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Clinical Investigation

A New Insight Into Pathophysiological Mechanism of Abdominal Aortic Aneurysm With Novel Parameters Salusin-β and Arterial Stiffness

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Background: *Abdominal aortic aneurysm (AAA) has risk factors similar to those of atherosclerosis. Salusin-β and arterial stiffness are novel parameters that have been shown to predict atherosclerosis and related cardiovascular disorders. However, their predictive value for detecting AAA remains unclear.*

Methods: *Forty-eight patients with AAA and 47 age- and sex-matched participants without AAA were enrolled in the study. Arterial stiffness parameters were obtained via an oscillometric Mobil-O-Graph PWA Monitor device (IEM GmbH) with integrated ARCSolver software (Australian Institute of Technology). Plasma salusin-β levels were analyzed using an enzyme-linked immunosorbent assay reagent kit (Abbkine, Inc). The measured salusin-β levels and arterial stiffness parameters of the AAA and control groups were compared.*

Results: *Salusin-β levels were significantly lower in patients with AAA (P = .014). There was a significant negative correlation between salusin-β levels and abdominal aorta diameter. No significant difference was detected between AAA and control groups in terms of arterial stiffness parameters (P > .05). In backward multiple regression analysis, the presence of AAA, platelet count, and augmentation index were found to be independent predictors of salusin-β levels (P = .006 and P = .023, respectively).*

Conclusion: *Arterial stiffness parameters were not found to be associated with AAA. Contrary to previous results regarding atherosclerosis and related cardiovascular disorders, salusin-β levels were found to be lower in patients with AAA. Although AAA is thought to have similar risk factors as atherosclerosis, the exact pathophysiologic mechanism remains unclear.* ***(Tex Heart Inst J. 2022;49(6):e217561)***

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An abdominal aortic aneurysm (AAA) is an enlarged area in the lower part of the aorta that supplies blood to the body. AAA is diagnosed when the diameter of the vessel, most exclusively infrarenal, exceeds 30 mm. The main etiology is a degenerative process that shares risk factors with atherosclerotic disorders. Besides established conventional risk factors, such as age, male gender, smoking, and hypertension, there is a growing interest in novel parameters.

Salusins are endogenous bioactive peptides with hemodynamic and mitogenic activities. Biosynthesis of 2 related peptides, salusin-α and salusin-β, occurs by proteolytic processing of prosalusin at the prosalusin C terminus.[1] Interestingly, the 2 isoforms of salusin were found to have opposite effects on the pathophysiologic processes of atherosclerosis in experimental studies. Salusin-β has systemic proatherogenic activity, and salusin-α has a contrasting antiatherogenic effect.[2]

Arterial stiffness also has value in the prediction of cardiovascular morbidity and mortality. There is a rapidly growing area of investigation on arterial stiffness, specifically aortic stiffness, as measured by the reference standard carotid-femoral pulse wave velocity (PWV).[3-5] Although the relationship between arterial stiffness and the ath-

erosclerotic process is well known, the impact of aortic elastic parameters on AAA remains unclear.

Abdominal aortic aneurysm is an insidious disease with a mostly asymptomatic course and devastating consequences. It deserves investigation of novel parameters that may provide earlier diagnosis and risk stratification. In this study, the pathophysiological mechanism of AAA with novel parameters, salusin-β and arterial stiffness, were investigated.

Patients and Methods

The study was conducted by the cardiology department of Giresun University Hospital between April 2019 and April 2020. A total of 48 patients with AAA were included in the study, and 47 age- and gender-matched participants without AAA constituted the control group. All patients underwent echocardiographic evaluation following documentation of medical history and baseline physical examination. The exclusion criteria were presence of malignancy, chronic obstructive pulmonary disease, chronic renal failure requiring dialysis, connective tissue or other chronic inflammatory diseases, rheumatic valvular disease, and prosthetic heart valves. The protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The study was approved by the local ethics committee, and informed consent was obtained from all participants.

Assessment of Salusin-β Levels

Venous blood samples from the participants were taken into ethylenediaminetetraacetic acid tubes. Following centrifugation, plasma samples were aliquoted and stored at −80 °C until the day of the study.

Plasma salusin-β levels were analyzed using an enzyme-linked immunosorbent assay reagent kit (Abbkine, Inc; catalog no. KTE60751, lot ATSJL1501). Plasma salusin-β levels were expressed in picograms per milliliter. The detection range of the method was reported to be 2.25 to 36 pg/mL, and the results obtained within this range were multiplied by the dilution factor with the recommended dilution ratio of 1:5.

Arterial Stiffness

The oscillometric method used to measure arterial stiffness and central hemodynamics has been shown to correlate well with the conventional tonometric method.[6] In our study, an oscillometric Mobil-O-Graph PWA monitor device (IEM GmbH) with integrated ARC-Solver software (Australian Institute of Technology) was used to obtain arterial stiffness parameters. Measurement of the arterial stiffness was based on the physiological process of pulse waves. A blood pressure cuff was placed on the left upper arm while the patient was in a resting supine position. The device measured the oscillometric blood pressure level, and then the pulse waves at the level of brachial artery were recorded. Measurements were taken after 30 minutes of rest. The ARCSolver algorithm, as implemented in the Mobil-O-Graph 24h PWA monitor, reconstructed the central pulse wave by applying a transfer function. Pulse wave velocity was estimated from the time difference between the derived forward and reflected waves after signal processing based on the waveform constraint criteria. The model used was linear with a continuous parameter space for arterial resistance, peripheral resistance, and arterial compliance. The software system provided quantification of aortic systolic blood pressure, aortic diastolic blood pressure, augmentation index (AIX), and PWV.

Assessment of Abdominal Aorta

The grayscale ultrasound examinations were performed by a single radiologist with 18 years of ultrasound experience who was blinded to the preliminary clinical findings. The patients were imaged carefully so that the largest diameter in supine and resting position could be obtained. All patients were imaged via an Aplio 500 sonography device (Toshiba Medical Systems; recently Canon) using a 3.5 to 5 MHz frequency range convex transducer. The transducer dispensed with gel was moved gently on the skin to avoid abdominal contractions. After obtaining the relevant grayscale image, the image was frozen. Inadequate images were not evaluated. The abdominal aorta was evaluated in both sagittal and axial planes for each patient. The largest diameter was measured in the sagittal plane, and each patient's results were recorded.

Statistical Analysis

Statistical analyses were performed using MedCalc version 20.106 (MedCalc Software Ltd). The suitability of continuous variables to normal distribution was investigated using the Kolmogorov-Smirnov test. Variables with Gaussian distribution were shown as mean (SD), whereas variables with non-Gaussian distributions were shown as the median. Student t test or Mann-Whitney U test was used for intergroup comparisons of variables with normal distribution. Pearson χ^2 test was used for comparisons of expected and observed frequencies. The directions and degrees of the relationship between variables were evaluated with Pearson correlation coefficient (*r*) or point-biserial correlation coefficient (*rpb*). Linear regression analysis was used to determine the parameters independently associated with plasma salusin-β. Statistical significance was evaluated at the $P < .05$ (2-tailed) level.

Results

A comparison of demographic characteristics, echocardiographic findings, and arterial stiffness parameters is

shown in Table I. There was no statistically significant difference between AAA and the control groups regarding age, sex, smoking status, or systolic or diastolic blood pressure. Prevalences of diabetes mellitus, hypertension, coronary artery disease, and rates of β-blocker, angiotensin-converting enzyme inhibitor, and calcium channel blocker use were also similar between the 2 groups. As expected, the abdominal aorta diameter was significantly higher in the AAA group ($P < .001$). Moreover, ascending aorta diameter and right ventricular diameter were also significantly higher ($P < .001$). Although PWV was found to be higher and AIX was found to be lower in the AAA group, the difference for both parameters did not reach statistical significance. A comparison of laboratory parameters is given in Table II. No significant difference was detected between the levels of the AAA and control groups except for salusin-β levels; the salusin-β level was significantly higher in the control group than in the AAA group ($P = .014$). In backward multiple-regression analysis, among the variables showing statistically significant correlation with salusin-β in correlation analysis (Table III), the parameters independently associated with salusin-β were abdominal aorta diameter, AIX, and platelet count (Table IV). Figure 1 shows the flowchart of the study, whereas Figure 2 shows scatter plot drawings between salusin-β levels and abdominal aorta diameters, ascending aorta diameter, AIX, and platelet count in their respective panels.

Discussion

The study results revealed that AAA was associated with lower levels of salusin-β. Moreover, salusin-β levels were negatively correlated with abdominal aortic diameter.

TABLE I. Comparison of Demographic Characteristics and Clinical Findings Between AAA and Control Groups

	AAA group (n = 48)	Control group (n = 47)	*P* value[a]
Age, mean (SD), y	66.9 (9.5)	64.7 (7.2)	.218
Sex			.374
Male, No. (%)	42 (87.5)	38 (80.9)	
Female, No. (%)	6 (12.5)	9 (19.1)	
BMI, mean (SD), kg/m^2	29.0 (4.9)	28.8 (3.1)	.862
DM, No. (%)	9 (18.8)	13 (27.7)	.303
HTN, No. (%)	36 (75.0)	30 (63.8)	.237
CAD, No. (%)	21 (43.8)	21 (44.7)	.927
Smoking status, No. (%)	10 (20.8)	8 (17.0)	.635
β-Blocker use, No. (%)	14 (29.2)	8 (17.0)	.161
Calcium channel blocker use, No. (%)	5 (10.4)	6 (12.8)	.720
ACE inhibitor use, No. (%)	26 (54.2)	12 (25.5)	.004
SBP, mean (SD), mm Hg	142.8 (26.6)	145.7 (19.9)	.551
DBP, mean (SD), mm Hg	82.7 (14.6)	78.2 (13.9)	.128
Heart rate, mean (SD), No./min	80.1 (18.5)	77.0 (11.3)	.331
Abdominal aorta, mean (SD), mm	38.7 (8.7)	20.3 (2.3)	<.0001
Ascending aorta, mean (SD), mm	3.54 (0.60)	3.14 (0.48)	<.001
Left atrium, mean (SD), mm	3.50 (0.76)	3.31 (0.47)	.140
Septum, mean (SD), mm	1.01 (0.16)	0.99 (0.20)	.535
Posterior wall, mean (SD), mm	1.03 (0.13)	0.99 (0.16)	.239
EDD, mean (SD), mm	5.03 (0.61)	4.81 (0.56)	.061
ESD, mean (SD), mm	2.95 (0.58)	2.96 (0.56)	.921
Right ventricle, mean (SD), mm	2.62 (0.40)	2.37 (0.27)	<.001
EF, mean (SD), %	59.4 (8.5)	60.9 (6.4)	.314
PWV, mean (SD), m/s	9.76 (1.45)	9.52 (1.35)	.408
AIX, mean (SD), %	21.0 (11.9)	24.1 (13.2)	.230

AAA, abdominal aortic aneurysm; ACE, angiotensin-converting enzyme; AIX, augmentation index; BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; DM, diabetes mellitus; EDD, end-diastolic diameter; EF, ejection fraction; ESD, end-systolic diameter; HTN, hypertension; PWV, pulse wave velocity; SBP, systolic blood pressure.

[a] $P < .05$ was regarded as significant.

TABLE II. Comparison of Laboratory Findings and Salusin-β Levels Between AAA and Control Groups

Finding[a]	AAA group (n = 48)	Control group (n = 47)	*P* value[b]
Glucose levels, median (IQR), mg/dL	108 (95-117)	104 (91-120)	.308
Urea levels, mg/dL	36.8 (10.4)	37.6 (10.9)	.714
Creatinine levels, mg/dL	0.92 (0.22)	0.92 (0.20)	.859
Total cholesterol, mg/dL	203.6 (46.4)	195.0 (51.3)	.392
Triglycerides, median (IQR), mg/dL	143 (92-210)	163 (111-225)	.577
HDL cholesterol, mg/dL	49.5 (17.3)	47.6 (14.3)	.561
LDL cholesterol, mg/dL	121.6 (43.1)	109.3 (42.9)	.166
AST levels, IU/L	23.1 (7.1)	21.5 (5.1)	.220
ALT levels, IU/L	18.8 (9.1)	18.4 (6.9)	.797
TSH, median (IQR), mIU/L	1.36 (0.99-1.86)	1.57 (1.04-2.09)	.313
FT_4, ng/dL	1.24 (0.18)	1.23 (0.20)	.803
WBC count, median (IQR), $\times 10^9$/L	7.32 (6.14-8.55)	7.55 (6.72-8.81)	.529
Hemoglobin levels, g/dL	14.2 (1.5)	14.2 (1.6)	.846
Hematocrit, %	43.2 (4.3)	42.8 (4.5)	.686
Plt count, $\times 10^9$/L	240.5 (64.6)	242.9 (60.6)	.855
Salusin-β, pg/mL	54.0 (20.8)	64.9 (20.8)	.014

AAA, abdominal aortic aneurysm; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FT_4, free thyroxine; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; Plt, platelet; TSH, thyroid-stimulating hormone; WBC, white blood cell.

[a] The data are expressed as mean (SD), unless otherwise indicated.

[b] The results were regarded as significant at $P < .05$.

TABLE III. Parameters Showing Statistically Significant Correlation With Salusin-β Among Overall Study Population and Subgroups[a]

	Control group		AAA group		Overall study population	
	r	*P* value	*r*	*P* value	*r*	*P* value
Abdominal aorta	−0.239	.114	−0.269	.071	−0.336	<.001
Ascending aorta	−0.242	.109	−0.277	.062	−0.321	.002
Calcium channel blocker use	0.184[b]	.227	0.289[b]	.059	0.242[b]	.021
Plt count	0.363	.014	0.219	.144	0.291	.005
AIX	0.401	.006	0.133	.377	0.290	.005

AAA, abdominal aortic aneurysm; AIX, augmentation index; Plt, platelet; *r*, Pearson correlation coefficient; *rpb*, point-biserial correlation coefficient.

[a] The results were regarded as significant at $P < .05$.

[b] *rpb* is reported here instead of *r*.

PWV and AIX, which reflect arterial stiffness, did not differ between AAA and control groups.

Abdominal aortic aneurysm is generally silent and incidentally detected if it does not end in rupture. Although the presence of conventional risk factors and family history for AAA raise suspicion and strict screening programs are highly recommended, most cases are overlooked. Moreover, in some cases, the course of the disease is unpredictable because enlargement can progress rapidly. More must be learned about AAA for earlier diagnosis and prognostic stratification.

Among many parameters being investigated to support the development of more powerful strategies against the atherosclerotic process, salusins have drawn particular attention. Salusin-β induces vasopressin and oxytocin release from the posterior pituitary, which results in a rapid and profound decrease in blood pressure and heart rate.[7,8] On the other hand, endogenous salusin-β in the vasculature accelerates the atherosclerotic process.[9]

TABLE IV. Backward Multiple-Regression Analysis of Parameters Showing Significant Correlation With Salusin-β[a]

Independent variables	B	SE	β	*P* value	R^2
Constant	43.64	10.42	–	<.001	
Abdominal aorta	−0.52	0.18	−0.27	.005	
Calcium channel blocker use	11.37	6.35	0.17	.077	0.521
Plt count	0.09	0.03	0.26	.006	
AIX	0.37	0.16	0.22	.023	

AIX, augmentation index; B, unstandardized regression coefficients; Plt, platelet

[a] The constant term in the regression equations was the value at which the regression line cuts the y-axis. The results were regarded as significant at $P < .05$.

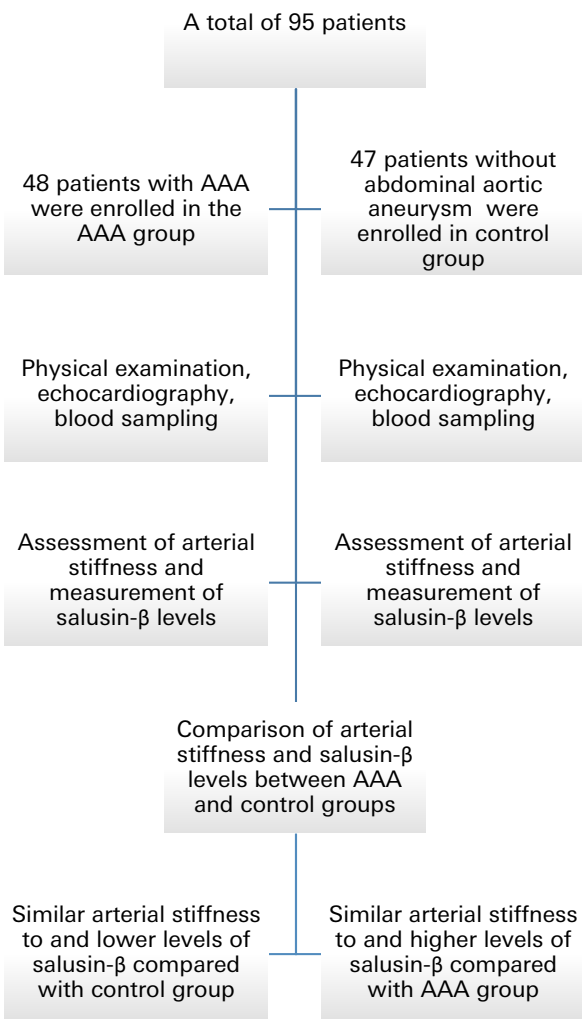

Fig. 1 *Flowchart for the study.*

AAA, abdominal aortic aneurysm.

Serum salusin-β level was found to be associated with the presence and severity of coronary artery disease.[10] Moreover, salusin-β is superior to salusin-α as a marker for evaluating coronary atherosclerosis.[11] Previous studies have revealed a positive correlation between salusin-β and triglycerides, low-density lipoprotein cholesterol, and triglyceride to high-density lipoprotein to cholesterol ratio.[12,13] Unfavorable effects of salusin-β in atherosclerosis and myocardial remodeling following ischemia-reperfusion injury were also demonstrated in animal models.[9,14] Moreover, proliferation of vascular smooth muscle cells and vascular fibrosis, which are closely linked with atherosclerosis, were found to be induced by salusin-β.[15] Because the atherosclerotic degenerative process is considered to be the main cause of AAA, the association between this clinical entity and salusin-β ought to be investigated further. Unexpectedly, our study results revealed that patients with AAA had lower levels of salusin-β. In addition to the abovementioned studies demonstrating a positive correlation between salusin-β levels and the atherosclerotic process, some contrary reports are also present in the literature. Some studies have revealed favorable effects of salusin-β against metabolic syndrome, cardiovascular disease, and renal ischemia/reperfusion damage.[16,17] These conflicting results may be a result of the multifaceted effects of salusin-β. The blood pressure–lowering effect is also a well-known feature of this endogenous peptide. For example, Sun et al[18] demonstrated that salusin-β contributes to vasodilatation in hypertensive rats. The lack of this favorable effect may contribute to the development of AAA.

Arterial stiffness is a well-established predictor of cardiovascular morbidity and mortality.[3-5] Although AAA is a vascular disease that shares common risk factors with atherosclerosis, a partly independent process through different pathogenic mechanisms is also involved in the etiology. Endothelial dysfunction, which was shown to be precisely reflected by PWV, is also implicated in this

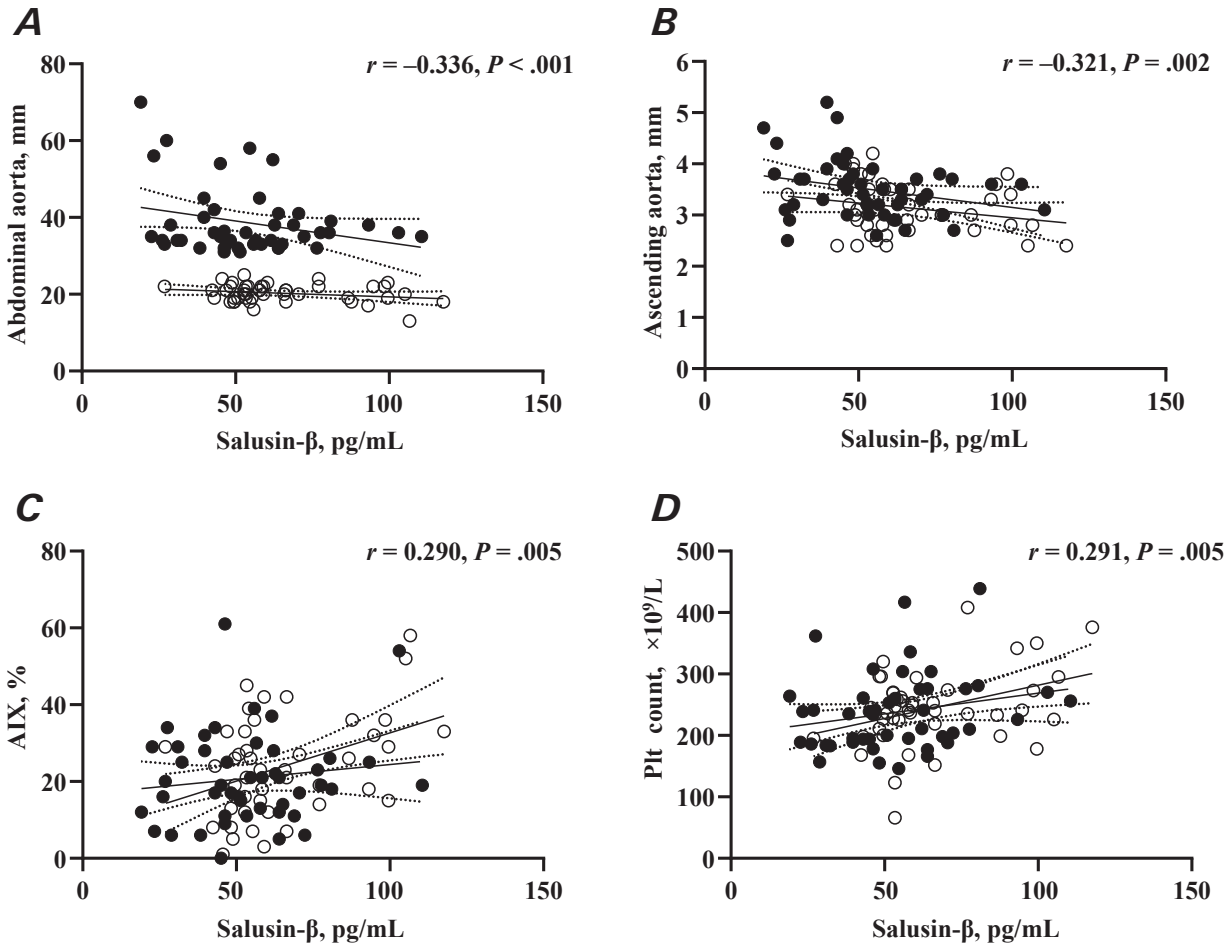

Fig. 2 *Scatter plot drawings between* ***A****) salusin-β levels and abdominal aorta diameter,* ***B****) ascending aorta diameter,* ***C****) AIX, and* ***D****) platelet count. Statistical significance was evaluated at the* P < .05 *(2-tailed) level. Filled and empty circles represent abdominal aortic aneurysm and control groups, respectively.*

AIX, augmentation index; Plt, platelet

pathophysiologic process.[19] Thus, arterial stiffness has been the focus of interest in recent AAA studies. Some studies have revealed increased arterial stiffness in patients with AAA.[20,21] On the contrary, Lee et al[22] concluded that PWV and AIX are not reliable parameters in patients with AAA because they found that patients with AAA had significantly lower PWV than did controls. Arterial stiffness parameters in patients with AAA were investigated to elucidate this debate, and although PWV was found to be increased in patients with AAA in the current study, the difference did not reach statistical significance. In line with the study by Lee et al,[22] there was no clear association between arterial stiffness parameters and AAA in the present study.

Because the concept of confounders is causal and thus cannot be defined in terms of correlations or relationships, age and gender were counted as confounders in most of the reviewed clinical trials. In this study, age and gender were also used as confounder variables and were matched between study and control groups.

Limitations

This was a single-center observational study with possible unknown confounders. The low number of participants and the mismatch in the number of participants in the control group can be considered limitations. However, AAA is generally asymptomatic and thus is not easy to detect. In this study, besides age and gender, there were quite a few other factors that could have been considered, as well. Lack of propensity-score matching between the groups using all relevant variables can also be considered a limitation. Other cardiovascular disorders, such as coronary artery disease, and medications used can be confounders as it relates to salusin-β levels. On the other hand, the similar frequency of these abovementioned factors might have diminished this confounder effect. This study was a case-control study in which participants were included according to certain criteria. There is a need for cross-sectional studies that can reveal the diagnostic properties (sensitivity, specificity, positive/negative predictive values) of salusin-β

levels for AAA and the prevalence of the population. In addition, further prospective cohort studies in healthy individuals with the defined risk factors are needed to determine the effect of salusin-β on the risk of future AAA development (relative risk). This study represents preliminary data, so further analysis should be undertaken to avoid potential bias.

Conclusion

Although AAA is thought to share similar pathophysiologic mechanisms with the atherosclerotic process, salusin-β levels, which have been shown to be a predictor of atherosclerosis, were found to be decreased in patients with AAA. Moreover, a clear association between arterial stiffness parameters and AAA was not found. The pathophysiologic mechanism of AAA requires a more comprehensive evaluation because conventional risk factors seem to be incapable to be used to determine the exact mechanism. A sophisticated interaction between conventional risk factors and novel parameters may be possible. Further studies excluding other disorders that may affect salusin-β levels and arterial stiffness—such as coronary artery disease—are needed to conclude whether there is a clear association between AAA and these novel parameters.

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