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Coronary Artery Disease

Relationship between Serum Salusin Beta Levels and Coronary Artery Ectasia

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Background: Local or diffuse dilatation of the coronary artery is defined as coronary artery ectasia (CAE). Salusin beta plays a role in the proliferation of cardiomyocytes, inhibition of apoptosis, and proliferation of vascular smooth muscle cells and fibroblasts. In this study, we aimed to investigate the relationship between serum salusin beta and CAE.

Methods: This study was conducted between July 2019 and December 2019 and included 71 patients with CAE (age 59.3 ± 11 years, 67.7% male) and 72 healthy subjects (age 57.1 ± 10.2 years, 69.4% male) with coronary artery angiography (CAG) findings. Venous blood samples of the participants were collected for serum salusin beta level evaluation. CAG examinations and the diagnosis of CAE were performed by two invasive cardiologists blinded to the clinical conditions of the patients.

Results: Mean systolic (SBP) and diastolic arterial blood pressures were significantly higher in the CAE group than in the control group, and the mean left ventricular ejection fraction (LVEF) was significantly lower (all $p < 0.05$). The median serum salusin beta value was statistically significantly higher in the CAE group compared to the control group [415 (interquartile range (IQR): 51.7) pg/mL vs. 365 (IQR: 55.8) pg/mL; $p < 0.001$]. In receiver operating characteristic curve analysis, a cut-off value of salusin beta ≥ 393 pg/mL had 78.9% sensitivity and 75.0% specificity for predicting CAE (area under the curve: 0.822; $p < 0.001$). Multivariate analysis demonstrated that serum salusin beta [odds ratio (OR): 1.011; $p = 0.002$], LVEF (OR: 0.816; $p = 0.001$) and SBP (OR: 1.041;$p = 0.001$) were independent predictors of CAE.

Conclusions: This study revealed a significant and independent relationship between serum salusin beta level and the presence of CAE.

Key Words: Atherosclerosis • Coronary artery ectasia • Salusin beta

INTRODUCTION

Local or diffuse dilatation of the coronary artery is defined as coronary artery ectasia (CAE). Anatomically, CAE occurs when the ratio of the ectatic coronary segment to the regular coronary segment is higher than 1.5.[1,2] The reported prevalence of CAE ranges from 1.4% to 5.3%.[2-4] Although many molecules and risk factors have been associated with CAE development, the underlying mechanism is not yet fully understood.[2-6] However, the underlying etiology in approximately half of CAE patients has been suggested to be atherosclerosis, with other common etiologies including inflammation and endothelial dysfunction.[2,6-8]

Salusin alpha and beta are bioactive peptides consisting of 28 and 20 amino acids, respectively, derived from the same prosalusin precursor.[9] Salusins are synthesized in many different tissues and organs such as the small intestine, adrenal medulla, central nervous system, heart, adrenal cortex, human vascular smooth

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muscle cells, and endothelial cells.[10-12] Interestingly, salusin is also expressed in human atherosclerotic plaques. Salusin beta plays a role in the proliferation of cardiomyocytes, inhibition of apoptosis, and proliferation of vascular smooth muscle cells and fibroblasts. In addition, salusin beta has been shown to facilitate the conversion of macrophages into foam cells, whereas salusin alpha has been shown to have an impeding effect.[10,13] Both peptides affect macrophage conversion via the activation (salusin beta) and suppression (salusin alpha) of the Acetyl-CoA Acetyltransferase 1 (ACAT-1) enzyme.[10] Thus, salusin alpha participates in the preventing and salusin beta contributes to the development of atherosclerosis.[14] In previous studies, patients with coronary artery disease (CAD) have been shown to have lower levels of salusin alpha and higher levels of salusin beta compared to those without CAD.[14,15]

To the best of our knowledge, serum salusin beta levels have not been studied in patients with CAE. Since the most common etiologies of CAE are atherosclerosis and inflammation, serum salusin beta may be an essential marker associated with CAE. Therefore, we aimed to investigate the relationship between serum salusin beta and CAE in this study.

METHODS AND MATERIALS

This study was conducted at Adana Health Practice and Research Center between July 2019 and December 2019. The files of the patients (n = 5451) who underwent coronary artery angiography (CAG) for angina pectoris, significant myocardial ischemia in a non-invasive stress test, or acute coronary syndrome were analyzed. Among them, 154 (2.8%) patients had a diagnosis of CAE. The exclusion criteria were as follows; having acute coronary syndrome, 50% stenosis in at least one coronary artery, a previous coronary intervention, systolic heart failure revealed by echocardiography [left ventricular ejection fraction (LVEF) < 40%], severe valvular heart disease, severe left ventricular hypertrophy, chronic infection, malignancy, chronic kidney failure, chronic liver disease, chronic obstructive pulmonary disease, autoimmune diseases, and inflammatory diseases. The remaining 81 patients diagnosed with CAE were invited to participate in the study by phone call. Ten patients could not be contacted by phone or refused to participate in the study. Venous blood samples for analysis of salusin beta were collected from 71 participants in the outpatient clinic. A total of 72 age- and gender-matched healthy subjects with normal CAG findings were included in the study as a control group.

The participants underwent echocardiography in accordance with the recommendations of the American College of Cardiology/American Heart Association echocardiography guide.[16] The demographic and medical characteristics of all patients were recorded from patient files or at the time of blood sample collection. The results of routine laboratory tests, analyzed at the time of CAG, were obtained from the patient files.

The patients with systolic blood pressure (SBP) ≥ 140 mm Hg, diastolic blood pressure (DBP) ≥ 90 mm Hg, with a history of hypertension or on anti-hypertensive medication were identified as having hypertension. The patients with fasting blood glucose ≥ 126 mg/dL or a history of anti-diabetic medications were identified as having diabetes mellitus. The patients with a serum total cholesterol value > 200 mg/dL or with a history of lipid-lowering therapy were identified as having dyslipidemia. The patients that smoked at least one cigarette a day for one year without interruption were defined as having a smoking history. The patients with one or more first-degree relatives having or experienced CAD or a history of sudden cardiac death at a young age (female < 65, male < 55 years), were identified as having a family history of CAD.

Angiographic analysis

Experienced invasive cardiologists at the clinic performed the Judkins technique for coronary angiography in all cases. All angiography images were recorded on the digital system of the angiography device (Siemens, Munchen, Germany). Two invasive cardiologists, who were unaware of the clinical status of the patients and the control group, examined the CAG images and made the diagnosis of CAE. Patients with coronary segments 1.5 times more dilated than the healthy coronary section were identified as having CAE. When there was no healthy section for comparison, especially in patients with diffuse CAE, the mean coronary artery diameter of the control group was taken as the standard value.

Blood sample collection and analysis

The blood samples for salusin analysis were collected into special tubes for salusin beta, and centrifuged at 4000 rpm for approximately 15 minutes to separate the serum. The serum samples were placed in Eppendorf tubes and preserved at -80 °C until further analysis. On the day of the sample analysis, all samples were warmed to room temperature and analyzed following dissolution. A serum salusin beta enzyme-linked immunosorbent assay (ELISA) kit (Salusin-β ELISA kit, Elabscience Biotech Co., Ltd., Wuhan, China) was used for the analysis. Results were reported in pg/mL.

Statistical analyses

The distribution of continuous variables was evaluated using the Kolmogorov Smirnov test. Continuous variables with normal distribution were reported as mean ± standard deviation, and those without normal distribution were reported as median, interquartile range (IQR). Continuous variables with normal distribution were compared among groups using the Student's t-test, whereas continuous variables without normal distribution were analyzed using the Mann-Whitney U test. Categorical variables were expressed as numbers and percentages. Categorical variables were compared among groups using the chi-squared test or Fisher's exact test. Receiver operating characteristic (ROC) curve analysis was performed to determine the salusin beta cut-off value for the development of CAE. Univariate and multivariate logistic regression analyses were performed to identify the independent predictors associated with the development of CAE. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS 20.0) for Windows (SPSS Inc., Chicago, Illinois, USA). A p-value < 0.05 was considered to be statistically significant.

RESULTS

A total of 143 cases, including 71 CAE patients (age 59.3 ± 11 years, 67.7% male) and 72 healthy subjects (age 57.1 ± 10.2 years, 69.4% male) as the control group were analyzed. The demographic and clinical characteristics of the groups are summarized in Table 1. There were no statistically significant differences between the groups in terms of age, gender, diabetes mellitus, hypertension, hyperlipidemia, smoking, and family history of CAD (p > 0.05). The mean SBP and DBP were significantly higher in the CAE group compared to the control group, whereas the mean LVEF was significantly lower (all p < 0.05). The median serum salusin beta value was significantly higher in the CAE patients compared to the control group [415 (IQR: 51.7) pg/mL vs. 365 (IQR: 55.8) pg/mL; p < 0.001] (Figure 1). In the ROC analysis, a cut-off value of salusin beta ≥ 393 pg/mL had 78.9% sensitivity and 75.0% specificity for predicting CAE [area under the curve: 0.822, 95% confidence interval (CI): 0.750-0.894; p < 0.001] (Figure 2).

The patients with CAE were divided into two groups according to the presence of atherosclerosis in CAG. Ten (14.1%) patients who had atherosclerosis were determined to have CAE with atherosclerosis, and the remaining 61 (85.9%) patients were identified as having isolated CAE. The mean salusin beta level was similar between the CAE patients with atherosclerosis and isolated CAE. In addition, the mean salusin beta level was significantly higher in both CAE groups compared to the control group (Figure 3).

Univariate and multivariate logistic regression analyses were performed to determine the risk factors for CAE, and the results are summarized in Table 2. In the univariate analysis, LVEF [odds ratio (OR): 0.795, 95% CI: 0.703-0.898; p < 0.001], SBP (OR: 1.036, 95% CI: 1.013-1.059; p = 0.002), DBP (OR: 1.030, 95% CI: 1.004-1.014; p = 0.037) and serum salusin beta level (OR: 1.009, 95% CI: 1.004-1.014; p < 0.001) were found to be predictors of CAE. The multivariate analysis included all these parameters, and the results showed that serum salusin beta level [OR: 1.011 (1.006-1.016); p = 0.002], LVEF (OR: 0.816, 95% CI: 0.727-0.915; p = 0.001) and SBP (OR: 1.041, 95% CI: 1.017-1.065; p = 0.001) were independent predictors of CAE.

DISCUSSION

In the present study, we found that serum salusin beta levels were significantly higher in CAE patients compared to the control group. In addition, we demonstrated that serum salusin beta level was an independent risk factor associated with the development of CAE.

Table 1. Baseline demographic and laboratory characteristics of studies groups

Variables	Patients with CAE (n = 71)	Control (n = 72)	p value
Age, years	59.3 ± 11	57.1 ± 10.2	0.473
BMI kg/m^2	24.9 ± 5.6	25.9 ± 6.3	0.291
Male gender %, (n)	67.7 (48)	69.4 (50)	0.813
Diabetes mellitus %, (n)	36.6 (26)	31.9 (23)	0.556
Hypertension %, (n)	62.0 (44)	52.2 (38)	0.266
Hyperlipidemia %, (n)	12.7 (9)	6.9 (5)	0.249
Smoking %, (n)	46.5 (33)	38.9 (28)	0.359
Family history of coronary artery disease %, (n)	9.9 (7)	15.3 (11)	0.329
Systolic blood pressure (mm Hg)	123 ± 19	114 ± 13	0.001
Diastolic blood pressure (mm Hg)	77 ± 11	73 ± 12	0.034
LVEF %	54.9 ± 7.4	59.9 ± 3.6	< 0.001
ASA %, (n)	15.5 (11)	20.8 (15)	0.408
Beta-blocker %, (n)	12.7 (9)	11.1 (8)	0.773
ACEI/ARB %, (n)	15.5 (11)	26.4 (19)	0.110
Statin %, (n)	9.9 (7)	12.5 (9)	0.616
CCB %, (n)	9.9 (7)	5.6 (4)	0.334
Hemoglobin, g/dL	13.7 ± 1.85	13.2 ± 1.60	0.138
Hematocrit, %	40 ± 5.2	39.4 ± 4.3	0.394
White blood cell count, ×10^3/mL	8300 ± 2200	7800 ± 2200	0.157
Platelet count, ×10^3/mL	259 ± 68	256 ± 45	0.772
Lymphocyte count, ×10^3/mL	2700 ± 1200	2500 ± 850	0.269
Neutrophil count, ×10^3/mL	4600 ± 1400	4400 ± 1300	0.334
Monocyte count, ×10^3/mL	687.36 ± 213.29	663.03 ± 184.32	0.467
Mean platelet volume, fL	8.58 ± 0.86	8.70 ± 0.96	0.409
Glucose (mg/dL)	121 ± 40	129 ± 37	0.195
Creatinine (mg/dL)	0.83 ± 0.16	0.77 ± 0.14	0.129
C-reactive protein (mg/L)	2.8 ± 2.71	2.2 ± 1.76	0.107
Troponin (ng/mL)	7.7 ± 2.1	5.6 ± 2.2	0.421
Total cholesterol (mg/dL)	211 ± 46	206 ± 31	0.492
HDL-cholesterol (mg/dL)	43 ± 9	44 ± 8.0	0.709
LDL-cholesterol (mg/dL)	144 ± 44	143 ± 24	0.890
Triglyceride (mg/dL)	192 ± 32	173 ± 41	0.207
Salusin (pg/mL), median (interquartile range)	415 (51.7)	365 (55.8)	< 0.001

ACEI/ARB, angiotensin converting enzyme/angiotensin receptor blocker; ASA, acetyl salicylic acid; BMI, body mass index; CAE, coronary artery ectasia; CCB, calcium channel blockers; HDL, high density lipoprotein; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction.

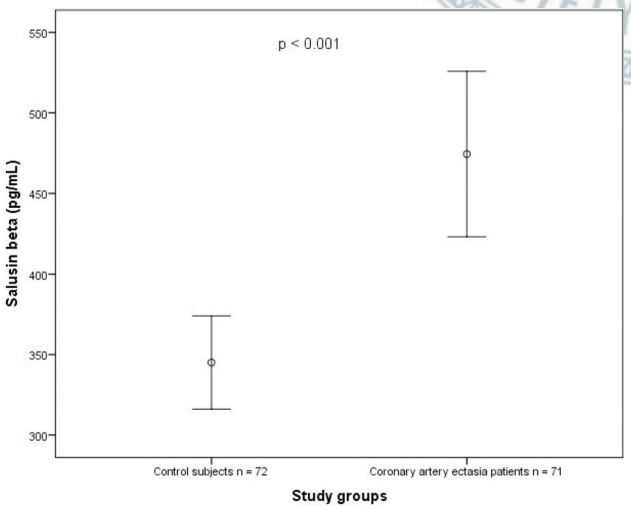

Figure 1. *Comparison of salusin beta levels between control subjects and coronary artery ectasia patients.*

Moreover, we found that the increased level of salusin beta in the CAE patients was independent of the underlying etiology of CAE. To the best of our knowledge, this study is the first in the literature to demonstrate the relationship between serum salusin beta level and CAE.

Coronary artery ectasia is defined as local or diffuse dilatation of the coronary arteries 1.5 times more than healthy coronary artery segments.[17] The prevalence of CAE has been reported to range from 1.4% to 5.3%.[4] Although the underlying etiology of CAE has not been fully elucidated, it has been reported to be atherosclerosis in approximately half of all patients, and therefore CAE is considered to be a variant of atherosclerosis.[4] Some CAE patients diagnosed with isolated CAE do not have apparent atherosclerosis accompanying the ectasia. In suchgroups, the possible underlying etiology may

be inflammation and endothelial dysfunction. However, since the role of vascular endothelial dysfunction and inflammation in the development of atherosclerosis is known, it is assumed that CAE and atherosclerosis may have a similar etiopathology.[18] Other rare underlying etiologies are congenital CAE, Marfan syndrome, Kawasaki disease, syphilis, connective tissue diseases, Takayasu arteritis, Polyarteritis nodosa, and infective septic emboli.[2] In previous studies, multiple risk factors, inflammatory markers, and peptides have been associated with CAE. In addition, various studies have indicated that hypertension, hyperlipidemia, and smoking, which have already been identified as risk factors for atherosclerosis, were also associated with CAE.[19-21] Moreover, either no relationship or an inverse relationship has been reported between CAE and diabetes mellitus, a well-known atherosclerotic risk factor.[22-24] In the current study, there was no significant difference between the groups in terms of hypertension history; however, we found that mean SBP and DBP were higher in the patients with CAE, and that SBP was an independent risk factor for CAE in multivariate analysis. This finding may be due to failure to manage the blood pressure in the CAE patients. Aksu et al. found no difference between patients with isolated CAE and CAE patients with accompanying atherosclerosis in terms of traditional risk factors for atherosclerosis.[25] This result was hypothesized to be because the underlying pathophysiological process is similar in both cases.

Salusin is a new class of bioactive peptides derived as alpha and beta from the same prosalusin precursor.[9] Salusins are synthesized in many different tissues and organs, including the small intestine, adrenal medulla, central nervous system, heart, adrenal cortex, human

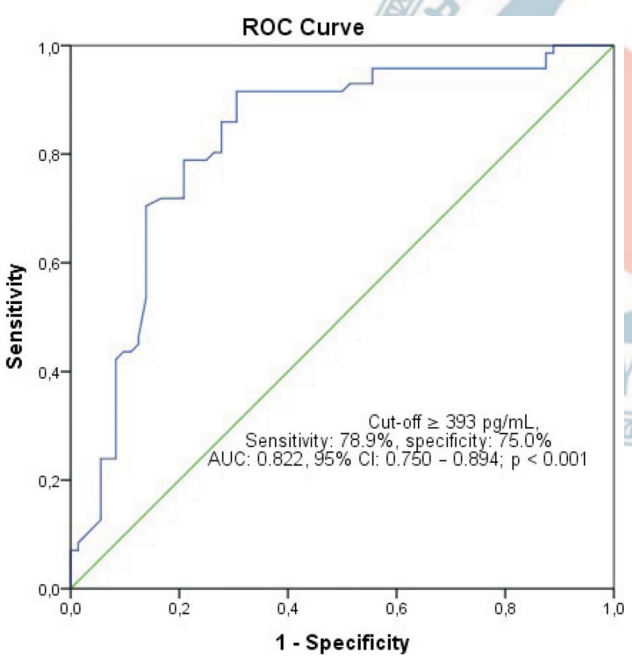

Figure 2. *Receiver operating characteristic curve analysis of salusin beta to predicting coronary artery ectasia. AUC, area under curve; CI, confidence interval.*

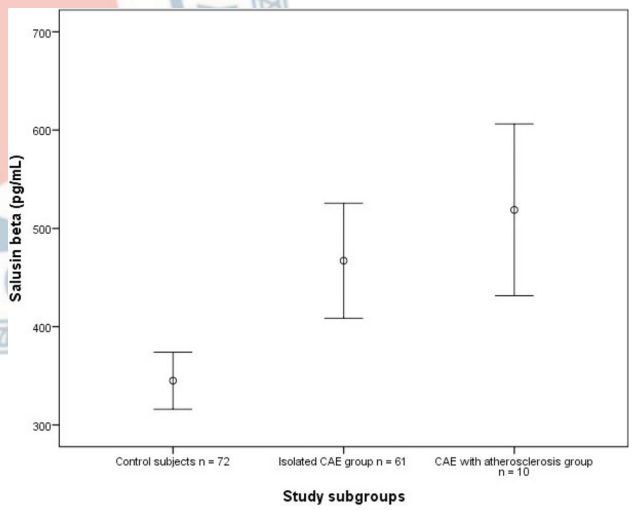

Figure 3. *Comparison of salusin beta levels between study subgroups. Isolated coronary artery ectasia (CAE) vs. CAE with atherosclerosis (467 ± 227 vs. 515 ± 139; p = 0.521). Isolated CAE vs. control subjects (467 ± 227 vs. 345 ± 123; p < 0.001). CAE with atherosclerosis vs. control subjects (515 ± 139 vs. 345 ± 123; p < 0.001).*

Table 2. Logistic regression analysis of possible predictors of coronary artery ectasia

Analysis	Univariate		Multivariate	
Variables	p value	OR [95% CI]	p value	OR [95% CI]
LVEF	< 0.001	0.795 (0.703-0.898)	0.001	0.816 (0.727-0.915)
Systolic blood pressure	0.002	1.036 (1.013-1.059)	0.001	1.041 (1.017-1.065)
Diastolic blood pressure	0.037	1.030 (1.002-1.060)	-	-
Salusin beta (per 1-pg/mL increase)	< 0.001	1.009 (1.004-1.014)	0.001	1.011 (1.006-1.016)

CI, confidence interval; LVEF, left ventricular ejection fraction; OR, odds ratio.

vascular smooth muscle cells and endothelial cells.[10-12] The relationship between atherosclerosis and salusin has been shown in human and experimental animal studies.[10,26,27] Watanabe et al. demonstrated that salusin alpha and beta had opposite effects on the transformation of macrophages to foam cells, which plays an essential role in the development of atherosclerotic plaques.[10] Salusin alpha inhibits the conversion of macrophages into foam cells by suppressing the ACAT-1 enzyme, which increases the accumulation of cholesterol esters into macrophage cells. Salusin beta, in contrast, increases the activity of the ACAT-1 enzyme and improves foam cell formation.[10] In another study by Watanabe et al., the authors examined the relationship between carotid intima-media thickness and salusin alpha levels in hypertension patients compared to healthy human subjects, and found a significant independent and negative correlation between salusin alpha and carotid intima-media thickness.[28] Moreover, Lui et al. demonstrated that average serum salusin beta levels of patients diagnosed with CAD on coronary angiography were significantly higher compared to levels of patients without CAD, and that there was an independent relationship between serum salusin beta and the presence of CAD.[29] Furthermore, in a recent study, patients with ST-segment elevation myocardial infarction were shown to have lower serum salusin alpha levels and higher serum salusin beta levels compared to healthy human.[30] Similarly, in experimental studies, the impacts of salusin alpha and salusin beta on atherosclerotic lesions demonstrated opposite effects.[26,27] Salusin alpha infusion for 4 to 8 weeks in apolipoprotein E-deficient (ApoE -/-) mice was shown to suppress atherosclerotic lesions in the aorta via reducing the transformation of macrophages to foam cells. In addition, the administration of salusin beta infusion to the mice for 4 to 8 weeks was shown to increase atherosclerotic lesions in the aorta and increase macrophage infiltration into the lesions.[27] In another study, subcutaneous injections of salusin beta once daily for 12 weeks in low-density lipoprotein receptor-deficient (LDLR -/-) mice resulted an aggravation of atherosclerosis formation.[26] These studies indicate that salusin alpha is protective against atherosclerosis, whereas salusin beta is atherogenic.[10,27]

Salusin beta has been shown to induce the mitogenesis of human vascular smooth muscle cells, which play a role in vascular fibrosis and maladaptive vascular remodeling.[31,32] In their in vitro research, Sun et al. showed the role and signal pathways of salusin beta in the proliferation of human vascular smooth muscle cells (HVSMCs), vascular fibrosis, and maladaptive vascular remodeling.[33] In addition, Salusin beta was also shown to promote HVSMC proliferation, and the overexpression of salusin beta in rats caused severe hypertension due to increased fibrosis and maladaptive vascular remodeling. Sun et al. also suggested that salusin beta increased collagen-1, collagen-3, and fibronectin mRNA expressions in the HVSCMs. Moreover, Sato et al. proposed a potential reaction between salusin beta and the inflammatory cytokine tumor necrosis factor-α.[34] Similarly, Koya et al. indicated that salusin beta might accelerate inflammatory responses in vascular endothelial cells via nuclear factor-κB signaling.[35]

Many possible etiologies have been determined for CAE, of which the two main etiologies are atherosclerosis and inflammation. In the present study, the majority of the patients had isolated CAE, and salusin levels did not differ significantly between those with isolated CAE and CAE with atherosclerosis. Therefore, salusin beta appears to play a vital role in promoting atherosclerosis and vascular remodeling, which are essential in CAE development. Our results are similar to the results of the previous studies. We found that there was no significant difference in salusin beta levels between the CAE patients with and without atherosclerosis. The similar pathophysiology in the development of CAE and the direct and indirect effects of salusin beta in the arterial vascular wall may explain these results. Salusin beta may promote CAE through the formation of atherosclerosis or direct vascular maladaptive remodeling.

Limitations

The limitations to the study were the small sample size and the inclusion of cases from a single center. Moreover, we could not analyze salusin alpha levels at the same time as salusin beta because the study was not funded, and only a limited number of kits were available for a limited number of patients. Another significant limitation is the small number of CAE patients with atherosclerosis. Finally, since long-term follow-up data of CAE patients were not available, the clinical implication of high salusin beta levels in CAE patients re-

mains unclear. Studies with a higher number of patients and long-term follow-up are required.

CONCLUSION

In this study, we demonstrated that serum salusin beta levels in CAE patients were significantly higher than in patients with healthy coronary arteries. We also found a significant and independent relationship between serum salusin beta level and the presence of CAE.

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CONFLICT OF INTEREST

All the authors declare no conflict of interest.

REFERENCES

1. Çekici Y, Kılıç S, Saraçoğlu E, et al. The relationship between blood viscosity and isolated coronary artery ectasia. *Acta Cardiol Sin* 2019;35:20-6.
2. Devabhaktuni S, Mercedes A, Diep J, et al. Coronary artery ectasia-a review of current literature. *Curr Cardiol Rev* 2016;12: 318-23.
3. Ozturk S, Yetkin E, Waltenberger J. Molecular and cellular insights into the pathogenesis of coronary artery ectasia. *Cardiovasc Pathol* 2018;35:37-47.
4. Dahhan A. Coronary artery ectasia in atherosclerotic coronary artery disease, inflammatory disorders, and sickle cell disease. *Cardiovasc Ther* 2015;33:79-88.
5. Roberts WC. Natural history, clinical consequences, and morphologic features of coronary arterial aneurysms in adults. *Am J Cardiol* 2011;108:814-21.
6. Antoniadis AP, Chatzizisis YS, Giannoglou GD. Pathogenetic mechanisms of coronary ectasia. *Int J Cardiol* 2008;130:335-43.
7. Erdoğan T, Kocaman SA, Çetin M, et al. Increased YKL-40 levels in patients with isolated coronary artery ectasia: an observational study. *Anadolu Kardiyol Derg* 2013;13:465-70.
8. Turhan H, Erbay AR, Yasar AS, et al. Comparison of C-reactive protein levels in patients with coronary artery ectasia versus patients with obstructive coronary artery disease. *Am J Cardiol* 2004;94:1303-6.
9. Shichiri M, Ishimaru S, Ota T, et al. Salusins: newly identified bioactive peptides with hemodynamic and mitogenic activities. *Nat Med* 2003;9:1166-72.
10. Watanabe T, Nishio K, Kanome T, et al. Impact of salusin-alpha and-beta on human macrophage foam cell formation and coronary atherosclerosis. *Circulation* 2008;117:638-48.
11. Suzuki N, Shichiri M, Tateno T, et al. Distinct systemic distribution of salusin-α and salusin-β in the rat. *Peptides* 2011;32:805-10.
12. Wang Z, Takahashi T, Saito Y, et al. Salusin β is a surrogate ligand of the mas-like G protein-coupled receptor MrgA1. *Eur J Pharmacol* 2006;539:145-50.
13. Thomas AC, Eijgelaar WJ, Daemen MJ, et al. Foam cell formation in vivo converts macrophages to a pro-fibrotic phenotype. *PLoS One* 2015;10:e0128163.
14. Sato K, Watanabe R, Itoh F, et al. Salusins: potential use as a biomarker for atherosclerotic cardiovascular diseases. *Int J Hypertens* 2013;2013:965140.
15. Niepolski L, Grzegorzewska AE. Salusins and adropin: new peptides potentially involved in lipid metabolism and atherosclerosis. *Adv Med Sci* 2016;61:282-7.
16. Cheitlin MD, Alpert JS, Armstrong WF, et al. ACC/AHA guidelines for the clinical application of echocardiography: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Application of Echocardiography) developed in collaboration with the American Society of Echocardiography. *Circulation* 1997;95: 1686-744.
17. Befeler B, Aranda JM, Embi A, et al. Coronary artery aneurysms: study of their etiology, clinical course and effect on left ventricular function and prognosis. *Am J Med* 1977;62:597-607.
18. Kundi H, Gök M, Çetin M, et al. Relationship between platelet-to-lymphocyte ratio and the presence and severity of coronary artery ectasia. *Anatol J Cardiol* 2016;16:857-62.
19. Lee HH, Lin TH, Su HM, et al. Recurrent thrombosis in a case of coronary ectasia with large thrombus burden successfully treated by adjunctive warfarin therapy. *Acta Cardiol Sin* 2013;29:462-6.
20. Çetin M, Kiziltunc E, Elalmış ÖU, et al. Predictive value of neutrophil lymphocyte ratio and platelet lymphocyte ratio in patients with coronary slow flow. *Acta Cardiol Sin* 2016;32:307-12.
21. Boles U, Rakhit R, Shiu MF, et al. Coronary artery ectasia as a culprit for acute myocardial infarction: review of pathophysiology and management. *Anadolu Kardiyol Derg* 2013;13:695-701.
22. Pinar Bermúdez E, López Palop R, Lozano Martínez-Luengas I, et al. Coronary ectasia: prevalence, and clinical and angiographic characteristics. *Rev Esp Cardiol* 2003;56:473-9.
23. Amirzadegan AR, Davoodi G, Soleimani A, et al. Association between traditional risk factors and coronary artery ectasia: a study

on 10057 angiographic procedures among Iranian population. *J Tehran Heart Cent* 2014;9:27-32.
24. Androulakis AE, Andrikopoulos GK, Kartalis AN, et al. Relation of coronary artery ectasia to diabetes mellitus. *Am J Cardiol* 2004;93:1165-7.
25. Aksu T, Uygur B, Kosar MD, et al. Coronary artery ectasia: its frequency and relationship with atherosclerotic risk factors in patients undergoing cardiac catheterization. *Anadolu Kardiyol Derg* 2011;11:280-4.
26. Zhou CH, Liu LL, Wu YQ, et al. Enhanced expression of salusin-β contributes to progression of atherosclerosis in LDL receptor deficient mice. *Can J Physiol Pharmacol* 2012;90:463-71.
27. Nagashima M, Watanabe T, Shiraishi Y, et al. Chronic infusion of salusin-α and-β exerts opposite effects on atherosclerotic lesion development in apolipoprotein E-deficient mice. *Atherosclerosis* 2010;212:70-7.
28. Watanabe T, Suguro T, Sato K, et al. Serum salusin-α levels are decreased and correlated negatively with carotid atherosclerosis in essential hypertensive patients. *Hypertens Res* 2008;31:463-8.
29. Liu J, Ren YG, Zhang LH, et al. Serum salusin-β levels are associated with the presence and severity of coronary artery disease. *J Investig Med* 2015;63:632-5.
30. Yilmaz M, Atescelik M, Ardic S, et al. Serum salusin levels in ST-segment elevation myocardial infarction. *Clin Lab* 2016;62:1717-23.
31. Shichiri M, Ishimaru S, Ota T, et al. Newly identified bioactive peptides with hemodynamic and mitogenic activities. *Nat Med* 2003;9:1166-72.
32. Sun HJ, Zhao MX, Ren XS, et al. Salusin-β promotes vascular smooth muscle cell migration and intimal hyperplasia after vascular injury via ROS/NFκB/MMP-9 pathway. *Antioxid Redox Signal* 2016;24:1045-57.
33. Sun HJ, Liu TY, Zhang F, et al. Salusin-β contributes to vascular remodeling associated with hypertension via promoting vascular smooth muscle cell proliferation and vascular fibrosis. *Biochim Biophys Acta* 2015;1852:1709-18.
34. Sato K, Fujimoto K, Koyama T, et al. Release of salusin-β from human monocytes/macrophages. *Regul Pept* 2010;162:68-72.
35. Koya T, Miyazaki T, Watanabe T, et al. Salusin-β accelerates inflammatory responses in vascular endothelial cells via NF-κB signaling in LDL receptor-deficient mice in vivo and HUVECs in vitro. *Am J Physiol Heart Circ Physiol* 2012;303:96-105.