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Assessment of ACE1 variants and ACE1/ACE2 expression in COVID-19 patients

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Contribution of the renin-angiotensinogen system in the risk of COVID-19 and related complications have been assessed by several groups. However, the results are not consistent. We examined levels of ACE1 and ACE2 in the circulation of two groups of COVID-19 patients (ICU-admitted and general ward-admitted patients) compared with healthy controls. We also genotyped two polymorphisms in ACE1 gene (the ACE1 I/D polymorphism rs1799752 and rs4359) to appraise their association with expression levels of ACE1 and ACE2. Expression level of ACE1 was significantly higher in ICU patients compared with non-ICU patients (P value = 0.02). However, its expression was not significantly different between total COVID-19 patients and total controls (P value = 0.34). ACE2 expression was not different either between two groups of COVID-19 patients (P value = 0.12) or between total COVID-19 patients and total controls (P value = 0.79). While distribution of rs1799752 and rs4359 alleles was similar between study groups, genotype frequencies of rs1799752 were differently distributed among total COVID-19 patients and controls (P value = 0.00001). Moreover, genotypes of the other polymorphism tended to be distinctly distributed among these two groups (P value = 0.06). In the total population of patients and controls, different ACE1 mRNA levels were observed among carriers of different rs1799752 genotypes; of note, ID genotype carriers showed a higher expression of ACE1 compared with II genotype carriers (P = 0.01). ACE1 polymorphisms might affect risk of COVID-19 and expression of ACE transcripts.

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as a global health problem since late 2019. This disorder has been associated with abnormal immune responses in some patients. Adult stem cells which have immunomodulatory and pro-reparative activities in the local environment [1,2], might be used as modulators of these response. Several research groups have aimed at identification of the underlying mechanism of susceptibility to this infection and development of severe forms of COVID-19 pointing to changes in the expression of certain genes or the presence of polymorphisms in genes mediating virus entry to target cells. Angiotensin-converting enzyme (ACE2) as the gene encoding the specific receptor of the SARS-CoV-2 has been at the center of attention. Expression level of ACE2 in the epithelial cells have been suggested as a factor for increasing susceptibility to COVID-19 [3]. Others have linked the lower risk of COVID-19 among children to the decreased levels of ACE2 receptor in them compared with adults [4].

Meanwhile, the presence of polymorphisms in renin-angiotensin system has been associated with risk of COVID-19 and disease course. For instance, ACE1-insertion/deletion (I/D) polymorphism has been shown to be strongly associated with COVID-19. Carriers of DD genotype have exhibited higher ACE1 levels and higher risk for development of acute respiratory distress syndrome and mortality [5,6]. In fact, D allele...
of this polymorphism has been found to be associated with progression of COVID-19 [7] and mortality rate from this infection [6].

Evidence suggests that SARS-CoV-2 interferes with normal balance of ACE1/ACE2 and induces the angiotensin II (Ang II)/Angiотensin II type 1 receptor (AT1R) pathway, resulting in severe COVID-19 consequences [8]. In addition, down-regulation of ACE2 and the imbalance between the renin-angiotensin system and ACE2/angiotensin-1-7/MAS following COVID-19 infection has been proposed to participate in the pathogenesis of multiple organ damage in this disorder [9].

In this study, we examined levels of ACE1 and ACE2 in the circulation of two groups of COVID-19 patients (ICU-admitted and general ward-admitted patients) compared with healthy controls. Moreover, we genotyped two polymorphisms in ACE1 gene (the ACE1-I/D polymorphism rs1799752 and rs4359) to appraise their association with expression levels of ACE1 and ACE2.

2. Material and methods

2.1. Cases and controls

The present genotyping and expression assay project was performed on 91 COVID-19 cases admitted to Nikan Hospital, Tehran, during 2020. COVID-19 was confirmed in all cases through RT-PCR method on nasopharyngeal swab samples. In addition, 91 control specimens were obtained from unaffected individuals without history of exposure to COVID-19 [7] and mortality rate from this infection [6].

2.2. Genotyping

Tetra-primer amplification-refractory mutation system-PCR method was used for identification of rs4359 genotypes according to our former research [10]. Primers were designed using Primer1 software. The sequences of primers were as follow: Forward inner primer (T allele): GGGTCAAGACAGAACTGGGTTCAATCT, Reverse inner primer (C allele): TCTCTGTTACCTGACCTTGGTTAA and Reverse outer primer: TGGCTAATGGTTACCTGACCTTGGTTAA. Second round of PCR was performed using TGTAAGCCACTGCTGGAGAG and TGGCCATCA GACGTGGCCATCACATTCGTCAGAT. Reverse outer primer: TAGAGAGTGTAGATGTTGGTGGTGTCCTG. Annealing step was set at 62 °C.

Two rounds of PCR and electrophoresis were used for genotyping of the rs1799752 (I/D) polymorphism. First round of PCR was accomplished with the following primers: TGGAGAGCCACTCCATCCTCTCT and GACGTGGCCATCACATTCGTCAGAT. Second round of PCR was performed using TGTAAGCCACTGCTGGAGAG and TGGCCATCA GACGTGGCCATCACATTCGTCAGAT as forward and reverse primers, respectively. The PCR program consisted an initial denaturing phase at 95 °C for 5 min; 35 cycles at 95 °C for 30 s, specific annealing temperature for 30 s and extension at 72 °C for 60 s. Finally, microtubes were incubated at 72 °C for 5 min. Genotyping results with confirmed with Sanger sequencing of a number of samples.

2.3. Expression assays

Blood samples were collected from COVID-19 patients and healthy controls in EDTA-containing tubes. Total RNA was extracted from all samples using GeneAll RNA extraction kit (Seoul, South Korea). Then, RNA was converted to complementary DNA using the BioFact™ kit (Seoul, South Korea). Levels of ACE1 and ACE2 genes were quantified in all samples in relation with expression of B2M gene. The RealQ Plus 2x Master Mix (Amplicon, Denmark) was used for preparation of reactions. Table 1 demonstrates the information about primers sequences and amplicons.

Table 1

| Gene | Primer sequence | Primer | Product size |
|------|----------------|--------|-------------|
| ACE1 | Forward primer | ACGTGAGGATACAGCAAAGGC | 20 | 75 |
| | Reverse primer | AGAGTTCCTGATGGCCTGTTG | 20 |
| ACE2 | Forward primer | ATCTACTCCAAGGCAAAGGT | 20 | 187 |
| | Reverse primer | TGCTGAGGGTGAAATACTCC | 20 |
| B2M | Forward primer | AGATGAGATGTGCCGCGCTG | 20 | 105 |
| | Reverse primer | GGGGATCTCTAAACACTCTCA | 20 |

2.4. Statistical methods

The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL) and SNP Analyzer 2.0 were used for statistical assessments. Graphics were created using GraphPad Prism version 9.0 for Windows (La Jolla California, USA). Expressions of ACE1 and ACE2 genes in each sample were calculated using the Efficiency adjusted Ct of normalizer gene (B2M) - Efficiency adjusted Ct of target genes (comparative –delta Ct method). Student t-test was used to compare expression levels of ACE1 and ACE2 between groups of COVID-19 patients vs. controls, and ICU patients vs. non-ICU patients. Mann Whitney’s U test or student t-test was used to compare laboratory data between subgroups of COVID-19 patient (ICU patients vs. non-ICU patients).

Allele and genotype frequencies were compared between groups by the chi-squared test. Relative risk (odds ratio (OR)) for effect alleles and genotypes was calculated by logistic regression. Adjusted relative risks were calculated considering gender and age as covariates. Associations between genomic variants and COVID-19 risk were assessed in codominant, dominant, recessive and over-dominant models. The results of association analysis were described as OR and 95% confidence interval of OR (95% CI), P-value and FDR adjusted q-values. The FDR adjusted q-values were calculated through analyzing a stack of p values in column analyses by GraphPad Prism version 9.0. P-values less than 0.05 were considered as statistically significant. Estimation of accuracy of genotype distributions with Hardy–Weinberg equilibrium, haplotype estimation, linkage disequilibrium (LD) blocking and were performed in SNP Analyzer 2.0.

The correlation of ACE2 and ACE1 expression levels with age, complete blood cells, ESR and CRP were analyzed using nonparametric spearman correlation test.

3. Results

3.1. General data of patients

First, we compared general laboratory data of ICU-admitted and general ward-admitted patients. This comparison showed higher levels of ESR and CRP in ICU-admitted group (P values = 0.011 and 0.000001, respectively). Moreover, ICU-admitted patients had lower lymphocyte count while higher neutrophil count (P values = 0.00492 and 0.000086, respectively) (Table 2).

3.2. Genotyping and expression assays

Expression level of ACE1 was significantly higher in ICU patients compared with non-ICU patients (P value = 0.02). However, its expression was not significantly different between total COVID-19 patients and total controls (P value = 0.34). ACE2 expression was not different ether between two groups of COVID-19 patients (P value = 0.12) or between total COVID-19 patients and total controls (P value =
3.3. Association between ACE1 genotypes and ACE1 and ACE2 expressions

The ACE1 rs1799752 polymorphism was associated with a high risk of COVID-19 in dominant and co-dominant models (Fig. 3). In the dominant model, the presence of at least one mutated (−) allele was tested against the homozygous wildtype genotype (wt/wt). The ACE1 rs1799752 polymorphism showed a significant protective effect against COVID-19 risk in over-dominant model. The total population of patients and controls, different ACE1 mRNA levels were observed among carriers of different rs1799752 genotypes; of note, ID genotype carriers showed a higher expression of ACE1 compared with II genotype carriers (P = 0.01).

ACE2 expression was significantly higher in ID genotype carriers than the II genotype carriers in total population. In fact, increase in ACE1 expression was associated with increase in the ACE2 expression in ID genotype carriers (Fig. 4).

The ACE1 rs4359 polymorphism was associated with a higher risk of COVID-19 in dominant and co-dominant models. The ACE1 rs4359 polymorphism showed a significant protective effect against the risk for COVID-19 in over-dominant model. However, in contrast to the rs1799752 genotypes, there was no significant difference in the ACE1 expression level between carriers of different rs4359 genotypes in the total population of patients and controls (Fig. 5).

There was no significant difference in ACE2 expression level among the rs4359 genotype carriers which was consistent with ACE1 expression levels among the rs4359 genotype carriers (Fig. 6).

There was no significant difference in distribution of rs4359 and rs1799752 variants between COVID-19 cases and control in allelic model.

Then, we appraised association between estimated haplotypes and COVID-19 risk in over-dominant model. In the total population of patients and controls, different ACE1 mRNA levels were observed among carriers of different rs1799752 genotypes; of note, ID genotype carriers showed a higher expression of ACE1 compared with II genotype carriers (P = 0.01).

ACE2 expression was significantly higher in ID genotype carriers than the II genotype carriers in total population. In fact, increase in ACE1 expression was associated with increase in the ACE2 expression in ID genotype carriers (Fig. 4).

The ACE1 rs4359 polymorphism was associated with a higher risk of COVID-19 in dominant and co-dominant models. The ACE1 rs4359 polymorphism showed a significant protective effect against the risk for COVID-19 in over-dominant model. However, in contrast to the rs1799752 genotypes, there was no significant difference in the ACE1 expression level between carriers of different rs4359 genotypes in the total population of patients and controls (Fig. 5).

There was no significant difference in ACE2 expression level among the rs4359 genotype carriers which was consistent with ACE1 expression levels among the rs4359 genotype carriers (Fig. 6).

There was no significant difference in distribution of rs4359 and rs1799752 variants between COVID-19 cases and control in allelic model.

Then, we appraised association between estimated haplotypes and COVID-19 risk. The results showed similar distribution of ACE1 haplotypes between COVID-19 cases and healthy controls (Table 5).
A strong positive correlation has been detected between ACE1 and ACE2 expression in COVID-19 patients, healthy controls as well as total population (Fig. 7). Finally, the correlation of ACE2 and ACE1 expression levels with age, blood cells counts, ESR and CRP was analyzed using nonparametric spearman correlation test. – delta Ct values in the figures were plotted as box and whisker plots (showing the median [line], interquartile range [box], and minimum and maximum values).

A strong positive correlation has been detected between ACE1 and ACE2 expression in COVID-19 patients, healthy controls as well as total population (Fig. 7).

Finally, the correlation of ACE2 and ACE1 expression levels with age, blood cells counts, ESR and CRP was analyzed using nonparametric spearman correlation test. – delta Ct values in the figures were plotted as box and whisker plots (showing the median [line], interquartile range [box], and minimum and maximum values).

Fig. 1. Distributions of alleles (a, c) and genotypes (b, d) of rs4359 and rs1799752 among normal controls (NC), COVID-19 patients, non-ICU and ICU-admitted cases. There was significant difference between genotypes distribution of rs1799752 among COVID-19 patients compared to matched controls.

Fig. 2. Relative expressions of ACE1 and ACE2 in COVID-19 patients (n = 91) compared with healthy controls (n = 91). There was no significant difference in expression of ACE1 or ACE2 between COVID-19 patients and healthy controls. However, a moderate increase in ACE1 expression was observed in ICU-admitted COVID-19 patients compared to other group of COVID-19 patients. – delta Ct values in the figures were plotted as box and whisker plots (showing the median [line], interquartile range [box], and minimum and maximum values).
4. Discussion

The importance of renin-angiotensin system in the pathogenesis of COVID-19 has been assessed by several studies. Over-activation of the renin-angiotensin-aldosterone has been suggested to participate in abnormal biochemical and clinical manifestations of SARS-CoV-2 infection [11]. The protective renin-angiotensin system medicated by ACE2 might be inhibited in COVID-19 [11]. ACE2 is regarded as a negative regulator of renin angiotensin system which converts Ang II to angiotensin 1–7 [12]. On the other hand, ACE1 catalyzes biogenesis of Ang II from Ang I [13]. Thus, ACE1/ACE2 level has a critical significance in the pathogenesis of disorders associated with renin-angiotensin system [14].

In the current study, we demonstrated higher levels of ACE1 in ICU patients compared with non-ICU patients. However, its expression was not significantly different between total COVID-19 patients and total controls. ACE2 expression was not different ether between two groups of COVID-19 patients or between total COVID-19 patients and total controls. These findings indicate imbalance in ACE1/ACE2 level in severely affected COVID-19 patients.

The ACE1 rs1799752 polymorphism was associated with a high risk of COVID-19 in dominant and co-dominant models. In the dominant model (II + ID versus DD), the presence of at least one mutated (−) allele was tested against the homozygous wildtype genotype (wt/wt). The ACE1 rs1799752 polymorphism was associated with a high risk of COVID-19 in dominant and co-dominant models. In the dominant model, the presence of at least one mutated (−) allele was tested against the homozygous wildtype genotype (wt/wt). The ACE1 rs1799752 polymorphism showed a significant protective effect against COVID-19 risk in over-dominant model.

(b) In the total population of patients and controls, different ACE1 mRNA levels were observed among carriers of different rs1799752 genotypes; of note, ID genotype carriers showed a higher expression of ACE1 compared with II genotype carriers (P = 0.01). The level of Odds Ratios was showed as FDR adjusted q-values. MAF: minor allele frequency.
The ACE1 rs4359 polymorphism was associated with a higher risk of COVID-19 in dominant and co-dominant models. The ACE1 rs4359 polymorphism showed a significant protective effect against the risk for COVID-19 in over-dominant model. There was no significant difference in the ACE1 expression level between rs4359 genotypes in the total population of patients and controls. Odds Ratios are shown as FDR adjusted q-values. MAF: minor allele frequency.

**Fig. 4.** ACE2 expression was significantly higher in ID genotype carriers than the II genotype carriers in total population.

**Fig. 5.** Association between ACE1 rs4359 gene polymorphism and COVID-19 risk as well as ACE1 mRNA levels by rs4359 genotypes. (a) The results of association tests under five different inheritance models are shown. The Odds Ratios (plus Confidence Intervals) are reported on the X axis in a linear scale. Data on the right of Y axis indicates causative effects toward the risk and the data on the left indicates protective effects. The ACE1 rs4359 polymorphism was associated with a higher risk of COVID-19 in dominant and co-dominant models. (b) There was no significant difference in the ACE1 expression level between rs4359 genotypes in the total population of patients and controls. Odds Ratios are shown as FDR adjusted q-values. MAF: minor allele frequency.

**Fig. 6.** ACE2 expression in carriers of different rs4359 genotypes in total population.
COVID-19 in over-dominant model. However, in contrast to the rs1799752 genotypes, there was no significant difference in the ACE1 or ACE2 expression level between carriers of different rs4359 genotypes in the total population of patients and controls. Thus, this polymorphism can be regarded as a non-functional polymorphism in this regard, although a previous study had reported the role of this polymorphism in modulation of response of patients to a certain ACE inhibitor medication [15].

A strong positive correlation has been detected between ACE1 and ACE2 expression in COVID-19 patients, healthy controls as well as total population. Thus, one can deduce that the balance between these two transcripts is only impaired in severely affected COVID-19 cases.

Finally, ACE2 expression levels were positively correlated with RBC, HB and HCT levels in COVID-19 patients. However, ACE2 expression levels had a negative correlation with ESR in COVID-19 patients. In contrast, ACE1 expression was only correlated with HCT. A previous study has demonstrated the impact of Ang II on enhancement of erythropoiesis [16]. In fact, ACE1 knockout mice have exhibited anemia in spite of having normal kidney function [16]. Considering the opposite impacts of ACE1 and ACE2 on Ang II levels [13,14], ACE1 correlation with HCT can be contributed to the impact of this enzyme on erythropoiesis. However, the underlying mechanism for the observed correlation between ACE2 levels and the mentioned parameters should be clarified in future.

Taken together, ACE1 polymorphisms might affect risk of COVID-19 and expression of ACE transcripts.

| rs4359 | rs1799752 | Case   | Control | Total | OR (95% CI) | P-value | FDR | q-Value |
|--------|-----------|--------|---------|-------|-------------|---------|-----|---------|
| C      | D         | 0.22   | 0.35    | 0.32  | 1.14 (0.75–1.74) | 0.52    | 0.525 |         |
| C      | I         | 0.31   | 0.24    | 0.23  | 0.48 (0.26–0.87)  | 0.014   | 0.057 |         |
| T      | D         | 0.34   | 0.21    | 0.23  | 0.81 (0.46–1.43)  | 0.47    | 0.525 |         |
| T      | I         | 0.11   | 0.19    | 0.19  | 1.55 (0.97–2.48)  | 0.06    | 0.121 |         |

Table 5
The results of haplotype analysis in COVID-19 patients and controls.

Fig. 7. Correlation between ACE1 and ACE2 expression levels. There was a strong positive correlation between ACE1 and ACE2 expression in COVID-19 patients (a), healthy controls (b), and total population (c).

Fig. 8. Correlation of ACE2 expression levels with age, RBC, HB, HCT, NEUT and ESR of COVID-19 patients. – delta Cts of ACE2 and log 2 of age and blood cells parameters were used for correlation tests.
Authors statement

SGF wrote the draft and revised it. MT designed and supervised the study. MA, GA, NA and BMH performed the experiment and collected the clinical data and samples. All the authors read and approved the submitted version.

Declaration of competing interest

The authors declare they have no conflict of interest.

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