Full Length Research Article

The relationship between the single-nucleotide polymorphisms rs1978124 and rs2074192 of the ACE2 gene in individuals with type 2 diabetes infected with COVID-19

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ABSTRACT

Background: Understanding of the complexity and importance of ACE2 gene from the perspective of two genotypes (rs1978124 and rs2074192) and their role in pancreatic deterioration is gaining prominence these days. The ACE2 role is considered important in characterizing different factors when diabetic patients interact with viruses like SARS-CoV-2.

Methods: Blood samples were collected from 120 participants and divided into three groups for a cross- sectional and observational study. The first group was admitted to the COVID-19 isolation wards, and 40 of them were infected with the SARS- CoV-2 virus. Most of them had diabetes, while the other groups included 40 patients with diabetes only, and 40 control samples. The test was performed using ARMS-PCR technology.

Result: The results showed differences in ACE2 genotype and allele frequencies among the study groups, with a statistically significant association observed only for the T allele of rs2074192 in COVID-19 patients with diabetes compared with healthy controls. When investigating rs2074192 genotype in COVID-19 patients with diabetes compared with diabetes- only patients, C/T (OR = 1.458) and TT (OR = 1.167) showed OR values above 1, but these findings were not statistically significant.

Conclusion: After the virus binds to the ACE2 receptor of pancreatic cells, it results in the destruction of beta cells and an increase in the rate of pancreatic fibrosis due to a decrease in blood flow in the blood vessels, and a decrease in insulin secretion, which leads to diabetes.

INTRODUCTION

Humans are readily infected by coronaviruses, with mild to severe respiratory infections [1]. This infection and spread were characterized by close personal contacts, such as direct contact with infected people or objects, and through droplet transmission during coughing and sneezing [2]. SARS- CoV-2 interacts with angiotensin- converting enzyme 2 (ACE2) receptor and opens a pathway for viral attachment and entry into the host cell. [3]. ACE2 receptor was highly and extensively expressed in organs with abundant capillaries, such as the lungs, which explains the strength and supremacy of the respiratory symptoms of COVID-19 [4].

The surface trimeric spike (S) glycoprotein of COVID-19 binds to the human cell receptor ACE2 and allows its entry to the host cell [5]. The binding mechanism involves S1 distal subunit's ability of identifying and connecting to its target, whereas fusion entry into the cell membrane of host is the characteristic of S2 subunit [6].

After COVID-19 enters the cytoplasm of the cell, it is activated and controls events in the cell's own cellular transcription mechanism to multiply. It was a particularly potent virus compared to previous hCoV pathogenic viruses.

ACE2 receptor’s comprehensive tissue expression gives rise to pulmonary and extra-pulmonary signs of viral infection in organs such as the heart, kidneys, and pancreas [7].

Genetic variations such as single-nucleotide polymorphisms (SNPs) are most common in the human genome. The total number of reported SNPs in the SNP databases can be estimated to be approximately 9 million, of which two SNPs studied here are rs1978124 and rs2074192. SNPs are important markers for many disease studies as they are associated with sequence changes of the phenotype.

There are active sites present in ACE2 gene that shut down when a molecular binding is detected [8]. Increased heritability is also found in the protein and gene of ACE2 [9]. The surface of the ACE2 receptor contains residues of histidine, glutamine, aspartate, glutamate, lysine, and tyrosine that provide a large and sufficient amount to increase interaction opportunities with RBD elevation protein variants [10].

The extent of viral infection is determined by the coronavirus’s spike (S) protein, which promotes entry of the virus into host cells by causing a direct fusion reaction involving the plasma membrane of the virus and the host cell membrane [7, 11]. The essential route was activated by the synergetic action of receptors with ACE2 [12]. Entry of membrane- encapsulated glycoproteins into endoplasmic reticulum or Golgi, the nucleocapsid is made from a mixture of genomic RNA, protein, and nucleocapsid [13].

ACE2 mRNA is expressed in numerous human organs, namely the pancreas, small intestine, heart, and kidney [7]. ACE2 behaves similarly to both variants of coronavirus (SARS- CoV and SARS- CoV-2) [14]. The ACE2 receptor in the second variant consists of a single metallopeptidase domain [15]. At the position Xp22.2 on the X chromosome, the ACE2 gene polymorphism rs1978124 SNP and rs2074192 were located within a region of 39.98 kb of genomic DNA (Genbank, NT 011757). Previous studies explained that ACE2 rs1978124 SNP was coupled with the severity of COVID-19 [16].

A recent study indicated that high concentrations of ACE2 increased susceptibility to COVID-19, along with increased occurrence and death rates [17]. Genotyping SNP markers are SNPs rs1978124 (gene region / Intron 1) and rs2074192 (gene region / Intron 16) [18].

In many different population studies, polymorphisms of ACE2 were associated with diabetes mellitus. Also, in another study reported, SNPs, rs1978124 and rs2074192, had a close association with T2D *[19]*. Possible ACE2 polymorphism is effective in controlling the virus's passage into the host cells by affecting its S1 protein interaction.

The rate of mutation is 100 - 10,000 times in RNA viruses, higher than that of DNA viruses. A process related to high mutation rate was highlighted as correlated with viral evolution related to lethal mutations [20].

By working on angiotensin receptor type 2 AT1R and AT2R, Ang2 plays a central role in RAS. The role of RAS in tissues is mainly to regulate the vasculature of the vehicle and inflammatory processes, including vascular permeability, and programmed cell death [21].

ACE2 is an enzyme that regulates its receptor / Ang (1-7). Homologous to ACE2 is ACE, and about 42% of it contributes in ACE's balancing. Ang2 forms to Ang (1-7) after which Ang1 becomes Ang (1-9), while ACE essentially inactivates Ang1 [22].

ACE2 is predominantly expressed in pancreatic islets and exterior endocrine tissues, suggesting that SARS-CoV-2 may significantly infect the pancreatic islets and alter glucose metabolism [23]. The research conducted by Yang *et al.* (2020) demonstrated a permitted SARS-CoV-2 entry into human alpha and beta cells affecting pancreas [24].

While the cytotoxic response of the immune system might not successfully eradicate the COVID-19 virus, it can lead to substantial organ tissue and healthy cell harm. It has been shown that SARS-CoV-2 infection induces inflammation of vascular endothelium of multiple organs through direct and indirect effects [25].

This type was one of the most common, about 90-95% of all cases of diabetes. It occurs due to the death of glucose captured in the patient's body as a result of insulin resistance or insulin deficiency [26]. Symptoms were similar to those of type 1 diabetes, but were less pronounced [27]. Approximately 422 million individuals globally are afflicted with diabetes, resulting in 1.5 million fatalities annually directly linked to the condition [28].

METHODS

The collection of samples of people infected with the SARS-CoV-2 virus started from the first day of January 2022 until the end of April 2022. Case–control study was conducted on 120 participants, who were divided into three groups. The age of these groups of participants was 18-75 years. SARS-CoV-2 infection was found in 40 patients with type 2 diabetes mellitus, 40 patients with diabetes alone who had no prior history of SARS-CoV-2 infection, and 40 healthy controls. The diagnostic method, ARMS PCR, was used.

Sample and research population

Patients with severe cases were collected from the designated center in Al-Diwaniyah Teaching Hospital, during the period (first - January - 2022 to the end of April - 2022).

Sample Collection

Venous blood samples of 3 mL were collected from each participant, including control groups, into a tube of anticoagulant (K3-EDTA). Then, the drawn blood sample was stored at -20°C.

Patient exclusion criteria

The study excluded patients under 18 years of age with other chronic diseases, such as high blood pressure and respiratory diseases, and patients who were treated with long-term oral corticosteroids. In addition, people vaccinated with the COVID-19 vaccines were also excluded.

Statistical analysis

Data was analyzed using Microsoft Office Excel 2010 and SPSS version 23, respectively. Statistical analysis was performed by various tests according to distribution pattern of the data. For data of a normally distributed continuous variable, an independent-samples t-test was used to compare the means of two groups, and one-way ANOVA was used for the comparison of means from more than two groups. Chi-square test conclusions were based on the following P-value criteria: not significant (NS) for $P > 0.05$, significant for $P \leq 0.05$, and highly significant (HS) for $P \leq 0.001$. If they were non-parametric, the Kruskal-Wallis test, in contrast, was employed to analyze differences in mean rank between any number of groups [29].

RESULTS

DNA Extraction

The gSYAN DNA extraction kit enabled researchers to isolate genomic DNA from blood samples before they determined DNA purity using a Nanodrop spectrophotometer at a wavelength of 260/280 nm.

Genotypic and Allelic Analysis for the studied gene in COVID-19 patients with diabetes and patients with only diabetes

No significant difference was noticed in the ACE2 (rs1978124) SNP genotypes and allele frequencies amongst the COVID-19 with diabetes and diabetes only cases (Table 1). Under the regime of co-dominance, the distribution of genotypes did not differ significantly among groups (p = 0.904). Risk analysis tried out showed that neither the homozygous TT genotype (OR = 0.821) nor the heterozygous C/T genotype (OR = 0.811) were risk elements.

Genotypic and Allelic Analysis for the studied gene in COVID-19 patients with diabetes and healthy controls

Comparative outcomes of ACE2 (rs1978124) SNP genotypes and allele distribution among diabetic COVID-19 patients and healthy controls displayed no dissimilarities (Table 2). At the co-dominant model, genotype distribution did not differ between groups (p = 0.229). The risk analysis revealed that neither the homozygous TT genotypes (OR = 0.626) nor the heterozygous C/T genotypes (OR = 0.397) are risk factors.

Genotypic and Allelic Analysis for the studied gene in COVID-19 patients with diabetes and only diabetes

Under the co-dominant model, comparison of ACE2 (rs2074192) SNP genotypes and allele frequencies revealed no significant distribution differences between diabetic patients and diabetic COVID-19 patients (Table 3). Risk assessment showed that heterozygous C/T (OR = 1.458) and homozygous TT (OR = 1.167) had OR values above 1, but these findings were not statistically significant.

Genotypic and Allelic Analysis for the studied gene in COVID-19 patients with diabetes and healthy controls

Comparison of genotypes and allele frequencies related to the ACE2 (rs2074192) SNP between diabetic COVID-19 patients and healthy controls is shown in Table 4. The difference is not significant in the frequency distribution of genotypes between COVID-19 patients with diabetes and healthy controls, with OR = 2.7 for TT and OR = 1.25 for C/T. Risk analysis revealed that TT and C/T genotypes were not significant risk factors, and the recessive TT comparison showed OR = 2.455 but remained not statistically significant. Whereas allele T was significant (p = 0.026) and (OR = 2.029).

Tables

Mode	ACE2 (rs1978124)	COVID-19 with diabetics *n* = 40	Diabetics patients *n* = 40	*P*	OR	95% CI
Co-dominant	TT	9 (22.5%)	10 (25.0 %)	0.904	0.821	0.28-2.41
	C/T	8 (20.0%)	9 (22.5 %)	¥	0.811	0.26 -2.49
	CC	23 (57.5 %)	21 (52.5 %)	NS	Reference	
Dominant	TT+C/T	17 (42.5 %)	19 (47.5 %)	0.653	Reference	
	CC	23 (57.5 %)	21 (52.5 %)	¥ NS	1.22	0.51 -2.95
Recessive	TT	9 (22.5%)	10 (25.0 %)	0.792 ¥	0.871	0.31 -2.44
	C/T+CC	31 (77.5%)	30 (75.0 %)	NS	Reference	
Alleles	T	26 (32.5%)	29 (36.3 %)	0.617	0.846	0.44 -1.62
	C	54 (67.5 %)	51 (63.7 %)	¥ NS	Reference	

Table 1: Patient Genotype Frequencies for COVID-19 Patients with Diabetes and Diabetes only Patients.

Mode	ACE2 (rs1978124)	COVID-19 with diabetics *n* = 40	Control *n* = 40	*P*	OR	95% CI
Co-dominant	TT	9 (22.5%)	10 (25.0 %)	0.229	0.626	0.27-1.88
	C/T	8 (20.0%)	14 (35.0 %)	¥	0.397	0.14 -1.16
	CC	23 (57.5 %)	16 (40.0 %)	NS	Reference	
Dominant	TT+C/T	17 (42.5 %)	24 (60.0 %)	0.117	Reference	
	CC	23 (57.5 %)	16 (40.0 %)	¥ NS	2.09	0.83 -4.9
Recessive	TT	9 (22.5%)	10 (25.0 %)	0.792 ¥	0.871	0.31 -2.44
	C/T+CC	31 (77.5%)	30 (75.0 %)	NS	Reference	
Alleles	T	26 (32.5%)	34 (42.5 %)	0.191	0.651	0.34 -1.24
	C	54 (67.5 %)	46 (57.5 %)	¥ NS	Reference	

Table 2: Comparison of Genotype Frequencies Between Diabetic COVID-19 Patients and Healthy Controls.

Mode	ACE2 (rs2074192)	COVID-19 with diabetics *n* = 40	Diabetics patients *n* = 40	*P*	OR	95% CI
Co-dominant	TT	18 (45.0%)	18 (45.0%)	0.829	1.167	0.427-3.20
	C/T	10 (25.0%)	8 (20.0 %)	¥	1.458	0.435 -4.88
	CC	12 (30.0 %)	14 (35.0 %)	NS	Reference	
Dominant	TT+C/T	28 (70.0 %)	26 (65.0 %)	0.633	Reference	
	CC	12 (30.0 %)	14 (35.0 %)	¥ NS	0.795	0.311 -2.03
Recessive	TT	18 (45.0%)	18 (45.0%)	1.000 ¥ NS	1.0	0.414 -2.41
	C/T+CC	22 (55.0%)	22 (55.0%)		Reference	
Alleles	T	46 (57.5%)	44 (55.0 %)	0.749	1.107	0.592-2.06
	C	34 (42.5 %)	36 (45.0 %)	¥ NS	Reference	

Table 3: ACE2 rs2074192 Polymorphism genotype frequency in COVID-19 patients with diabetes and only diabetic patients.

Mode	ACE2 (rs2074192)	COVID-19 with diabetics *n* = 40	Control *n* = 40	*P*	OR	95% CI
Co-dominant	TT	18 (45.0%)	10 (25.0 %)	0.160	2.7	0.93-7.82
	C/T	10 (25.0%)	12 (30.0 %)	¥	1.25	0.41 -3.80
	CC	12 (30.0 %)	18 (45.0%)	NS	Reference	
Dominant	TT+C/T	28 (70.0 %)	22 (60.0 %)	0.166	Reference	
	CC	12 (30.0 %)	18 (45.0%)	¥ NS	0.523	0.208 -1.31
Recessive	TT	18 (45.0%)	10 (25.0 %)	0.060 ¥	2.455	0.95 -6.33
	C/T+CC	22 (55.0%)	30 (75.0 %)	NS	Reference	
Alleles	T	46 (57.5%)	32 (40.0 %)	0.026	2.029	1.08 -3.80
	C	34 (42.5 %)	48 (60.0 %)	¥ S	Reference	

Table 4: ACE2 rs2074192 Polymorphism genotype frequency in COVID-19 patients with diabetes and healthy controls.

DISCUSSION

The ACE2 SNPs rs1978124 and rs2074192 were evaluated for their possible link to COVID-19 infection in individuals with type 2 diabetes. This finding is consistent with Acharya (2020), which showed the linkage relationship of ACE2 SNP rs1978124 and rs2074192 with T2D [30].

According to this study, ACE2 polymorphism may have a role in type 2 diabetes in COVID-19 patients. Genetic variation can be explained as a permanent change in the genetic structure due to mutations and recombination in DNA mutations called single- nucleotide polymorphisms (SNPs) through insertions, deletions, copies, and permutations, Models were also displayed by Yan *et al.* (2022), who revealed that these SNPs and COVID-19 are closely related [31]. The current study is consistent with the reported association of Miriam *et al.* (2020) [32]. Genetic variation is passed on to daughter cells during cell division. Acquired mutations may occur due to environmental factors or infection with a virus and are not inherited from the parents. Variation in allele frequency across populations around the world indicates several common genetic variants of established functional significance. These distinctions can be used to identify population differences in the spread of COVID-19 as well as in the clinical characteristics of the progression of this disease.

The expression level of genes essential for establishing vulnerability to SARS-CoV-2 is impacted through genetic modification. Among the evidence is the extent of the effect of infection with the virus and its relationship to the pancreatic damage. According to Ma *et al.* (2022), diabetes elevated the expression of ACE2, and this would facilitate infection with COVID-19 and the occurrence of its complications [33]. A study by Pal *et al.* (2020), which is identical to the current study, found that the ACE2 mRNA expression in many human tissues, including the pancreas, is higher than in the lungs [34]. Evidence is consistent with Pal (2020) that increased ACE2 expression leads to increased SARS infection and inflammation, which leads to an increase in the chance of contracting COVID-19 and the occurrence of its complications [35]. Angiotensin-converting enzyme 2 receptors that are more prevalent make it easier for viruses to enter cells, which raises the risk of infection. This indicates the strong association between this SNP and

diabetes mellitus due to SARS- CoV-2 infection. ACE2 rs1978124 Polymorphism genotype frequency in COVID-19 patients with diabetes and diabetes only patients, the current association study relates this ACE2 SNP to diabetes mellitus. In ACE2 rs1978124 genotype frequency polymorphism in diabetic patients and diabetic COVID-19 patients, results indicate CC genotypes OR = 1.22. The results did not agree with Al Ghatrif *et al.* (2021) that homozygous genotypes of TT were dominant [36].

This suggests a possible association between the SNP and diabetes in the context of SARS-CoV-2 infection, in line with previous reports on ACE2-SNP links with diabetes mellitus.

When compared to ACE2 rs1978124 polymorphism genotype frequency in diabetic patients with COVID-19 and healthy controls, diabetic patients and COVID-19 healthy controls showed a non-significant increase in CC genotype frequency (OR = 2.09). According to Faridzadeh *et al.* (2022), the risk factor for SARS- CoV-2 infection in people with diabetes is that their mortality rate increases when severe symptoms occur [37]. Increased oxidative stress and consumption in diabetes (DM) is caused by endothelial damage caused by high concentrations of Ang II [38]. The risk of contracting the virus increases with high blood sugar. In addition, this accelerates progress to multiple organ failure and septic shock [39].

Genotypic and allelic investigation of ACE2 (rs2074192) in individuals with COVID-19 and type 2 diabetes mellitus compared to diabetic people without COVID-19 indicated that both C/T and TT genotypes had OR values above 1, although these findings were not statistically significant. These genetic variants may also worsen diabetes disease progression by accelerating pancreatic β-cell demise [40].

As for the results of the comparison between diabetic patients and the control group, there was no significant difference in the frequency distribution of genotypes among diabetic patients. The homozygous TT genotype showed OR = 2.455, but this result was not statistically significant, while the other genotypes also showed no significant effect. This may suggest a possible association of the TT genotype with susceptibility to infection; however, this comparison did not reach statistical significance in the present study. ACE2 SNPs are associated with diabetes mellitus (DM) in the contemporary study.

rs1978124 and rs2074192 are the most widespread genetic variants of SARS- CoV-2 in individuals with DM [41]. This is consistent with previous work showing the linkage relationship of ACE2 SNP rs1978124 and rs2074192 with T2D [42].

Through the action of virus spike proteins, the viral entry into human cells occurs by unlocking the ACE2 receptor. The ACE2 membrane is bound by these spikes, allowing the virus to enter the human cell. ACE2 and spike proteins have a strong affinity.

The associated genetic variations found in patients with diabetes mellitus may be related to COVID-19 susceptibility. In this study, homozygous TT genotypes at the ACE2 SNPs rs1978124 and rs2074192 were evaluated, but not all comparisons were statistically significant. These genetic polymorphisms may be useful candidates for further investigation in assessing susceptibility to SARS- CoV-2 infection. Higher expression, polymorphisms, mutations, and deletions of several genes are linked to COVID-19 risk, severity, and clinical implications. Early treatment and prevention are important for people with genetic predispositions. For the development, prevention, and treatment of identifying people who are vulnerable to severe forms of COVID-19, it is crucial to comprehend the RAS system and, in particular, the function that ACE2 plays in the pathogenesis.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

AUTHOR CONTRIBUTIONS

Ghaleb Hussein Obaid Al-Saeedi: Patient sample collection, laboratory testing, and manuscript preparation. Wisam Salih Abood: Study supervision, Data analysis, Data interpretation, feedback, and editing. Both authors revised, edited, and approved the final version of the manuscript for submission.

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ETHICS STATEMENT

The collection of blood samples to conduct the study from patients in the isolation wards designated for accepting COVID-19 patients at Al-Diwaniyah Teaching Hospital was consented with respective individuals and approval was also obtained from the Institutional Ethics Committee / Health Authority.

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