Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(5), 2434-2441 | ISSN:2251-6727

ACE I/D Polymorphism And Premature Coronary Artery Disease: Evidence From Young Indian Patients

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(Received: 25 August 2025 Revised: 27 September 2025 Accepted: 14 October 2025)

KEYWORDS

Coronary artery disease (CAD), Young-onset CAD, ACE gene polymorphism, Insertion/deletion (I/D)

ABSTRACT:

Introduction: Coronary artery disease (CAD) is the leading global cause of mortality and affects South Asians a decade earlier than Western populations. Beyond conventional risk factors, genetic determinants—particularly the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism—may influence susceptibility. This study assessed the association of ACE I/D polymorphism in young-onset CAD patients and its relation to biochemical parameters.

Methods: A case–control study included 100 angiographically proven CAD patients aged ≤45 years and 100 age- and sex-matched healthy controls. Demographic, clinical, and biochemical data were collected, and ACE I/D genotyping was performed using polymerase chain reaction. Genotype and allele frequencies were compared, and associations with fasting glucose and lipid profile were analyzed. Odds ratios with 95% confidence intervals were calculated.

Results and Conclusion: The distribution of ACE genotypes differed significantly between CAD patients and controls. The DD genotype was more frequent in CAD patients, while the II genotype was more common in controls. The D allele frequency was significantly higher in cases (0.56) compared to controls (0.375). The DD genotype conferred increased risk under both dominant and recessive models (OR=0.32 and 0.45, respectively). Biochemical analysis revealed that ID+DD carriers had higher fasting glucose and significantly lower HDL-C compared to II carriers, both in cases and controls. The ACE I/D polymorphism, particularly the DD genotype and D allele, is strongly associated with young-onset CAD in the study population. Incorporating genetic screening into risk stratification may facilitate early identification and preventive interventions in high-risk individuals.

1. Introduction

Coronary artery disease (CAD) is the leading global cause of mortality and is increasingly affecting younger populations in developing countries, especially South Asia, where onset occurs nearly a decade earlier than in the West [1,2]. This early manifestation imposes prolonged risks of recurrent cardiac events and considerable economic and social burdens, highlighting the urgency to identify risk factors beyond traditional lifestyle contributors [2].

While established risk factors such as hypertension, diabetes, dyslipidemia, smoking, and obesity are critical contributors to CAD, they do not fully explain its occurrence in younger individuals, suggesting a substantial role for hereditary factors—estimated to account for 40 to 60% of disease risk [3]. Among genetic pathways implicated, the renin–angiotensin–aldosterone system (RAAS) plays a central role in cardiovascular regulation, and its constituent, the angiotensin-converting enzyme (ACE), has been extensively investigated for its involvement in atherogenic mechanisms [4].

ACE is a zinc metalloproteinase that catalyzes the conversion of angiotensin I into angiotensin II—a potent vasoconstrictor—and promotes degradation of the vasodilator bradykinin, thus affecting vascular tone and endothelial function. Elevated ACE activity contributes to inflammation, oxidative stress, and vascular remodelling, accelerating atherosclerotic plaque development and progression [5, 6].

A functional polymorphism in the ACE gene—characterized by an insertion (I) or deletion (D) of a 287-bp Alu repeat in intron 16—defines three genotypes (II, ID, DD). These genotypes influence ACE levels in a codominant manner: DD > ID > II [7, 8]. Consequently, the polymorphism is a plausible contributor to CAD, and

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JCHR (2025) 15(5), 2434-2441 | ISSN:2251-6727

numerous studies have examined its impact on disease susceptibility. [9-11]

Several investigations have found an association of the D allele and DD genotype with higher CAD risk, particularly in young cohorts; for example, Gardemann A [11] et al observed significant enrichment of the D allele in individuals under 62 years with CAD, but not in older patients [7]. Studies in South Asian populations have shown similar associations, strengthening the relevance of ACE variants in these ethnic contexts [4, 10]. Nevertheless, findings remain inconsistent, especially in certain Western populations, indicating that the effect may be modulated by population-specific genetic backgrounds, environmental exposures, or gene–gene interactions [3].

In the ethnically diverse Indian population—with its high burden of premature CAD—regional studies have produced mixed outcomes: some report strong DD associations with disease, while others find weaker effects [4, 10]. Notably, many of these analyses did not focus specifically on young-onset CAD, where genetic factors may play a more prominent role relative to cumulative environmental influences.

Young CAD patients often present without long-standing comorbidities, making them an ideal group to assess genetic contributions more clearly. ACE polymorphisms, potentially interacting with metabolic factors like glucose and lipid levels, may trigger early atherosclerosis in this group, supporting the case for integrated risk models combining genetic and traditional determinants. Despite extensive literature, there remains a deficit of age-specific data from South Asia targeting young CAD populations. Filling this gap can enhance our understanding of ACE I/D's role in early disease, and guide tailored prevention approaches.

This study evaluates the association of the ACE I/D polymorphism with CAD in young Indian patients by comparing genotype and allele frequencies with age- and sex-matched healthy controls. We also examine whether ACE genotypes correlate with clinical and biochemical markers—such as lipid profile and glucose metabolism—to assess their utility in risk stratification for premature CAD.

2. Methods

The present study was conducted in the Department of Biochemistry, Dr. Rajendra Gode Medical College, Amravati. A case–control design was adopted to evaluate the association of angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism with the risk of coronary artery disease (CAD) in young individuals. Prior approval was obtained from the Institutional Ethics Committee of the institute, and written informed consent was taken from all study participants before enrolment.

The study population comprised a total of 200 individuals, including 100 clinically confirmed young CAD patients as cases and 100 healthy subjects as controls. The cases were recruited from cardiology and medicine departments of affiliated teaching hospitals, and the diagnosis of CAD was established based on clinical history, electrocardiographic changes, elevated cardiac biomarkers, and/or angiographic evidence of coronary artery stenosis. Only patients aged 45 years or younger at the time of diagnosis were included in the study, irrespective of gender. Exclusion criteria included patients with congenital heart disease, cardiomyopathies, valvular disease, chronic kidney disease, or systemic illnesses likely to influence ACE activity. The control group consisted of age- and gender-matched individuals without any history or clinical evidence of CAD, recruited from hospital staff, voluntary blood donors, and routine health check-up attendees. Controls with hypertension, diabetes mellitus, dyslipidemia, or family history of premature CAD were excluded to minimize confounding influences.

Demographic and clinical data were collected from all participants using a structured proforma. Information regarding age, sex, family history of CAD, smoking and alcohol consumption, dietary habits, and presence of hypertension or diabetes mellitus was recorded. Anthropometric measurements such as body mass index (BMI) and waist-to-hip ratio were taken and fasting venous blood samples were collected for biochemical analysis. Serum lipid profile, fasting blood glucose, and other relevant routine investigations were carried out using standard enzymatic methods to assess conventional risk factors.

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JCHR (2025) 15(5), 2434-2441 | ISSN:2251-6727

Genotyping

The genotyping methodology for the ACE I/D polymorphism has been comprehensively described in our previous publication. [12] Genomic DNA was extracted from peripheral venous blood using an established salt extraction method. [13] The ACE I/D polymorphism, located in intron 16 of the ACE gene, was analyzed via polymerase chain reaction (PCR) amplification. Specific primers, custom-synthesized by Eurofins Genomics (Germany), were used to target the polymorphic region. The PCR reaction was conducted in a 25 µl volume, incorporating QIAGEN PCR Master Mix, primers, DNA template, and sterile distilled water, with thermal cycling parameters optimized for amplification. Amplified products were separated by 2% agarose gel electrophoresis and visualized under UV transillumination using a Gel DocTM XR+ system (Bio-Rad, United States). Genotypes were identified based on distinct band patterns: a 597 bp band for the I/I homozygote, a 319 bp band for the D/D homozygote, and both bands for the I/D heterozygote.

Statistical analysis was performed using SPSS software (version 26). Genotype and allele frequencies were calculated for both cases and controls. Comparison of genotype and allele frequencies between cases and controls was carried out using the chi-square test. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to assess the strength of association of the ACE I/D polymorphism with CAD risk. The differences in the means of biochemical parameters between wild type and carriers was tested using student's 't' test. A p-value of less than 0.05 was considered statistically significant for all tests.

3. Results

The present study included 100 young patients with angiographically proven coronary artery disease (CAD) and 100 age- and gender-matched healthy controls. The demographic characteristics of the study participants are summarized in Table 1. The mean age of young CAD patients was 42.1 ± 4.8 years, while that of controls was 41.7 ± 5.1 years. The difference in mean age between the two groups was not statistically significant (p=0.58), indicating that cases and controls were well matched with respect to age. With regard to gender distribution, 78 (78%) of the CAD patients were males and 22 (22%) were females, whereas in the control group 76 (76%) were males and 24 (24%) were females. The difference in male-to-female ratio between the two groups was not statistically significant (p=0.74). (Table 1)

Table 1: Demographic Characteristics of Study Participants

Parameter		Young CAD (n=100)	Controls (n=100)	p-value
Age (years, mean ± SD)		42.1 ± 4.8	41.7 ± 5.1	0.58
Gender	Male	78 (78%)	76 (76%)	0.74
	Female	22 (22%)	24 (24%)	

The distribution of ACE I/D genotypes among young CAD patients and controls is shown in Table 2. In the CAD group, the frequencies of II, ID, and DD genotypes were 22%, 44%, and 34%, respectively, while in controls the corresponding frequencies were 39%, 47%, and 14%. Statistical analysis revealed that the overall genotype distribution differed significantly between the two groups ($\chi^2 = 13.17$, $p = 0.0014$).

Table 2: Frequencies of Genotypes and Alleles of ACE Gene I/D Polymorphism in Young CAD Patients and Controls

Genotypes / Alleles	Young CAD (n=100)	Controls (n=100)	P value
II	22 (22%)	39 (39%)	0.0014
ID	44 (44%)	47 (47%)	
DD	34 (34%)	14 (14%)	
I (allele)	0.44	0.625	0.0002
D (allele)	0.56	0.375	

When allele frequencies were analyzed, the I allele was observed at a frequency of 0.44 in CAD patients and 0.625 in controls, whereas the D allele occurred at a frequency of 0.56 in CAD patients compared to 0.375 in controls. This difference in allele distribution was statistically significant ($\chi^2 = 13.75$, $p = 0.0002$), indicating a higher prevalence of the D allele among young CAD patients.

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JCHR (2025) 15(5), 2434-2441 | ISSN:2251-6727

To further evaluate the association of ACE I/D polymorphism with CAD, odds ratios (OR) were calculated (Table 3). The OR for the allelic model (D vs I) was 2.13. For the dominant model (II vs ID+DD), the OR was 2.27. In the codominant model, the OR for II vs DD was 4.31, while for II vs ID, the OR was 1.65. (Table 3)

Table 3: Odds Ratio and 95% Confidence Interval for ACE Gene I/D Polymorphism in Young CAD Patients and Controls

Model	Allele/ Genotypes	Young CAD (n=100)	Controls (n=100)	OR
Allelic	D Vs I	112 Vs 88	75 Vs 125	2.13
Dominant model	II vs ID+DD	22 vs 78	39 vs 61	2.27
Codominant model	II vs DD	22 vs 34	39 vs 14	4.31
Codominant model	II vs ID	44 vs 22	47 vs 39	1.65

When biochemical parameters were compared across ACE I/D genotypes (dominant model) in the overall study population (cases and controls combined), some notable trends were observed (Table 4). Individuals with the ID+DD genotypes had a significantly higher mean fasting blood glucose level (99.19 ± 11.65 mg/dL) compared to those with the II genotype (94.91 ± 10.61 mg/dL; p = 0.012). Total cholesterol and triglyceride levels were marginally higher in the II genotype group (191.17 ± 35.46 mg/dL and 165.51 ± 32.95 mg/dL, respectively) compared to ID+DD carriers (189.89 ± 36.74 mg/dL and 162.48 ± 40.58 mg/dL), but these differences were not statistically significant (p = 0.817 and p = 0.579, respectively).

A significant difference was observed in HDL-C, with individuals carrying the II genotype having higher mean levels (42.34 ± 7.58 mg/dL) than those with ID+DD genotypes (37.95 ± 7.52 mg/dL; p = 0.0003). Differences in means of LDL-C and VLDL-C levels did not differ significantly between patients and controls (p = 0.528 and p = 0.583, respectively).

When biochemical parameters were compared across ACE I/D genotypes separately in young CAD patients and controls, certain differences were observed (Tables 5 and 6). In the CAD group, fasting blood glucose levels were slightly higher in ID+DD carriers (99.65 ± 12.38 mg/dL) compared to those with the II genotype (96.62 ± 11.63 mg/dL), but this difference was not statistically significant (p = 0.295). Total cholesterol and triglyceride levels were marginally higher in the II genotype group (200.70 ± 40.88 mg/dL and 169.73 ± 24.05 mg/dL, respectively) than in ID+DD carriers (192.63 ± 38.40 mg/dL and 165.05 ± 41.56 mg/dL, respectively), though the differences did not reach statistical significance (p = 0.414 and p = 0.504 respectively). A significant finding was noted in HDL-C levels, where patients with the II genotype had higher mean values (40.80 ± 7.12 mg/dL) compared to ID+DD genotypes (37.15 ± 7.15 mg/dL; p = 0.041). LDL-C and VLDL-C were slightly higher in the II group but without significant differences (p = 0.738 and p = 0.502, respectively).

Table 4: Comparison of Biochemical Parameters Across ACE I/D Genotypes in study population (cases + controls)

	II		ID+DD		p values
	Mean	SD	Mean	SD	
Fasting blood glucose	94.91	10.61	99.19	11.65	**0.012**
Total cholesterol	191.17	35.46	189.89	36.74	0.817
Triglycerides	165.51	32.95	162.48	40.58	0.579
HDL-C	42.34	7.58	37.95	7.52	**0.0003**
LDL-C	115.73	37.84	119.44	38.82	0.528
VLDL-C	33.10	6.59	32.50	8.12	0.583

Table 5: Comparison of Biochemical Parameters Across ACE I/D Genotypes in Young CAD Patients

CAD	II		ID+DD		p values
	Mean	SD	Mean	SD	
Fasting blood glucose	96.62	11.63	99.65	12.38	0.295
Total cholesterol	200.70	40.88	192.63	38.40	0.414
Triglycerides	169.73	24.05	165.05	41.56	0.504
HDL-C	40.80	7.12	37.15	7.15	**0.041**
LDL-C	125.95	43.06	122.47	41.17	0.738
VLDL-C	33.95	4.81	33.01	8.31	0.502

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Among the control group, fasting blood glucose was significantly higher in individuals with ID+DD genotypes (98.60 ± 10.61 mg/dL) compared to the II genotype (93.95 ± 9.87 mg/dL; p = 0.028). Total cholesterol and triglycerides showed nearly identical values across genotypes, with no significant differences (p = 0.929 and p = 0.611, respectively). Similar to the CAD group, HDL-C levels were significantly higher in the II genotype (43.20 ± 7.69 mg/dL) compared to ID+DD carriers (38.98 ± 7.85 mg/dL; p = 0.009). LDL-C and VLDL-C levels did not differ significantly between the two genotypic groups (p = 0.424 and p = 0.611, respectively).

Table 6: Comparison of Biochemical Parameters Across ACE I/D Genotypes in Controls

Controls	II		ID+DD		p values
	Mean	SD	Mean	SD	
Fasting blood glucose	93.95	9.87	98.60	10.61	**0.028**
Total cholesterol	185.80	30.72	186.39	34.18	0.929
Triglycerides	163.14	36.82	159.19	39.04	0.611
HDL-C	43.20	7.69	38.98	7.85	**0.009**
LDL-C	109.97	33.19	115.57	35.21	0.424
VLDL-C	32.63	7.36	31.84	7.81	0.611

4. Discussion

CAD continues to be the most common cause of morbidity and mortality worldwide, and in India it increasingly affects younger individuals due to a convergence of genetic susceptibility and lifestyle changes. [14] While conventional risk factors such as diabetes, hypertension, smoking, and dyslipidemia are well established, [15, 16] genetic determinants may play a particularly important role in premature disease where the cumulative burden of acquired risks is relatively lower. [17] The angiotensin-converting enzyme (ACE) gene insertion/deletion (I/D) polymorphism is one such variant that has been extensively studied, as the D allele is associated with increased ACE activity, enhanced angiotensin II production, and downstream effects that accelerate atherogenesis. [18]

In the present study involving 100 young angiographically proven CAD patients and 100 age- and sex-matched healthy controls, demographic analysis confirmed comparability between groups. The mean age did not differ significantly, and male predominance was observed in both groups, consistent with the known higher burden of premature CAD in men. This careful matching minimized confounding from age and sex, as emphasized in previous angiographic case–control studies. [19, 20]

Evaluation of genotype frequencies demonstrated a significantly elevated prevalence of the DD genotype in young coronary artery disease (CAD) patients compared to the control group (34% vs. 14%; P < 0.05). Concurrently, the D allele frequency was notably higher in the CAD cohort (0.56) relative to controls (0.375), suggesting an association between the D allele and increased CAD susceptibility in this population. These observations align with findings by Gardemann A [11] et al. who reported a pronounced association of the D allele with elevated CAD risk in younger (<61.7 years) individuals, with the effect size attenuating in older age groups. Comparable associations have also been documented in Indian cohorts. Similar to findings of present study, Bhatti GK [4] et al. observed that the D allele and DD genotype were more frequent in CAD patients than controls (40 vs 28.3 %) from north India. While Dhar S [10] et al. showed both DD and ID genotypes of the ACE gene to be significantly associated with the development of CAD.

According to Beohar N [19] et al ACE genotype DD was present in 47% of patients with CAD as compared to 30% in the general population, with significant difference in the frequencies. The frequency of allele D was 0.68 in patients with CAD, comparable to present study findings and 0.55 in general population. Our findings align with these studies, suggesting that the D allele may be an important genetic determinant of premature CAD across diverse Indian subgroups.

On the other hand, in contrast to present study, Pfohl M [20] et al found no association between the ACE genotypes and coronary artery disease, extent of coronary artery disease, or myocardial infarction among the patients with coronary artery disease.

In the present study, the D allele of the ACE I/D polymorphism was found to be significantly associated with young CAD. The allelic model (D vs I) demonstrated an odds ratio of 2.13, indicating a higher frequency of the D allele among CAD patients compared to controls. Similarly, the dominant model (II vs ID+DD)

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showed an OR of 2.27, suggesting that carriers of the D allele (heterozygous or homozygous) were at increased risk. The codominant analysis revealed an even stronger association when comparing II vs DD genotypes (OR = 4.31), further emphasizing the role of the DD genotype as a genetic risk factor. The II vs ID comparison also indicated elevated risk (OR = 1.65), though the effect was less pronounced.

These findings are consistent with previous reports that have identified the D allele, particularly the DD genotype, as a susceptibility factor for coronary artery disease. Cambien F [21] et al. first demonstrated an association of the ACE DD genotype with myocardial infarction in a large European cohort, while Rigat B [22] et al. described the molecular basis of the I/D polymorphism and its effect on ACE plasma levels. Subsequent meta-analyses and population-based studies have supported this association in different ethnic groups. [23] A large meta-analysis by Zintzaras E [3] et al also reported modest positive association between the D allele and CAD, though they highlighted heterogeneity across populations. Logistic regression analysis by Bhatti GK [4] et al demonstrated that DD genotype was associated with 1.8-fold increased risk of development of CAD in Asian Indians. Our results strengthen this evidence in the young CAD cohort, suggesting that ACE I/D polymorphism may contribute to premature disease onset. The stronger signal observed in relatively young, ethnically homogeneous cohort may reflect an age-dependent genetic effect, as suggested by Gardemann A [11] et al.

It is noteworthy that not all studies have replicated these associations. For example, some Western cohorts reported weak or absent associations between ACE I/D and CAD, [3] highlighting population-specific differences in allele frequencies and environmental exposures. The stronger associations seen in Indian and East Asian populations may reflect higher prevalence of the D allele, gene–diet interactions, or interactions with conventional risk factors that are highly prevalent in these settings.

However, some studies in other populations have shown conflicting results, with no significant association between ACE I/D polymorphism and CAD. [24, 25] Such discrepancies may be explained by differences in genetic background, environmental risk factors, sample size, and selection criteria across studies. Nevertheless, the strength of association observed in our study, particularly under the recessive and codominant models, supports the potential utility of ACE I/D genotyping as a marker for CAD risk assessment in younger individuals.

The evaluation of biochemical parameters across genotypes provided additional insights into the potential metabolic correlates of ACE I/D polymorphism. In the combined analysis of cases and controls, carriers of the ID+DD genotypes exhibited significantly higher fasting blood glucose and lower HDL-C compared to the II genotype. This is consistent with the biological role of ACE activity in modulating insulin resistance and lipid metabolism. Similar to present study Bhatti GK [4] et al no significant difference was observed in the clinical and biochemical characteristics of CAD patients and controls when the data was stratified according to the genotypes of ACE gene. A recent study by Susilo H [26] et al. demonstrated increased ACE activity in D allele carriers, contributing to plaque instability.

When CAD patients were analyzed separately, fasting glucose was modestly higher and HDL-C significantly lower in ID+DD genotypes compared to II, while total cholesterol, triglycerides, and LDL-C did not differ significantly. Similar observations were made in controls, where fasting glucose was again higher and HDL-C lower in ID+DD carriers. The consistency of the HDL-C association across both patients and controls strengthens the likelihood of a true genotype effect rather than a consequence of established disease. A study by Meiling Y [27] et al. confirmed role of higher triglycerides and lower HDL-C levels in CAD patients. According to Tran DC [28] et al, there was no significant difference in clinical and laboratory parameters between ACE I/D genetic polymorphism categories. Similarly, Vargas-Alarcón G [29] et al in the total group of patients with DD genotype showed moderate increased values of total cholesterol, LDL-cholesterol, triglycerides and VLDL cholesterol, however, these values were not statistically increased. Our finding supported by previous studies of significantly lower HDL-C in DD carriers in both CAD and control groups suggests that the D allele may exert an atherogenic effect even in apparently healthy individuals.

Taken together, the findings of our study support a significant association between the ACE D allele and

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premature CAD in an Indian population, with accompanying metabolic alterations that further increase risk. These results add to the growing evidence that genetic predisposition plays a major role in early-onset CAD and that identification of such variants can help stratify risk in young individuals who may otherwise be missed by traditional risk screening. From a societal perspective, early recognition of genetically at-risk individuals allows for the implementation of preventive measures such as lifestyle modification, aggressive risk factor control, and possibly tailored pharmacotherapy targeting the renin–angiotensin system. Such approaches may help reduce the burden of premature CAD in India, where the disease strikes at a younger age than in most Western populations and contributes to substantial loss of productive life-years.

In conclusion, this study demonstrates that the ACE I/D polymorphism, particularly the DD genotype and D allele, is significantly associated with CAD in young Indian patients and is linked to unfavourable metabolic profiles, notably lower HDL-C and higher fasting glucose. These findings emphasize the role of genetic susceptibility in premature CAD and highlight the potential benefit of incorporating genetic markers into risk assessment strategies for early identification and prevention.

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