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Pentraxin 3 is Associated with Worse Outcome in Non-ST-Segment Elevation Myocardial Infarction

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ABSTRACT

Background: Pentraxin 3 (PTX3) is a more specific marker of vascular inflammation than C - reactive protein (CRP).

Objectives: The present study aimed to demonstrate the association between PTX3 and markers of adverse events and poor prognosis in patients with Non-ST-segment Elevation Myocardial Infarction (NSTEMI).

Patients and Methods: This case-control study was conducted on 36 patients (10 females, mean age: 58 ± 11 years) with NSTEMI who had admitted to the Cardiology Clinic of Kartal Koşuyolu Heart Research Hospital and 35 age- and gender-matched healthy controls (26 females, mean age: 56 ± 9 years) between January and May 2013. PTX3 levels were measured in the controls and at the 8th and 24th hours of chest symptoms in the patients undergoing coronary angiography during admission.

Results: The patients group had significantly higher PTX-3 levels at both 8th and 24th hours compared to the control group (2.6 ± 3.1 vs. 1.9 ± 2.1 ng/mL, $P < 0.001$ at the 8th hour; 4.8 ± 7.6 vs. 1.9 ± 2.1 ng/mL, $P < 0.010$ at the 24th hour). The results showed a significant correlation between PTX3 level and Killip class ($r = 0.34$, $P = 0.040$ at the 8th hour; $r = 0.43$, $P = 0.009$ at the 24th hour). Besides, serum PTX3 level was positively correlated to the SYNTAX score ($r = 0.57$, $P < 0.001$ at the 8th hour) and negatively correlated to hemoglobin level ($r = -0.37$, $P = 0.020$).

Conclusions: Among the patients with NSTEMI, PTX3 level was associated with markers of higher risk and worse prognosis (GRACE score, hsCRP, age, NT-proBNP, and hemoglobin). Thus, PTX3 level might be used as a novel cardiac biomarker to determine high-risk patients.

►*Implication for health policy/practice/research/medical education:*
Pentraxin 3 is a novel biomarker that is in the same family as C-reactive protein (Crp). It seems to be used in prognostication of various cardiovascular disorders. We aimed to demonstrate if there is any association between Pentraxin 3 levels and worse outcome measures in patients with non-ST-segment elevation myocardial infarction.

1. Background

Inflammation has a significant role in atherosclerotic plaque formation, progression, rupture, and eventual thrombus occurrence on the plaque (1-3). Pentraxin 3 (PTX3) has been known as a novel biomarker assumed to be more specific to vascular inflammation than other proteins in the pentraxin family, such as C-Reactive Protein (CRP) (4). It is an early indicator of activation of both immune and inflammatory responses. Its plasma levels rapidly increase during Cardiovascular (CV) events as a consequence of immediate synthesis by various cell types (5-8). It is found also in the intact myocardium, increases in the blood of patients with acute Myocardial Infarction (MI), and represents an early marker of irreversible injury of myocytes in ischemic cardiomyopathy (8).

PTX3 is a more specific biomarker than Neutrophil Activating Peptide-2 (NAP-2) and 22troponin I in unstable angina pectoris, Non-ST-segment Elevation

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Myocardial Infarction (NSTEMI), and ST-segment Elevation Myocardial Infarction (STEMI) (9). PTX3 serum concentration reaches the peak levels earlier compared to CRP plasma levels up to 7 hours after the onset of symptoms in patients with STEMI (8). PTX 3 has anti-inflammatory, anti-atherosclerotic, and cardioprotective effects (10-12). It is produced in and secreted from the vascular tissue and is related to development of atherosclerosis (13).

Increased PTX3 levels are associated with worse CV outcomes in cardiac patients (6, 14). The biologic probability of its role in cardiac risk is supported by its presence in atherosclerotic plaques (13, 15) as well as in the coronary sinus of patients with heart failure. The Killip class as a component of the Global Registry of Acute Coronary Events (GRACE) score and a marker of the severity of Acute Coronary Syndromes (ACS) is independently associated with PTX3 concentrations in subjects with all ACS subsets (16).

Elevated PTX3 level in patients with STEMI treated with primary percutaneous coronary intervention is related to complicated coronary plaques and decreased myocardial perfusion (17). Similar to its role in ACS, it was demonstrated that PTX3 was related to the complexity and severity of coronary artery disease in patients with stable angina pectoris (18).

Whether PTX3 is correlated to high-risk markers [CRP, GRACE score, Ejection Fraction (EF), Killip class, and N-Terminal pro-Brain Natriuretic Peptide (NT- proBNP)] or not in patients with NSTEMI has not been well studied.

2. Objectives

The present study aims to investigate whether PTX3 is related to markers of adverse events and poor prognosis.

3. Patients and Methods

The present study was conducted on 36 patients who presented with NSTEMI in Kartal Koşuyolu Heart Research and Training Hospital and 35 age- and gender-matched outpatient healthy controls with a negative treadmill or myocardial perfusion scan test between January and May 2013. The inclusion criteria of the study were resting pain lasting for more than 10 minutes together with transient ST elevation of 0.1 mV (< 30 minutes), ST depression of at least 0.05 mV, T wave inversion of 0.1 mV in two adjacent derivations, or cardiac troponin I elevation (> 0.1 ng/mL). On the other hand, the patients with a persistent (> 30 min) ST-segment elevation of at least 0.1 mV in at least two contiguous leads or a presumed new left bundle branch block, renal failure (serum creatinine concentration > 2.0 mg/dL), malignancy, or acute/chronic inflammatory disease and those treated with non-steroidal anti-inflammatory drugs or steroids were excluded from the study.

The study was approved by the local ethics board of Kartal Koşuyolu Heart Research and Training Hospital, and all the participants provided written informed consents prior to enrolment. The Gensini score was used to assess the severity of coronary artery lesions. Treatments were carried out according to the USAP/NSTEMI guidelines. All the patients underwent selective coronary artery angiography after appropriate patient preparation. Coronary angiographic examination was performed using Judkins method via the femoral approach.

Initially, the participants' clinical and demographic characteristics, such as age, gender, coronary risk factors, previous MI history, Killip classification at the time of admission, the performed procedure, and systolic and diastolic blood pressures, were recorded. Venous blood samples were taken from all the patients at the 8th and 24th hour after onset of pain. The samples were then placed in tubes containing EDTA and were stored at 70 ˚C. The samples were studied using Quantified PTX3 ELISA method (produced by R&D SYSTEMS, United States of America). The minimum value of PTX3 that can be measured by this method is 0.007 - 0.116 ng/mL, with the mean value of 0.025 ng/mL. The plasma level of PTX3 is 0.65 ng/mL in normal adults. CK, CK-MB, troponin I (during presentation and at the 8th and 24th hours), creatinine, hemoglobin, glucose, NT-proBNP (at the 8th and 24th hours), and lipid values were measured among the patients. Acute MI was defined as a cardiac troponin I level > 0.1 ng/mL of the upper reference limit on admission or 8 h after admission.

Echocardiography was conducted for all the patients at the 24th hour and the Wall Motion Score Index (WMSI) was calculated. The GRACE risk score was calculated, as well. The patients were divided into two groups of high and low according to the GRACE risk scores (high risk > 130, low risk < 130).

The SYNTAX score was used to grade the complexity of coronary artery disease. Coronary artery lesions with a stenosis diameter of ≥ 50% were calculated in ≥ 1.5 mm vessels. The latest online updated version (2.11) was used for computation of the SYNTAX scores (www.syntaxscore.com). The SYNTAX scores were classified as low (≤ 22), intermediate (23 - 32), and high (≥ 33). It should be noted that all the angiographic variables of the SYNTAX scores were computed by two experienced cardiologists who were blinded to the procedural data and clinical outcomes. The final decision was made by consensus in case of conflicts.

3.1. Statistical Analysis

All the statistical analyses were performed using the SPSS statistical software, version 17 (SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation, whereas the categorical ones were presented as percentages. The differences between the normally distributed continuous variables were evaluated using student's t-test, while non-normally distributed variables were analyzed by Mann-Whitney U-test or Kruskal-Wallis analysis as appropriated. Besides, chi-square test was used to compare the categorical variables. Moreover, correlations among the variables were assessed using Spearman's test. P value < 0.05 was considered as statistically significant.

4. Results

Baseline and clinical characteristics of the patients and controls have been presented in Table 1. Accordingly, the study population consisted of 26 female and 10 male patients with NSTEMI with the mean age of 58 ± 11 years and 26 female 9 male healthy controls with the mean age of 56 ± 9 years (P = 0.300). Besides, 19 patients were 60

Table 1. Socio-Demographic and Clinical Characteristics of the Patients and Healthy Controls

Characteristics	Patients (N = 36)	Controls (N = 35)	P value
Age (years)	58 ± 11	56 ± 9	0.300
Sex, male, n (%)	10 (27.8)	9 (25.7)	0.210
Hypertension, n (%)	24 (66.7)	22 (62.8)	0.400
Diabetes, n (%)	15 (41.7)	13 (37.1)	0.320
Hyperlipidemia, n (%)	16 (44.4)	14 (40)	0.250
Current smoker, n (%)	17 (47.2)	15 (42.8)	0.260
Creatinine, mg/dL	0.87 ± 0.36	0.85 ± 0.34	0.340
Ejection fraction (%)	62 ± 4.3	64 ± 6.2	0.280
Killip class > 1, n (%)	3 (8.3)	NA	
SYNTAX score (low/intermediate/high) (%)	25/39/36	NA	

The data are expressed as means ± SD, number (n), or percent.

years old or above. The patients' PTX3 levels at the time of admission, the 8th hour, and the 24th hour were compared to the control group's plasma PTX3 levels, and the differences were found to be statistically significant (2.6 ± 3.1 vs. 1.9 ± 2.1 ng/mL, P < 0.001 at the 8th hour; 4.8 ± 7.6 vs. 1.9 ± 2.1 ng/mL, P < 0.010 at the 24th hour) (Table 2).

PTX-3 levels were higher in the high SYNTAX group compared to the intermediate SYNTAX group (N = 14) (3.4 ± 3.3 vs. 2.3 ± 3.1 ng/mL, P < 0.010 at the 8th h) and the low SYNTAX group (3.4 ± 2.7 vs. 2.1 ± 2.9 ng/mL, P < 0.001 at the 8th h). However, PTX3 levels were comparable between the low and intermediate SYNTAX groups (2.1 ± 2.9 vs. 2.3 ± 3.1 ng/mL, P = 0.060). PTX3 level was positively correlated to the SYNTAX score (r = 0.57, P < 0.001 at the 8th hour).

When the patients were grouped according to electrocardiographic (ECG) findings as with dynamic ECG changes, without dynamic ECG changes, and with transient ST elevation, no statistically significant relationship was found between the ECG findings and PTX3 levels (P = 0.700 at the 8th hour, P = 0.090 at the 24th hour).

According to the Killip classification system, the patients were categorized as class 1 and class 2 (3 patients were in class 2). Based on the results, the PTX3 level was higher in the patients in class 2 compared to those in class 1 at the 8th and 24th hours (P = 0.04 at the 8th hour, P = 0.009 at the 24th hour). Also, the PTX3 levels were higher in the patients aged above 60 years compared to the young ones (P = 0.006).

Moreover, the PTX3 levels were significantly higher in the patients with CRP levels > 0.9 mg/mL at the 24th hour (P = 0.020). Furthermore, the PTX3 levels were significantly higher among the patients with high compared to those with low GRACE risk scores (P = 0.030).

The results showed a moderate correlation between age and the 24th hour PTX3 level (r = 0.43, P < 0.009). Also, a linear correlation was found between the patients' Killip class and PTX3 levels at the 8th and 24th hours (r = 0.34, P = 0.04 at the 8th hour; r = 0.43, P < 0.010 at the 24th hour). Besides, a correlation was observed between the CRP levels and the 24th hour PTX3 level (r = 0.37, P < 0.020). In addition, PTX3 level at the 8th hour was significantly related to WMSI (r = 0.35, P = 0.032) (Table 3).

The study findings revealed a moderate correlation between the 24th hour PTX3 level and both GRACE risk score and NT proBNP levels (GRACE: r = 0.40, P = 0.010; NT- proBNP: r = 0.38, P = 0.020). An inverse correlation was also found between the 24th hour PTX3 level and hemoglobin level (r = -0.37, P = 0.020). However, no significant correlations was observed between the PTX3 level and presence of diabetes mellitus, hypertension, dyslipidemia, cigarette smoking, gender, previous coronary artery disease, congestive heart failure, chronic renal failure, and systolic and diastolic blood pressure levels.

5. Discussion

Inflammation is a primary player of events leading to atherosclerotic plaque rupture and myocardial damage in NSTE-ACS. It is a reasonable choice to measure inflammatory biomarkers to promote the management of these patients. As most of the inflammatory biomarkers are not specific to CV pathologies and as they often produce only moderate prognostic value, their clinical benefit is limited. PTX3 has been proposed to be a promising biomarker in this regard. PTX3 is synthesized at the location of damage and might therefore be a useful indicator of localized cardiovascular inflammatory processes. PTX3 is produced by a number of cells (peripheral leukocytes, vascular endothelial cells, and smooth muscle cells) and is produced in response to both inflammatory (IL-1, tumor necrosis factor-α, toll-like receptor agonists, and lipopolysaccharide) and anti-inflammatory stimuli (IL-10 and HDL) (19). PTX3 and CRP play roles in different processes of inflammation in atherosclerosis and other diseases and they represent different pathways. CRP is synthesized mainly in the liver in response to various inflammatory stimuli (20). On the other hand, PTX3 is produced by different cells located in atherosclerotic lesions in response to inflammatory mediators (21, 22). Thus, PTX3 is considered as a specific marker of localized

Table 2. Comparison of PTX3 Levels at Admission, 8th Hour, and 24th Hour in the Patients with NSTEMI and Controls

	Controls	Patients	P value
PTX3 level at the 8th hour (ng/mL)	1.9 ± 2.1	2.6 ± 3.1	P < 0.001
PTX3 level at the 24th hour (ng/mL)	1.9 ± 2.1	4.8 ± 7.6	P < 0.001

Table 3. Univariate Correlations between PTX3 Levels at the 8th and 24th Hours and Other Parameters

		PTX3 at the 8th hr	PTX3 at the 24th hr
Age	r	0.270	0.429
	P	0.112	0.009 [a]
Sex	r	0.23	0.14
	P	0.26	0.270
SBP	r	0.112	0.079
	P	0.326	0.520
CK	r	0.091	0.296
	P	0.599	0.079
Killip Class	r	0.343	0.431
	P	0.040 [b]	0.009 [b]
CK MB	r	0.282	0.302
	P	0.096	0.073
DBP	r	0.185	-0.027
	P	0.279	0.876
Hemoglobin	r	-0.317	-0.376
	P	0.060	0.024 [b]
Creatinine	r	-0.004	0.276
	P	0.983	0.104
hsCRP	r	0.048	0.373
	P	0.779	0.025 [b]
LDL	r	0.007	-0.106
	P	0.24	0.320
Troponin I	r	0.169	0.267
	P	0.324	0.116
EF	r	-0.282	0.095
	P	-0.045	0.794
WMSI	r	0.357	0.071
	P	0.032 [b]	0.682
GRACE	r	0.161	0.412
	P	0.349	0.013 [b]
NT-proBNP	r	0.160	0.380
	P	0.351	0.022 [b]
Glucose	r	-0.276	-0.050
	P	0.103	0.773

Abbreviations: CK, Creatine kinase; CK MB, Creatine kinase myocardial band fraction; CHF, Congestive heart failure; DBP, Diastolic blood pressure; EF, Ejection fraction; F, Female; hsCRP, high sensitive C-reactive protein; LDL, Low density lipoprotein; M, Male; NT-proBNP, amino terminal pro brain natriuretic peptide; SBP, Systolic blood pressure; WMSI, Wall motion score index. [a] $P < 0.05$, [b] $P < 0.005$

vascular inflammation. Growing evidence shows that PTX3 serves an important role as both diagnostic and prognostic biomarkers of CV diseases (4, 23, 24). Complicated coronary plaque compared to fibroatheroma has higher PTX3 levels. In contrast, CRP was found to be at similar levels in complicated plaque and fibroatheroma (15).

A morphological analysis was conducted on an autopsy series of patients with STEMI. CRP level in STEMI was found to be related to the severity of MI. However, PTX3 was not found to be correlated to localization and extent of STEMI. Inflammatory factors play a role in development, progression, and rupture of atherosclerotic plaque. PTX3 and CRP are independent predictive factors of death caused by all CV events (15).

According to the findings of the present study, PTX3 levels were significantly elevated in the NSTE-ACS patients, which is in agreement with the previous studies on NSTE-ACS patients (7, 8, 25). The results also revealed that PTX-3 level was associated with the complexity and severity of coronary artery disease in the patients with NSTEMI. Circulating PTX3 level changes in a time-dependent manner in the acute phase of MI (8). In our study, we found a similar trend in PTX3 level; it increased significantly at the 8th h and reached its maximum level at the 24th h. Moreover, the results indicated that PTX3 levels were higher in the patients aged above 60 years, which is consistent with the results of a previous study conducted on the issue (24).

It was suggested that PTX3 might be an early marker of irreversible injury in ischemic cardiomyopathy (8). In elderly patients who do not have CV disease, PTX3 is related to increased CV deaths (23). It was reported that in patients with stable congestive heart disease, PTX3 was strongly related to all-cause mortality, CV events, and incidental heart failure, independent from known demographic characteristics, classic CV risk factors, and CRP (14).

Although PTX3 was reported to be associated with dyslipidemia and smoking (14, 26), it showed no relationships with subclinical atherosclerosis indices (26). In a study, it was proposed that PTX3 levels in NSTE-ACS were mainly determined by ischemic myocardial injury and not by the conditions leading to its occurrence;

i.e., development and rupture of coronary atherosclerotic plaques (25).

PTX3 was significantly elevated in patients with heart failure with both reduced and preserved EF (27, 28). This predicts adverse clinical events in such patients. It should also be noted that PTX3 level was positively correlated to New York Heart Association (NYHA) functional class (29).

In a regression analysis including age, NYHA class III-IV, hsCRP, and NT- proBNP, PTX3 was presented as an important predictor of cardiac events (27). In another study on heart failure, PTX3 was found to be correlated to in hospital and 6th month deaths caused by MI in ACS (16). These results demonstrated that PTX3 might play an important role in pathophysiology of congestive heart failure (27).

In the current study, the patients with elevated PTX3 levels tended to have a higher Killip class on admission, which is similar to the previous studies (16, 17, 24). Decreased myocardial perfusion is associated with myocardial injury, resulting in endothelial swelling and protrusion, myocyte swelling, and tissue edema with the subsequent microvascular obstruction (30). PTX3 may modulate reperfusion-related inflammation and myocardial injury as PTX3 was found to be released from several cell types in AMI lesions, such as macrophages and endothelial cells around necrotic myocardium (12). Increased level of PTX3 might also play a compensatory cardioprotective role in lesions with impaired myocardial perfusion (12, 31). The positive correlation between PTX3 and worse Killip class in our study can be described with impaired myocardial perfusion in ACS patients with elevated PTX3 as in the mentioned studies.

Hemoglobin, glucose, troponin, and creatinine are high-risk markers in ACSs. The findings of the present study demonstrated a weak-moderate correlation between these parameters and PTX3. It was previously demonstrated that NT-proBNP was a mortality marker in ACSs similar to congestive heart failure (32). Moreover, research indicated that NT- proBNP could be used together with GRACE risk score to determine the 30th day and 6th month mortalities in ACSs (33-35). PTX3 together with age > 70 and Killip class > 1 was found to be an independent predictor of three-month mortality in STEMI in contrast to CRP, creatine kinase, troponin, and NT-proBNP (14). GRACE risk score is a predictor of 6th month and even five-year hospital mortality in ACSs (16). In the current study, PTX3 level was found to be higher in the patients with high GRACE risk scores.

The correlation between PTX3 and CRP might be directive in understanding the effects of these markers on physiopathology of ACSs. These results showed that PTX3 might be a biomarker in determining high-risk patients. PTX3 concentrations during acute cardiac events provide clinicians with an estimation of long- term prognosis of patients at the early phase of ACS.

PTX3 was found to be high in the patients with NSTEMI. Among these patients, higher PTX3 concentrations were associated with high-risk and poor prognostic markers (GRACE score, hsCRP, age, NT- proBNP, and hemoglobin). Thus, PTX3 might be a biomarker to determine high-risk patients. Overall, PTX3 concentrations during acute cardiac events could provide clinicians with an estimation of long-term prognosis of patients in the early phase of ACS. However, these findings should be confirmed in large scale and prospective studies.

5.1. Limitations

An important limitation of our study was the small number of patients and healthy controls. Absence of the results of long-term follow-up was the other limitation of the current study.

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Authors' Contribution

Study concept and design: Tahir Bezgin, Ali Elveran, Ali Metin Esen; Acquisition of data: Tahir Bezgin, Ali Elveran; Analysis and interpretation of data: Tahir Bezgin; Drafting of the manuscript: Ali Karagöz; Critical revision of the manuscript for important intellectual content: Tahir Bezgin, Ali Metin Esen; Statistical analysis: Tahir Bezgin; Administrative, technical, and material support: Tahir Bezgin, Ali Metin Esen; Study supervision: Ali Metin Esen

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