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Angiotensin-Converting Enzyme Gene Polymorphism (Insertion/Deletion) in Patients with Chronic Obstructive Pulmonary Disease and Hypertension Among the Indian Population

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ABSTRACT:

Chronic Obstructive Pulmonary Disease (COPD) is regarded as one of the major global health issues. It is a complex, heterogeneous condition that results from both genetic and environmental factors. The mechanisms involved in its pathophysiology are still not fully understood. The present study aims to investigate Angiotensin-Converting Enzyme Gene Polymorphism (Insertion/Deletion) in patients with Chronic Obstructive Pulmonary Disease and Hypertension Among Indian Population. The current study included 300 patients, divided into three groups: 100 with COPD, 100 with COPD and hypertension, and 100 with hypertension alone. Additionally, a control group of 100 healthy individuals was included. The ACE I/D gene was typed using Mutation-Specific Polymerase Chain Reaction (MSP). PCR products were analyzed by gel electrophoresis on 1% agarose gel, and the results were visualized using a UV Gel Doc. The results revealed that a notable correlation existed between the D allele and COPD (odds ratio [OR] = 4.987, $p \leq 0.001$), for the patients with a combination of COPD and HTN (odds ratio [OR] = 2.691, $p \leq 0.001$), and for hypertensive patients only (OR = 2.136, p-value ≤ 0.01). Nonetheless, non-significant association recorded between the homozygous II, heterozygous ID, and homozygous DD genotypes and the incidence of COPD or HTN ($p \leq 0.05$). Based on the findings, the study concludes that a significant correlation existed between the D allele in the ACE gene with an increased risk of developing HTN and COPD in patients. The study suggested that this allele may be associated with a higher likelihood of occurrence of both COPD and HTN.

Keywords: *Chronic Obstructive Pulmonary Disease (COPD); Hypertension (HTN); Angiotensin Converting Enzyme (ACE); insertion/deletion (I/D) polymorphism; Mutation-Specific Polymerase Chain Reaction (MSP)*

INTRODUCTION:

COPD is one of the global health crises that poses significant challenges. This debilitating respiratory condition is difficult to reverse. COPD presents symptoms such as breathlessness, chronic cough, and acute exacerbations linked to airway damage and emphysema. It is a complex and diverse disease resulting from intricate interactions among various cellular and molecular pathways, influenced by genetic in addition to environmental factors. Although research continues, to establish the fundamental mechanisms underlying this phenomenon remain unclear (1,2). Cardiovascular disease (CVD), particularly hypertension (HTN), often occurs alongside COPD and increases the risk of death. Statistics show that 35% of COPD patients also have HTN; when COPD is combined with coronary artery disease, it accounts for approximately 62% of the morbidity of COPD patients (3).

COPD is classified as the third most common cause of death globally. COPD impacts millions and imposes substantial socioeconomic challenges, particularly in low- and middle-income countries (LMICs). In 2020, approximately 10.6% of individuals aged 40 and older were affected, which translates to around 480 million cases worldwide. The situation in India is particularly severe, with the nation representing 16.7% of global COPD cases and an unequal percentage of deaths (28.6%) and Disability-Adjusted Life Years (DALYs) (30.1%). India leads the world in COPD-related Disability-Adjusted Life Years (DALYs), amounting to 24 million, and ranks second in both prevalence, with 35.8 million cases, and mortality, with 1.06 million annually. The true burden may be even greater than what is recorded (4,5).

The Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) in 2017 highlighted genetic factors as significant contributors to COPD risk, with the ACE gene identified as a crucial factor. Variations in the ACE gene, particularly the I/D

polymorphism, can significantly impact enzyme activity, potentially contributing to inflammation and the development of COPD. Angiotensin II (Ang II), produced by ACE, exacerbates the condition through its harmful effects on vascular function and inflammation (6).

The renin-angiotensin system (RAS) plays a crucial role in lung health, with ACE being essential for generating angiotensin II (Ang II). Disruptions in ACE levels can lead to severe complications. The I/D polymorphism notably influences ACE concentration, especially in individuals having the DD genotype, who experience significantly higher levels associated with various lung diseases, including COPD and COVID-19. Importantly, the ACE2/Ang 1-7/MasR axis counterbalances the adverse effects of Ang II, highlighting the need for a balanced response within the RAS (7). COPD and HTN are conditions influenced by genetics, involving various genes, gene combinations, and gene interactions, as well as epigenetic factors that contribute to their development (6–9). Numerous previous studies have examined the connection between the gene polymorphism related to ACE and COPD, yet the findings have been inconsistent (10–12). Both conditions, COPD and HTN, highlight the influence of genetic factors and their interactions. (13–17).

The ACE gene polymorphism (I/D) affects the risk of developing both conditions, with the D allele potentially increasing the risk in some ethnic groups. However, results vary and lack a consistent consensus, especially across different populations, underscoring the need for further research intervention.

MATERIALS AND METHODS

This is a case–control study involving 400 participants. The study was conducted in the "Department of Biochemistry, School of Medical Sciences and Research, Sharda Hospital, Greater Noida, UP, India". Study participants were categorized into four groups: 100 diagnosed with COPD, 100 patients with a combination of both COPD and HTN, 100 patients with HTN only, and 100 healthy individuals as controls. The study participants, aged between 30 and 60 years at the screening phase, were diagnosed with COPD and/or Hypertension (HTN) and had provided written informed consent before participating. The diagnosis of COPD was conducted in accordance with the guidelines established by the American Thoracic Society and the European Respiratory Society (GOLD, 2017). Exclusion criteria included patients with other significant respiratory diseases, malignancies, severe comorbid conditions, or pregnancy. The gene typing of the ACE I/D gene was carried out using MSP for ACE-rs4646994 I/D. Approximately 3 mL of peripheral blood was collected into an EDTA tube. DNA was isolated using the Qiagen kit. The DNA samples were kept at -20°C until further analysis. NanoDrop™ checked the quality and integrity of DNA. Primers were designed using the Primer3 software, as mentioned in a previous study (18). The primers for the PCR reaction were provided by Eurofins Genomics India Pvt Ltd in India. The PCR products were separated by 1% agarose gel electrophoresis, and the results were visualized with an Ultraviolet (UV) Gel Doc as shown in Figure 1. The statistical analyses were performed using SPSS software (SPSS Inc., Chicago, USA). The analysis of categorical variables was conducted using the chi-square test. The calculation of the odds ratio, together with a 95% confidence interval, is employed to determine the level of risk. A p-value ≤ 0.05 was considered statistically significant.

RESULTS:

The PCR products separated by 1% agarose gel electrophoresis were visualized with an Ultraviolet (UV) Gel Doc (Figure 1). The distribution of polymorphic genotype frequencies of ACE and the assessment of their conformity to the Hardy-Weinberg equilibrium were conducted in patients with COPD, COPD+HTN, HTN, and controls. The genotype and allelic frequencies are detailed in Table 1.

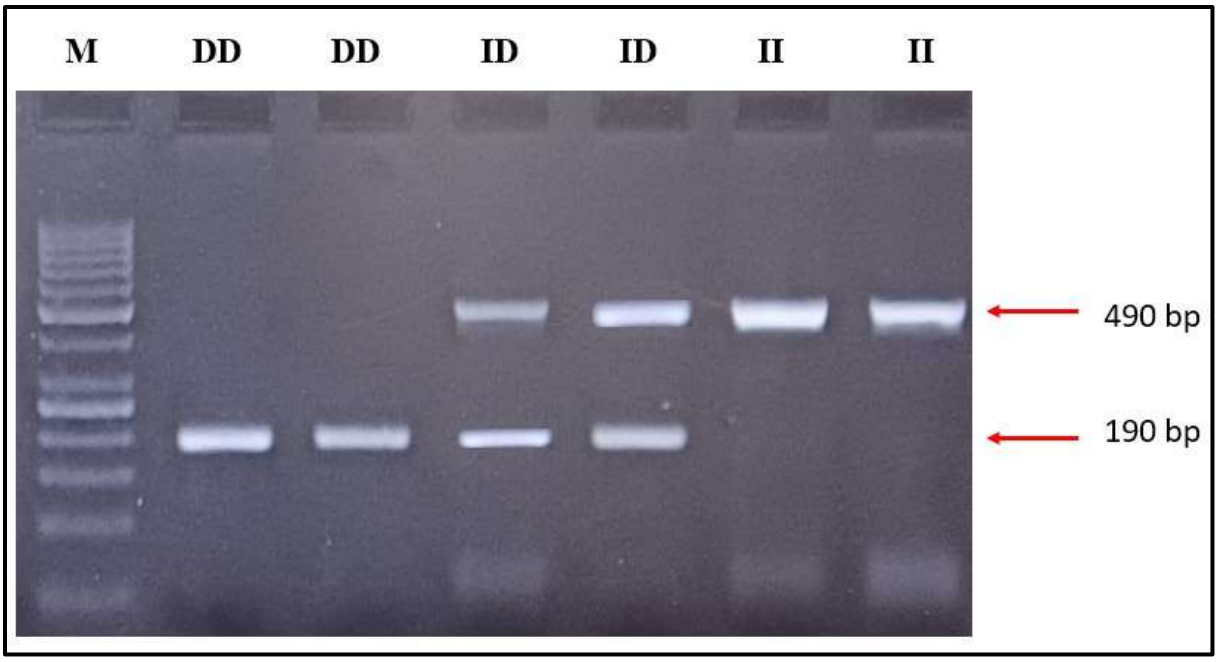

Figure 1:Gel Electrophoresis bands visualized with UV Gel Doc.

The chi-square and estimation of risk (OR) with 95% Confidence Intervals for homozygous II, heterozygous ID, and homozygous DD genotypes in different study groups versus the control are shown in Table 2. The results indicate that there were no significant correlations between genotypes and the risk of disease occurrence.

The study results of the chi-square test and estimation of risk (OR) with a 95% confidence interval for the ACE I/D allele in different study groups compared to controls are presented in Table 3. The p-value indicates a significant correlation between the D allele and the disease in COPD, COPD + HTN, and HTN compared to controls.

Table 1. Hardy-Weinberg equilibrium of genotype frequencies related to homozygous II, heterozygous ID, or homozygous DD genotypes among individuals with COPD, COPD+ HTN, HTN, and controls

	COPD		COPD+HTN		HTN		Control	
Genotype	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected
Homozygotes(II)	21	16.81	30	22.09	38	29.16	31	27.56
Heterozygotes (ID)	40	48.38	34	49.82	32	49.68	43	49.88
Homozygotes (DD)	39	34.81	36	28.09	30	2.160	26	22.56
Allele frequency	%	n	%	n	%	n	%	n
ACE I allele	41	82	47	94	54	108	52.5	105
ACE D allele	59	118	53	106	46	92	47.5	95
Chi-square p-value	0.0833		0.0015		0.0004		0.1681	

%: percentage; n: number

Table 2: The chi-square and estimation of risk (OR)with a 95% Confidence Interval

Group	Homozygotes II				Heterozygotes ID				Homozygotes DD			
			95% Confidence Interval				95% Confidence Interval				95% Confidence Interval	
	P	OR	Lower	Upper	*P*	OR	Lower	Upper	*P*	OR	Lower	Upper
COPD	0.146	0.592	0.312	1.123	0.774	0.884	0.503	1.552	0.070	1.82	0.998	3.319
COPD+ HTN	1.000	0.954	0.522	1.742	0.243	0.683	0.385	1.211	0.169	1.601	0.874	2.933
HTN	0.372	1.364	0.760	2.450	0.144	0.624	0.35	1.111	0.637	1.22	0.657	2.264

Table 3: Chi-square value and estimation of risk (OR) with a 95% Confidence Interval

Group	ACE Alleles							
	I allele				D allele			
			95% Confidence Interval				95% Confidence Interval	
	P	OR	Lower	Upper	*P*	OR	Lower	Upper
COPD	0.070	0.550	0.301	1.002	0.001	4.987	2.674	9.299
COPD+HTN	0.219	0.653	0.356	1.197	0.001	2.691	1.515	4.782
HTN	0.637	0.820	0.442	1.522	0.011	2.136	1.229	3.807

DISCUSSION:

ACE is produced by epithelial, endothelial, and neuronal cells. It is an endopeptidase that contains two catalytic domains. It exists in both soluble and membrane-bound forms (5,13). The primary role of ACE is connected to the RAS system, where it helps convert angiotensin I, a non-vasoactive precursor, into Ang II, a vasoconstrictor, while also aiding in breaking down the vasodilator bradykinin (17,18).

The current study demonstrates that there is no significant correlation between the presence or absence of II, ID, or DD genotypes in cases versus controls (Table 2). However, previous research suggests that the DD genotype of the ACE gene is typically associated with higher levels of both cellular and circulating ACE, as well as an increased risk of cardiovascular problems (19-22). In contrast, the results showed a significant association between the presence of the D allele and the incidence of COPD, with OR = 4.987 ($p \leq 0.001$) (Table 3). The same finding was reported in the meta-analysis of the Asian population, with a similar result (OR = 1.30, 95% CI 1.08, 1.56); however, no associations were observed in other genetic models (7). In the case of patients having both COPD and HTN, as well as within the patients having only HTN, the odds ratios (ORs) were 2.691 and 2.163, respectively, with p-values < 0.05 (Table 3). A similar analysis of odds ratios across various studies indicated that the D allele and D/D genotype of the ACE gene are correlated with an elevated risk of hypertension and COPD (16,23-26). The correlation between the DD gene polymorphism of the ACE gene and the risk for COPD is a current and extensively researched topic; however, the available data require further clarification and supplementation (6,10,12,13). ACE activity primarily occurs in lung tissue, with levels rising in chronic hypoxia, often seen in COPD (27–30). This suggests that pulmonary ACE could contribute to COPD-related pulmonary hypertension. Kanazawa et al. demonstrated a connection between the insertion/deletion (ID) polymorphism in the ACE gene and elevated plasma ACE levels (31), other studies investigated the relationship between the ACE gene insertion/deletion polymorphism and the likelihood of developing COPD, suggesting that there is no significant link between the I/D polymorphism and the onset of COPD (19-22,27).

Importantly, those with II and ID genotypes showed considerably reduced circulating ACE levels in comparison to individuals carrying the DD genotype (23-25). In this study, a significant association was found between the D allele and patients with COPD, as

well as those with both COPD and HTN, or those with only HTN. The likely connection between the D allele of the ACE gene and the incidence of COPD and HTN is due to the fact that the D allele activates ACE production, which leads to the activation of angiotensin II, along with altered endothelial responses, increased capillary permeability, and degradation of bradykinin. As it has been concluded that the D allele is associated with higher ACE levels in plasma, as reported in previous studies. Another study suggested that a protective I allele may act against comorbidities in patients with HTN and COPD (3,10).

CONCLUSIONS:

The study revealed a significant correlation between the D allele in the ACE gene and an increased risk of developing HTN and COPD in patients. This suggests this allele may be associated with a higher likelihood of occurrence of both COPD and HTN. Therefore, extensive and comprehensive studies with a large sample size are required to establish ACE gene polymorphisms in COPD and HTN**.**

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