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Combined Effect Of COL1A1 And EDN1 Gene Polymorphisms On The Risk Of Developing Cardiological Complications

Zokirova Muborakkhon Bobir kizi

Republican Scientific and Practical Medical Center of Hematology, Tashkent State Medical University, Uzbekistan

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Abstract: Background: Cardiological complications are a leading cause of adverse outcomes in patients with systemic diseases. Genetic factors, particularly those influencing myocardial structure and vascular regulation, play a significant role in individual susceptibility. Polymorphisms in the COL1A1 gene are associated with myocardial fibrosis and remodeling, while variations in the EDN1 gene are linked to endothelial dysfunction and vasoconstriction. However, the combined effect of these polymorphisms on cardiovascular risk remains underexplored.

Objective: To assess the association of COL1A1 and EDN1 gene polymorphisms with the risk of developing cardiological complications and to evaluate their combined effect on structural and vascular abnormalities.

Materials and Methods: An observational case-control study included 199 participants: 102 patients with an underlying disease (subdivided into 64 with and 38 without cardiological complications) and 97 healthy controls. Cardiological complications were diagnosed based on clinical, ECG, echocardiographic, and laboratory criteria. Genotyping of COL1A1 and EDN1 polymorphisms was performed using PCR. Statistical analysis included allele frequency comparison, odds ratios (OR), and risk stratification.

Results: Carriers of the minor A allele of COL1A1 and the Asn allele of EDN1 showed a trend toward increased risk of complications (OR=1.22, 95% CI: 0.67–2.22 and OR=1.36, 95% CI: 0.70–2.64, respectively). Combined carriage of both unfavorable alleles was associated with a higher frequency of complications and demonstrated

an additive risk increase compared to isolated variants.

Conclusion: Polymorphisms in COL1A1 and EDN1 are associated with an elevated risk of cardiological complications, with combined carriage resulting in additive risk. These findings support an integrated genetic approach to cardiovascular risk prediction and may inform personalized prevention strategies.

Keywords: COL1A1, EDN1, gene polymorphism, cardiological complications, cardiovascular risk, myocardial remodeling, endothelial dysfunction.

1. Introduction: Cardiological complications remain one of the leading causes of adverse outcomes in patients with various somatic and systemic diseases, including combined pathology accompanied by metabolic, inflammatory, and vascular disorders. In recent years, increasing attention has been paid to the role of genetic factors in shaping individual susceptibility to cardiovascular system damage [1–3]. Particular importance in the pathogenesis of cardiological complications is attributed to processes of myocardial extracellular matrix remodeling, fibrosis formation, and disruption of collagen fiber structure, which are directly associated with impaired diastolic function and reduced myocardial elasticity [4–6]. In this context, the COL1A1 gene, encoding the α1 chain of type I collagen, is considered one of the key regulators of myocardial structural organization. Polymorphisms of this gene are associated with fibrotic changes, tissue remodeling, and an increased risk of cardiovascular complications [7–9].

In parallel, endothelial dysfunction plays a significant role in the development of cardiac pathology, being accompanied by disturbances in vascular tone, microcirculation, and tissue perfusion. One of the key molecular regulators of vascular homeostasis is endothelin-1, encoded by the EDN1 gene, which exerts pronounced vasoconstrictive, pro-ischemic, and proliferative effects [10,11]. Genetic variations in the EDN1 gene have been linked to the development of arterial hypertension, endothelial dysfunction, ischemic myocardial injury, and an increased risk of cardiovascular events [12–14].

Contemporary studies emphasize that the combined effect of genetic polymorphisms affecting both myocardial structural components and vascular regulation contributes to the formation of the most unfavorable cardiovascular risk phenotype [15–17]. However, despite growing interest in multigene models, data on the joint role of COL1A1 and EDN1 gene polymorphisms in the development of cardiological complications remain limited and fragmented, particularly in clinical and genetic studies that stratify patients according to the presence of complications.

In this regard, a comprehensive investigation of the associations between COL1A1 and EDN1 gene polymorphisms and the development of cardiological complications appears to be highly relevant. Such an approach may deepen the understanding of the molecular and genetic mechanisms underlying cardiotoxicity, myocardial remodeling, and vascular dysfunction, and may also provide a basis for personalized risk prediction and prevention of cardiovascular complications.

Objective

To assess the association of COL1A1 and EDN1 gene polymorphisms with the risk of developing cardiological complications, as well as to determine their combined effect on the formation of structural and vascular abnormalities of the cardiovascular system.

2. Methods

The study was conducted as an observational analytical case–control study. The analysis aimed to evaluate the association of COL1A1 and EDN1 gene polymorphisms with the development of cardiological complications.

A total of 199 individuals were enrolled in the study, including 102 patients in the main group and 97 apparently healthy individuals in the control group. The main group was further divided into two subgroups according to the presence of cardiological complications: a subgroup of patients with cardiological complications (n = 64) and a subgroup of patients without cardiological complications (n = 38).

Inclusion criteria for the main group were: presence of the underlying disease, age over 18 years, and written informed consent to participate in the study.

Exclusion criteria included congenital heart defects, severe concomitant cardiovascular diseases in the decompensation stage, and acute inflammatory or infectious processes.

The control group consisted of individuals matched by sex and age, with no clinical signs of cardiovascular pathology or chronic diseases.

Cardiological complications were diagnosed based on a combination of clinical, instrumental, and laboratory

data, including clinical symptoms (dyspnea, chest pain, palpitations), electrocardiography (ECG) findings, echocardiographic parameters (left ventricular ejection fraction, cardiac chamber dimensions, and signs of diastolic dysfunction), and, when necessary, biochemical markers of myocardial injury.

All participants underwent analysis of polymorphic variants of the COL1A1 and EDN1 genes. Genomic DNA was extracted from peripheral venous blood using a standard method. Genotyping of the polymorphisms was performed using polymerase chain reaction (PCR) followed by analysis of the amplified fragments. For each gene, allele frequencies and genotype distributions were determined.

Statistical analysis was performed using standard methods of variation statistics. Allele and genotype frequencies were expressed as absolute values and percentages. Differences between groups were assessed using Pearson's χ^2 test. The association between genetic variants and the risk of cardiological complications was evaluated by calculating odds ratios (ORs) with 95% confidence intervals (95% CIs). Differences were considered statistically significant at $p < 0.05$.

3. Results

A comparative analysis of subgroups within the main cohort revealed that the frequency of the A allele of the COL1A1 gene was higher in patients with cardiological complications (37.5%) compared with patients without complications (32.9%). Calculation of the odds ratio showed that carriage of the A allele was associated with an increased risk of developing cardiological complications (OR = 1.22, 95% CI: 0.67–2.22). Although the difference did not reach statistical significance ($p > 0.05$), a trend toward a higher frequency of the unfavorable allele was observed in patients with complications, suggesting a possible involvement of the COL1A1 gene in myocardial remodeling and the development of cardiac pathology.

Association of EDN1 gene polymorphism with cardiological complications.

Analysis of allele distribution of the EDN1 gene demonstrated that the frequency of the Asn allele in patients with cardiological complications was 28.1%, whereas in the subgroup without complications it was 22.4%. Assessment of the risk of cardiological complications associated with carriage of the Asn allele revealed an OR = 1.36, 95% CI: 0.70–2.64. These findings indicate a trend toward an increased risk of cardiological complications in carriers of the Asn allele, which is consistent with the role of the EDN1 gene in the regulation of vascular tone and the development of endothelial dysfunction.

Table. Association of COL1A1 and EDN1 gene polymorphisms with the risk of cardiological complications

Gene	Analyzed allele	OR	95% CI
COL1A1	A vs C	1.22	0.67–2.22
EDN1	Asn vs Lys	1.36	0.70–2.64

For both genes (COL1A1 and EDN1), a unidirectional trend toward an increased risk of cardiological complications was observed in carriers of the minor alleles (A and Asn, respectively). The EDN1 gene demonstrated a more pronounced risk effect compared with COL1A1.

Combined analysis of COL1A1 and EDN1 gene polymorphisms.

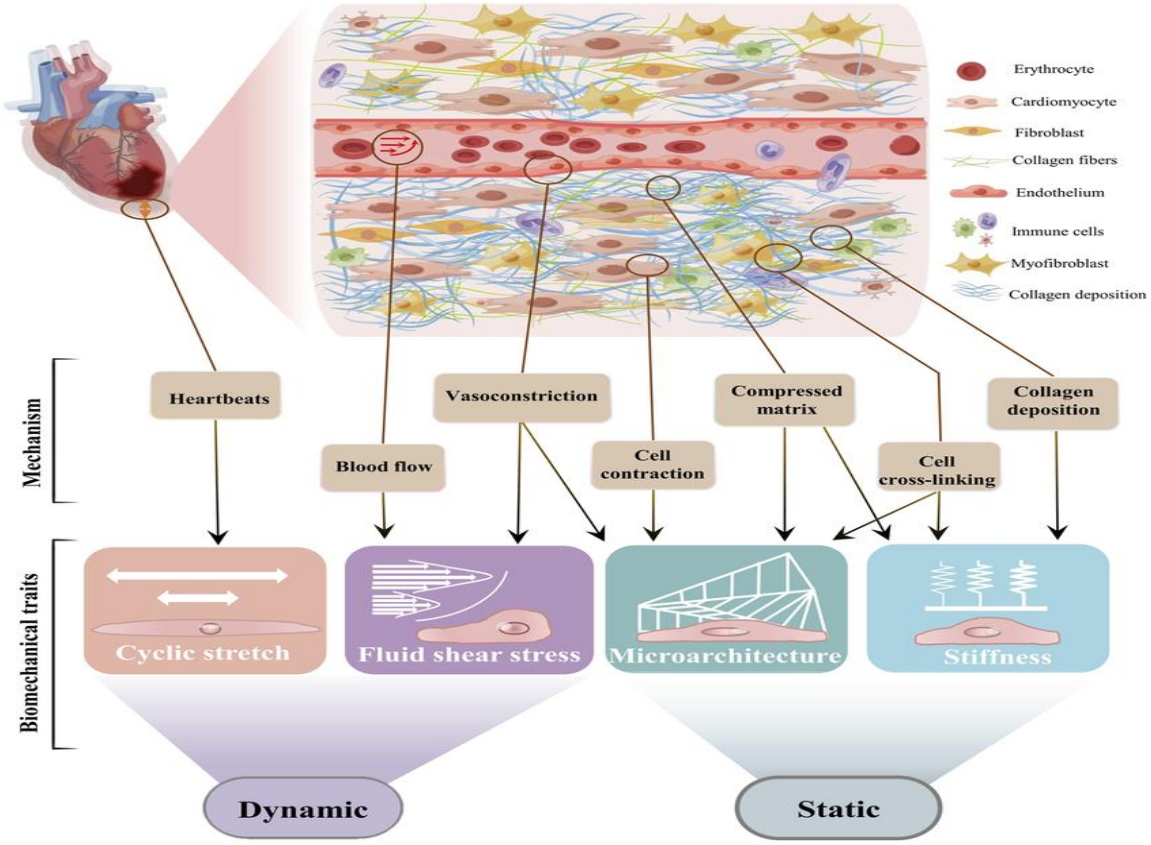
To assess the potential synergistic influence of structural and vascular genetic factors, a combined analysis of COL1A1 and EDN1 gene polymorphisms was performed in subgroups of patients with and without cardiological complications.

Combined genetic risk stratification. All patients in the main group were conditionally stratified into three categories of genetic risk. Low genetic risk included carriers of protective genotypes only (COL1A1 C/C and EDN1 Lys/Lys). Moderate genetic risk was defined as carriage of an unfavorable variant of one of the studied

genes: COL1A1 C/A or A/A in combination with EDN1 Lys/Lys, or EDN1 Lys/Asn or Asn/Asn in combination with COL1A1 C/C. High genetic risk included patients with simultaneous carriage of unfavorable variants of both genes (COL1A1 C/A or A/A combined with EDN1 Lys/Asn or Asn/Asn).

Results of the combined analysis. Patients with cardiological complications demonstrated a higher frequency of combined carriage of unfavorable alleles of COL1A1 and EDN1 compared with patients without complications and the control group. Combined carriage of the A allele of COL1A1 and the Asn allele of EDN1 was associated with a higher proportion of patients with clinical and instrumental signs of cardiological complications.

Integral risk assessment. Based on individual odds ratios for each gene, isolated carriage of the A allele of COL1A1 was associated with an approximately 22% increase in the risk of cardiological complications, while isolated carriage of the Asn allele of EDN1 was associated with an approximately 36% increase in risk. Combined carriage of both alleles demonstrated an additive increase in the estimated risk compared with isolated carriage of either allele.



Schematic representation of the pathogenetic mechanism underlying the development of cardiological complications in combined carriage of COL1A1 and EDN1 gene polymorphisms.

Polymorphism of the COL1A1 gene contributes to impaired type I collagen synthesis, development of fibrosis, and increased myocardial stiffness, whereas polymorphism of the EDN1 gene is associated with endothelial dysfunction, vasoconstriction, and impaired microcirculation. The combined action of these mechanisms leads to structural and vascular remodeling of the heart and the development of cardiological complications.

4. Discussion

The present study provides a comprehensive analysis of the association between polymorphisms of the COL1A1 and EDN1 genes and the development of cardiological complications, allowing evaluation of the contribution of both structural and vascular mechanisms to cardiovascular pathology. The obtained results demonstrate a unidirectional trend toward an increased frequency of the minor alleles A (COL1A1) and Asn (EDN1) in patients with cardiological complications compared with patients without complications and with the control group.

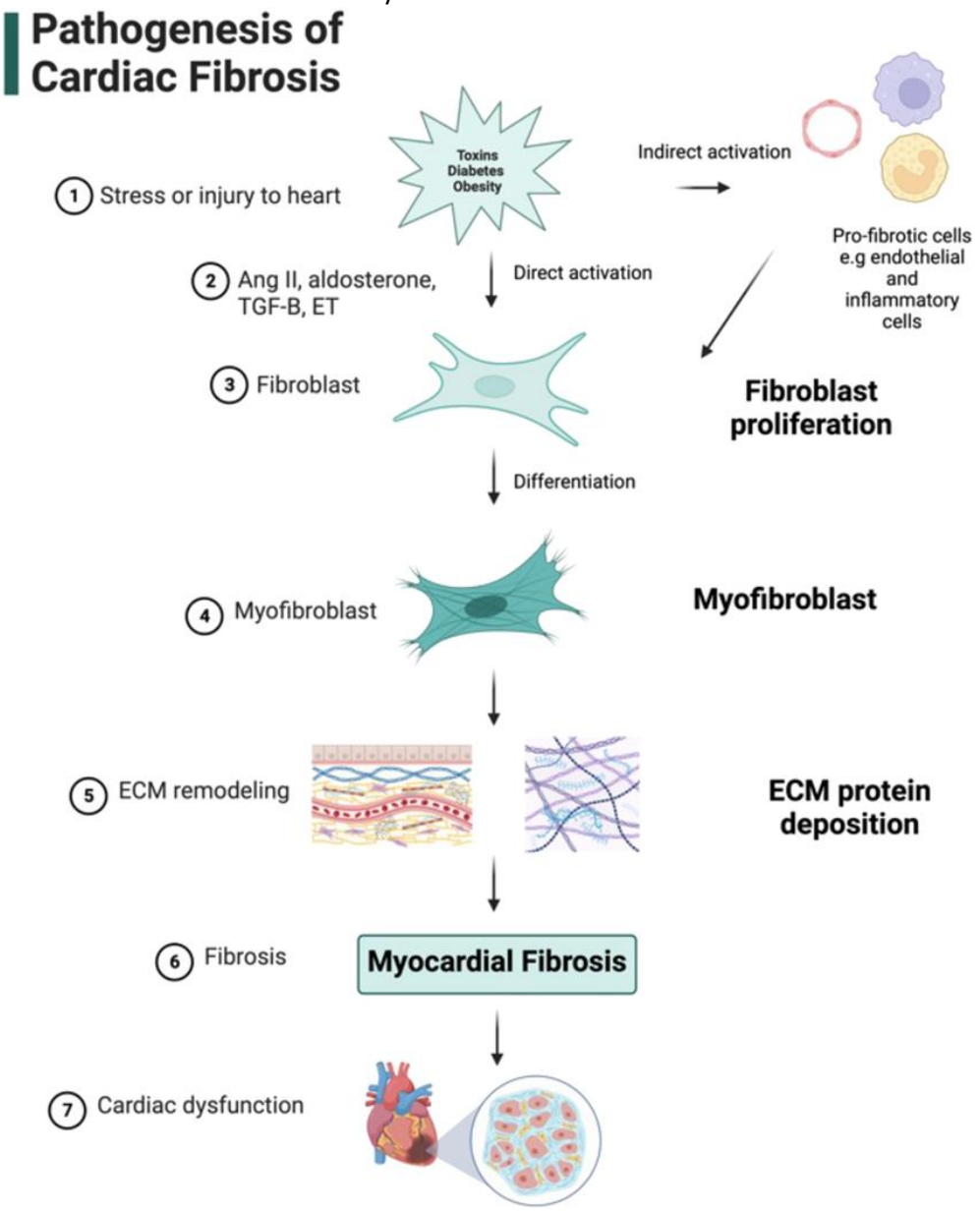
Polymorphism of the COL1A1 gene is associated with alterations in type I collagen synthesis, a key component of the myocardial extracellular matrix. The increased prevalence of the A allele and A/A genotype in patients

with cardiological complications may reflect a predisposition to myocardial fibrosis, increased myocardial stiffness, and impaired diastolic function. These mechanisms are consistent with current concepts regarding the role of collagen remodeling in the progression of structural cardiac abnormalities.

In turn, polymorphism of the EDN1 gene, which encodes endothelin-1, is considered an important genetic factor contributing to endothelial dysfunction. The increased frequency of the Asn allele in patients with cardiological complications suggests a potential enhancement of vasoconstrictive effects, impaired microcirculation, and the development of myocardial ischemia. These processes create an unfavorable hemodynamic background that promotes the progression of functional and structural cardiac changes.

Of particular interest is the combined analysis of COL1A1 and EDN1 polymorphisms, which demonstrated an additive nature of their effects. Simultaneous impairment of myocardial structure (through fibrosis and remodeling) and vascular regulation (through endothelial dysfunction and vasoconstriction) forms a unified pathogenetic cascade leading to structural and vascular remodeling of the heart. This synergy, illustrated in the schematic pathogenetic model, may explain the higher frequency of cardiological complications observed in carriers of unfavorable variants of both genes.

The absence of statistically significant differences in odds ratio calculations may be related to the limited sample size, highlighting the pilot nature of the study. Nevertheless, the observed trends are of clinical relevance and support the feasibility of further investigations with larger sample sizes and the inclusion of multifactorial analysis.



5. Conclusion

Polymorphisms of the COL1A1 and EDN1 genes are associated with an increased frequency of cardiological complications. Carriage of the A allele of the COL1A1 gene is linked to alterations in structural myocardial remodeling, whereas the Asn allele of the EDN1 gene reflects the vascular component of cardiac involvement. The combined effect of these genetic variants results in an additive risk of developing cardiological complications. The obtained findings confirm the relevance of a comprehensive genetic approach to cardiovascular risk assessment. The identified associations may be applied in the future development of personalized strategies for the prevention and monitoring of cardiological complications.

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