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Genetic Polymorphism of The Natriuretic Peptide System and Long-Term Outcomes of Coronary Artery Stenting

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Abstract

The study evaluated the association between genetic polymorphisms of the natriuretic peptide system and long-term outcomes after coronary artery stenting. A total of 112 patients with coronary artery disease who underwent drug-eluting stent implantation were examined. Genetic testing included NPPA rs5065, NPPB rs198389, and NPR3 rs2270915 polymorphisms. The follow-up period was 24 months. Major adverse cardiovascular events were observed in 28 patients, recurrent angina in 31 patients, in-stent restenosis in 17 patients, and repeat revascularization in 14 patients. NPPA rs5065 C allele carriage was associated with a higher risk of adverse cardiovascular events, while NPR3 rs2270915 G allele carriage was associated with in-stent restenosis. NPPB rs198389 C allele carriage was associated with increased NT-proBNP levels.The results indicate that polymorphisms of the natriuretic peptide system may be useful markers for risk stratification and personalized follow-up after coronary artery stenting.

Keywords: Coronary artery disease, coronary stenting, natriuretic peptides, genetic polymorphism, NPPA, NPPB, NPR3, in-stent restenosis.

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1. Introduction

Coronary artery disease remains one of the leading causes of cardiovascular morbidity and mortality. Coronary artery stenting is widely used to restore coronary blood flow and reduce myocardial ischemia. However, despite the use of modern drug-eluting stents, long-term complications may still occur. In the present study, 112 patients with coronary artery disease who underwent coronary artery stenting were analyzed. The mean age of the patients was 61.2 ± 9.4 years. The study group included 76 men and 36 women. Among the examined patients, arterial hypertension was detected in 89 patients, diabetes mellitus in 38 patients, previous myocardial infarction in 44 patients, and multivessel coronary artery disease in 51 patients. These clinical factors are known to increase the risk of recurrent ischemic events, in-stent restenosis, repeat revascularization, and heart failure progression after coronary intervention. During 24 months of follow-up, major adverse cardiovascular events were registered in 28 patients. Recurrent angina was observed in 31 patients, in-stent restenosis in 17 patients, repeat revascularization in 14 patients, myocardial infarction in 6 patients, and hospitalization due to heart failure in 9 patients. These findings indicate that unfavorable long-term outcomes remain clinically relevant even after technically successful stent implantation. The natriuretic peptide system plays an important role in the regulation of vascular tone, blood pressure, myocardial

remodeling, endothelial function, and cardiovascular homeostasis. Genetic polymorphisms of NPPA, NPPB, and NPR3 genes may influence NT-proBNP levels, vascular remodeling, inflammatory response, and individual susceptibility to adverse cardiovascular outcomes. Therefore, assessment of natriuretic peptide system polymorphisms may improve risk stratification and personalized follow-up after coronary artery stenting.

Objective of the Study

The objective of the study was to assess the role of NPPA rs5065, NPPB rs198389, and NPR3 rs2270915 polymorphisms in predicting major adverse cardiovascular events, in-stent restenosis, recurrent angina, repeat revascularization, and changes in NT-proBNP levels during 24-month follow-up after coronary artery stenting.

2. Methods

The study was conducted at the Republican Scientific and Practical Center of Nephrology and Hemodialysis. A total of 112 patients with coronary artery disease who underwent coronary artery stenting were included in the study. The age of the patients ranged from 43 to 78 years, with a mean age of 61.2 ± 9.4 years. The study group included 76 men and 36 women. All patients underwent clinical, laboratory, instrumental, and genetic examination. Clinical assessment included the analysis of cardiovascular risk factors, previous myocardial infarction, arterial hypertension, diabetes mellitus, dyslipidemia, smoking status, and the presence of multivessel coronary artery disease. Arterial hypertension was detected in 89 patients, diabetes mellitus in 38 patients, previous myocardial infarction in 44 patients, and multivessel coronary artery disease in 51 patients. Laboratory examination included complete blood count, fasting blood glucose, glycated hemoglobin, lipid profile, serum creatinine, estimated glomerular filtration rate, and NT-proBNP level. Instrumental examination included electrocardiography, echocardiography, and coronary angiography. Left ventricular ejection fraction was assessed by echocardiography. Genetic testing was performed to identify polymorphisms of the natriuretic peptide system. The analyzed polymorphisms included NPPA rs5065, NPPB rs198389, and NPR3 rs2270915. Genotyping was carried out using polymerase chain reaction-based methods. The follow-up period after coronary artery stenting was 24 months. Long-term outcomes included major adverse cardiovascular events, recurrent angina, in- stent restenosis, repeat revascularization, myocardial infarction, and hospitalization due to heart failure. Statistical analysis was performed using descriptive and comparative methods. Quantitative variables were presented as mean ± standard deviation, while qualitative variables were expressed as absolute numbers. The significance of differences between groups was assessed using standard statistical tests. A p-value of less than 0.05 was considered statistically significant.

3. Results

During the 24-month follow-up period, major adverse cardiovascular events were recorded in 28 patients. Recurrent angina was observed in 31 patients, in-stent restenosis in 17 patients, repeat revascularization in 14 patients, myocardial infarction in 6 patients, and hospitalization due to heart failure in 9 patients. The distribution of NPPA rs5065 genotypes was as follows: TT genotype was detected in 72 patients, TC genotype in 34 patients, and CC genotype in 6 patients. Carriers of the C allele had a higher frequency of major adverse cardiovascular events compared with patients with the TT genotype. Adverse cardiovascular events were detected in 15 C allele carriers and in 13 patients with the TT genotype, $p = 0.03$. The distribution of NPPB rs198389 genotypes was as follows: TT genotype was detected in 39 patients, TC genotype in 52 patients, and CC genotype in 21 patients. Patients carrying the C allele had higher NT-proBNP levels compared with patients without this allele: 198.4 ± 74.6 pg/ml versus 142.7 ± 59.3 pg/ml, $p = 0.01$. The distribution of NPR3 rs2270915 genotypes was as follows: AA genotype was detected in 64 patients, AG genotype in 39 patients, and GG genotype in 9 patients. Carriers of the G allele had a higher frequency of in-stent restenosis. Restenosis was detected in 9 G allele carriers and in 8 patients with the AA genotype, $p = 0.04$. Patients with adverse long-term outcomes had higher NT-proBNP levels and lower left ventricular ejection fraction. The mean NT-proBNP level in patients with major adverse cardiovascular events was 236.8 ± 91.5 pg/ml, while in patients without adverse events it was 151.2 ± 68.4 pg/ml, $p < 0.001$. The mean left ventricular ejection fraction was 49.6 ± 7.8 in patients with adverse events and 56.3 ± 6.9 in patients without adverse events, $p < 0.01$. The obtained results indicate that NPPA rs5065 C allele carriage, NPR3 rs2270915 G allele carriage, elevated NT-proBNP level, reduced left ventricular ejection fraction, diabetes mellitus, and multivessel coronary artery disease were associated with an increased risk of unfavorable long-term outcomes after coronary artery stenting.

4. Discussion

The results of the present study indicate that genetic

polymorphisms of the natriuretic peptide system may be associated with long-term outcomes after coronary artery stenting. During the 24-month follow-up period, major adverse cardiovascular events were recorded in 28 patients, recurrent angina in 31 patients, in-stent restenosis in 17 patients, repeat revascularization in 14 patients, myocardial infarction in 6 patients, and hospitalization due to heart failure in 9 patients. These data confirm that adverse cardiovascular events remain clinically relevant even after successful percutaneous coronary intervention. According to current recommendations, coronary artery stenting is an important method of myocardial revascularization in patients with coronary artery disease. However, long-term prognosis after stenting depends not only on procedural success, but also on clinical, angiographic, biochemical, and genetic factors [1,2]. In the present study, diabetes mellitus, multivessel coronary artery disease, elevated NT-proBNP level, reduced left ventricular ejection fraction, and unfavorable genetic variants were associated with a higher risk of adverse outcomes. The natriuretic peptide system plays an important role in cardiovascular regulation, including blood pressure control, vascular tone, natriuresis, myocardial remodeling, endothelial function, and inhibition of fibrosis. Genetic variants in the NPPA and NPPB gene region have been shown to influence circulating natriuretic peptide levels and blood pressure regulation [3]. These mechanisms may be important in patients after coronary stenting, because vascular remodeling, endothelial dysfunction, and myocardial stress are closely related to restenosis and recurrent ischemic events. In our study, carriers of the NPPA rs5065 C allele had a higher frequency of major adverse cardiovascular events compared with patients with the TT genotype. This may indicate the possible influence of NPPA polymorphism on atrial natriuretic peptide activity, endothelial response, vascular tone, and myocardial remodeling. Previous studies have also reported associations between natriuretic peptide gene variants and cardiometabolic and cardiovascular phenotypes [3,4]. The NPPB rs198389 polymorphism was associated with higher NT-proBNP levels. Patients carrying the C allele had significantly higher NT-proBNP values compared with patients without this allele. Similar data have been reported in the literature, where the NPPB promoter polymorphism was associated with elevated NT-proBNP concentrations and blood pressure-related phenotypes [5]. In the present study, this polymorphism was more strongly related to biomarker expression than to independent prediction of clinical events after adjustment for other risk factors. The NPR3 rs2270915 G allele was associated with a higher frequency of in-stent restenosis. NPR3 encodes the natriuretic peptide clearance receptor, which participates in the regulation of natriuretic peptide availability and vascular remodeling. Literature data indicate that NPR3 polymorphisms may be associated with blood pressure regulation and cardiovascular structural changes [6,7]. Therefore, the observed association between NPR3 rs2270915 and restenosis may be explained by altered vascular response to injury, endothelial dysfunction, smooth muscle cell proliferation, and neointimal hyperplasia after stent implantation. An important finding of the study was the association between elevated NT-proBNP level and adverse long-term outcomes. Patients with major adverse cardiovascular events had higher NT-proBNP levels and lower left ventricular ejection fraction. NT-proBNP is widely used as a marker of myocardial stress and heart failure risk, and its elevation after coronary intervention may reflect subclinical myocardial dysfunction, residual ischemia, or increased cardiovascular risk [8]. The obtained results suggest that the combination of genetic testing and traditional clinical assessment may improve risk stratification after coronary artery stenting. Patients with NPPA rs5065 C allele carriage, NPR3 rs2270915 G allele carriage, elevated NT-proBNP level, diabetes mellitus, reduced left ventricular ejection fraction, and multivessel coronary artery disease may require closer follow-up and more intensive secondary prevention. Thus, genetic polymorphisms of the natriuretic peptide system may serve as additional molecular markers for predicting unfavorable long-term outcomes after coronary artery stenting. The integration of molecular-genetic markers with clinical, angiographic, and biochemical predictors may contribute to the development of a personalized approach to the management of patients with coronary artery disease after percutaneous coronary intervention.

5. Conclusions

1. Genetic polymorphisms of the natriuretic peptide system are associated with long-term outcomes after coronary artery stenting in patients with coronary artery disease.

2. NPPA rs5065 C allele carriage was associated with a higher frequency of major adverse cardiovascular events during the 24-month follow-up period.

3. NPPB rs198389 C allele carriage was associated with increased NT-proBNP levels, reflecting greater myocardial stress and higher cardiovascular risk.

4. NPR3 rs2270915 G allele carriage was associated with a higher frequency of in-stent restenosis, suggesting a

possible role of natriuretic peptide receptor signaling in vascular remodeling after stent implantation.

5. Combined assessment of genetic markers, NT-proBNP level, left ventricular ejection fraction, diabetes mellitus, and multivessel coronary artery disease may improve personalized risk stratification and follow-up after coronary artery stenting.

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