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The Relationship between Serum Pentraxin-3 Levels and Severity of Coronary Heart Disease

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Abstract

Background: Clinical data suggested that pentraxin-3 is a biomarker for atherosclerosis due to its role in inflammatory processes since it exerts unfavorable effects on the course of atherosclerosis, stimulates plaque formation, and augments vascular inflammation. **Objective:** The aims of this study were to measure the level of serum pentraxin-3 in patients with suspected coronary artery disease (CAD) and to determine whether it was associated with the severity of CAD. **Material and Methods:** The serum pentraxin-3 level was measured by enzyme-linked immunosorbent assay in 80 patients who were referred for elective coronary angiography due to positive stress test results. SYNTAX score was used to determine the severity of CAD. **Results:** The study cohort consisted of 45 (56.25%) males and 35 (43.75%) females with a mean age of 55 ± 9.8 years. The mean serum pentraxin-3 level was 3.79 ± 1.38 ng/ml, and the mean SYNTAX score was 15.8 ± 11.3. A significant correlation was observed between pentraxin-3 level and SYNTAX score ($r = 0.459$, $p < 0.001$). The level of pentraxin-3 was significantly higher in patients with SYNTAX scores of ≥33 compared with patients who scored 23 - 32 or ≤22 ($p = 0.002$). **Conclusion:** The serum level of inflammatory marker pentraxin-3 is increased in patients with CAD and is correlated with the severity of CAD.

Keywords

Coronary Artery Disease, Pentraxin-3, SYNTAX Score

1. Introduction

Pentraxin-3 is a glycoprotein originally identified in the endothelial cells of human umbilical veins and fibroblasts [1]. It is an inflammatory protein that is plentifully released in vascular plaques and cardiomyocytes. It is induced by cyto-

kines in endothelium, macrophages, smooth muscle cells, and dendritic cells [2].

Clinical data suggested that pentraxin-3 is a biomarker for atherosclerosis due to its role in inflammatory processes since it produces unfavorable effects on the course of atherosclerosis, stimulates plaque formation, and augments vascular inflammation [3]. Patients with vulnerable coronary plaque showed higher pentraxin-3 levels than those with stable plaque [4].

Patients with endothelial dysfunction exhibited elevated pentraxin-3, and the serum level of pentraxin-3 was associated with the degree of the endothelial dysfunction [5]. In addition, elevated pentraxin-3 was reported in patients with systemic hypertension [6]. Furthermore, pentraxin-3 was stated to be a biomarker of acute myocardial injury [7].

Clinicians use SYNTAX score to identify the severity of CAD. It yields predictive data about the outcomes of patients with CAD, and indicates the type of coronary revascularization (*i.e.*, percutaneous or surgical) [8] [9].

A few studies have explored the association between pentraxin-3 and the degree of coronary atherosclerosis. One study reported a significant correlation between serum levels of pentraxin-3 and the number of diseased coronary arteries. Another one reported an association between pentraxin-3 levels and Gensini score [10] [11]. The aims of this study were to measure the level of serum pentraxin-3 in patients with suspected CAD and to determine whether it was associated with the severity of CAD.

2. Methods

2.1. Study Population

A total of 80 patients (mean age: 55 ± 9.8 years) were recruited in this study. The inclusion criteria were patients with suspected CAD who were referred for elective coronary angiography due to positive results of a stress test between May 2017 and March 2018. The exclusion criteria were defined as acute coronary syndrome, previous coronary revascularization, significant valvular heart disease, preexisting cardiomyopathies, chronic kidney disease, liver cirrhosis, and patients with CAD and a SYNTAX score of 0 (*i.e.*, stenosis of less than 50%). The study was approved by the local ethics committee. Informed consent was obtained from the patients before they became involved in the study.

As part of the study, risk factors of CAD (diabetes mellitus, hypertension, dyslipidemia, family history, and smoking) were reported, and body mass index was calculated. In addition, the echocardiographic data, including the left ventricular ejection fraction, was reviewed and reported. Further, the serum levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, serum creatinine, and fasting glucose were analyzed.

2.2. Measurement of Serum Pentraxin-3

The protein concentration in serum samples collected after 12 h of fasting was

estimated using the BCA protein estimation kit (ThermoFisher Scientific, USA). Appropriate sample dilution was performed prior to enzyme-linked immunosorbent assay (ELISA) of pentraxin-3. Standard stock was serially diluted, and all samples were loaded onto a pre-coated ELISA plate. The procedure was performed according to the instructions on the datasheet of the human pentraxin-3 ELISA kit (#SEK411Hu, Cloud-Clone Corp., Katy, TX, USA). The concentration of pentraxin-3 in control and patient samples was determined using the standard curve equation.

2.3. Cardiac Catheterization

Cardiac catheterization was performed using a radial approach in 72 patients and a femoral approach in 8 patients. Usual views of coronary angiography were taken. The assessment of coronary artery stenosis was done according to the recommendations of American Heart Association. The extent of disease is defined as left main disease, one-vessel, two-vessel, or three-vessel disease. Significant coronary lesion was defined by the presence of a stenosis of ≥50% diameter reduction [12]. Coronary angiograms were stored on compact discs in DICOM format. SYNTAX score was used to determine the severity of CAD. An online computer program (http://www.syntaxscore.com/calculator/start.htm) consisting of 12 sequential questions was used to calculate the score. Any lesion causing ≥50% stenosis in a vessel ≥ 1.5 mm in diameter was included [13]. The main factors used to calculate the score of each lesion are as follows: dominant coronary artery, diseased segments, total occlusion, trifurcation or bifurcation, lesions leading to severe tortuosity, lesion with aorto-ostial site, lesion more than 20 mm in length, severe calcification of the lesion, presence of thrombus, and diffusely diseased and narrowed segment. Patients who had a normal coronary angiogram were included in the control group. Patients with CAD were subdivided into three groups according to their SYNTAX scores. The first group included patients with mild CAD (SYNTAX score: ≤22), the second group included those with moderate CAD (SYNTAX score: 23 - 32), and the third group included those with severe CAD (SYNTAX score: ≥33). Patients with a score of 0 were excluded.

2.4. Statistical Analysis

The data were analyzed using the IBM SPSS software package, version 20.0 (IBM Corp, Armonk, NY, USA). The Kolmogorov-Smirnov, Shapiro-Wilk, and D'Agostino tests were used to verify the normality of the distribution of the variables, and comparisons between groups were assessed using a chi-squared test (Fisher or Monte Carlo) for the categorical variables. A Student's t-test was used to compare the groups in terms of normally distributed quantitative variables, and the Mann-Whitney U test was used to compare the groups in terms of abnormally distributed quantitative variables. Spearman's and Pearson's coefficient tests were used to determine the correlations between the variables. Results below 0.5 were considered to be significant.

3. Results

3.1. Patient's Characteristics

The study cohort consisted of 45 (56.25%) males and 35 (43.75%) females with a mean age of 55 ± 9.8 years. Of the cohort, 31 (38.75%) patients were smokers, 17 (21.25%) patients had a family history of CAD, 34 (42.5%) patients were hypertensive, and 33 (41.25%) patients were diabetic. The mean SYNTAX score was 15.8 ± 11.3, and the mean serum pentraxin-3 level was 3.79 ± 1.38 ng/ml.

Based on the results of coronary angiography, 12 (15%) patients with normal coronary angiography—5 males and 7 females with a mean age of 53.5 ± 9.5 years—and served as a control group. 68 (75%) patients—40 males and 28 females with a mean age of 55.3 ± 10 years—had CAD. No significant difference was found between the two groups regarding age, gender, prevalence of CAD risk factors, lipid profile, or serum creatinine ($p > 0.05$). The mean pentraxin-3 level was 3.1 ± 0.9 ng/ml in control group and 3.9 ± 1.4 ng/ml in CAD group ($p = 0.038$) (Table 1 and Table 2, Figure 1).

Table 1. Comparison between control and cases according to different parameters

Variable	Control (n = 12)	Cases (n = 68)	p
Age (y)	53.5 ± 9.5	55.3 ± 10	0.569
Sex			
Male, n, (%)	5 (41.7%)	40 (58.8%)	0.269
Female, n, (%)	7 (58.3%)	28 (41.2%)	
BMI (kg/m^2)	26.7 ± 3.2	28.3 ± 3.6	0.143
HTN, n, (%)	3 (25%)	31 (45.6%)	0.269
DM, n, (%)	4 (33.3%)	29 (42.6%)	0.752
FBS (mg/dl)	5 (41.7%)	36 (52.9%)	0.471
Dyslipidemia, n, (%)	2 (16.7%)	15 (22.1%)	1.000
FH of CAD, n, (%)	4 (33.3%)	27 (39.7%)	0.758
Smoking, n, (%)	57.5 ± 4.4	57.1 ± 4.4	0.748
LVEF%	1.09 ± 0.29	1.1 ± 0.3	0.802
Creatinine (mg/dl)	102.4 ± 20.4	111 ± 24.5	0.254
LDL-C (mg/dl)	133.7 ± 29.4	135 ± 34.8	0.901
HDL-C (mg/dl)	38.8 ± 8.3	39.8 ± 8.4	0.716
TG (mg/dl)	142.9 ± 56	153.5 ± 65.2	0.509
TCH (mg/dl)	201.2 ± 34.8	206.9 ± 37.5	0.623
Pentraxin-3 (ng/ml)	3.1 ± 0.9	3.9 ± 1.4	0.038
SYNTAX score	-	15.8 ± 11.3	

BMI: Body mass index, HTN: Hypertension, DM: Diabetes mellitus, FH of CAD: Family history of coronary artery disease, LVEF: left ventricular ejection fraction, FBS: Fasting blood sugar, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, TG: Triglycerides, TCH: Total cholesterol.

Table 2. Comparison between the studied groups according to extent of CAD.

Variable	SYNTAX score				P
	Control (n = 12)	≤22 (n = 42)	23 - 32 (n = 17)	≥33 (n = 9)	
Age (y)	53.5 ± 9.5	53.8 ± 10.78	55.6 ± 7.1	61.7 ± 9.6	0.165
Men, n, (%)	7 (58.3%)	16 (38.1%)	8 (47.1%)	4 (44.4%)	0.649
BMI (kg/m^2)	26.7 ± 3.2	26.7 ± 3.2	29 ± 3.7	29.1 ± 5.3	0.284
HTN, n, (%)	3 (25%)	18 (42.9%)	9 (52.9%)	4 (44.4%)	0.517
DM, n, (%)	4 (33.3%)	15 (35.7%)	8 (47.1%)	6 (66.7%)	0.347
FBS (mg/dl)	102 ± 20.4	107 ± 22.7	112.3 ± 22.4	127.6 ± 31.1	0.074
Dyslipidemia, n, (%)	5 (41.7%)	21 (50%)	9 (52.9%)	6 (66.7%)	0.772
FH of CAD, n, (%)	2 (16.7%)	8 (19%)	4 (23.5%)	3 (33.3%)	0.764
Smoking, n, (%)	4 (33.3%)	16 (38.1%)	7 (41.2%)	4 (44.4%)	0.942
LVEF%	57.5 ± 4.4	57.8 ± 4.7	56.5 ± 3.9	54.8 ± 2.4	0.272
Creatinine (mg/dl)	1.09 ± 0.29	1.1 ± 0.2	1.1 ± 0.3	1.1 ± 0.3	0.834
LDL-C (mg/dl)	134 ± 29.4	133.2 ± 36.5	137.1 ± 33.3	139.4 ± 32.3	0.952
HDL-C (mg/dl)	38.8 ± 8.3	40.4 ± 7.9	38.8 ± 8.8	38.9 ± 10.6	0.873
TG (mg/dl)	142.9 ± 56	148.8 ± 43.8	167 ± 104.3	153.8 ± 58.5	0.911
TCH (mg/dl)	201 ± 34.8	205.6 ± 39.8	209.1 ± 36.1	208.9 ± 32.7	0.947
SYNTAX score	-	7.8 ± 4.1	24.8 ± 2.2	35.9 ± 3.1	

BMI: Body mass index, HTN: Hypertension, DM: Diabetes mellitus, FH of CAD: Family history of coronary artery disease, LVEF: Left ventricular ejection fraction, FBS: Fasting blood sugar, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, TG: Triglycerides, TCH: Total cholesterol.

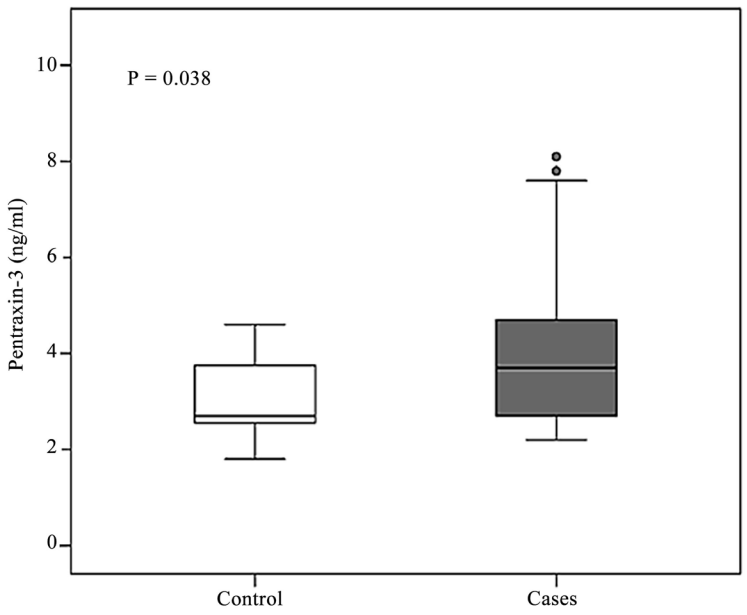

Figure 1. Comparison between control and cases according to serum pentraxin-3 level.

3.2. Serum Pentraxin-3 Levels in the Studied Groups and Association with SYNTAX Score

The mean serum pentraxin-3 levels in Groups I, II, and III were 3.5 ± 1.1, 4.3 ± 1.3, and 5.4 ± 2 ng/ml, respectively (p = 0.002) (Table 3 and Figure 2). Pentraxin-3 level was associated with SYNTAX score (r = 0.459, p < 0.001). There was also a significant association between serum pentraxin-3 and LDL cholesterol (r = 0.285, p = 0.018) (Table 4 and Figure 3).

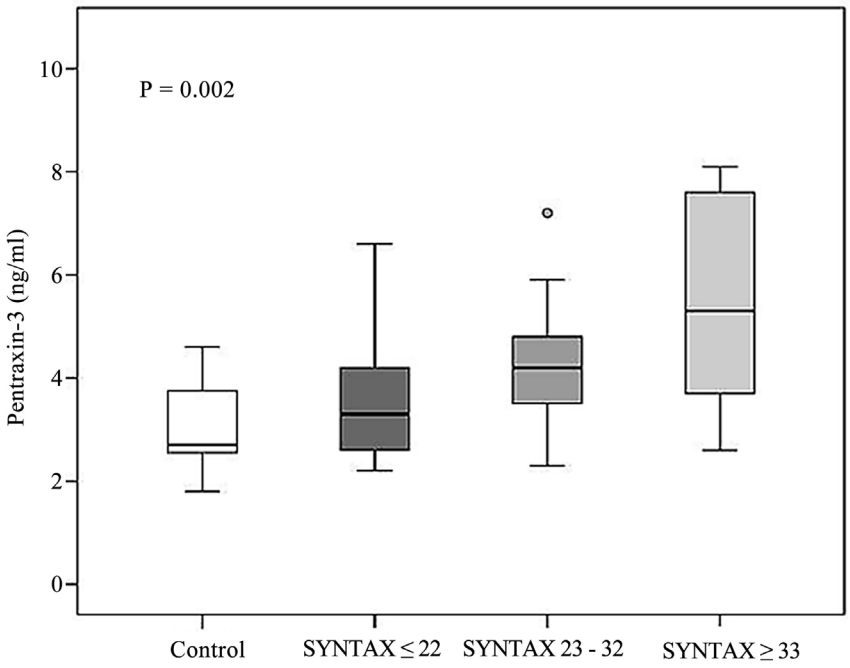

Figure 2. Comparison between the studied patients according to serum pentraxin-3 level.

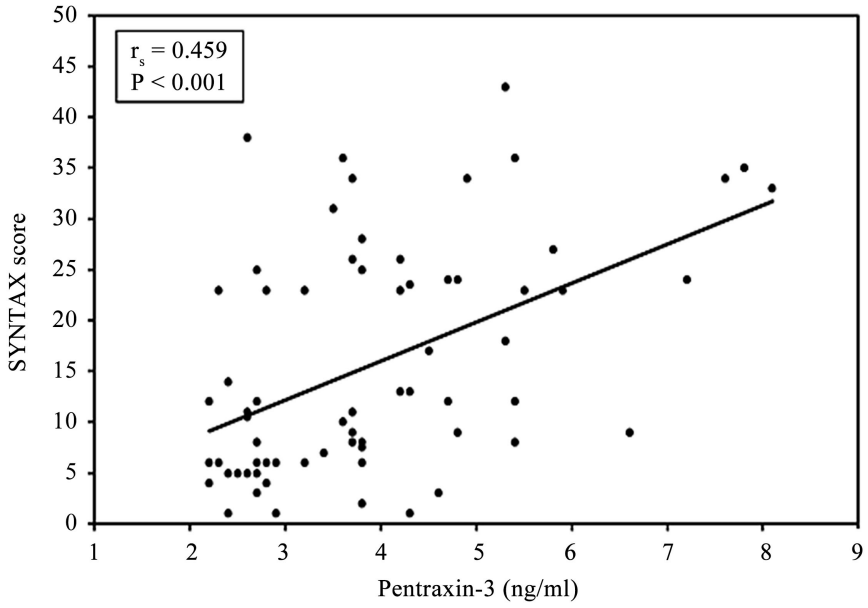

Figure 3. Correlation between pentraxin-3 and SYNTAX score in CAD patients (n = 68).

Table 3. Serum Pentraxin-3 levels in studied groups.

	SYNTAX score				
	Control (n = 12)	≤22 (n = 42)	23 - 32 (n = 17)	≥33 (n = 9)	P
Pentraxin-3 (ng/ml)	3.1 ± 0.9	3.5 ± 1.1	4.3 ± 1.3	5.4 ± 2	0.002

Table 4. Correlation between pentraxin-3 and studied parameters in CAD patients (n = 68).

	Pentraxin-3	
Variable	rS	p
Age (y)	0.165	0.180
BMI (kg/m^2)	0.024	0.845
LVEF%	−0.041	0.737
Creatinine (mg/dl)	−0.014	0.910
FBS (mg/dl)	0.176	0.150
LDL-C (mg/dl)	0.285	0.018
HDL-C (mg/dl)	−0.146	0.236
TG (mg/dl)	0.056	0.651
TCH (mg/dl)	0.238	0.049
SYNTAX score	0.459	<0.001

BMI: Body mass index, LVEF: Left ventricular ejection fraction, FBS: Fasting blood sugar, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, TG: Triglycerides, TCH: Total cholesterol.

4. Discussion

Considered an acute-phase immunity protein due to its role in innate immunity, pentraxin-3 is a protein released by polymorphonuclear neutrophils, macrophages, and vascular endothelium [14] [15]. It also initiates an inflammatory state that leads to cardiovascular disease [16] [17] [18] [19] [20]. Atherosclerotic arteries produce a high level of pentraxin-3, mainly from macrophages and endothelial cells. In addition, oxidized LDL-cholesterol stimulates the production of pentraxin-3 by smooth muscle cells inside plaque [21] [22]. In turn, pentraxin-3 activates the complement system and has a subsequent chemotactic effect [23] [24]. As macrophages and vascular cells are the main cells that are recruited by the intimal layer of arteries during the process of atherosclerosis [25], and as these cells are known to release pentraxin-3, various studies have investigated pentraxin-3 as a modulator of vascular damage. The aim of this study was to measure the serum level of pentraxin-3 in patients with suspected CAD and to identify its association with the severity of CAD. The serum levels of pentraxin-3 were measured in 80 patients who were referred for coronary angiography due to their positive results on a stress test. The control group was comprised of 12

patients with normal coronary angiography, and the second group included 68 patients with CAD. SYNTAX score was used to determine the extent of CAD. The serum pentraxin-3 level was significantly higher in diseased patients than in the controls. Furthermore, patients with high SYNTAX scores demonstrated higher levels of pentraxin-3 than those with lower scores. Therefore, serum pentraxin-3 level was correlated with SYNTAX score, which could reflect the degree of inflammatory reaction which initiate and extend CAD.

The results of this study agree with other researches. For instance, Nerkiz *et al.* reported higher levels of pentraxin-3 in patients with CAD than in those without. In their study, they did not use SYNTAX score to assess the severity of CAD, but the number of affected vessels (≤50% stenosis; disease in one, two, three, or four vessels). They concluded that pentraxin-3 level was significantly increased proportionate to the number of affected coronary arteries [10]. In addition, Liu *et al.* investigated the association between C-reactive protein and pentraxin-3 and the extent of CAD by examining the Gensini score of 60 patients who underwent elective coronary angiography. They reported a significant association between pentraxin-3 and Gensini score, but not between C-reactive protein and Gensini score. Patients with a Gensini score of >90 demonstrated higher pentraxin-3 levels than those with a score of 45 - 90 or <45. A similar correlation was reported in a subgroup of patients with underlying renal impairment [11]. Karakas *et al.* compared the serum levels of pentraxin-3 in 160 patients with symptoms of angina pectoris to 50 age- and sex-matched controls, reporting a significant difference between the controls and CAD patients. The severity of CAD was evaluated by both SYNTAX and Gensini scores, and they found significant associations between pentraxin-3 level and both SYNTAX score ($r = 0.87$) and Gensini score ($r = 0.75$) [26]. Koga *et al.* studied the relationship between pentraxin-3 and the vulnerability of plaque. The authors reported significantly increased pentraxin-3 levels in subjects with thin cap plaque, as assessed by optical coherence tomography, concluding that serum pentraxin-3 level could be used to determine plaque vulnerability [27].

The prognostic role of pentaraxin-3 was investigated by Jenny *et al.*, who studied the link between pentraxin-3 and asymptomatic cardiovascular disease and reported higher pentraxin-3 levels in patients with asymptomatic cardiovascular disease compared to healthy subjects. Furthermore, they found a positive correlation between pentraxin-3 and both cardiovascular disease and cardiovascular mortality [28].

The serum pentraxin-3 level was not only investigated in relation to stable CAD but also reported to be increased in patients with acute coronary syndrome, especially those with worse outcomes [29] [30] [31] [32], LV failure with reduced or preserved systolic function [33] [34], and ischemic stroke [35].

5. Limitations of the Study

SYNTAX score depends on visual assessment of coronary lesions. Therefore, it is

better to use intravascular coronary ultrasonography to evaluate coronary plaque. The small number of patients is another limitation. Further, the present study had no prognostic value. Finally, it would have been better to estimate other documented inflammatory markers, such as C-reactive protein.

6. Conclusion

The serum level of inflammatory marker pentraxin-3 is increased in patients with CAD and is correlated with the severity of CAD.

Conflict of Interest

The authors declare no conflicts of interest.

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