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Original Article

Can Serum Endocan Levels Predict the Presence and Severity of Coronary Artery Ectasia?

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ABSTRACT

Background: The aim of this study was to investigate the relationship between serum endothelial cell-specific molecule-1 endocan levels and coronary artery ectasia (CAE).

Methods: This cross-sectional study was conducted on 99 patients. According to angiographic data, the patients were divided into 3 groups: 1) patients with isolated CAE (n = 33), 2) patients with documented coronary artery diseases without CAE (n = 33), and 3) those with normal coronary arteries (n = 33). The endocan concentration was measured via the ELISA technique.

Results: patients with isolated CAE had significantly lower levels of endocan than did the controls (261.30 ± 61.34 vs 564.58 ± 81.69; $P < 0.05$). There was no significant correlation between endocan levels and the severity of CAE according to the Markis classification ($P > 0.05$). The patients who used opium had a significantly higher prevalence rate of CAE (65.6% vs 35.3%; $P = 0.012$). Moreover, in the group with ectasia, by comparison with the non-ectatic group, significantly high levels of serum triglyceride, cholesterol, and LDL levels, as well as low HDL levels, were detected.

Conclusions: Among our study population, a decrease in endocan levels was a sensitive and accurate indicator for predicting the presence of CAE, although the level of this marker was not very effective in determining the severity of ectasia. In addition to a drop in endocan expression levels, the use of opium and also an abnormal lipid profile were the other predictors of CAE. ***(Iranian Heart Journal 2019; 20(3): 20-26)***

KEYWORDS: Coronary artery ectasia, Endocan, Endothelial cell

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Coronary artery ectasia (CAE) is characterized by abnormal epicardial coronary dilatation exceeding 1.5 times the normal range. [1] This phenomenon is a well-defined, pathological, and non-obstructive defect detectable through coronary angiography or computed tomography angiography. [2, 3] CAE has been significantly less studied than has

coronary artery disease (CAD). This phenomenon is classified as a diffuse, full-length coronary artery or local involvement. [4] The frequency of this disease varies from 0.2% to 10% in different studies. [5-7] All the clinical manifestations of ectasia can imitate coronary heart diseases such as angina pectoris and the acute coronary syndrome secondary to thrombosis or vasospasm. [8, 9]

The underlying mechanism for ectasia has not yet been identified. In light of previous reports, it appears that there is more than 1 mechanism involved. [10, 11] In this regard, it has been shown that ectasia associated with obstructive CAD is seen in about 85% of cases. Given the co-occurrence of CAE and CAD, histologic findings of the 2 diseases have shown similarities such as the destruction and reduction of both elastic fibers and internal and external lamina elastic fibers. [12, 13] Occasionally, ectasia appears to be a subset of atherosclerosis. Celik et al [14] showed that the increased thickness of the intima-media layer could be a common mechanism between ectasia and CAD.

Various molecules and parameters correlate with the incidence of CAE have been reported, mainly related to inflammatory factors. An increase in the distribution of red blood cells in peripheral blood vessels has been associated with the incidence and severity of ectasia. [15] Additionally, a rise has been reported in the count of monocytes and also the volume of platelets in these patients. [16] The severity of CAE is associated with an increase in the ratios of neutrophils to lymphocytes and the ratios of platelets to lymphocytes. [18, 19] The activation of some cell surface markers such as CD11b, CD11c, CD54, CD83, CD86, and MHC Class II has been reported to be abundant in these patients, especially in association with CAD. In this regard, a substance released from the endothelium, termed “endocan” or “endothelial cell-specific molecule-1 (ESM-1)”, has been associated with these increases, reflecting endothelial disorders in the field of CAE. [20]

ESM-1 or endocan is a soluble proteoglycan (50 kDa), secreted by human vascular endothelial cells. Endocan can be detected in the circulation and is an indicator of angiogenesis and endothelial cell activation. Endocan is secreted by vascular endothelial cells, especially from the inflamed endothelium Thus, endocan may lead to inflammatory and vasculoprotective actions, which may play a role in the process of atherosclerosis. [21]

The overexpression of endocan in various tissue defects such as lungs, the endothelial cells of the vessels especially coronary arteries, skin, and the adipose tissue has been fully confirmed. [21, 22] It appears that endothelial dysfunction may play an important role in the pathophysiology of CAE. Given the evidence of the association between endocan as an inflammatory mediator and vascular endothelial dysfunction, we sought to investigate the relationship between endocan levels and CAE in southeastern Iran (Kerman province).

METHODS

This was a cross-sectional study. The study population was comprised of all the patients candidated for coronary angiography in Shafa Hospital in Kerman between 2017 and 2018. The exclusion criteria comprised acute or chronic active infection, the presence of underlying inflammatory diseases, heart failure with a left ventricular ejection fraction (LVEF) < 40%, atrial fibrillation, renal insufficiency, the presence of any malignancy, a history of cirrhosis or hepatic failure, a history of any revascularization (coronary artery bypass grafting or percutaneous coronary intervention), and the incidence of the acute coronary syndrome in a recent month. The purpose of the study was fully explained to the patients and informed consent was obtained. The stud population’s characteristics were recorded using a checklist that included demographic information, screening records, and drug use, as well as clinical features and the manifestations

of the patients. Thereafter, the patients were assessed via coronary angiography (Siemens, Axiom Zee and Axiom Arties Model, Germany) and classified as one of the following 3 groups: 1) patients with isolated CAE (n = 33), 2) patients with documented CAD without coronary ectasia (n = 33), and 3) those with normal coronary arteries (n = 33). In each group, peripheral venous blood samples were taken from each patient immediately after coronary angiography. The plasma was separated by centrifugation at 3000 rpm for 10 minutes. Then, the endocan concentration was measured via the ELISA method and the ESM1-ELISA Kit. In addition, other biochemical parameters were measured using the Cobas Kit (Roche Diagnostics GmbH, D-68298 Mannheim, Germany). Finally, the severity of ectasia was determined according to the Markis classification system as follows: Type 1 (diffuse ectasia of 2 or 3 vessels), Type 2 (diffuse ectasia in 1 vessel and localized disease in another), Type 3 (diffuse ectasia in 1 vessel only) or Type 4 (localized or segmental involvement).

Descriptive analysis was used to describe the data, including the mean ± the standard deviation (SD) for the quantitative variables and frequencies (percentages) for the categorical variables. The χ^2 test, the ANOVA test, or the Kruskal–Wallis H test was used to compare the variables. The value of endocan to predict CAE was assessed using the receiver operating characteristic (ROC) curve analysis. For the statistical analyses, the statistical software IBM SPSS Statistics for Windows, version 22.0, (IBM Corp, Released 2013, Armonk, New York) was used. A *P* value <0.05 was considered statistically significant.

RESULTS

In the present study, 3 groups were evaluated: the CAD group (n=33), the normal coronary artery group as the control group (n=33), and the CAE group, (n=33). As is shown in Table 1, there was no difference in some baseline parameters such as gender, the body mass index, a history of cardiovascular diseases, diabetes mellitus, smoking, and some laboratory parameters including coagulation indices, fasting blood sugar, the white blood cell count, and serum creatinine. The patients with CAD were significantly older, had lower LVEFs, had longer disease durations, and had higher prevalence rates of hypertension than did those with ectatic or normal coronary arteries. A history of opium use was reported more frequently in the patients with CAD or coronary ectasia than in those with normal coronary states. Interestingly, the patients with CAE had significantly higher serum triglyceride, low-density lipoprotein (LDL), and total cholesterol levels as well as lower high-density lipoprotein (HDL) levels than did the other groups. In addition, the platelet count and the hemoglobin level were both lower in the CAD group than in the other 2 groups.

In the group with CAE, 24.2% of the patients were classified as the Markis I, 24.2% as the Markis II, 27.3% as the Markis III, and 24.2% as the Markis IV classes. Ectasia in 1, 2, and 3 coronary vessels was also revealed in 48.5%, 30.3%, and 21.2%, respectively (Table 2). The mean level of serum endocan in the CAD group, the normal coronary group, and the ectasia group was 388.98 ± 66.39, 564.58 ± 81.69, and 261.30 ± 61.34, respectively, with a significant difference. The Tokay analysis showed a lower level of endocan in the CAE group than in the normal coronary group (*P* = 0.009), with no difference between the CAD group and the CAE group (*P* = 0.429) or between the CAD group and the normal coronary group (*P* = 0.191).

Table 1. Underlying features of the patients in the 3 study groups

Indicator	Coronary Artery Disease Group	Normal Coronary	Ectasia Group	*P* value
Male gender	23 (69.7)	22 (66.7)	23 (69.7)	0.954
Mean age	62.27 ± 9.78	54.97 ± 9.74	57.52 ± 9.74	0.011
Body mass index	25.66 ± 3.05	26.43 ± 3.46	26.32 ± 2.15	0.554
Left ventricular ejection fraction	51.22 ± 6.23	55.76 ± 2.83	55.15 ± 3.85	0.001
History of heart disease	33 (100)	15 (45.5)	16 (48.5)	0.001
Disease duration	30.59 ± 48.20	6.75 ± 13.48	20.07 ± 41.48	0.001
Cardiac death < 65 y in family	4 (12.1)	2 (6.1)	4 (12.1)	0.565
Cardiac death < 55 y in family	1 (3.0)	4 (12.1)	4 (12.1)	0.333
Hypertension	18 (56.2)	14 (42.4)	7 (21.2)	0.014
Diabetes	9 (27.3)	6 (18.2)	4 (12.1)	0.290
Smoking	6 (18.2)	7 (21.2)	11 (33.3)	0.315
Expose to smoke	10 (30.3)	9 (27.3)	9 (27.3)	0.951
Opium use	21 (63.6)	11 (33.3)	21 (63.6)	0.017
Fasting blood sugar	97.19 ± 16.83	104.55 ± 23.67	103.31 ± 25.21	0.371
Triglyceride	141.18 ± 69.00	163.22 ± 58.60	200.33 ± 70.14	0.002
Low-density lipoprotein	97.94 ± 27.49	88.06 ± 30.49	142.94 ± 73.99	0.001
High-density lipoprotein	44.61 ± 18.38	46.19 ± 17.83	39.06 ± 7.82	0.152
Cholesterol	162.64 ± 42.19	171.45 ± 40.67	197.42 ± 50.10	0.006
Partial thromboplastin time	27.76 ± 5.71	27.67 ± 3.77	29.00 ± 4.27	0.763
Prothrombin time	12.55 ± 0.78	12.51 ± 0.80	12.47 ± 0.41	0.962
International normalized ratio	1.04 ± 0.07	1.03 ± 0.08	1.03 ± 0.05	0.859
WBC count	6719.3 ±2511.9	6858.0 ± 1128.6	6966.25 ± 1156.8	0.740
Hemoglobin	13.37 ± 2.26	14.68 ± 1.31	14.46 ± 1.30	0.006
Platelet count	227.42 ± 68.16	264.29 ± 71.36	266.91 ± 61.29	0.038
Serum creatinine	1.05 ± 0.19	0.97 ± 0.17	1.02 ± 0.15	0.219

Table 2. Characteristics of ectasia in the patients with CAE

Indicator	CAD Group
Markis class	
I	8 (24.2)
II	8 (24.2)
III	9 (27.3)
IV	8 (24.2)
Number of coronary arteries involved	
One vessel	16 (48.5)
Two vessels	10 (30.3)
Three vessels	7 (21.2)
Pattern of involvement	
LAD, LCX, RCA	7 (21.2)
LAD, LCX	5 (15.2)
LAD, RCA	5 (15.2)
LAD	8 (24.2)
LCX	4 (12.1)
RCA	4 (12.1)

CAE, Coronary artery ectasia; LAD, Left anterior descending; LCX, Left circumflex; RCA, Right coronary artery

The level of serum endocan was not different between the men and the women (P = 0.163). There was no significant relationship between the serum level of endocan and the other parameters such as age (P = 0.428), the body mass index (P = 0.695), hypertension (P = 0.100), diabetes mellitus (P = 0.792), smoking (P = 0.592), opium use (P = 0.813), the LVEF (P = 0.331), blood sugar (P = 0.622), triglyceride (P = 0.270), LDL (P = 0.112), HDL (P = 0.523), total cholesterol (P = 0.275), the partial thromboplastin time (P = 0.879), the prothrombin time (P = 0.652), the white blood cell count (P = 0.459), the hemoglobin level (P = 0.444), the platelet count (P = 0.467), and the creatinine level (P = 0.635).

In the patients with CAE, the mean endocan level was not different across the Markis classes of I, II, III, and IV (P = 0.554) (Table 3).

Table 3. Relationship between the endocan concentration and the ectasia-related factors

Indicator	Endocan Level	*P* value
Markis class		
I	224.50 ± 77.56	0.554
II	321.46 ± 157.07	
III	136.61 ± 85.66	
IV	371.84 ± 178.62	
Number of coronary arteries involved		
One vessel	146.22 ± 39.08	0.553
Two vessels	302.29 ± 142.12	
Three vessels	350.24 ± 182.62	
Pattern of involvement		
LAD, LCX, RCA	350.24 ± 182.62	0.647
LADو LCX	472.80 ± 313.54	
LAD , RCA	165.88 ± 57.16	
LAD	170.33 ± 39.29	
LCX	304.81 ± 149.69	
RCA	129.85 ± 24.38	

LAD, Left anterior descending; LCX, Left circumflex; RCA, Right coronary artery

As is indicated in Table IV, the patients who used opium had a significantly higher prevalence rate of CAE (65.6% vs 35.3%; *P* = 0.012). In the group with ectasia, in comparison with the non-ectatic group, significantly high levels of serum triglyceride, cholesterol, and LDL, as well as low levels of HDL, were detected (Table 4).

Table 4. Predictors of the presence of ectasia

Factor	Ectatic Group	Non-Ectatic Group	*P* value
Triglyceride	200.33 ± 70.14	163.22 ± 58.60	0.024
LDL	142.94 ± 73.99	88.06 ± 30.48	0.001
HDL	39.06 ± 7.82	46.19 ± 17.83	0.040
Cholesterol	197.42 ± 50.09	171.45 ± 40.67	0.027
Endocan	261.30 ± 61.34	564.58 ± 81.69	0.005

LDL, Low-density lipoprotein; HDL, High-density lipoprotein

Based on the analysis of the area under the ROC curve, the determination of the endocan concentration had a high value in predicting the presence of CAE (AUC = 0.756, *P* = 0.001). The best cutoff value for endocan to predict ectasia in coronary arteries was 300, yielding a sensitivity of 75% and a specificity of 70% (Fig. 1).

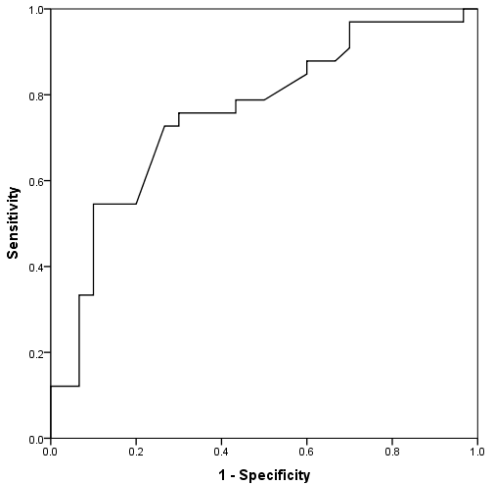

Figure 1. Receiver operating characteristic (ROC) curve analysis to determine the value of endocan to predict coronary ectasia

DISCUSSION

In the present study, we investigated the relationship between the serum level of endocan and CAE. According to the results, endocan levels in the patients with ectasia were far lower than those in the patients with normal coronary arteries. We also observed a decrease in the endocan level in the patients with CAD. It appears, firstly, that the decreased expression of this marker in the vascular bed is essentially related to the pathophysiology of vascular ectasia. Secondly, the simultaneous decrease of the marker in the CAD group and the ectatic group somehow justifies some commonalities in the pathophysiology of the 2 diseases. Additionally, in the group with ectasia, by comparison with the non-ectatic group, significantly high levels of serum triglyceride, cholesterol, and LDL levels, as well as low HDL levels, were detected. Sudhir et al [24] reported that CAE was 6 times more frequent among their patients with familial hypercholesterolemia than in their control group, suggesting a link between an abnormal lipid profile and CAE. Another important point was that the other risk factors for CAD such as hypertension, diabetes mellitus, smoking, familial history of CAD, and changes in the count of leukocytes and platelets did not play a

role in the prediction of ectasia in our patients. Therefore, along with decreased levels of endocan, the use of opium and an abnormal lipid profile were the other predictors of CAE. Contrary to our results, other studies have revealed a positive relationship between CAE and increased serum endocan levels.

In a study by Baysal et al, [25] the endocan level was 1.19 ± 0.18 in patients with ectasia and 1.07 ± 0.18 in the subjects without ectasia, indicating a higher level of this marker in patients with ectasia; however, there was no correlation between the endocan level and the Markis score. In a study by Turan et al, [26] the serum endocan level in the 2 groups was 18.9 ± 7.33 and 15.66 ± 3.60, respectively, which demonstrated a significant difference between the groups. Furthermore, based on the Markis classification system for ectasia, the authors reported a significant relationship between the level of endocan and the degree of ectasia. In a study by Gök et al [27] in 2018, serum endocan along with C-reactive protein predicted CAE; nonetheless, there was no relationship between the endocan level and the severity of CAE based on the Markis system, which is completely inconsistent with the results of our study.

Endocan is a soluble proteoglycan secreted by endothelial cells, primarily inflamed endothelial cells. In total, endocan appears to be a major determinant of endothelial inflammation, vascular endothelial dysfunction, and atherosclerosis. Due to the close relationship between the incidence of coronary ectasia with the degeneration of the extracellular matrix, the vascular tropical depletion of the tonica media following severe inflammation, and vascular glandular degeneration, the relationship between increased endocan levels and the risk of ectasia is also expected. Nevertheless, we found a significant relationship between decreased serum endocan levels and CAE. Further longer studies are, therefore, required to assess this association in different ethnic populations.

CONCLUSIONS

In our study population, a decrease in the endocan level was a sensitive and accurate indicator for predicting the presence of CAE, although the level of this marker was not very effective in determining the severity of ectasia. Alongside a reduction in the endocan expression, the use of opium and also impairment in the lipid profile were the other predictors of CAE.

REFERENCES

1. LaMotte, L.C. and V.S. Mathur, Atherosclerotic coronary artery aneurysms: eight-year angiographic follow-up. Texas Heart Institute Journal, 2000. 27(1): p. 72.
2. Bermúdez, E.P., et al., Coronary ectasia: prevalence, and clinical and angiographic characteristics. Revista espanola de cardiologia, 2003. 56(05): p. 473-479.
3. Díaz-Zamudio, M., et al., Coronary artery aneurysms and ectasia: role of coronary CT angiography. Radiographics, 2009. 29(7): p. 1939-1954.
4. Swanton, R., et al., Coronary artery ectasia--a variant of occlusive coronary arteriosclerosis. Heart, 1978. 40(4): p. 393-400.
5. Aintablian, A., et al., Coronary ectasia: incidence and results of coronary bypass surgery. American heart journal, 1978. 96(3): p. 309-315.
6. Befeler, B., et al ,.Coronary artery aneurysms: study of their etiology, clinical course and effect on left ventricular function and prognosis. The American journal of medicine, 1977. 62(4): p. 597-607.
7. Swaye, P.S., et al., Aneurysmal coronary artery disease. Circulation, 1983. 67(1): p. 134-138.
8. Krüger, D., et al., Exercise-induced myocardial ischemia in isolated coronary artery ectasias and aneurysms ("dilated coronaropathy"). Journal of the American College of Cardiology, 1999. 34(5): p. 1461-1470.

9. Manginas, A. and D.V. Cokkinos, Coronary artery ectasias: imaging, functional assessment and clinical implications. European heart journal, 2006. 27(9): p. 1026-1031.

10. Bohórquez, R., et al., Aneurysmatic coronary artery disease: Presentation of a case and review the literature. Acta Medica Colombiana, 2009. 34(1): p. 38-41.

11. Abou Sherif, S., et al., Coronary artery aneurysms: a review of the epidemiology, pathophysiology, diagnosis, and treatment. Frontiers in cardiovascular medicine, 2017. 4: p. 24.

12. Markis, J.E ,.et al., Clinical significance of coronary arterial ectasia. American Journal of Cardiology, 1976. 37(2): p. 217-222.

13. Yetkin, E. and J. Waltenberger, Novel insights into an old controversy. Clinical research in cardiology, 2007. 96(6): p. 331-339.

14. Erkan, H., et al., Coronary artery calcification score is increased in patients with isolated coronary artery ectasia. Clinical & Investigative Medicine, 2013. 36(4): p. 191-196.

15. Keser, A., et al., Relationship between red cell distribution with levels and severity of coronary artery ectasia. European review for medical and pharmacological sciences, 2016. 20: p. 1571-1574.

16. Demir, M., C. Demir, and S. Keceoglu, The relationship between blood monocyte count and coronary artery ectasia. Cardiology research, 2014. 5(5): p. 151.

17. Kundi, H., et al., Relationship between platelet-to-lymphocyte ratio and the presence and severity of coronary artery ectasia. Anatolian journal of cardiology, 2016. 16(11): p. 857.

18. Varol, E., et al., Mean platelet volume has a prognostic value in patients with coronary artery ectasia. Clinical and Applied Thrombosis/Hemostasis, 2012. 18(4): p. 387-392.

19. Delehedde, M., et al., Endocan in cancers: a lesson from a circulating dermatan sulfate proteoglycan. International journal of cell biology, 2013. Article ID 705027, 11 pages.

20. Tsai, J.C., et al., Cloning and characterization of the human lung endothelial-cell-specific molecule-1 promoter. Journal of vascular research, 2002. 39(2): p. 148-159.

21. Aitkenhead, M., et al., Identification of endothelial cell genes expressed in an in vitro model of angiogenesis: induction of ESM-1, βig-h3, and NrCAM. Microvascular research, 2002. 63(2): p. 159-171.

22. Scherpereel, A., et al., Endocan, a new endothelial marker in human sepsis. Critical care medicine, 2006. 34(2): p. 532-537.

23. Abbas AK, Lichtman AH, Pillai S. Basic immunology: functions and disorders of the immune system: Elsevier Health Sciences; 2014.

24. Sudhir, K., et al., Increased prevalence of coronary ectasia in heterozygous familial hypercholesterolemia. Circulation, 1995. 91(5): p. 1375-1380.

25. Baysal, S., et al., Endothelium biomarkers endocan and thrombomodulin levels in isolated coronary artery ectasia. European review for medical and pharmacological sciences, 2018. 22: p. 4677-4682.

26. Turan, T., et al., Plasma endocan levels in patients with isolated coronary artery ectasia. Angiology, 2016. 67(10): p. 932-936.

27. Gök, M., et al., The relationship between serum endocan levels and the presence/severity of isolated coronary artery ectasia. Cardiovascular Endocrinology & Metabolism, 2018. 7(2): p. 42-46.