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Association of *OCT1* (rs628031) with COVID-19 Severity in Diabetic Individuals

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Abstract

Background: The surge in blood glucose levels in COVID-19 patients has been linked to worse outcomes, as hyperglycemia may aid SARS-CoV-2 entry. Acute hyperglycemia caused complications like kidney failure, liver dysfunction, and increased infection risk, especially in diabetic COVID-19 patients which was validated by deranged biochemical parameters. Metformin, an antidiabetic drug with anti-inflammatory properties, has been beneficial to COVID-19 patients. The organic cation transporter 1 (*OCT1*) polymorphism, rs628031, may influence metformin efficacy, but its role in severity of diabetic COVID-19 patients remains unclear. Thus, this study explored the link between *OCT1* (rs628031), biochemical markers, and COVID-19 severity in diabetic individuals.

Materials and Methods: We collected 50 diabetic COVID-19 patients' (RT-PCR confirmed) blood samples (17 mild, 33 severe) with their consent, from Era's Medical College and Hospital (ELMC&H), Lucknow. Biochemical analysis was performed at hospital lab services (HLS), ELMC&H, and results were noted from hospital records. Genotyping of *OCT1* (rs628031) was performed by PCR-RFLP and validated by Sanger sequencing followed by statistical analysis.

Results: Our study did not find any association between allele or genotype frequencies of *OCT1* rs628031 among mild and severe patients. Additionally, we found that patients with higher erythrocyte sedimentation rate (ESR) ($p = 0.011$) and blood urea ($p = 0.012$), as well as lower total protein ($p = 0.007$) and serum albumin ($p = 0.05$) levels were more prone to severity in diabetic COVID-19 patients.

Clinical Significance: Biomarkers not only help in early screening of disease and its severity but also aid in better patient management. Thus, some potent biomarkers must be discovered so that timely intervention may be provided and severity of infections like COVID-19 can be prevented

Conclusion: In conclusion, Erythrocyte Sedimentation Rate (ESR), blood urea, total protein, and serum albumin levels may serve as biomarkers for the severity of COVID-19 or related infections; however, further studies on larger cohorts may yield significant results.

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INTRODUCTION

Multiple fatalities have been attributed to COVID-19 ever since its outbreak in December, 2019.[1] Several studies have proved that diabetes served as a potent risk factor for developing COVID-19 infection and those who were diabetic were at a higher risk of reaching severity of the infection than non-diabetic or non-hyperglycemic COVID-19 patients.[2-4] Some pathways have been proposed to explain how hyperglycemia causes severity of COVID-19. First is the inflammatory cytokines storm that is accompanied by hyperglycemia which may lead to multiple organ failure.[5] Secondly, hyperglycemia leads to glycosylation of ACE2 receptor, which facilitates severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry into the host cell and causes the severity of the infection.[5] Lastly, dipeptidyl peptidase-4 (DPP-4), a major enzyme in glucose metabolism, may also anchor SARS-CoV-2.[6] Individuals with hyperglycemia had greater levels of DPP-4, which increases their risk of developing a severe COVID-19 infection.[7]

Metformin serves as the first-line treatment for diabetes and may have beneficial effects in COVID-19 patients owing to its anti-inflammatory properties.[8] Several studies revealed that metformin reduces the risk of both severity and mortality in COVID-19 patients either through AMPK pathway or inhibition of the m-TOR-mediated signaling pathway.[8,9] However, metformin action is greatly influenced by the variations in its transporter genes like organic cation transporter (*OCT*) genes.[10] OCT1 is the primary hepatic transporter of metformin and other cationic drugs encoded by solute carrier family 22 member 1 (*SLC22A1)* gene, also known as *OCT1* gene. This is a distinctly polymorphic gene and its single nucleotide polymorphisms have been largely attributed to T2DM susceptibility and response to metformin.[10,11] One of the most widely studied non-synonymous polymorphisms of *OCT1* gene is rs628031 (Met408Val, c.1222A) present on exon 7.[10] Shikata *et al.*,(2007) showed increased efficacy of metformin with this polymorphism whereas Tarasova *et al.* (2012) revealed that rs628031 was associated with metformin-related gastrointestinal side-effects.[12,13] Thus, different studies revealed variable outcomes concerning this polymorphism. To the best of our knowledge, no research has been found that links *OCT1* (rs628031) to the severity of COVID-19. Thus, the purpose of this study was to investigate the relationship between the severity of COVID-19 infection and the *OCT1* polymorphism rs628031 as well as clinical parameters.

MATERIALS AND METHODS

Subjects and Sample Collection

The Ethics Committee, Era University, India, gave its approval to this study. 50 RT-PCR-confirmed COVID-19 patients who were enrolled at Era University's Lucknow Medical College and Hospital (ELMC&H) were recruited. According to the standards established by the Indian Council of Medical Research (ICMR), New Delhi, India, the participants were split into two study groups, each consisting of mild and severe COVID-19 patients with diabetes mellitus. Severe patients with pneumonia had a respiratory rate of >30/min and a SpO_2 of less than 90% on room air, while mild patients had a respiratory rate of < 24/min and a SpO_2 of greater than 94%. 2 mL of venous blood was drawn with the participants' permission, placed in anticoagulant vials (EDTA vials), and kept at –20°C until needed. Following each patient's informed consent, a self-administered questionnaire was used to gather demographic information, and a qualified clinician assisted in gathering clinical information from hospital records. Individuals who met the inclusion criteria—RT-PCR-confirmed COVID-19 patients aged >20-years with diabetes as a comorbidity—and exclusion criteria—non-diabetic COVID-19 patients aged <20 years and >70-years—were chosen as participants.

Genotyping

For genotyping, polymerase chain reaction (PCR) was used followed by restriction fragment length polymorphism (RFLP). The PCR primers used were as follows: 5′-TTTCTTCAGTCTCTGACTCATGCC-3′ and 5′-AAAAAACTTTGTAGACAAAGGTAGCACC-3′, respectively with the following amplification conditions: An initial denaturation at 94°C (5 min), 32 denaturation cycles at 94°C (30 sec), annealing at 68°C (45 sec) and extension at 72°C (1 min) and final extension at 72°C (5 min). The amplified products of size 397bp were analyzed on 2% agarose gel in a Gel Documentation System (EZ, BioRad) and then subjected to restriction digestion using enzyme *MscI*, followed by incubation at 37°C for 1-hour. The digested products were then analyzed on 3% agarose gel wherein the 397bp product either showed retention of whole amplicon (GG condition) partial digestion resulting in three bands of sizes 397, 210, and 187bp corresponding to heterozygous condition (AG) or complete digestion with 2 resulting bands of 210 and 187bp suggestive of homozygous recessive condition (AA). These genotyping results were validated using Sanger sequencing.

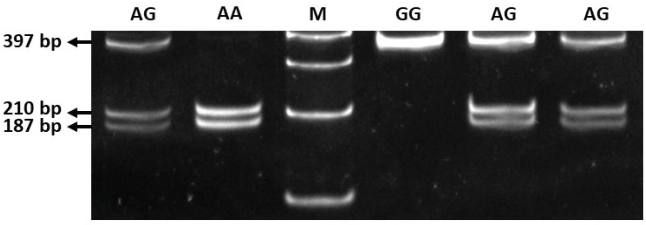

Figure 1: Agarose gel (3%) showing digested (RE= *MscI*) PCR products of *OCT1*(rs628031). [GG: 397bp; AG: 397bp, 210bp, 187bp; AA: 210bp, 187bp; M: DNA ladder (100bp)]

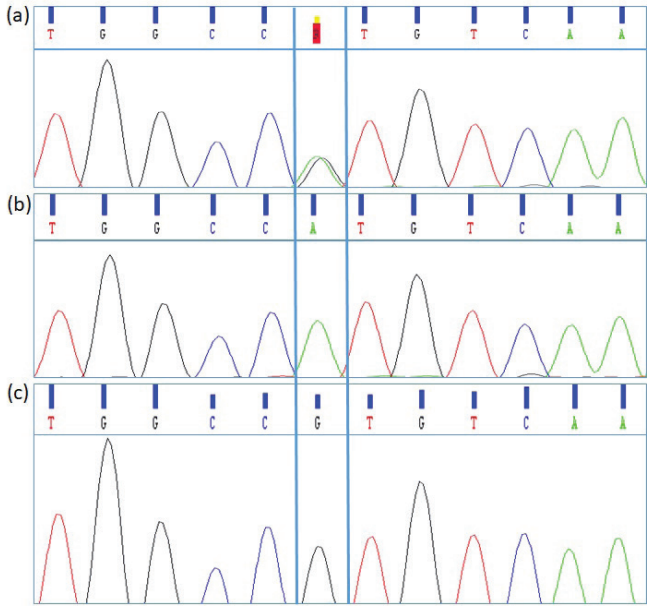

Figure 2: Electropherograms from Sanger sequencing runs of *OCT-1* polymorphism, rs628031. Figures show the following conditions: (a) Heterozygous (AG); (b) Homozygous wild type (AA); (c) Homozygous mutant (GG).

Statistical Analysis

SPSS software (version 21) was used to conduct the statistical analysis. The clinical and demographic details were compared using Fisher's exact test and χ2 analysis. Fisher's exact test was used to compare the genotype and allele frequencies of mild and severe patients using a 2x2 contingency table. *p*-values were considered statistically significant if they were less than or equal to 0.05.

Table 1. Analysis of demographic and clinical parameters of mild (*n* = 17) and severe (*n* = 33) diabetic COVID-19 patients.

Parameters	Mild (n = 17)	Severe (n = 33)	*p-value*
Age (Years)			
≤45	4 (23.5%)	4 (12.1%)	(1.0)Ref
>45	13 (76.5%)	29 (87.9)	0.751
Gender			
Male	11 (64.7%)	24 (72.7%)	(1.0) Ref
Female	6 (35.3%)	9 (27.3%)	0.567
HTN			
No	13 (76.5%)	18 (54.5%)	(1.0) Ref
Yes	4 (23.5%)	15 (45.5%)	0.136
Clinical Parameters			
Calcium/Serum Calcium (mg/dL)	8.4118 ± 0.6183	8.3030 ± 0.6366	0.566
Haemoglobin (g/dL)	12.29 ± 2.085	11.8 ± 2.455	0.499
WBC (cells/µL)	8223.5234 ± 2695.0254	10185.4978 ± 4343.5269	0.096
RBC (million/mm^3)	4.53 ± 0.624	4.12 ± 0.893	0.099
ESR (min)	83.38 ± 10.321	91.47 ± 9.883	**0.011***
Blood Urea (mg/dL)	41.06 ± 24.969	89.79 ± 74.859	**0.012***
Creatinine (mg/dL)	2.00 ± 2.449	2.76 ± 3.103	0.386
Na+ (mmol/L)	138.24 ± 4.070	137.76 ± 4.744	0.725
K+ (mmol/L)	4.24 ± 0.562	4.12 ± 0.781	0.596
Serum Bilirubin (Total) (mg/dL)	0.65 ± 0.702	0.0.53 ± 0.507	0.524
S.G.P.T./ALTV (U/L).	41.12 ± 23.563	49.94 ± 35.380	0.361
S.G.O.T./AST (U/L).	44.88 ± 19.974	61.19 ± 31.881	0.061
Serum Alkaline Phosphatase (IU/L)	110.88 ± 36.881	131.84 ± 70.824	0.261
Serum Albumin (g/dL)	3.71 ± 0.686	3.00 ± 0.559	**0.05***
Total Protein (g/dL)	7.00 ± 0.816	6.31 ± 0.780	**0.007***

CI = Confidence interval; OR = Odds ratio; 1.0 = Reference; *= significant *p-value* ($p \leq 0.05$)

RESULTS

General Characteristics and Clinical Parameters

A total of 50 diabetic COVID-19 patients were included in the study, of whom 17 were mild (11 males and 6 females) and 33 were severe (24 males and 9 females). The results that we obtained in comparing demographic and clinical parameters of mild and severe COVID-19 patients have been summarised in table 1. We found no significant association between parameters like age, gender, presence or absence of hypertension, serum calcium, haemoglobin, etc. ($p > 0.05$).

However, comparatively higher levels of blood urea ($p = 0.012$) and erythrocyte sedimentation rate (ESR) ($p = 0.011$), as well as slightly lower levels of total protein ($p = 0.007$) and serum albumin ($p = 0.05$) were significantly associated with severity of the infection in diabetic COVID-19 patients.

Association of OCT1 rs628031 with Severity of COVID-19 Infection

The distribution of *OCT1* rs628031 alleles and genotypes as well as the carriage rates of alleles in mild and severe COVID-19 patients having diabetes is shown in table 2. The frequencies of AA and GG genotypes were lower in mild patients than in severe patients as compared to AG genotype (AA: 17.6% vs 27.3%; GG: 17.6% vs 21.2%; AG: 64.7% vs 51.5%). Frequency of A allele was 32.7% and 67.3% whereas G allele frequency was 41.5% and 58.5% in mild and severe patients respectively ($p > 0.05$). We also analysed the carriage rates of alleles in mild and severe patients where the carriage rate of G allele was found to be greater in mild patients (82.4%) than in severe patients (72.7%). However, *OCT1* rs628031 polymorphism had no significant association with COVID-19 severity in diabetic COVID-19 patients (Table 2).

DISCUSSION

One of the main causes of morbidity and death in the world is diabetes. It has long been known that infectious diseases and diabetes are clinically related.[14] Infections are more common and more severe in older adults with type-2 diabetes (T2DM), particularly influenza and pneumonia.[15] Patients infected with various viruses, such as the 2009 pandemic influenza A (H1N1),[16] SARS-CoV,[17] and MERS-CoV, had diabetes and uncontrolled glycaemia as significant predictors of severity and mortality.[18] Studies conducted during the current SARS-CoV-2 pandemic have not conclusively linked diabetes to serious illness.[19] Diabetes patients who contract SARS-CoV-2 may experience elevated stress levels and a greater release of hyperglycaemic hormones, such as catecholamines and glucocorticoids, which raise blood glucose levels and cause abnormal glucose variability.[20]

National and international guidelines recommend metformin as the first-line treatment for diabetes mellitus, although there are other pharmacological interventions available as well.[21] Numerous genetic variations have been found to contribute to the variation in clinical response to

Table 2: Analysis of genotype, allele frequencies, and carriage rate of *OCT1* (rs628031) in mild (n=17) and severe (n=33) diabetic COVID-19 patients.

Genotypes	Mild, n(%) (n = 17)	Severe, n(%) (n = 33)	*p*-value	Unadjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)
AA	3 (0.176)	9(0.273)	1.0 (Ref)			
AG	11 (0.647)	17 (0515)	0.390	0.515 (0.114 - 2.334)	0.558	0.614(0.12 - 3.144)
GG	3 (0.176)	7 (0.212)	0.793	0.778 (0.119 - 5.1)	0.956	1.062(0.127 - 8.872)
Allele						
A*	17 (32.7%)	35 (67.3%)	1.0 (Ref)			
G*	17 (41.5%)	24 (58.5%)	0.384	0.686 (0.293-1.604)		
Carriage rate						
A+	14 (82.4%)	26 (78.8%)	1.0 (Ref)			
A-	3 (17.6%)	7 (21.2%)	0.766	1.256 (0.280-5.633)	0.241	5.106 (0.334-78.146)
G+	14 (82.4%)	24 (72.7%)	1.0 (Ref)			
G-	3 (17.6%)	9 (27.3%)	0.454	1.75 (0.405-7.562)	0.528	1.905 (0.257-14.112)

CI = Confidence interval; OR = Odds ratio; 1.0 = Reference; Allele*, Total number of alleles in mild = 34, severe patients = 66

metformin treatment for diabetes mellitus, thanks to recent developments in genome-wide association studies.[22] The literature has also documented a number of genetic variations of organic cation transporter1 (OCT1), some of which have been demonstrated to affect how well metformin treats diabetes mellitus.[23] Furthermore, little research has been done on how these SNPs individually and in combination affect Asian patients' glycaemic response to metformin treatment of DM. Recent studies have explored the possible role of *OCT1* gene polymorphisms on various drugs and disease phenotypes. Among these genetic variants is *OCT1* rs628031, which has important relevance in studies related to diseases such as T2DM, polycystic ovary syndrome (PCOS), and transport of drugs such as metformin and imatinib, etc., is shown.[13,24] A UK-based study performed on chronic myeloid leukemia (CML) patients suggested that the effect of rs35191146 (420del), which reduces imatinib uptake, was reversed if rs628031 (A allele) was also present (p <0.05).[24] Minor allele, i.e., A allele, of the same polymorphism showed metformin-related gastrointestinal side-effects, however, it did not affect its efficacy (p = 0.012; OR [95% CI] =.389 (0.186-0.815)).[13,24] Low levels of the transporter are suggestive of lower transport activity which may result in increased toxicity of the drug. Some anti-COVID-19 drugs such as ritonavir and remdesivir have been shown to inhibit OCT1 expression, which can lead to associated hepatotoxicity.[24] Similar results were observed in our study, all our subjects who were on remdesivir reached severity of the infection. This led to the conclusion that in accordance with the mentioned study our subjects may either have decreased expression of *OCT1* gene or it was inhibited by anti-COVID-19 drugs. The minor allele frequency of rs628031 was found to be 0.67 in a south Indian study which was similar to that in the Javanese population, i.e., 0.60.[26] In our study, we included 50 diabetic COVID-19 patients, out of which 17 were mild and 33 were severe. Among the carriers of A allele, 32.7% were mild and 67.3% were severe whereas 41.2% of patients having G allele were mild and 58.5% were severe. Thus, there was no significant difference in allele frequencies among the two groups (p = 0.384). Concerning genotype frequencies, AA genotype was present in 17.6% mild and 27.3% of severe patients, AG genotype was present in 64.7% mild and 51.5% severe patients whereas GG genotype was present in 17.6% mild and 21.2% severe patients. This suggested that heterozygous genotype (AG) was higher in mild patients than severe patients as compared to homozygous genotypes (AA and GG). However, these results were not statistically significant (p>0.05). In other study they found that minor allele of rs628031 (A allele) to be significantly associated with hypoglycemic events (p =0.046; OR [95% CI] =0.51 (0.26-0.99)) in T2DM.[27] Additionally, our study assessed the clinical features of individuals with severe COVID-19 and diabetes mellitus and discovered a correlation between mild COVID-19 and diabetes mellitus. Patients with severe COVID-19 and diabetes exhibited clinical signature patterns that were comparable to those of severe COVID-19 patients without diabetes, according to another study. The study's clear laboratory abnormalities included a decrease in lymphocytes and an increase in leukocytes and neutrophils in patients with severe COVID-19 and diabetes, as opposed to severe COVID-19 patients without diabetes. Additionally, we discovered that in diabetic COVID-19 patients, the severity of the infection was significantly correlated with higher blood urea (p =0.012), erythrocyte sedimentation rate (ESR) (p =0.011), and slightly lower levels of total protein (p = 0.007) and serum albumin (p = 0.05). We did not find any association between parameters like age, gender, presence or absence of hypertension, serum calcium, haemoglobin, etc. (p >0.05) with severe covid-19 patients with diabetes. Though we did not find a significant association between OCT1 rs628031, some clinical parameters included high

ESR (min) (p =0.011) and blood urea (p =0.012), and lower serum albumin (p =0.05) and total protein levels (p =0.007) showed significant association with COVID-19 severity. These findings were similar to those observed by Zhao *et al.,* (2020) where they found increased C-reactive protein (CRP), ESR, fibrinogen degradation products (FDP), and neutrophils as well as decreased levels of albumin, total protein, lymphocytes, and SOD in severe COVID-19 patients (p <0.05).[28] Hypoalbuminemia or low serum albumin has been associated with terminally ill patients and mortality in several studies.[29] Our results were in accordance with previous studies that suggested low levels of serum albumin increased the risk of COVID-19 severity (p <0.05).[30] These findings can be further justified by studies on larger cohorts involving multiple centres.

CONCLUSION

Our study suggests that OCT1 polymorphisms may have a possible role in COVID-19 severity, however, studies on larger cohorts and involving multiple centres are required to justify the same. In addition, increased ESR (min) and blood urea, and decreased serum albumin and total protein levels may prove to be significant biomarkers for the severity of COVID-19 and similar infections.

CLINICAL SIGNIFICANCE

Studying the implications of genetic polymorphisms in COVID-19 and similar infections may provide biomarkers for disease severity and aid in tailoring treatment plans based on the genetic makeup. Thus, better disease management could be achieved at an early stage with cost-effective and more potent interventions.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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