterozygote *SLC22A1 rs35191146* and heterozygote (GA) *SLC22A3 rs2292334* genotypes. These genotypes showed higher C max, AUC 0-∞ and lower kel when compared to volunteers who had other combined *SLC22A1* and *SLC22A3* genotypes [37].

rs12194182

Among a total of 197 subjects that were screened for the SNP in a study conducted on Jordanians previously diagnosed with Type 2

Diabetes Mellitus. They were followed up and assessed in a diabetes clinic. Adequate glycaemic control was achieved in 77 patients and inadequate glycaemic control was seen in 120 patients. Minor allele frequency(C) was found to be 0.09. Subjects with *CC* genotype reported lower mean HbA1c levels, while patients with the *CT* and *TT* genotypes reported higher levels. However, the SNP did not affect the adequate or inadequate control of glycaemic response [40].

rs8187722

It was also conducted by Hakooz et al. in Arab Jordanian population. The mutant allele frequency was found to be 0.22 and the study concluded that there was a higher C_{max} and AUC levels but it had no effect on half-life and K_{el} in the heterozygous (G/A) and homozygous variants after assessing 26 samples on metformin pharmacokinetics. This allele was not within the Hardy-Weinberg equation showing $\chi 2$, $p < 0.05$ [37].

131 C>T rs68187715

In a study conducted by L. Chen et al. coding region of *OCT3* gene was examined using DNA of 247 ethnically diverse individuals. The frequency of polymorphism was 0.006 in African American and European American samples and 0.143 in Pacific Islander samples in the study. Cells expressing the 131C>T variant showed an increase in metformin uptake and significant increase in V_{max} while K_m was similar in variant and wild type [37].

-1603G >A rs520685, -1547T >G rs520829, -29G > A rs555754 and -993C > G

A study was conducted in 45 Koreans subjects to find out the effect of haplotype in *OCT3* promoter region on pharmacokinetics of metformin out of 48 subjects evaluated for frequency of genetic variations. Participants with homozygous or heterozygous variant gene of *rs520685, rs520829* or *rs555754* showed significantly higher AUC and C_{max} of metformin, while there was no significant difference in bioavailability, elimination half-life, T_{max}, or clearance. Subjects with homozygous variant gene showed the highest AUC and C_{max}, the minor allele frequencies of the variants, -1603G > A, -1547T > G rs520829, -29G > A rs555754 and -993C > G were 0.260, 0.260, 0.293 and 0.021 respectively.

However, there were no significant pharmacodynamic differences due to these variants [38].

Negative impact

rs2076828

A study was conducted on 57 healthy volunteers and it has detected 11 SNPs and only *rs2076828* had an effect on luciferase activity, where the minor allele G showed significantly lower activity. The variant had no significant effect on metformin pharmacokinetics parameters, even after adjusting for creatinine clearance, age, and gender. The variant associated with pharmacodynamics showed reduced response to metformin during oral glucose tolerance test in healthy volunteers. Healthy volunteers with minor G allele had significantly smaller changes in the glucose AUC. Results showed that there was a significant association between variant allele and metformin response [19].

1199 C>T rs8187725

1199 C>T *rs8187725* polymorphism was studied in an in vitro study conducted by L. Chen et al. among the 247 ethnically diverse population assessed for the SNP, a single sample of European American origin had shown a variant 1199C>T(T400I). Metformin uptake was found to be reduced by 80% and there was a slight decrease in V_{max} and a significant rise in K_m values in the variant sample [33].

V423F

There was a 50% decrease in metformin uptake in variant alleles and slight decrease in V_{max} with a significant raise in K_m value as reported in the study involving 247 ethnically diverse individuals by Chen et al. minor allele frequency of the variant allele was not mentioned int the study (Chen et al. 2010).

No impact

rs2292334

In a study conducted by Al-Eitan et al. 209 Jordanians were screened for *rs2292334* polymorphism (G>A) and 84 patients showed adequate glycaemic control and there was inadequate control in 129. Minor allele frequency (A) was found to be 0.28. this study has not found any significant association

between the presence of SNP and HbA1c or glycaemic control [40].

rs2504927

Al-Eitan et al. have also studied *rs2504927* polymorphism (G>A) in 194 patients among which 75 showed adequate glycaemic control and 119 did not. Minor allele frequency (A) was 0.48. The study has concluded that there was no significant relationship between the SNP and metformin response. Hba1c and glycaemic control were used to assess the response to metformin in patients (Al-Eitan et al. 2019).

rs3123634

rs3123634 (C>T) polymorphism was studied in 209 patients; 84 and 125 patients have shown adequate and inadequate glycaemic responses respectively in a study which was also conducted by Al-Eitan et al. Minor Allele Frequency (T) was found to be 0.37 in Jordanian Type 2 Diabetes Mellitus patients. This SNP has not shown any significant effect on either Hba1c levels or glycaemic control of metformin [40].

rs183669984

It has been studied by Hakooz et al. at 2017. This study in Jordan has tried to assess the effect of this polymorphism on metformin but no variants were detected in the study population, which had a sample size of 116 [37].

L423F (c.1267G>T), A116S (346G>T), L186F (558G>T), and V388M (1162G>A)

A116S (346G>T) allele frequency was 1.7% in African American population in a sample of 247 ethnically diverse population and had a frequency of 5.4% according to data obtained from 1000 Genomes Project.

L423F (c.1267G>T) variant had an allele frequency of 6.8% in Chinese and Japanese population from Beijing and Tokyo respectively. L186F (c.558G>T) had a frequency of 7.6% and 4.5% respectively in DNA samples of Chinese and Japanese samples and African samples. V388M (c.1162G>A) polymorphism was seen in a single sample in Caucasian population.

This data was obtained from 1000 Genomes Project for a study conducted by L. Chen et al. The above four missense alleles showed a similar metformin response and uptake, V_{max} and K_m when compared to reference *OCT3* used [33].

Discussion

Metformin is the best oral anti-diabetic drug for use as monotherapy in patients with Type 2 Diabetes Mellitus (T2DM). *OCT3* plays a major role in the uptake of metformin into multiple tissues, which affects therapeutic and toxicological effects of metformin peripherally. Several studies were identified on *OCT3* genetic variants that underlie inter individual variants, but no review has been conducted to assess its impact. From the data extracted, we identified 19 genetic variations from different ethnic groups.

The frequencies of the genetic polymorphisms varied when studied in more than 1 ethnic group. *Rs3088442* showed a non-significant yet protective effect on the action of metformin in an Iranian study and a significant protective effect on metformin action in a Pakistani study. *Rs2292334* polymorphism showed a positive effect on pharmacodynamics of metformin in an Iranian study and increased pharmacokinetic parameters in Arab Jordanian population. In another study in Jordan, no significant link was found between polymorphism and glycemic control of metformin.

Rs12194182 polymorphism showed an increased reduction in the HbA1c levels in a Jordanian population. *Rs8187722* polymorphism showed an increase in pharmacokinetic parameters in a Jordanian population. *Rs68187715* polymorphism showed an increased metformin uptake in an ethnically diverse population. *rs520685*, *rs520829*, *rs555754*, -993C > G polymorphisms have shown a positive effect on the pharmacokinetic parameters (AUC and C_{max}) of metformin when studied in a Korean population.

Rs2076828 polymorphism study in Koreans found no significant changes in the pharmacokinetic parameters of metformin but there was a significant decrease in the pharmacodynamic parameters of metformin. *rs8187725*, V423F have shown deleterious effects on the pharmacokinetics of metformin.

They showed reduced C_{max} and metformin uptake. No significant link between the polymorphisms and pharmacodynamics was

found for *rs2504927* and *rs3123634* variants in a Jordanian study. L423F, A116S, L186F, V388M showed similar results when compared to reference OCT3 in an ethnically diverse sample. There was a study where the assessors could not find a polymorphism (*rs183669984*) in their study population (Jordanian). We focused on the effects of *OCT3* polymorphisms on the pharmacokinetics and pharmacodynamics of metformin in treating Type 2 Diabetes Mellitus and found that the results and frequencies varied among different ethnic groups.

The result may be affected entirely by the genetic make-up or by other confounding factors such as age, disease condition, environmental factors etc. A genotype – phenotype relationship cannot be derived from the studies due to conflicting results. The limitations of this review are that a small number of studies have been included due to limited research conducted and the sample sizes of the studies varied. A few studies have small sample size which may not be adequate to obtain a significant result regarding the distribution and effect of the polymorphism.

Further research would provide a better insight into the effects of polymorphisms. The impact of genetic polymorphisms of *OCT3* showed both positive and negative associations with PK (Pharmacokinetics) & PD (Pharmacodynamics) of metformin. Also, the literature reveals few others off label indications of metformin besides Diabetes mellitus. In this context, this assessment in larger population could help the healthcare team in designing individualised dosage regimen of metformin for different labelled and off-labelled indications, in *OCT3* polymorphic group that aligns with the concepts of precision medicine.

Conclusion

Influence of *OCT3* polymorphisms on metformin responses were found to have positive and negative effect which was unique to the population. This recommends new research requirement on association between *OCT3* polymorphism and Metformin in different populations to create ethnicity-specific references for metformin responses and to provide a solid foundation for the effective clinical decision and therapeutic outcomes of Metformin for T2DM & in other off-labeled indications.

Author Contributions

Swathi Swaroopa B is the first author who executed the idea of manuscript, drafted and reviewed the manuscript. Arun K P is the corresponding author who conceptualized and had overseen the overall work including drafting and critically reviewing the manuscript. Chebrolu Bhavya, Poojitha T, Sujin Bright F J and Sadagoban G K are the co-authors who collected, synthesised and reviewed the literature and assisted in synthesizing the results, conclusion.

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