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FGF-21: a novel biomarker predicting no-reflow in ST-segment elevation myocardial infarction

D. KOPRULU[1], K. TOPRAK[2], G. GENC TAPAR[3], M. OCAK[4]

[1]Department of Cardiology, Ordu State Hospital, Ordu, Turkiye
[2]Cardiology Department, Faculty of Medicine, Harran University, Şanlıurfa, Turkiye
[3]Department of Cardiology, Tokat Gaziosmanpasa University, Tokat, Turkiye
[4]Department of Emergency Medicine, Samsun Education and Training Hospital, Samsun, Turkiye

Abstract. – OBJECTIVE: Primary percutaneous coronary intervention (pPCI) is the most effective reperfusion therapy in the treatment of ST-elevation myocardial infarction (STEMI). Although the infarct-related artery of STEMI patients is effectively revascularized during pPCI, effective reperfusion in the myocardial tissue may not be achieved. This condition is called the no-reflow (NR) phenomenon. FGF-21 is a circulating hormone-like molecule primarily secreted by the liver and has been proven to be the main metabolic regulator of glucolipid metabolism and insulin sensitivity. The aim of this study was to investigate the predictive effect of FGF-21 on the development of the NR phenomenon in STEMI patients undergoing pPCI.

PATIENTS AND METHODS: This study included 91 patients with acute STEMI who underwent pPCI and 45 healthy participants. Patients with acute STEMI were split into two groups: 46 patients in the NR phenomenon group and 45 patients in the non-NR phenomenon group. Serum levels of FGF-21 were measured in all study groups.

RESULTS: Serum FGF-21, white blood cell count, and high-sensitivity C-reactive protein (hs-CRP) values were considerably different amongst the groups ($p = 0.001$, $p = 0.001$, and $p = 0.003$, respectively). In comparison to patients without NR and the control group, STEMI patients with NR had considerably higher FGF-21 levels. In addition, the FGF-21 level of STEMI patients without NR was significantly higher than that of the control group. In multivariate logistic regression analysis, hs-CRP [odds ratio (OR) 2.106% 95% confidence interval (CI) (0.002-0.069) $p = 0.038$], age [OR 2.147; 95% (CI) (0.001-0.015); $p = 0.0035$], and serum FGF-21 levels [OR 4.644; 95% CI (0.003-0.006); $p < 0.001$] were independent predictors of NR formation. For FGF-21 ≥ 92.2 pg/MI, 87% sensitivity and 88% specificity were found in predicting NR formation (area under the curve: 0.897, 95% CI: 0.841-0.954; $p < 0.001$).

CONCLUSIONS: Our study demonstrates a strong association between the NR phenomenon, a key indicator of poor prognosis in acute STEMI patients, and an elevated FGF-21 level. These findings indicate FGF-21 as a novel and potent predictor of NR development in STEMI patients.

Key Words:
ST-elevation myocardial infarction, No-reflow phenomenon, FGF-21, Primary percutaneous coronary intervention.

Introduction

Acute myocardial infarction (AMI) is a leading cause of death worldwide. The most severe clinical manifestation of AMI, ST-elevation myocardial infarction (STEMI), necessitates prompt identification and intervention[1]. The primary objective of AMI treatment remains early revascularization of the culprit coronary artery lesion, with primary percutaneous coronary intervention (pPCI) being the most effective reperfusion strategy[2,3].

Despite successful revascularization of the infarction-related artery during pPCI, STEMI patients can experience inadequate myocardial reperfusion, a phenomenon termed no-reflow (NR)[3]. Previous studies[4,5] have reported a prevalence of NR ranging from 1-40%. This phenomenon is significantly associated with adverse outcomes in AMI patients, such as early and delayed cardiac mortality, congestive heart failure, and malignant arrhythmia. Although the exact pathogenesis of NR remains unclear, several hypotheses have been proposed, including distal microembolization of thrombus fragments due to local platelet activation, microvascular spasm, and ischemia or reperfusion injury[6,7].

Although advancements in pPCI have significantly improved outcomes, NR is associated with a significantly poor prognosis in STEMI patients[8]. Previous studies[1,4,8] have identified predictors of the NR phenomenon, potentially guiding

Corresponding Author: Diyar Koprulu, MD; e-mail: ordudhs9@saglik.gov.tr; drkoprulu12@icloud.com

treatment strategies and improving outcomes for STEMI patients undergoing pPCI.

Fibroblast growth factor (FGF) plays a crucial role in maintaining body glycolipid metabolism balance and in endocrine functions. It regulates various pathophysiological processes, including cell proliferation, body development, vascular proliferation, and wound healing. FGF-21 is expressed primarily in the liver and adipose tissues[9].

FGF-21, a circulating hormone-like molecule secreted primarily by the liver, is a member of the FGF-19 subfamily and a key metabolic regulator of glucolipid metabolism and insulin sensitivity[10,11]. Previous studies[12,13] have further elucidated its metabolic effects, demonstrating elevated serum FGF-21 levels in obesity, metabolic syndrome, and diabetes mellitus. Furthermore, recent studies[14-16] have revealed an active role of FGF-21 in critical conditions, such as AMI, acute kidney failure, congestive heart failure, septic shock, and acute liver injury.

We evaluated the value of FGF-21 as a predictor of the NR phenomenon in STEMI patients undergoing pPCI.

Patients and Methods

Study Design

This case-control study enrolled 91 STEMI patients who underwent pPCI and 45 healthy controls. The STEMI patients were categorized into non-NR (n = 45) and NR (n = 46) groups. Patients with preexisting coronary artery disease, heart failure, severe heart valve disease, cancer, hematological and rheumatic disorders, kidney failure, and liver disease or those who declined participation were excluded. The Local Ethics Committee approved the study protocol. The study was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients.

According to the fourth universal definition of myocardial infarction, the diagnosis of STEMI was confirmed, and therapy was administered in accordance with the recommendations of the American Heart Association. The NR phenomenon was defined as a Thrombolysis in Myocardial Infarction score < 2 without dissection or stenosis. The anatomical extent and severity of coronary artery disease were calculated using the SYNTAX score, accessed from http://www.syntaxscore.com.

Primary Percutaneous Intervention

All participants underwent coronary angiography using the Judkins technique. pPCI was performed using a 6F or 7F guiding catheter via the femoral artery or a 6F guiding catheter via the radial artery. Before the procedure, patients were administered ticagerol 180 mg (AstraZeneca, İstanbul, Turkiye), aspirin 300 mg (Ali Raif, İstanbul, Turkiye), and an intravenous bolus of unfractionated heparin 70 U/kg (Gensenta, İstanbul, Turkiye). During the procedure, additional intravenous heparin was administered to maintain an activated clotting time > 250 s, ensuring effective anticoagulation. A drug-eluting stent was implanted in the culprit artery responsible for the infarction. Treatment for patients in the NR group followed current guidelines[17]. Intracoronary vasodilators and glycoprotein IIb/IIIa inhibitors (Farma-Tek, İstanbul, Turkiye) were used depending on the operator's preference.

Biochemical Analysis and Serum FGF-21 Measurement

After the initial electrocardiography assessment, blood samples were obtained from drug-free patients without additional interventions. The blood samples were centrifuged at 3,000 rpm for 10 min, and serum aliquots were stored at -80°C until analysis of laboratory values. Standard laboratory techniques were used to measure blood glucose, electrolyte, total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglyceride levels. Serum FGF-21 levels were determined using an enzyme-linked immunosorbent assay following the manufacturer's instructions.

Statistical Analysis

Statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). The normality of data was assessed using the Kolmogorov-Smirnov test. Continuous variables are expressed as the mean ± standard deviation. Two groups were compared using the Mann-Whitney U test or Student's *t*-test, whereas three groups were compared using the Kruskal-Wallis test or one-way analysis of variance. The Chi-square test was used to compare categorical variables. Correlation analysis was performed to determine the relationship between the FGF-21 level and other continuous variables. Univariate analysis was used to identify potential risk factors for NR development, and multivariate logistic regression was used to identify independent predictors of NR development. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal FGF-21 level threshold for predicting NR development

following pPCI in STEMI patients. *p*-values < 0.05 were considered statistically significant.

Results

Table I presents the clinical and laboratory characteristics of the study population. Although no significant differences were observed in sex, body mass index, or diabetes, hypertension, and smoking statuses ($p > 0.05$), age and the SYNTAX score demonstrated significant variations $p = 0.029$ and $p = 0.05$, respectively). Significant differences were observed among the three groups in the first acceptable serum measurement of FGF-21, white blood cell count, and high-sensitivity C-reactive protein level ($p = 0.001$, $p = 0.001$, and $p = 0.003$, respectively). Pairwise comparisons were conducted to elucidate the clinical significance of the FGF-21 level further. The FGF-21 level was significantly higher in STEMI patients with NR than in those without NR or the control group. Furthermore, STEMI patients without NR exhibited a significantly higher FGF-21 level compared with the control group (Figure 1).

Correlation analysis revealed that the FGF-21 level was positively correlated with age (r

Table I. Baseline characteristics of the study population.

Variables	NR+STEMI group (n: 46)	STEMI (not NR) group (n: 45)	Control Group (n: 45)	*p*-values
Age (years)	63.7 ± 7.1	57.5 ± 16.3	58.8 ± 9.6	0.029
Male gender (%)	34 (74)	21 (47)	26 (58)	0.043
Body mass index (kg/m²)	26.3 ± 4.9	26.7 ± 4.1	25.8 ± 3.5	0.641
Hypertension (%)	15 (33)	11 (24)	14 (31)	0.872
Hemoglobin (g/dL)	13.6 ± 1.7	13.9 ± 1.6	13.1 ± 1.5	0.055
WBC (10^3/µL)	11.76 ± 3.4	11.58 ± 3	7.65 ± 2.5	0.001
Platelets (10^3/µL)	259 ± 62	264 ± 73	254 ± 57	0.775
Total cholestrol (mg/dL)	170 ± 41	178 ± 53	179 ± 61	0.673
HDL (mg/dL)	39 ± 11	46 ± 18	43 ± 17	0.091
LDL (mg/dL)	114 ± 39	118 ± 42	116 ± 41	0.851
hs-CRP (mg/dL)	4.3 ± 3.3	3.2 ± 1.8	1.69 ± 1.9	0.001
FGF-21 (pg/mL)	132.3 ± 54	88.55 ± 19	78.95 ± 13	0.001
Syntax score	28.8 ± 7.1	25.5 ± 8.5	0	0.05
Stent length (mm)	28.9 ± 7.6	27.5 ± 6.4	0	0.340

WBC: White blood cell. HDL: High-density lipoprotein. LDL: Low-density lipoprotein. FGF-21: Fibroblast growth factor 21. hs-CRP: High-sensitive C-reactive protein.

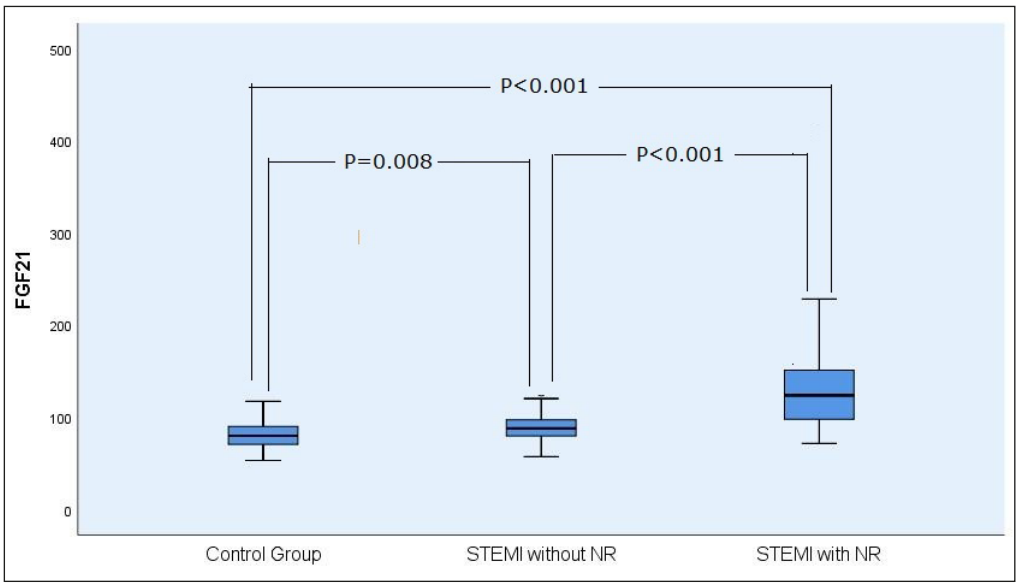

Figure 1. Comparison of FGF-21 level among all groups.

= 0.163, p = 0.063), SYNTAX score (r = 0.246, p = 0.019), high-sensitivity C-reactive protein level (r = 0.195, p = 0.025), and white blood cell count (r = 0.300, p = 0.001) but negatively correlated with systolic blood pressure (r = 0.158, p = 0.067). Univariate regression analysis identified age, SYNTAX score, high-sensitivity C-reactive protein level, and FGF-21 level as potential risk factors for NR development. Subsequently, multivariate logistic regression analysis confirmed the serum FGF-21 level as an independent predictor of NR (odds ratio 4.644; 95% confidence interval 0.003-0.006; $p < 0.001$; Table II). ROC analysis was used to determine the optimal FGF-21 threshold value for predicting NR development following pPCI in STEMI patients. An FGF-21 level of ≥ 92.2 pg/mL exhibited high sensitivity (87%) and specificity (88%) for predicting NR, with an area under the curve of 0.897 (95% confidence interval 0.841-0.954; $p < 0.001$; Figure 2).

Discussion

Our study demonstrates that the FGF-21 level is a potent independent predictor of the NR phenomenon in STEMI patients. Notably, the FGF-21 level was significantly higher in STEMI patients without NR compared with the control group. A threshold FGF-21 level of ≥ 92.2 pg/mL exhibited 87% sensitivity and 88% specificity in predicting NR in this population. To our knowledge, this is the first study to investigate the potential of FGF-21 to predict NR in STEMI patients. This novel insight contributes to our understanding of the NR phenomenon and its implications for treatment and follow-up strategies in STEMI patients.

NR is associated with poor prognosis and adverse cardiac events in STEMI patients treated with pPCI[1]. Although the exact mechanisms underlying NR remain unclear, several contributing factors have been proposed. Distal embolization is considered the primary driver, with microvascular spasm and ischemia/reperfusion injury potentially playing roles in NR development. Moreover, thrombus size, age, pain-to-balloon time, and stent length have been associated with NR development. Multiple studies[1,4-8] have demonstrated the ability of these factors to predict NR in STEMI patients undergoing pPCI. FGF-21, produced in the liver, pancreas, skeletal muscle,

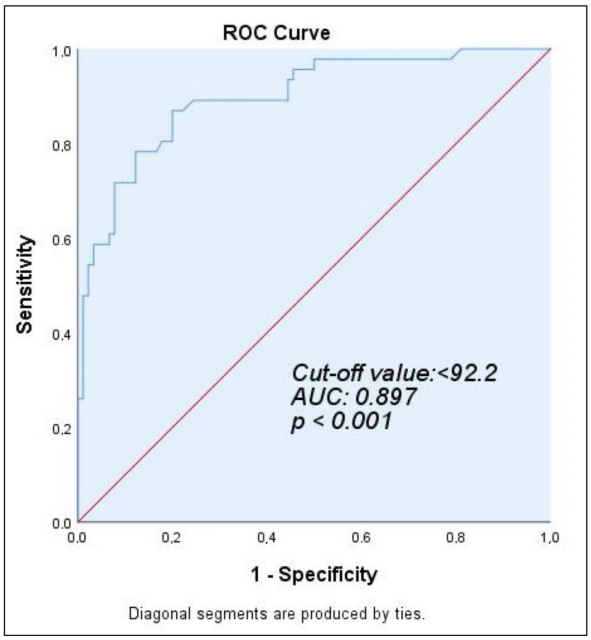

Figure 2. ROC of FGF-21 and the no-reflow phenomenon.

Table II. Univariate and multivariate logistic regression analysis representing the independent predictors of NR phenomenon.

	Univariate		Multivariate	
Variables	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
hs-CRP	1.174 (0.997-1.382)	0.054	1.115 (0.89-1.396)	0.362
Syntax score	1.054 (.999-1.113)	0.056	1.015 (0.974-1.087)	0.674
FGF-21	1.063 (1.035-1.092)	0.0001	1.058 (1.028-1.088)	< 0.001
Diabetes mellitus	1.368 (0.554-3.375)	0.497		
Hypertension	1.276 (0.504-3.228)	0.607		
Stent length	1.029 (0.97-1.092)	0.339		
Body mass index	0.983 (0.896-1.077)	0.706		
Platelet	0.999 (0.993-1.005)	0.728		
Age	1.043 (1.005-1.082)	0.027	1.036 (0.997-1.077)	0.091

FGF-21: Fibroblast growth factor 21. hs-CRP: High sensitive c reactive protein.

and adipose tissue, originates mainly in the liver under normal metabolic conditions. Liver FGF-21 synthesis is induced by prolonged fasting, stimulating ketogenesis, gluconeogenesis, and hepatic fatty acid oxidation[18]. FGF-21 synthesis in skeletal muscle increases under stress conditions, including mitochondrial myopathies. Several studies[19] have demonstrated that FGF-21 enhances skeletal muscle insulin sensitivity by enhancing glucose uptake. Furthermore, intracerebroventricular FGF-21 injection in rats[20] increases sympathetic activity, insulin sensitivity, and energy expenditure. The FGF-21 level is elevated in various human diseases, including metabolic syndrome, obesity, cardiovascular diseases, non-alcoholic fatty liver disease, diabetes mellitus, mitochondrial myopathies, and cold exposure[14]. However, the mechanisms underlying its cardioprotective properties remain unclear; potential cardioprotective effects include lowering blood pressure, improving lipid profiles, and regulating glucose and insulin homeostasis[21]. Previous studies[22,23] have demonstrated that FGF-21 autocrine upregulation of genes, such as uncoupling protein 3 and superoxide dismutase 2, reduces oxidative stress in cardiomyocytes. Conversely, several studies[9,11,15,16] have demonstrated significantly elevated FGF-21 levels in coronary artery disease, heart failure, and cardiometabolic disorders, suggesting a potential association with poor prognosis. Consistent with prior studies in the literature, our study confirmed an elevated FGF-21 level in STEMI patients. Furthermore, NR, a key indicator of poor prognosis in STEMI patients, was elevated in all groups.

Limitations

Our study has several limitations. The primary limitation is its single-center design and recruitment of a limited number of patients. In addition, the lack of serial FGF-21 measurements after pPCI and investigations into the association of FGF-21 with in-hospital and out-of-hospital mortality or prognosis warrants further studies.

Conclusions

Our study demonstrates a strong association between the NR phenomenon, a key indicator of poor prognosis in acute STEMI patients, and an elevated FGF-21 level. These findings indicate FGF-21 as a novel and potent predictor of NR development in STEMI patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding

None.

Data Availability

All data generated or analyzed during this study are included in this published article (and/or its supplementary material).

Authors' Contributions

Concept: D. Koprulu, G. Genc Tapar, K.Toprak. Design: D. Koprulu, G. Genc Tapar, K. Toprak. Supervision: D. Koprulu, G. Genc Tapar, K. Toprak, M. Ocak. Materials: D. Koprulu, G. Genc Tapar, K. Toprak, M. Ocak. Data collection and/or processing: D. Koprulu, G. Genc Tapar, K. Toprak, M. Ocak. Analysis and/or interpretation: D. Koprulu, K. Toprak, M. Ocak. Literature search: D. Koprulu, G. Genc Tapar, K. Toprak, M. Ocak. Writing: D. Koprulu, G. Genc Tapar, K. Toprak, M. Ocak. Critical review: M. Ocak, K. Toprak.

Ethics Approval

This study was approved by the Harran University Faculty of Medicine Ethics Committee (Date: 27/03/2023; No.: 23/05/11).

Informed Consent

Informed consent was obtained from all the study participants.

ORCID ID

Diyar Koprulu: 0000-0002-0001-5080
Kenan Toprak: 0000-0001-8923-8709
Gulsen Genc Tapar: 0000-0001-6840-5459
Metin Ocak: 0000-0002-9978-0216

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