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Prognostic Value of Endothelin-1 Level in Diabetic Patients with Coronary Artery Disease

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Abstract: Objective: The aim of this work is to study the prognostic value of the plasma level of the new marker, endothelin-1 (ET-1), in diabetic patients with coronary artery disease. Background: Endothelin 1 (ET-1) has been demonstrated to play a role in endothelial dysfunction and inflammation, both of which are actively involved in the pathophysiology of the onset and progression of coronary artery disease (CAD). Diabetes mellitus increases the risk of CAD and has unfavorable effects on the vascular endothelium, hence the importance of assessing this plasma marker and its relation to the severity of CAD in diabetic patients. Patients & method: This is a cross sectional study in which data was collected from January 2019 to December 2019 and was carried out on patients selected from catheterization laboratory, faculty of medicine, Minoufia university hospital, Egypt. A total of seventy patients, 35 diabetics (groupI, GI) and 35 non-diabetics (groupII, GII), with coronary artery lesions of not less than 50% in at least one main coronary artery plus twenty patients with normal coronaries as a control group (groupIII, GIII) were enrolled. The severity of coronary artery lesions were assessed by GINSINI score (GS) and the relationship between ET-1 level and GS was evaluated. Results: The ET-1 levels were significantly higher in GI with higher GS values of 34.29+ 11.7 points and SYNTAX scores of 18.4+11.17 points, than in GII with lower GS values of 23.23+8.14 points and SYNTAX of scores 12.06+12.11 points (ET-1 was 187.93+146.61 ng/L in GI versus 76.30+91.83ng/L in GII, P value=0.001). ET-1 levels were significantly higher in GI than in GIII (187.93+146.61ng/L versus 26.16+7.32 ng/L, P value=0.001). ET-1 levels were significantly higher in GII than in GIII (76.30+91.83 ng/L versus 26.16+7.32 ng/L, P value=0.001). Conclusion: There is a positive correlation between DM and both ET-1 levels and the severity of coronary artery lesions, P value 0.001.

Keywords: Plasma Endothelin-1, Coronay Artery Disease, Risk Factors

1. Introduction

Coronary artery disease (CAD) is recognized as a health threat worldwide and remains a leading cause of both morbidity and mortality [1].

Hence, understanding its predictors would greatly aid in disease prevention and treatment, and the possible relationship between various plasma markers and CAD had intensively been investigated [2].

Among these markers, endothelin 1 (ET-1) has been demonstrated to play a role in endothelial dysfunction and inflammation [3], both of which are actively involved in the pathophysiology of the onset and progression of CAD, from the formation of acute coronary syndrome (ACS) and heart

failure following myocardial infarction [4].

Moreover, it has been reported that the baseline plasma ET-1 level can be used to predict the short- or long-term outcomes in patients with ACS and/or acute heart failure [5].

More importantly, little studies focusing on the diagnostic value of the plasma ET-1 level for discriminating the severity of CAD have been conducted.

Recently, big ET-1, the biological precursor of ET-1, with a longer half-life has been reported to be a more accurate indicator.

Therefore, in this study we tried to explain the usefulness of the plasma big ET-1 level in predicting the severity of CAD in diabetic patients.

2. Patients and Methods

2.1. Study Population

This is a cross sectional study in which data was collected from January 2019 to December 2019 from patients selected from cardiology department, faculty of medicine, Minoufia university hospital, Egypt. The current study included 90 patients who were divided, according to the presence or absence of diabetes mellitus (DM) and coronary artery disease (CAD), into three groups:

Group I (GI): 35 Diabetic patients with CAD.

Group II (GII): 35 Non-diabetic patients with CAD.

Group III (GIII control group): 20 Non-diabetic patients with normal coronary angiography.

2.2. Design of the Study

Sampling: The study group was chosen by convenient sample technique.

Data collection:

A case record form was used.

A written informed consent was obtained from all subjects.

2.2.1. History and Laboratory Tests

All subjects were submitted to the following:

1. Full history taking.
2. Full clinical examination.
3. Surface 12-lead ECG using CONTEC ECG100G machine.
4. Fasting, postprandial blood sugar and HbA1C measurement.
5. Lipid profile.
6. Serum levels of endothelin-1 (ET-1) was measured before coronary angiography using a highly sensitive and specific commercial sandwich enzyme immunoassay and was correlated with scoring assessment of coronary arteries.

2.2.2. Echocardiography

It was done using VIVID S5 machine stressing on EF, RWMA and scoring of the 16 LV segments according to American society of echocardiography as follows: normokinesia (1 point): normal wall thickening and endocardial excursion, hypokinesia (2 points): reduced wall thickening and endocardial excursion, akinesia (3 points): absence of wall thickening and endocardial excursion, dyskinesia (4 points): systolic outward stretching or thinning. Then the WMSI was calculated by dividing the total points over the number of LV wall segments, 16, where WMSI of 1 is normal, 1.5, 2, 2.5 being mild, moderate and severe hypokinesia respectively and finally 3 for akinesia [6].

2.2.3. Coronary Angiography

It was done using PHILIPS catheterization device, and Scoring of coronary artery lesions using SYNTAX and GINSINI scoring systems for each patient.

2.2.4. Statistical Analysis of the Collected Data [7]

Results were collected, tabulated and statistically analyzed by an IBM compatible personal computer with SPSS statistical package version 23 (SPSS Inc. Released 2015. IBM SPSS statistics for windows, version 23.0, Armnok, NY: IBM Corp.). Categorical data were expressed as number and percentage. Continuous data were expressed as mean and standard deviation. Suitable tests of significance were calculated. Comparison between groups was done using the Chi-square test or Fishers Exact test for categorical data and student t-test or ANOVA (F) test when suitable for Continuous data. The accepted level of significance in this work was 0.05.

3. Results

This study included 59 male patients (65.6%) and 31 female patients (34.4%) with 32-75 (mean: 58.21+8.46 and median 59) years of age. Analysis of anginal symptoms showed that 74 patients (82.2%) had chest pain and 16 patients (17.8%) had exertional dyspnea as shown in Table 1.

Patients were divided into three groups and were compared regarding sex, age, risk factors and their complaints as shown in Table 2.

Group I includes 35 diabetic patients of which 24 patients (68.6%) were males and 11 patients (31.4%) were females with 47-75 (mean: 61+6.27 and median age of 63) years of age. 8 patients (22.9%) had dyslipaedemia. 26 patients (74.3%) were complaining of exertional chest pain and 9 patients (25.7%) were complaining of exertional dyspnea.

Group II includes 35 patients of which 18 patients (51.4%) are males and 17 patients (48.6%) are females with 42-74 (mean: 59.03+8.8 and median age of 59) years of age. 26 patients (74.3%) had HTN, 8 patients (22.9%) were smokers and 18 patients (51.4%) had dyslipaedemia. 28 patients (80%) were complaining of exertional chest pain and 7 patients (20%) were complaining of exertional dyspnea.

Group III includes 20 patients of which 15 patients (75%) are males and 5 patients (25%) are females with 32-70 (mean: 58.9+8.1 and median age of 57) years of age. 13 patients (65%) had HTN, 7 patients (35%) were smokers. These patients were complaining of chest pain.

In our study we did Comparison of ejection fraction (EF), laboratory investigations and scoring systems of CAD among the three groups as shown Table 3.

There was no significant difference regarding the (EF) between group I and group II (43.69+5.38% versus 45.29+5.09%, P=0.194) while there was a high significant difference between G1 and GIII regarding EF (43.69+5.38 versus 63.5+4.65, p <0.001) and between GII and GIII. There was a high significant difference between GII and GIII regarding EF (45.29 +5.09% versus 63.5+4.65, p=0.001).

There was no significant difference regarding the WMSI between group I and group II (P=0.194) while there was a high significant difference between G1 and GIII regarding EF (p=0.001) and between GII and GIII (p <0.001) as shown in figure 1.

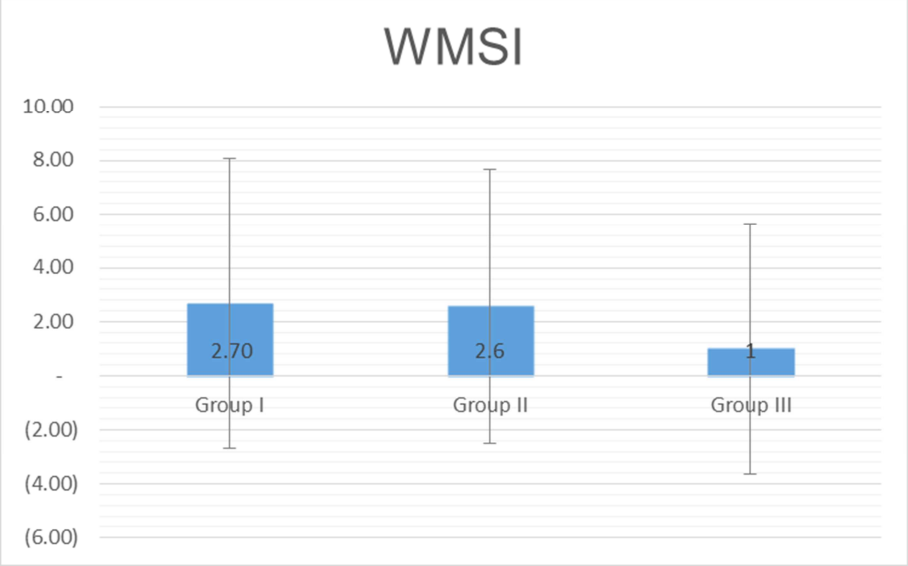

Figure 1. *Comparison of wall motion scoring index (WMSI) among studied groups.*

There was a positive correlation between the WMSI and the level of ET-1 and SYNTAX and GINSINI scores which were higher in GI and GII compared to GIII (p=0.001).

Importantly, the ET-1 levels were significantly higher in GI with high GS values of 34.29+ 11.7 points and SYNTAX scores of 18.4+11.17 points, than in GII with lower GS values of 23.23+8.14 points and SYNTAX of scores 12.06+12.11 points (187.93+146.61 ng/L in GI versus 76.30+91.83ng/L, P value=0.001).

ET-1 levels were significantly higher in GI than in GIII (187.93+146.61ng/L versus 26.16+7.32 ng/L, P value 0.001). ET-1 levels were significantly higher in GII than in GIII (76.30+91.83 ng/L versus 26.16+7.32 ng/L, P value 0.001). ET-1 levels were significantly higher in GII than in GIII (76.30+91.83 ng/L versus 26.16+7.32 ng/L, P value=0.001).

This means that there is a positive correlation between DM and both the severity of coronary artery lesions and ET-1 levels.

There was a positive correlation between plasma levels of ET-1 and the number of coronary arteries affected (P value 0.001) as its levels were the highest among patients with multivessel CAD (ET-1 219.34+14.65ng/L) followed by LM lesions (172.87+17.2) then two vessel CAD (157.31+16.79) then CTO lesions (113.16+12.13) and at last one vessel CAD (69.28+7.77) as shown in Table 4 and figure 1.

The plasma ET-1 level indicated a strong discriminatory power for predicting a high GS, and the optimal cutoff value of the plasma ET-1 level for predicting a high GS was 48.36 ng/L, with a sensitivity of 77.1% and specificity of 80%. Higher levels of ET-1 were detected in diabetic patients with CAD, group I, compared to non-diabetic patients with CAD, group II as shown in Table 5.

Table 1. *Demographics and compliants of studied groups.*

Variable	No.(90)	%
Gender		
Male	59	65.6
Female	31	34.4
Compliant		
Chest pain	74	82.2
Exertional dyspnea	16	17.8
Age		
Mean±SD*	58.21±8.46	
Range	32-75	
Median	59	

*standard deviation.

Table 2. *Comparison of demographic data, risk factors and complaints of the studied groups.*

Variable	Group I		Group II		Group III		Test of significance	P value
	No=35		No=35		No=20			
	No	%	No	%	No	%		
Gender								
Male	24	68.6	18	51.4	15	75	χ^2	0.15
Female	11	31.4	17	48.6	5	25	3.73	NS
Age								

Variable	Group I No=35		Group II No=35		Group III No=20		Test of significance	P value
	No	%	No	%	No	%		
Mean±SD	61±6.27		59.03±8.8		58.90±8.1		F	0.078
Range	47-75		42-74		32-70		2.9	NS
Median	63		59		57			
Compliant								
Chest pain	26	74.3	28	80	20	100	FXT	0.03
Exertional dyspnea	9	25.7	7	20	0	0	6.79	S
DM								
Yes	35	100	0	0	0	0	χ^2	<0.001
No	0	0	35	100	20	20	90	HS
HTN								
Yes	0	0	26	74.3	13	65	χ^2	<0.001
No	35	100	9	25.7	7	35	44.4	HS
Smoking								
Yes	0	0	8	22.9	7	35	FXT	<0.001
No	35	100	27	77.1	13	65	14.9	HS
Dyslipedemia								
Yes	8	22.9	18	51.4	0	0	χ^2	<0.001
No	27	77.1	17	48.6	20	20	17.4	HS

χ^2=chi-square test FXT=Fisher's exact test F=Anova test NS=non- significant S=significant HS=highly significant DM=diabetes mellitus.

Table 3. *Comparison of investigations, EF%, WMSI, ET-1, coronary angiographic scoring among studied groups.*

Variable	Group I No=35		Group II No=35		Group III No=20		Test of sig.	P value
	No	%	No	%	No	%		
LDL								
Mean±SD	136.31±25.4		151.8±36.03		68.60±5.74		F	<0.001
Range	110-200		100-250		55-77		60.39	HS
Median	128		140		69			
Post Hoc	P1=0.022 P2=<0.001 P3=<0.001							
HbA1C								
Mean±SD	12.19±1.48		4.72±0.24		--------		t	<0.001
Range	9-15		4.30-5.20				29.42	HS
Median	12		4.7					
ET-1 (ng/L)								
Mean±SD	187.93±146.61		76.30±91.83		26.16±7.32		K	<0.001
Range	29-428		26-385		15-37		46.32	HS
Median	141		40.4		24.26			
Post Hoc	P1=<0.001 P2=<0.001 P3=<0.001							
EF%								
Mean±SD	43.69±5.38		45.29±5.09		63.5±4.65		F	<0.001
Range	30-52		30-53		56-72		108.4	HS
Median	44		46		62.5			
Post Hoc	P1=0.194 P2=<0.001 P3=<0.001							
WMSI								
Mean±SD	2.7±0.38		2.6±0.42		1		F	<0.001
Range	1.5-3		1.5-3				108.4	HS
Median	2.5		2.5					
Post Hoc	P1=0.194 P2=<0.001 P3=<0.001							
SYNTAX score							U	
Mean±SD	18.40±11.17		12.06±12.11		-------		2.42	<0.001
Rang	2-38		2-38					HS
Median	20		6					
GINSINI score							U	
Mean±SD	34.29±11.7		23.23±8.14		-------		4.44	<0.001
Rang	20-60		12-40					HS
Median	32		20					

F=Anova test t=Student's t test U=Mann-whiteny test K=Kruskual wails test HS=High significant WMSI=wall motion scoring index EF=ejection fraction.
Group I=Diabetic patients with CAD.
Group II=Non-Diabetic patients with CAD.
Group III=Control.
P1=Group I versus Group II.
P2=Group I versus Group III.
P3=Group II versus Group III.

Table 4. *Relationship between coronary artery lesion and ET-1.*

Coronary artery lesion site	ET-1	Test of significance	P value
	Mean±SD		
1 vessel	69.28±7.77	K	0.001
LM	172.87±17.2	13.32	S
2 vessels	157.31±16.79		
MVD	219.34±14.65		
CTO	113.16±12.13		
Lesion severity			
Moderate	82.19±5.59	U	0.046
Severe	138.56±14.54	2.11	S

ET-1=Endothelin-1 U=Mann-whiteny test K=Kruskual wails test S=significant.
LM=left main artery CTO=chronic total occlusion.

Table 5. *Validity of Endothelin-1 (ET-1) as a predictor of the severity of coronary artery disease (CAD) in diabetic patients.*

	AUC	P value	Cutoff point	Sensitivity	Specificity	PPV	NPV
ET-1	0.84	0.001	≥48.36	77.10%	80%	71%	86%

AUC=area under the curve PPV=positive predictive value NPV=negative predictive value.

4. Discussion

The endothelium plays an integral role in the regulation of vascular tone, platelet activity, leukocyte adhesion, and thrombosis and is intimately involved in the development of atherosclerosis. Endothelial dysfunction has been observed in patients with established coronary artery disease or coronary risk factors, both in the coronary and peripheral vasculature [8, 9]. Coronary endothelial dysfunction in epicardial or resistance vessels is typically accompanied by myocardial perfusion defects suggestive of ischemia. In patients with dysfunctional endothelium, the loss of flow-mediated and catecholamine-stimulated nitric oxide (NO) release and increased production of endothelin-1 permits unopposed constriction to catecholamines. Thus, the loss of nitric oxide (NO) and increased levels of endothelin-1 may contribute to impaired dilation or constriction of epicardial and resistance vessels.

Endothelial dysfunction and reduced NO with increased levels of endothelin-1 in particular, may play an important role in destabilizing atherosclerotic plaques as well. Endothelial dysfunction, increased production of endothelin-1 and deficiency of NO exacerbates myocardial ischemia in patients with stable angina or acute ischemic syndromes. In addition, endothelial dysfunction may predispose to a transition from stable to unstable ischemic syndromes [10, 11]. The aim of this work was to study the prognostic value of a new marker, endothelin-1 (ET-1), level in diabetic patients with coronary artery disease and to determine its relation to the clinical presentation, cardiovascular risk factors and the extent, severity and angiogarphic lesion morphology of coronary atherosclerosis. Seventy patients with coronary artery disease were included, 35 with diabetes mellitus (DM) (group 1) and 35 without DM (group 2), versus twenty patients with normal coronary arteries as a control group (group 3). This study showed that plasma endothelin-1 levels are significantly elevated in patients with DM and CAD as compared to those without DM [12, 13].

There was a significant association between plasma endothelin-1 levels and the number of arteries affected by atheroma in humans. In the present study, the demonstration of significantly higher levels of plasma endothelin-1 in patients with DM and CAD than in normal persons (187.93±146.61 versus 26.16±7.32 ng/L, p=0.001) suggests a role for this peptide in the pathophysiology of coronary atheroma [14].

The trend towards an association between elevated plasma endothelin levels and severity of coronary artery disease observed in this study may, therefore, reflect the degree of associated endothelial dysfunction [15]. The present study demonstrates a positive correlation between the plasma endothelin-1 level and the severity & number of diseased coronary segments.

In our study we examined the relation between plasma endothelin-1 and the angiogarphic equivalent of diabetic patients with CAD. The plasma endothelin-1 level was significantly elevated in patients with DM and CAD when compared with healthy control subjects (187.93±146.61 versus 26.16±7.32 ng/L, p=0.001) and patients without DM but with CAD (76.30±91.83 ng/L, p=0.001). This observation indicates that endothelin-1 has a good predictive value for the severity of CAD in diabetic patient.

5. Conclusion

1. Plasma endothelin-1 levels were significantly higher in diabetic patients with CAD when compared with normal persons.
2. Plasma endothelin-1 levels were significantly higher in non-diabetic patients with CAD when compared with normal persons.
3. Plasma endothelin-1 levels were significantly higher in diabetic patients with CAD when compared with non-diabetic patients with CAD.
4. A positive correlation between the plasma endothelin-1 level and the severity of coronary artery disease as assessed by SYNTAX and Ginsini scores had been identified.

6. Recommendations

Plasma endothelin-1 may be used as a surrogate marker for the severity of coronary artery disease in diabetic patients with evidence of ischaemic heart disease (IHD).

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