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Original Research Article

Influence of SLC22A1 gene polymorphisms on gastrointestinal adverse effects with metformin therapy in South Indian type 2 diabetes mellitus patients

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ABSTRACT

Background: Metformin, a first-line agent in Type 2 diabetes mellitus, causes gastrointestinal adverse effects in 20-30% of patients, leading to discontinuation in 5-10% of them. Organic cation transporter 1 (OCT1) encoded by SLC22A1, transports metformin from the enterocytes into the bloodstream. Reduced function OCT1 variants could lead to increased luminal concentration of metformin leading to gastrointestinal adverse effects. Two single nucleotide polymorphisms in the SLC22A1 gene were studied in this cross-sectional study with cases and controls. Objective was to determine the association between genetic polymorphisms rs628031 (1222A>G) and rs622342 (1386C>A) in SLC22A1 gene and gastrointestinal adverse effects to metformin therapy in South Indian type 2 diabetes mellitus patients.
Methods: The study was conducted in JIPMER, Puducherry, India in T2DM patients (n=300) of South Indian origin, who were categorized into case (N=100) and control (N=200) groups, based on their gastrointestinal tolerance to metformin. DNA was extracted from the patients using whole blood by phenol-chloroform method and genotyping was done using real-time PCR.
Results: Minor allele frequency of rs628031 (A allele) and rs622342 (C allele) were 33.8% and 26.5% respectively. Genotype frequencies did not differ significantly between the case and control groups (rs628031, p=0.45, rs622342, p=0.28). Female gender (AOR 3.77; 95% CI 2.07, 6.85; p<0.001) and proton pump inhibitor usage (AOR 7.66; 95% CI 3.01, 19.47; p<0.001) had higher association with metformin intolerance.
Conclusions: No significant association was found between the genotypes of single nucleotide polymorphisms (rs628031 and rs622342) in the SLC22A1 gene and gastrointestinal adverse effects to metformin therapy in South Indian type 2 diabetes mellitus patients.

Keywords: Gastrointestinal adverse effects, Metformin, rs628031, rs622342, SLC22A1, South India, T2DM

INTRODUCTION

Type 2 diabetes mellitus results from resistance to insulin and is showing an increasing trend in developing countries. In the year 2017, 72.9 million Indians had diabetes, with a prevalence of 8.8% and this number is expected to rise to 123.5 million by the year 2040.[1,2] Metformin is the first line pharmacological agent in the management of type 2 diabetes mellitus.[3] Although it is a good drug in terms of safety and efficacy, there are

differences in response to metformin between individuals and this is could be genetically determined.[4] In spite of several benefits, metformin is known to be associated with gastrointestinal adverse effects (GI-ADR), taste disturbances, deficiency of vitamin B12 and rarely, lactic acidosis.[5,6]

The gastrointestinal symptoms usually include diarrhoea, bloating, abdominal pain and may vary from being mild to intolerable, leading to decreased compliance, decreased quality of life and can affect the treatment outcome Gastrointestinal adverse effects have been reported in around 20-30% of patients receiving metformin.[7] Severe intolerance may end up in termination of metformin therapy in 5-10% of the patients.[8] Metformin is a substrate for several transporters-organic cation transporters (OCT1, OCT2 and OCT3), plasma monoamine transporter (PMAT), multi-antimicrobial extrusion protein (MATE1 and MATE2).

Table 1: Baseline demographics among cases and controls.

Characteristic	Controls (N=200)	Cases (N=100)	P value
Age (years)*	55 (48, 61)	50 (44, 59)	0.001
Gender (%)			
Males	70.5	33	<0.001
Females	29.5	67	
BMI categories (%)			
Underweight (<18.5)	3	2	
Normal (18.5-24.9)	55	43	0.03
Overweight (25-29.9)	35	38	
Obese (>30)	7	17	
Positive family history of diabetes (%)	69.5	71	0.78
Age at onset of diabetes (years)**	45.6±8.3	45.63±9.6	0.951
Duration of diabetes (months)*	72 (48, 120)	48 (14.5, 66)	<0.001
Duration of metformin (months)*	72 (48, 120)	36 (12, 60)	<0.001
Initial dose of metformin (grams)*	1 (0.5, 1)	1 (0.5, 1)	-
Current dose of metformin (grams)*	2 (2, 2.25)	1 (0.5, 1)	<0.001
Fasting blood glucose (mg/dl)**	136.48 ±47.20	145.35 ±48.85	0.13
Postprandial blood glucose (mg/dl)**	235.57 ±67.82	241.95 ±60.0	0.40
Comorbidities (%)			
Hypertension	38	32	0.31
Hypothyroidism	8	16	0.03
Diabetic neuropathy	27	17	0.05
Coronary artery disease	6	5	0.72
Concomitant medications			
Insulin	27	24	0.57
Sulfonylurea	76.5	81	0.38
Statin	85	62	<0.001
Aspirin	6	5	0.72
Amitriptyline	16	14	0.65
Gabapentin	12.5	4	0.02
Proton pump inhibitor	6	27	<0.001
ACE inhibitor	43	29	0.02
Levothyroxine	8	16	0.03

*Values expressed as median with interquartile range, **Values expressed as mean±SD

These transporters engage in the various steps of transport of metformin from the lumen of the gut into the enterocytes, subsequently into hepatocytes and to the kidneys for its elimination.[9] The mechanism by which metformin causes GI-ADR is still unclear. The various proposed mechanisms are: decreased absorption of bile salts, increase in GLP-1 (Glucagon-like peptide-1) concentration, decrease in serotonin transport via the serotonin transporter (SERT) which contributes to cumulating levels of luminal serotonin and also by modifying the gut microbiome.[10] The gene SLC22A1 (Solute carrier family) which codes for OCT1 is located on chromosome 6 (6q25.3) and has important single nucleotide polymorphisms (SNPs).[11] This transporter engages in moving metformin from enterocytes to bloodstream. In the presence of polymorphisms in SLC22A1, the function of OCT1 may be affected. It is hypothesized that metformin intolerance is induced by increase in the metformin levels in the intestinal tissue. The association between OCT1 variants and the presence of gut related side effects of metformin in a study suggests that OCT1 could be involved in the development of the

gastrointestinal adverse effects in metformin users.[12] With this background, we intended to determine the association between the SNPs rs622342 and rs628031 in SLC22A1 gene and gastrointestinal adverse effects to metformin in South Indian type 2 diabetes mellitus population.

METHODS

Study design

This was an analytical, cross-sectional study with cases and controls. The participants were recruited from the diabetes clinics run by departments of Endocrinology and Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), a tertiary care government hospital in South India, from December 2017 to September 2019. The study was conducted in accordance with the principles of Declaration of Helsinki and the Good Clinical Practice guidelines of International Conference on Harmonization. Type 2 diabetes mellitus patients of South Indian origin who were current users or who used metformin but discontinued due to documented gastrointestinal adverse effects were recruited for this study. Patients with history of three generations living in any of the southern states (Puducherry, Tamil Nadu, Kerala, Karnataka, Andhra Pradesh and Telangana) and speaking the respective local language as mother tongue were considered as South Indians. Cases and controls were defined based on the documented tolerance profile to metformin. Cases were patients who had documented GI-ADR to metformin (Immediate release tablets) and required either dose reduction or discontinuation of metformin by their treating physician. Controls were patients who were able to tolerate ≥2 grams of metformin (immediate release tablets) for at least six months, without any documented complaints of GI-ADR.

Patient eligibility criteria

Patients of either sex, between 18 to 65 years of age with type 2 diabetes mellitus of South Indian origin were recruited in the study. Patients with history of treatment with metformin (IR formulation) dose of 2 g per day for at least 6 months duration were recruited under control group and those with documented gastrointestinal adverse effects to metformin (IR formulation) who required either dose reduction or discontinuation of metformin were recruited under case group. We excluded patients with hepatic or renal dysfunction (liver transaminase >2.5 times upper normal limit, serum creatinine >2 mg/dl), pregnant and lactating women and those with history of chronic gastrointestinal disorders including chronic liver disease, chronic pancreatitis, inflammatory bowel disease, gastro duodenal ulcer and alcohol dependence

Sample size calculation

Sample size was calculated to be 300 (100 cases and 200 controls) using PS Power and Sample Size Calculations Software, version 3.1.2, (Vanderbilt University, Nashville, Tennessee, USA) Power was set at 0.8, α=0.05, probability of outcome (variant genotype) in control=0.4, control to case ratio of 2 and odds ratio of 2.

Study procedure

Patients were screened based on the inclusion and exclusion criteria and eligible participants were explained in detail about the study such as the study procedure, risks and benefits in the local language. After obtaining written informed consent, patient details such as age, gender, family history of diabetes, onset of diabetes, duration of metformin usage, dose of metformin presence or absence of gastrointestinal adverse effects and if present, the symptom(s) experienced were noted in the case record form. Other details that were obtained included comorbidities, concomitant medications. Parameters noted were anthropometric data, fasting blood glucose and postprandial blood glucose.

Sample collection and processing

Five ml of venous blood was collected under strict aseptic precautions in EDTA (ethylene diamine tetra acetic acid) tubes. Samples were centrifuged for 10 minutes at 2500 rpm at 4°C, plasma was removed and the cellular component were stored at -30°C until further analysis could be carried out. Genomic DNA was extracted using standard phenol-chloroform method and DNA was stored in tris-buffer. DNA samples were diluted to a concentration of 50 ng/µl. Genotyping for rs628031 and rs622342 in the SLC22A1 gene was done using Real Time thermocycler (ABI Prism 7300, Foster city, CA, USA) using TaqMan SNP genotyping assay method. The well volume was made up to 20 microliters for which 10 µl of TaqMan® PCR Universal master mix (2x), 0.5 µl of 40x working stock of TaqMan® genotyping assay, 5 µl of 50 ng/µl genomic DNA, 4.5 µl of deionized water were added together. The SNP genotyping assay ID used for rs628031 was C-8709275-60 (Applied biosystems, Foster city, CA, USA). The SNP genotyping assay ID for rs622342, an intron variant (1386 C>A) was C-928527-20, (Applied biosystems, Foster city, CA, USA).

Statistical analysis

Data was analysed using SPSS version 19.0 and R software version 3.5.2. A p value of <0.05 was considered statistically significant. Parametric data was expressed as mean±SD, non-parametric data as median (interquartile range), categorical data was expressed as number (percentage). Chi square test was used to analyse categorical data, Independent T test was used for continuous variables following normal distribution and Mann Whitney U test for data not following normal distribution Comparison of allele and genotype frequencies between cases and controls, assessment of genotype frequencies for Hardy Weinberg equilibrium were done using Chi square test. Association between the genotypes and development of GI-ADR between cases and

controls was determined using chi square test and expressed as odds ratio with 95% confidence interval. Effect of covariates was analysed by multiple binary logistic regression.

RESULTS

Baseline demographics

Three hundred T2DM patients who were on metformin (currently or previously) either as monotherapy or in combination with other antidiabetic drugs were recruited in this study, as controls (N=200) and cases (N=100).

The mean age of the overall population was 52.3 years and females were higher in proportion in the cases group (67%). Body mass index (BMI) was categorized based on WHO classification. Baseline characteristics of the study population are given in (Table 1).

The baseline characteristics among cases and controls showed significant differences with respect to gender, body mass index, duration of diabetes, current dose of metformin and concomitant medications such as statin, proton pump inhibitor, ACE inhibitors and gabapentin.

Frequency of gastrointestinal adverse effects with metformin

The frequency of various GI-ADR reported in the metformin intolerant patients in the study are given in (Table 2). Some patients had more than one GI-ADR. Heartburn was reported as the most common adverse effect with metformin (54%) in our study.

Frequency distribution of SLC22A1 gene polymorphism rs628031 and rs622342 in the present study population and other populations

Genotyping for rs628031 and rs622342 in SLC22A1 was done for 300 patients with type 2 diabetes mellitus. The genotype frequencies were found to be in Hardy-Weinberg equilibrium (rs628031 p=0.60 and rs622342 p=0.55). The allele and genotype frequencies of rs628031 and rs622342 of other populations as per 1000 genome project. Ensembl browser was used to obtain the data of the 1000 Genomes Project for rs628031 and rs622342.[13,14]

Association between rs628031 and rs622342 polymorphism in SLC22A1 and gastrointestinal adverse effects to metformin therapy

The genotype frequency distribution in rs628031 and rs622342 in SLC22A1 were compared between cases and controls and the association between the genotypes and development of GI-ADR was analysed by calculating the odds ratio by using the most appropriate genetic model based on Akaike Information Criterion (AIC). The result of the analysis is shown in (Table 3).

Table 2: Frequency of various gastrointestinal adverse effects reported with metformin therapy among cases.

Gastrointestinal adverse effect	Cases (N=100)
Heartburn	54
Abdominal pain	42
Abdominal bloating	38
Diarrhoea	34
Vomiting	3
Constipation	2

*Values are expressed as percentages

Regression analysis

Multiple logistic regression analysis of factors such as age, gender, duration of metformin usage, categories of BMI, genotypes, proton pump inhibitor, amitriptyline and gabapentin were carried out to analyze the effect of these co-variates on the outcome.

Proton pump inhibitor and amitriptyline were specifically chosen because they are OCT1 inhibitors. The coefficient of correlation between duration of diabetes and metformin usage was found to be 0.96, hence duration of metformin use was chosen as the co-variate. Female gender and proton pump inhibitors were found to have a significant association with the development of gastrointestinal adverse effects (p<0.001).

Table 3: Association between gastrointestinal adverse effects to metformin and SNP rs628031 and rs622342 in SLC22A1 gene using dominant model.

Genotype	Cases (N=100) Frequency (%)	Controls (N=200) Frequency (%)	Odds ratio OR (95%CI)	P value
rs628031				
GG	40 (40)	89 (44.5)	1.00	0.45*
AG-AA	60 (60)	111 (55.5)	1.2 (0.74, 1.96)	
rs622342				
AA	59 (59)	105 (52.5)	1.00	0.28*
AC-CC	41 (41)	95 (42.5)	0.77 (0.47, 1.25)	

*Test statistic: Chi- square test

DISCUSSION

In our study, no significant association was found between the genotypes of single nucleotide polymorphisms (rs628031 and rs622342) in SLC22A1 gene and gastrointestinal adverse effects to metformin therapy in South Indian Type 2 diabetes mellitus patients. The allele frequencies of the two single nucleotide polymorphisms did not vary significantly between the case and control groups (rs628031, p=0.91, rs622342, p=0.84). The apical uptake of metformin in the enterocytes is carried out by organic cationic transporters OCT1, OCT2 and OCT3, plasma monoamine transporter (PMAT), choline high affinity transporter (CHT) and serotonin reuptake transporter (SERT).[15] The OCTs are involved in absorption, distribution and excretion of the cationic drugs and belong the solute carrier (SLC) membrane transport proteins. OCT1, OCT2 and OCT3 are coded by the SLC22A1, SLC22A2 and SLC22A3 genes respectively. OCT1 and OCT3 are present in the intestine and their levels are lower when compared to those in kidneys or the liver.[16] The human OCT1 (hOCT1) is the major transporter in the hepatocytes whilst hOCT2 plays a major role in the kidneys.[17] SLC22A1 which encodes for OCT1 is located in chromosome 6q25.3 containing 11 exons and spans over 37 kb. Many polymorphisms in SLC22A1 have been described with varying frequency in different populations. Of the several polymorphisms reported in SLC22A1, rs628031 (Met408Val) located in Chr6: 160,139,813) is a missense variant in exon 7 and rs622342 located in Chr6: 160,151,834 is an intron variant between exons 8 and 9.[18] These SNPs result in reduced function OCT1 and have been studied for metformin response in several studies previously. The minor allele frequency (MAF) 'A' in rs628031 (33.8%) is similar to the allele frequency reported in the 1000 genome project in the South Asian population (39%) and to the frequency in Sri Lankan Telugu in UK (37.7%).[13] However, the MAF in our study differs from that (19.7%) reported by Umamaheswaran et al in healthy volunteers in South Indian Tamil population. They reported no 'AA' genotype in their study population. This could be due to the smaller sample size (N=112) in their study.[19]

Presence of 'A' allele in rs628031 had an OR of 0.389 (p=0.012) of developing adverse effects related to GI tract in a study conducted in Latvian population.[12] In contrast, our study found no association between the genotypes in rs628031 and gastrointestinal intolerance status in South Indian type 2 diabetes mellitus patients (p=0.45). The MAF 'C' in rs622342 (26.5%) in our study is in agreement with the MAF (24.5%) previously reported by Umamaheswaran et al in South Indian type 2 diabetes mellitus patients.[20] In our study, the commonest gastrointestinal symptom reported in the metformin intolerant group was heartburn (54%). Whereas, in previous studies, diarrhea was found to be the predominant GI ADR to metformin.[21,22] Among cases, 83% required dose reduction and 17% required discontinuation of metformin. The median age of participants in this study was significantly different between both groups (55 vs 50 years in controls and cases respectively, p=0.001) However, the mean age was much higher (58.9 vs. 63.8 years among controls and cases respectively) in the study by Tarasova et al.[12] Likewise, the mean age in the study by Dujic et al was higher (58 vs. 67.8 years among controls and cases respectively).[23] This difference could be because of the earlier onset of type 2 diabetes in Indians which could explain why our study population was of a younger age.[24] The body mass index was found to be statistically different between the two groups, with the case group having a relatively higher body mass index (p=0.03). Univariate logistic regression showed higher risk of GI intolerance in obese individuals whose BMI was greater than 30 (OR 3.1; 95% CI 1.40, 6.84, p=0.005). In a meta-analysis by Eusebi et al it was reported that increased obesity (OR 1.73; 95% CI 1.46 to 2.06) per se has a modest association with gastroesophageal reflux disease (GERD) and other risk factors include age ≥50 years, smoking and usage of NSAIDS.[25] However, when adjusted for other co-variates, this factor became insignificant. In contrast, Dujic et al reported lower body mass index as a phenotype of metformin intolerant patients in their study.[23]

Females were found to have an increased risk for development of gastrointestinal intolerance to metformin, which remained significant after adjusting for other variables, AOR 3.77; 95% CI 2.07, 6.85 (p<0.001). Female gender was noted to be a risk factor for metformin GI intolerance in a study by Dujic et al.[23] Possible explanation could be due to the delayed intestinal transit time in females when compared to males due to effects of progesterone.[26,27] Gut microbiome is also found to differ between the genders. This could also explain the gender-based differences in gastrointestinal intolerance to metformin.[28] Among the cases and controls, there was a significant difference in the current dose of metformin, the median dose of metformin in the control group was 2 g in comparison to a median dose of 1 g of metformin in cases. This could be explained by the dose dependent gastrointestinal adverse effects exerted by metformin in the intolerant group.

The concomitant drug usage also varied between both the groups. Proton pump inhibitor usage was found to have a higher association with metformin intolerance AOR 7.66; 95% CI 3.01, 19.47 (p<0.001). Although proton pump inhibitors are known to inhibit OCT1, they were also prescribed to patients in our study to alleviate symptoms such as heartburn which occurs due to metformin. In our study, the proton pump inhibitor most commonly used was omeprazole. Statins, ACE inhibitors and gabapentin usage was significantly higher in the control group compared to case group (p<0.001). Possible explanation could be that patients who tolerated metformin better, belonged to the control group which in turn had a longer median duration of diabetes meaning higher prevalence of complications of diabetes. A study by Hermans et al also reported higher statin usage in the metformin tolerant group due to a higher prevalence of coronary artery disease in the metformin

tolerant group.[29] Gabapentin was also included for multiple logistic regression as this drug has shown some benefit in functional dyspepsia.[30] However, when adjusted for other factors, gabapentin showed no statistical significance.

The strengths of our study include a large sample size (n=300) in comparison to previous studies in South Indian population that studied these specific polymorphisms, larger sample size allowed us to establish the allele frequencies of the SNPs in the South Indian population better, confounding factors such as older age (>65 years), alcoholism were avoided in our study by excluding patients who had history of same. Several comorbidities were considered in our study and interestingly, hypothyroidism, on univariate analysis showed an OR 2.19; 95% CI 1.05, 4.59 (p=0.03).

Hypothyroidism may per se cause slow intestinal motility and can explain some symptoms. However, our patients were on thyroxine replacement therapy and we did not assess the current thyroid function status of those patients. This prevents us from commenting on a possible risk of hypothyroid patients developing GI intolerance to metformin therapy. The main limitation of our study was lack of assessment of compliance to metformin using a robust method such as a validated questionnaire or by methods like pill counting. Future directions could include protein expression studies of OCT1 in order to assess the effect of various genotypes. Epigenetic studies and transporter variant studies of PMAT and SERT can be done in future to gain better insights into the role of these transporters in metformin intolerance.

CONCLUSION

In our study, we found no significant association between the genotypes of single nucleotide polymorphisms (rs628031 and rs622342) in the SLC22A1 gene and gastrointestinal adverse effects to metformin therapy in South Indian type 2 diabetes mellitus patients. Female gender was found to have a higher risk of developing metformin intolerance. Proton pump inhibitor usage was more in the metformin intolerant patients which possibly could be attributed to its use to alleviate gastrointestinal adverse effects in this group.

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