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Investigating the Relationship between COVID-19 Vaccination and ACE2 Gene Expression in Cardiovascular Disease

Nabaa Sattar Shihab Shihab[1], Havva Cobanogullari[2], Aya Badeea Ismail[3], Ozlem Balcioglu[4], Mahmut Cerkez Ergoren[3]

[1]*Department of Molecular Medicine, Near East University, Nicosia, Cyprus*
[2]*Department of Biological Sciences, Eastern Mediterranean University, Famagusta, Cyprus*
[3]*Department of Medical Genetics, Near East University, Nicosia, Cyprus*
[4]*Department of Cardiovascular Surgery, Near East University, Nicosia, Cyprus*

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Corresponding author:
Mahmut Cerkez Ergoren.
E-mail: mahmutcerkez.ergoren@neu.edu.tr.
ORCID: 0000-0001-9593-9325.

ABSTRACT

Background: Cardiovascular disease (CVD) is a major global health problem and the angiotensin-converting enzyme 2 (ACE 2) gene plays a crucial role in SARS-CoV-2 cell entry and cardiovascular homeostasis. Although COVID-19 vaccines are widely used, their potential effects on ACE2 gene expression in individuals with pre-existing cardiac disease remain incompletely understood.

Objective: The aim of this study was to investigate whether ACE2 gene expression is altered by COVID-19 vaccination in cardiac patients compared with healthy controls.

Methods: A total of 90 participants were studied, including 47 healthy controls and 43 patients with confirmed heart disease. Venous tissue samples were obtained, total RNA extracted and reverse-transcribed to cDNA and ACE2 expression levels were determined by quantitative real-time PCR (qPCR) with ACTB as the reference gene. Relative expression, fold-change and correlation analyses were performed for statistical evaluation.

Results: ACE2 mRNA expression was detectable in venous tissue samples from both patient and control groups. No statistically significant difference in normalized ACE2 expression was observed between healthy controls and patients with cardiovascular disease ($p>0.05$). Correlation analyses showed no significant association between ACTB and ACE2 expression in either group. Although considerable inter-individual variability and high coefficients of variation were observed in ACE2 mRNA levels, fold-change analysis did not reveal a consistent directional difference between groups.

Conclusion: Under the conditions of this study, COVID-19 vaccination was not associated with a statistically significant group-level difference in ACE2 mRNA expression in venous tissue from patients with cardiovascular disease or healthy individuals However, the findings should be interpreted cautiously because of the lack of post-vaccination time stratification and high inter-individual variability. Larger multicentre longitudinal studies are needed to clarify tissue-specific ACE2 regulation and its potential clinical implications following vaccination.

Keywords: ACE2 gene, cardiovascular disease, COVID-19 vaccine, gene expression, qPCR

Introduction

Cardiovascular diseases such as heart failure, stroke and coronary heart disease are still one of the main causes of morbidity and mortality worldwide. Angiotensin-converting enzyme 2 not only plays a central role in the regulation of the renin-angiotensin system (RAS), but also acts as a functional receptor for SARS-CoV-2 and thus establishes a link between cardiovascular homeostasis and viral pathogenesis [1,2].

ACE2 is highly expressed in various organs, particularly in the heart, vascular endothelium, intestine and lungs [3]. ACE2 neutralizes the pro-inflammatory and vasoconstrictive effects of angiotensin II in cardiovascular tissues and therefore has a protective effect in atherosclerosis, myocardial injury and hypertension [4,5]. This expression of ACE2 can be downregulated by SARS-CoV-2 infection, which can disrupt this balance. As a result, cardiovascular damage and exacerbated inflammation can be observed. Importantly, reduced ACE2 levels have been observed in vivo models and in cells due to infection [6,7]. These findings may emphasize increased susceptibility and poor outcomes in patients with CVD [1,7].

Although the role of ACE2 in the pathophysiology of COVID-19 is well understood, it is not clear how the expression of ACE2 is affected by COVID-19 vaccination in people with pre-existing heart problems. Preliminary data show that serum ACE2 levels are elevated in vaccinated individuals along with biomarkers such as TNF-α and AngII, suggesting possible systemic immunological modulation following vaccination [8]. In addition, transient modulation of ACE2 expression could be induced by certain spike-based vector vaccines, but this does not necessarily lead to cardiac dysfunction in experimental models [9].

Based on these findings, it is both clinically relevant and biologically possible to investigate whether ACE2 is expressed differently in heart patients compared to healthy controls due to COVID-19 vaccination. This study aims to fill this knowledge gap by comparing the expression of the ACE2 gene in healthy controls and patients with diagnosed cardiovascular disease (CVD) after COVID-19 vaccination.

Methods

Study Design and Participants

This study was designed as a retrospective comparative observational study. The study included 90 participants (43 patients with clinically diagnosed CVD and 47 healthy controls). Patients with CVD were recruited from the cardiology clinics of a single tertiary hospital. A confirmed diagnosis of cardiovascular diseases such as cardiac arrhythmia, previous myocardial infarction and coronary heart disease were the inclusion criteria. Immunosuppressive therapy, autoimmune disease, active or recent infection malignancy and known systemic inflammatory disorders were the exclusion criteria. All participants had received at least one dose of a COVID-19 vaccine prior to tissue sampling. Due to the retrospective nature of the study, information regarding vaccine type and the exact time interval between tissue collection and vaccination was not uniformly available for all participants.

All participants provided a written informed consent. The institutional ethics committee approved the study and the study was conducted in accordance with the Declaration of Helsinki (Application No: YDU/2024/124-1843) and conducted in accordance with the Declaration of Helsinki.

Venous Tissue Collection

Miniphlebectomy procedures were used to obtain venous tissue samples at Near East University Hospital. Particularly, small segments of superficial lower-extremity veins, consistent with tributaries of the great saphenous vein, were collected for analysis. Immediately after excision, venous tissue specimens were placed into RNA-free tubes, stabilized in an RNA preservation solution and stored at –80 °C until further processing. Although venous endothelial tissue offers practical accessibility in a clinical setting, ACE2 expression is known to be cell- and tissue-type-specific, which should be considered when interpreting the findings beyond venous tissue.

RNA Extraction and Quality Assessment

TRIzol reagent (Invitrogen, USA) was used to extract total RNA from venous tissue according to the manufacturer's protocol. Approximately 50-100 mg of the tissue was homogenized in 1 ml TRIzol and then extracted with chloroform and precipitated with isopropanol. The RNA pellet was washed with 75% ethanol, air-dried and resuspended in RNase-free water.

The purity and concentration of RNA was determined spectrophotometrically using a NanoDrop instrument (Thermo Fisher Scientific, USA) at A260/A280. Samples with an A260/A280 ratio between 1.8 and 2.0 were used for downstream analyses. 1.5% agarose gel electrophoresis was used to check the integrity of the RNA.

Complementary DNA (cDNA) Synthesis

1 µg of total RNA was used in a 20 µl reaction with a Hibrigen cDNA synthesis kit (Hibrigen, Turkey) for reverse transcription according to the manufacturer's instructions. The reaction mixture contained reaction buffer, nuclease–free water, random hexamer primer and reverse transcriptase enzyme mix. The protocol included incubation at 42°C for 60 min, followed by enzyme inactivation 80°C for 10 min. Synthesized cDNA samples were stored at -20°C until further analysis.

PCR and Primer Optimization

Initial and gradient PCR assays were used to optimize primer annealing temperatures and concentrations. The primer sequences were designed to specifically amplify the housekeeping gene ACTB (β-actin), which was used as an internal control and the ACE2 gene as target gene. In order to determine the optimum annealing temperature, a gradient PCR was performed in the range of 56-62°C. Primer optimization involved testing final concentrations of 0.2-0.5 µM. The specificity of the amplification was confirmed by agarose gel electrophoresis and single amplicons of the expected size was ensured by this way. Although ACTB was used as a single reference gene in this study, it has been widely reported as a stable housekeeping gene in endothelial and vascular tissues. Nonetheless, the use of a single reference gene is acknowledged as a limitation and future studies may benefit from incorporating multiple housekeeping genes in accordance with MIQE guidelines.

Quantitative Real-Time PCR (qPCR)

SYBR Green-based quantitative real-time PCR (qPCR) on a StepOnePlus™ Real-Time PCR System (Applied Biosystems, USA) was used to quantify gene expression. Each 20 µL reaction contained 10 ng of cDNA template, 0.2 µM of each primer, 1.25 µL MgCl2, 10 µL of 2× SYBR Green Master Mix. An initial denaturation at 95 °C for 10 min, followed by 40 cycles of denaturation at 95 °C for 15 s and annealing/extension at 60-62

°C for 30 s and extension at 72°C for 45s constituted the cycling conditions. Amplification specificity was confirmed by melting curve analysis.

Samples demonstrating abnormal melting curves or non-specific amplification were excluded from the final analysis. Consequently, the number of valid Ct values slightly between study groups and genes.

Data Analysis

The 2^−ΔΔCt method (10) was used to calculate relative gene expression. The expression of ACE2 was normalized using ACTB as a reference gene. GraphPad Prism 10 (version 10.1.2) was used for statistical analysis. All qPCR reactions were performed in technical replicates.

Normality of data distribution was assessed prior to comparative analyses. As gene expression data did not follow a normal distribution, group comparisons were conducted using appropriate non-parametric tests. Correlation analyses were performed using Spearman's rank correlation coefficient. Sample sizes (n) for each analysis, exact p-values and 95% confidence intervals are reported in the Results section. A p-value < 0.05 was considered statistically significant.

Results

Participant Characteristics

A total of 90 participants were included in the study, comprising 47 healthy controls and 43 patients with cardiovascular disease (CVD). Due to exclusion of samples with insufficient RNA quality or non-specific qPCR amplification, the number of valid Ct measurements varied slightly between analyses and genes.

qPCR Quality Control and Amplification Specificity

Quantitative real-time PCR analysis confirmed successful amplification of both the reference gene (ACTB) and target gene (ACE2) in venous tissue samples from all studied participants. Amplification plots demonstrated consistent exponential amplification across samples, while melting curve analysis revealed single, specific peaks for each amplicon, indicating non-specific products, absence of primer-dimer formation and high amplification specificity.

Samples exhibiting insufficient amplification efficiency or abnormal melting curves were excluded from further analysis. As a result, the final number of valid samples included in each analysis differed slightly between study groups and genes, as indicated in the corresponding tables.

Table 1 Correlation analysis between ACTB and ACE2 expression in control and patient groups

Comparison	n	Spearman (r)	95%CI	p(two-tailed)
Controls: ACTB vs ACE2	42	0.05066	-0.2659 to 0.3573	0.7500
Patients: ACTB vs ACE2	43	0.2175	0.09773 to 0.4930	0.1612

No statistically significant correlation was observed between ACTB and ACE2 expression in either the control or patient groups based on Spearman's rank correlation analysis (p > 0.05 for both). These findings indicate that normalization using ACTB did not introduce systematic bias in the assessment of ACE2 expression. The total number of participants was 90 however due to exclusion of samples with missing data and non-specific products or amplification quality, the number of valid Ct measurements (N) slightly differed between groups and genes.

Table 2 Mean Ct values of ACE2 and ACTB in Venous Tissue Samples

Gene	N (Controls)	Mean±SD (Controls)	N (Patients)	Mean±SD (Patients)	p-value
ACTB	42	33.32 ± 1.303	47	32.38 ± 1.466	>0.05
ACE2	43	31.54 ± 2.900	43	25.16 ± 1.023	>0.05

Ct values represent unnormalized raw cycle threshold values obtained from qPCR analysis. Samples with abnormal melting curves or non-specific amplification were excluded from the analysis. Because raw Ct values are influenced by technical and sample-specific variation, biological interpretation was based primarily on ACTB-normalized relative expression rather than on unadjusted Ct values alone. Although numerical Ct differences were observed between groups, these differences did not translate into statistically significant differences after normalization and appropriate statistical testing

Table 3 Relative ACE2 mRNA Expression ($2^{-}\Delta\Delta Ct$) in Controls and CVD Patients

Metric	Controls	Patients
Median (2^−ΔΔCt)	4.07	266.10
Mean (2^−ΔΔCt)	123.9	522.8
Standard Deviation	471.6	621.5
Coefficient of Variation	380.7%	118.9%

Relative ACE2 expression was calculated using the $2^{-}\Delta\Delta Ct$ method after normalization to ACTB. Because expression values showed a substantial inter-individual variability and non-normal distribution, medians are presented alongside means. The high coefficients of variation in both groups indicate marked dispersion of ACE2 expression values, which limits the ability to identify a consistent directional group difference between patients and controls.

Table 4 Correlation Between ACTB and ACE2 Expression

Group	n	Correlation (r) 95%CI	p-value
Controls	42	0.0507 -0.27 to 0.36	0.75
CVD Patients	43	0.2175 0.10 to 0.49	0.16

Correlation analysis was performed using normalized ΔCt values derived from ACTB-normalized qPCR data. No statistically significant correlation was observed between ACTB and ACE2 expression in either group, indicating that normalization using ACTB did not introduce systematic bias.

Comparison of ACTB Expression Between Groups

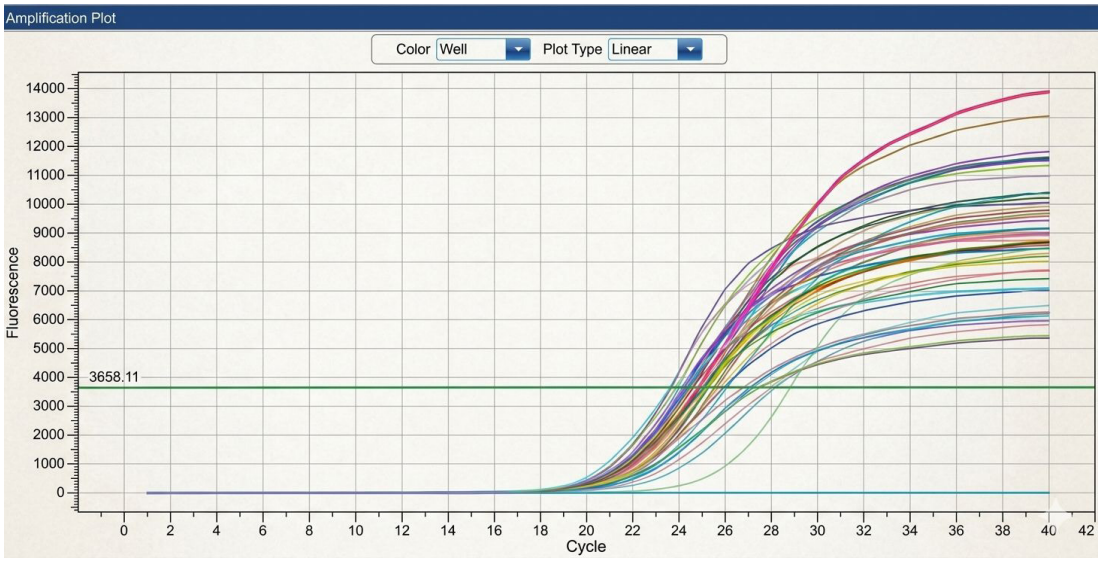
The stability of the reference gene ACTB was first evaluated to ensure reliable normalization of ACE2 expression. Mean Ct values of ACTB were comparable between the control group (mean ± SD: 33.32 ± 1.30; n = 42) and CVD group (32.38 ± 1.47; n = 47), with no statistically significant difference observed between groups (p > 0.05).

These findings indicate stable ACTB expression across venous tissue samples from both patients with cardiovascular disease and healthy controls, supporting its use as an internal reference gene in this study.

ACE2 mRNA Expression in Venous Tissue

ACE2 mRNA expression was detectable in venous tissue samples from both control participants and patients with cardiovascular disease. Although the raw Ct values of ACE2 showed numerical differences between the control group and patient group, these values should be interpreted cautiously

A



B

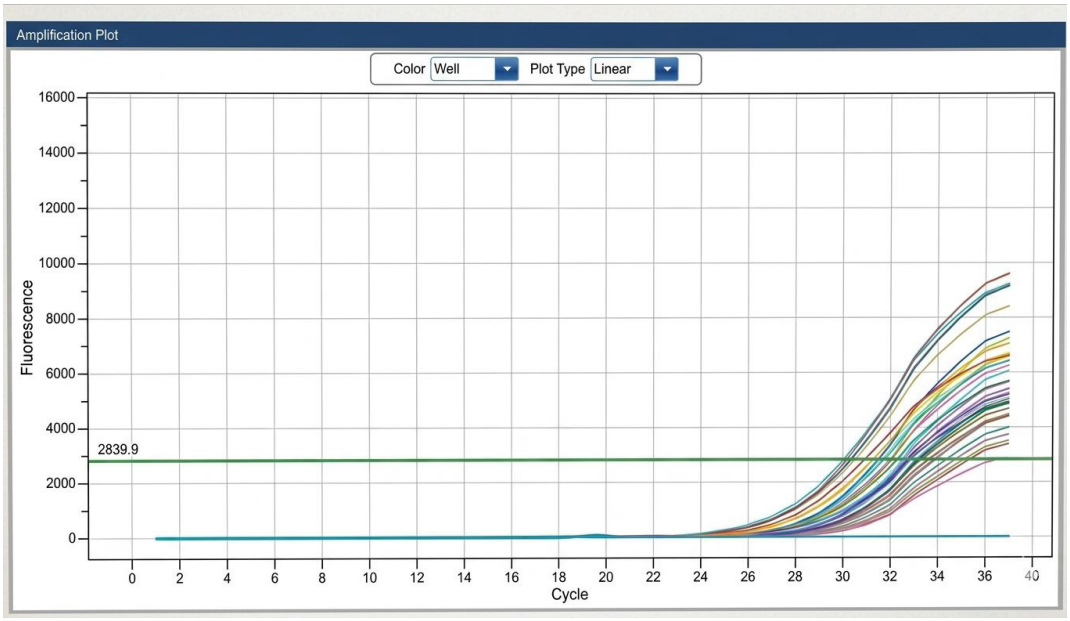


Figure 1 – qPCR amplification plots for patients (A) and controls (B), each including negative controls

Each curve represents amplification from an individual sample. Negative controls confirm the absence of non-specific amplification. The amplification curves demonstrate consistent exponential amplification patterns and assay performance across samples, supporting the reliability of downstream Ct-based analyses.

because Ct values were subsequently normalized to the reference gene ACTB. After non-parametric analysis and normalization, no statistically significant group-level difference in ACE2 expression was observed between patients with cardiovascular disease and healthy controls ($p>0.05$). Therefore, the observed numerical differences in raw Ct values were not considered sufficient evidence of a biologically meaningful difference at the normalized expression level.

Variability and Fold Change Analysis of ACE2 Expression

Although no statistically significant group-level difference was detected, ACE2 expression showed significant inter-individual variability in both groups. Fold change analysis demonstrated a wide dispersion of ACE2 expression values, with coefficients of variation of 118.9% in the patient group and 380.7% in the control group (Table 3). Median ACE2 expression values were 266.1 in patients and 4.07 in controls, whereas mean values were 522.8 and 123.9, respectively. These findings indicate substantial heterogeneity within both groups. Therefore, the fold-change results should be interpreted cautiously, and the numerical differences observed between groups should not be overinterpreted as robust biological group effects.

Correlation Analysis Between ACTB and ACE2 Expression

Correlation analysis was performed to assess the relationship between ACE2 and ACTB expression levels. No significant correlation was observed between ACE2 and ACTB expression in either the patient group (Spearman $r = 0.2175$, 95% CI: 0.10 to 0.49, $p = 0.16$) and the control group (Spearman $r = 0.0507$, 95% CI: −0.27 to 0.36, $p = 0.75$) as summarized in Table 1. These findings indicate that normalization using ACTB did not introduce systematic bias into the assessment of ACE2 expression.

Discussion

In the present study, no statistically significant group-level difference in ACTB-normalized ACE2 expression was detected between vaccinated individuals with cardiovascular disease and healthy controls. Although raw Ct values and fold-change estimates showed numerical variability, these findings should be interpreted cautiously because of the high inter-individual dispersion observed across samples. In addition, no meaningful correlation was observed between ACE2 and the internal control gene ACTB, supporting the consistency of the normalization approach used in the study.

These results do not provide evidence of a statistically significant alteration in venous tissue ACE2 mRNA expression under the conditions of this study. However, the substantial inter-individual variability observed in both groups suggests that subtle biological effects cannot be completely excluded. Therefore, the present findings should be interpreted as indicating the absence of a robust detectable group-level difference rather than definitive evidence of no biological effect.

ACE2 plays a central role in the regulation of the renin-angiotensin system (RAS). It neutralizes the harmful effects of angiotensin II by converting it into angiotensin-(1-7), a peptide with anti-fibrotic, anti-inflammatory and vasodilatory properties. In addition to its crucial role in the cardiovascular system, scientists have paid global attention to ACE2 because it is the functional receptor for SARS-CoV-2, which enables the SARS-CoV-2 virus to enter host cells [11,12].

During acute infection, ACE2 has been shown to be downregulated leading to an imbalance in the RAS and contributing to poor outcomes in patients with cardiovascular comorbidities myocardial injury and endothelial dysfunction [13].This dual role of ACE2 has raised concerns about whether COVID-19 vaccines, especially those encoding spike protein antigens could affect the expression of ACE2 in vaccinated individuals. In the present study, no statistically significant group-level difference in venous tissue ACE2 mRNA expression was detected after normalization, suggesting that any potential effect, if present, is unlikely to be large under the conditions examined.

Clinical observations have shown that there may be a transient increase in the concentration of soluble ACE2 in vaccinated individuals, which is likely due to protein excretion and immunomodulation rather than upregulation of ACE2 at the transcriptional level in tissues [8,14]. In this context, our findings do not support a statistically significant change in venous tissue ACE2 mRNA expression. Although rare cardiovascular adverse events have been reported after COVID-19 vaccination, the present data do not suggest that such events are mediated through a major shift in tissue-level ACE2 transcription.

The marked variability observed in ACE2 expression, including the high coefficients of variation, warrants careful consideration. This degree of dispersion may reflect substantial biological heterogeneity among participants, including differences in age, genetic background, clinical status, and disease characteristics at the time of sampling. While this variability limits the ability to detect subtle and consistent directional changes between groups, the absence of a significant correlation between ACTB and ACE2 suggests that the observed dispersion is unlikely to be explained by systematic normalization bias alone. Nevertheless, these findings should be interpreted within the context of venous endothelial tissue and extrapolation to arterial or myocardial ACE2 regulation should be made with caution.

The strengths of this study include the use of validated qPCR methodology with internal normalization, the inclusion of both patients with cardiovascular disease and healthy controls and the focus on tissue-specific gene expression. However, several limitations should also be acknowledged. One of the major limitations of the present study is the lack of time stratification according to the interval between tissue sampling and COVID-19 vaccination. Because ACE2 expression may vary dynamically over time after vaccination, the absence of a defined post-vaccination sampling window limits the biological interpretation of our findings. Therefore, the results should be interpreted as cross-sectional observations rather than evidence excluding time-dependent vaccine-related effects on ACE2 expression.

Another important limitation is the numerical inconsistency and high coefficient of variation observed in Ct values across samples. These factors reduce the statistical power to detect small differences in gene expression and indicate that venous tissue ACE2 levels may be subject to substantial individual fluctuation. Consequently, the lack of a statistically significant group-level difference should be interpreted cautiously. In addition, the retrospective and observational design of the study limits the ability to infer a causal relationship between ACE2 expression and cardiovascular disease status. Although the total study population comprised 90 participants, the effective sample size differed slightly across analyses and genes because some qPCR reactions were excluded due to poor melting curves or failed amplification. This is a recognized limitation in qPCR-based studies and should be considered when interpreting the findings. Furthermore, participants were not stratified according to vaccine type, which may also influence immune responses and ACE2 regulation.

Future research should involve larger, longitudinal and multicentre studies with sampling at defined intervals after vaccination. Comparisons across different vaccine platforms would also be informative, particularly if gene expression findings are integrated with clinical cardiovascular outcomes and circulating biomarkers. Such approaches may help clarify whether these changes have clinical relevance in different cardiovascular populations and whether subtle molecular changes occur after vaccination.

Conclusion

In conclusion, no statistically significant difference in venous tissue ACE2 mRNA expression was detected between healthy controls and vaccinated individuals with cardiovascular disease in this cohort. However, high inter-individual variability, the cross-sectional design and the absence of post-vaccination time stratification limit biological interpretation. Larger, time-stratified, longitudinal studies are needed to clarify whether COVID-19 vaccination influences tissue-specific ACE2 regulation.

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