Relationship of serum salusin beta levels with coronary slow flow

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Abstract

Objective: The pathophysiology of coronary slow flow (CSF) has not been clarified. Salusin-β is released predominantly from the atheroma plaques and influences the pathophysiologic processes of atherosclerosis. Therefore, this study aimed to determine serum salusin-β levels in CSF and its correlation with CSF.

Methods: The study included 39 patients with CSF, and the control group (n=42) consisted of consecutive subjects with normal coronary arteriogram. We measured salusin-β and thrombolysis in myocardial infarction frame count (TFC).

Results: Age, body mass index (BMI), systolic blood pressure, diabetes, hyperlipidemia, and smoking rates were similar (p values>0.05) in both groups. High sensitive C-reactive protein (2.80±1.2 vs. 2.21±1.2 mg/dL, p=0.011), salusin-β [1205 (330–2092) vs. 162 (29–676), pg/ml, p<0.001], corrected TFC of left anterior descending coronary artery (29±9 vs. 19.7±3.7, p<0.001), circumflex artery TFC (25±10 vs. 15±3.2, p<0.001), right coronary artery TFC (28±7.1 vs. 13±3.3, p<0.001), and mean TFC (28±4.4 vs. 16±3.7, p<0.001) were significantly higher in the CSF group. In univariate and multivariate regression analysis, only BMI (unstandardized β±SE=0.178±0.08, p=0.036) and salusin-β levels (unstandardized β±SE=0.006±0.01, p<0.001) were determined as predictors of CSF. There was a good correlation between serum salusin-β and mean TFC values (r=0.564; p<0.001).

Conclusion: There is an association between serum salusin-β levels and CSF. *(Anatol J Cardiol 2019; 22: 177-84)*

Keywords: atherosclerosis, coronary slow flow, salusin-β, endothelial dysfunction

Introduction

Coronary slow flow (CSF) is a disease that can be detected by the late distal arrival of opaque material despite absence of significant coronary artery stenosis in the coronary angiography (CAG) (1). Tambe et al. (2) first described it, and they attributed this condition to microvascular resistance. Goel et al. (3) reported that incidence of CSF as 1%–7% in patients undergoing CAG. Microvascular and endothelial dysfunction, atherosclerosis, inflammation, and platelet dysfunction are considered to play role in the etiology of CSF (4, 5). Although endothelial dysfunction is the common denominator of conditions such as diffuse atherosclerosis, systemic inflammation, and microvascular disease, no definite cause has been identified. Most patients are admitted to the hospital with complaints such as angina pectoris, exertional shortness of breath, or fatigue. Therefore, it is possible to perform multiple CAG procedures. Sometimes it may even lead to ST elevation myocardial infarction (6). Due to its association with fragmented QRS, which is a marker of sudden cardiac death and life-threatening arrhythmias on electrocardiography (7), CSF has also been shown to be a potential predictor of sudden death (8).

Salusins, defined as salusin-α and salusin-β, are related bioactive peptides of the amino acids 28 and 20, respectively, produced from the same prosalusin precursor molecule (9). Salusin-β increases macrophage foam cell formation while salusin-α has the opposite action (10). Salusin-β has a stronger mitogenic effect on vascular smooth muscle cells and fibroblasts than salusin-α. It aggravates atherosclerotic lesions, induces endothelial cell inflammation, and causes endothelial dysfunction. It has been suggested that in patients with CAD, increase in salusin-β level contributes to pathogenesis on atherosclerosis, while a decrease in level of salusin-α has anti-inflammatory effects on atherosclerosis, in patients with coronary artery disease (CAD). Salusin-β infusion in mice with serum high-density lipoprotein cholesterol (HDL-C) receptor defect has been shown to rapidly increase in low-density lipoprotein cholesterol (LDL-C) level and lipid load in the atherosclerotic plaque (10-12). Therefore, they were closely related to atherosclerosis. Salusin-β is released predominantly from the atheroma plaques. It activates

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inflammation by activating the nuclear factor kappa beta (NF-KB) pathway (11). In a recent study, Wang et al. (13) showed a positive correlation between salusin-β and CSF.

Considering atherosclerosis and endothelial dysfunction, the major causes of CSF, we hypothesized that salusin-β may be an important biomarker associated with CSF. Therefore, we investigated the relationship between serum salusin-β levels and CSF.

Methods

This study was prospectively conducted between December 2016 and January 2018. The Local Ethics Committee approved the study (no. 2016.16.09.08). All participants were informed about the study protocol; and informed volunteer consent form was received from every participant prior to enrolment. A total of 39 patients with angiographically proven CSF were enrolled in the study (Fig. 1, flowchart). To meet the age characteristics of the CSF group, the control group (n=42) was formed among those (>30 years old) with a completely normal coronary arteriogram. The control group consisted of consecutive subjects without heart failure, acute or chronic inflammation, and thyroid disorders. Three cardiologists who did not know the study protocol performed the selection of the participants. The patients with any epicardial coronary artery lesion with 50% or more stenosis were excluded from the CSF group regardless of whether obstructive lesion was in the CSF artery or not. The exclusion criteria were as follows: history of myocardial infarction, acute coronary events, any rhythm other than sinus, intracardiac conduction defect or branch block, left ventricular systolic dysfunction (LVEF≤50%), moderate or severe valve disease, chronic renal failure (estimated GFR<60 mL/min/1.73 m^2), acute or chronic inflammation, concomitant coronary ectasia or aneurysm, chronic lung or liver disease, thyroid disorder, or cancer, and those who have taken nonsteroidal or steroid-derived anti-inflammatory drugs within the last month.

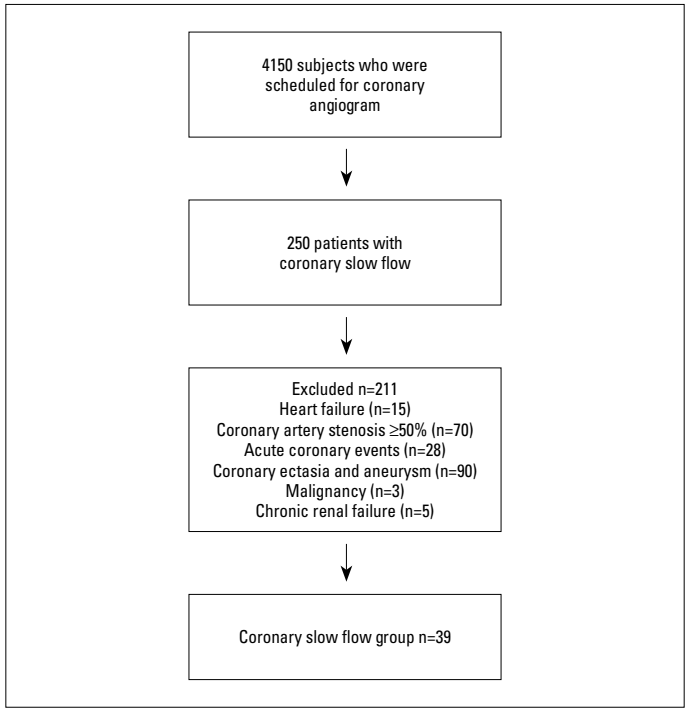

Figure 1. Diagram shows the selection of the study groups

Use of the medications, such as beta-blockers, acetylsalicylic acid, statin, calcium channel blockers, and angiotensin converting enzyme inhibitors (ACEI), and angiotensin receptor blockers (ARB) was recorded. Demographic characteristics and cardiovascular risk factors were recorded in each study' participants. Body mass index (BMI) was calculated by body weight (kg) / meter squared (m^2).

Diabetes mellitus was diagnosed as fasting blood glucose of higher than 126 mg/dL or taking any antidiabetic medication (14). The diagnosis of hypertension was considered as systolic pressure ≥140 mm Hg and/or diastolic pressure ≥90 mm Hg or use of any antihypertensive medication (15). Hyperlipidemia was defined as total cholesterol (TC) ≥200 mg/dL, LDL-C ≥130 mg/dL, triglyceride (TG) ≥150 mg/dL, HDL-C≤40 mg/dL, as described earlier (16).

Coronary angiographic examination and diagnosis of CSF

The CAG procedures were performed according to the standard protocol. For this purpose, after right femoral artery cannulation, left coronary arteries were imaged by 6 or 7 F Judkins catheters with at least four projections (Spider position, right oblique, antero-posterior cranial, and left oblique) and right coronary arteries (RCA) with at least two exposures (left oblique and left cranial). Images were shot at a rate of at least 80 image frames and recorded at a rate of 25 frames per second. Additional projections were taken in suspicious lesions and confirmed whether there was any lesion or not. Six to eight milliliters of opaque material were given by hand for each exposure. A total of 50–100 cc non-ionic radiopaque substance was used for each patient. At least two cardiologists examined coronary anatomic examination records offline (Artiz Zee, Siemens, Munich, Germany). The decision of the majority was accepted in the case of a conflict. Coronary blood flow velocity was determined by the quantitative number of frame count as described by Gibson et al. (17). It is a reliable method in all cardiology laboratories. We measured the thrombolysis in myocardial infarction frame count (TFC) as the difference of cine frames counts between proximal and distal coronary artery opacification. Bifurcation at the distal end of the left anterior descending coronary artery (LAD), and the point where the longest branch is distal to the circumflex artery (CX) (usually the branching of the optic margin branch or posterior descending branch separation), and posterolateral artery for the RCA are accepted as a distal point (17). The normal TFC ranges were previously reported as 36.28±2.6 for the LAD, 22.28±4.1 for the CX, and 20.48±3.0 for the RCA. When there is an epicardial coronary artery with TFC higher than two standard deviations from the normal range, CSF is considered. Therefore, the cut-off values in diagnosis of CSF for LAD, CX, and RCA were

determined as 41.48, 30.48, and 26.48, respectively. As LAD is 1.7 times longer than CX and RCA, the calculated TFC value for LAD is divided by 1.7, and the corrected TFC is obtained as 24.4. The mean TFC value is obtained by dividing the total TFC value by 3 (17). For inter-observer variability, 15 randomly selected participants (10 with CSF and five healthy controls) were re-evaluated by the same observer blinded to the first measurements. The intra-observer variability was calculated by comparison of the values determined by two different cardiologists. The inter- and intra-observer correlation coefficients of the mean TFC were ≥0.95.

Blood collection and biochemical analysis

Fasting venous blood samples were collected during the morning hours (between 08:00 and 11:00) prior to CAG for further analysis. A total of 10 cc serum sample was taken for salusin-β measurements after obtaining blood from the tubes for routine biochemical and blood count. Since salusins could be destroyed by proteases enzymes, aprotinin (500 kallikrein units per milliliter) was added into the biochemistry tubes before taking a blood sample (18). Routine biochemical tests were performed for the measurements of fasting glucose, HDL-C, LDL-C, TC, TG, creatinine, uric acid, and high-sensitivity-C-reactive protein (hs-CRP). A blood sample was also analyzed for the hemogram.

Blood samples were stored at -80° within 2 h to prevent salusin-β deterioration following centrifugation performed for 10 min at 4000 rpm. Serum salusin-β levels were measured by commercially available enzyme-linked immunosorbent assay kit ELISA- (Salusin-β ELISA kit, Elabscience Biotech Co., Ltd, Wuhan, China).

According to the information obtained from the catalog of the factory producing kits, the salusin-β kit analysis inter- and intra-assay coefficients of variation for the assay were less than 10%, and the detection range was between 31.25 and 2000 picogram per milliliter levels.

Statistical analysis

The predictive Analysis Software Statistics 25 (SPSS Inch, Chicago, Illinois, USA) was used for the analysis of the study variables. The Shapiro–Wilk test was used to control the variable distributions. Two independent sample t tests were used for normally distributed data, and Mann–Whitney U test was used to compare non-normally distributed data. Categorical data were compared by the Chi-square test, and Fisher's exact test was used if it was needed. Spearman and Pearson correlation analyses were performed to determine the association between different parameters with the salusin-β levels and mean TFC as appropriate. Logistic regression analysis was performed to assess predictors of the CSF. Receiver operating characteristic (ROC) curve analysis was performed to determine the salusin-β predictive value for CSF. Those variables with p<0.1 by univariate logistic analysis were entered in the multivariate logistic analysis by Backward LR method. A two-tailed p<0.05 was considered significant.

Results

When the characteristics of the CSF and control groups were compared, age, BMI, systolic blood pressure, diabetes, hyperlipidemia, smoking rates were similar (all p values>0.05). Male sex ratio [31 (79%) vs. 17 (40.5%)], diastolic blood pressure (74.5±6.4 vs. 69.2±7.7 mm Hg, p=0.005), hypertension rates [21 (53.8%) vs. 12 (28%), p=0.021] were higher in the CSF group. When biochemical variables of the CSF group and the control group were compared, the values of fasting glucose, TC, TG, HDL-C, LDL-C, uric acid, creatinine, and hemoglobin were similar (p>0.05 for all values). However, both hs-CRP (2.80±1.6 vs. 2.2±1.2 mg/dL, p=0.011) and salusin-β [1205 (330–2092) vs. 162 (29–676) pg/mL, p<0.001] were significantly higher in the CSF group (Table 1).

Compared to both groups' TFC values, corrected LAD TFC (29±9 vs. 19±3.7, p<0.001), CX TFC (25±10 vs. 15±3.2, p<0.001), RCA TFC (28±7.1 vs. 13±3.3, p<0.001), and the mean TFC (28±7.4 vs. 16±3.7, p<0.001) was significantly higher in the CSF group than in the control group (Table 1).

When the rates of cardiovascular drug use of both groups were compared, the rates of beta-blockers, acetyl salicylic acid, statin, calcium channel blockers, and ACEI/ARB drug use were similar (all p values>0.05) (Table 1). Mean TFC was correlated with serum salusin-β (r=0.564; p<0.001) (Fig. 2) and BMI (r=0.306; p=0.006). Additionally, salusin-β was not correlated with BMI and hs-CRP (p>0.05) (Table 2).

When gender, BMI, diastolic blood pressure, hypertension, hyperlipidemia, smoking, and salusin-β parameters were taken into univariate and multivariate logistic regression analysis, BMI [odds ratio (OR)=1.81; 95% confidence interval (CI), 1.31–2.32; p=0.005] and salusin-β levels (OR=1.92; 95% CI, 1.43–2.69; p<0.001) were detected as predictors of CSF presence (Table 3). In ROC analysis, the values of serum salusin-β above 516 pg/mL

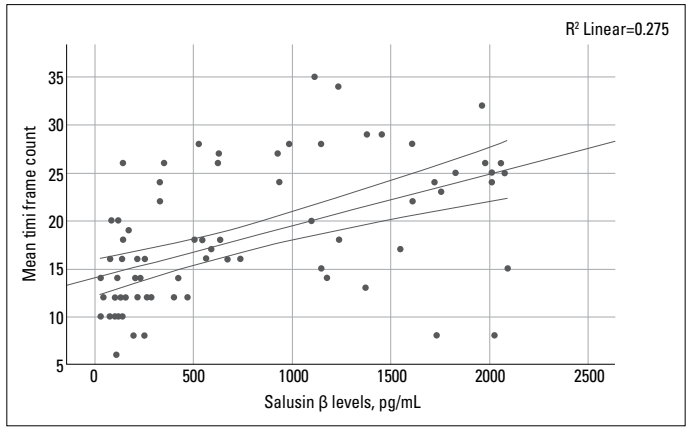

Figure 2. Relation of mean TIMI frame count and serum salusin-β levels

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Table 1. Comparison of demographic, anthropological, biochemical, and angiographic features of the coronary slow flow and the control group

Variables	Coronary slow flow group n=39	Control group n=42	*P* value
Age, year	57±10.9	54.3±8.0	0.490*
Gender, % (n=male)	31 (79.5)	17 (40.5)	0.001†
Body mass index, kg/m^2	28.8±6.03	26.8±4.7	0.074*
Systolic blood pressure, mm Hg	133±17	127±16	0.116*
Diastolic blood pressure, mm Hg	74.5±6.4	69.2±7.7	0.005*
Diabetes mellitus, n (%)	10 (25.6)	12 (28.6)	0.767†
Hypertension, n (%)	21 (53.8)	12 (28.6)	0.021†
Hyperlipidemia, n (%)	16 (41)	10 (23.8)	0.097†
Smoking, n (%)	12 (30.8)	6 (14.3)	0.075†
Fasting glucose, mg/dL	99±20.5	103±28.8	0.290*
Total cholesterol, mg/dL	188±40	186±39.5	0.688*
Triglycerides, mg/dL	156±91	159±80	0.533‡
HDL-cholesterol, mg/dL	47.8±16	46.3±17	0.408*
LDL-cholesterol, mg/dL	112±31	132±67	0.083*
Uric acid, mg/dL	5.9±1.4	5.1±1.3	0.147*
Creatinine, mg/dL	0.98±0.28	0.97±0.25	0.482*
Hemoglobin, mg/dL	13.9±1.5	13.1±1.1	0.566*
Salusin-β, pg/mL	1205 (330-2092)	162 (29-676)	<0.001‡
Hs-CRP, mg/dL	2.8±1.6	2.2±1.2	0.011*
Corrected LAD TFC	29±9	19 ±3.7	<0.001*
CX TFC	25±10	15 ±3.2	<0.001*
RCA TFC	28±7.1	13±3.3	<0.001*
Mean TFC	28±7.4	16 ±3.7	<0.001*
Drug use, n (%)			
Beta blockers	6 (15.4)	6 (14.3)	0.101†
Acetyl salicylic acid	5 (12.8)	1 (2.4)	0.085‖
Statins	3 (7.7)	4 (9.5)	0.542‖
Calcium channel blockers	2 (5.1)	0 (0)	0.229‖
ACEI/ARB	7 (17.9)	8 (19)	0.192†

*Student t test; †Chi-square test; ‡Mann–Whitney U test; ‖Fisher's test; ACEI/ARB - angiotensin-converting-enzyme inhibitor/angiotensin-receptor blocker; LAD - left anterior descending artery; CX - circumflex artery; RCA - right coronary artery; Hs-CRP - high sensitive C-reactive protein; HDL - high-density lipoprotein; LDL - low-density lipoprotein; TFC - thrombolysis in myocardial infarction frame count

predicted the presence of CSF with a 79.5% of sensitivity and 85.7% of specificity. The area under the curve was 0.801 (95% CI: 0.696–0.906, p<0.001) (Fig. 3).

Discussion

The most important finding of this study was that among various risk factors, increased BMI and serum salusin-β levels were the two determinants of CSF. We have shown that the values of serum salusin-β above 516 pg/mL suggest presence of CSF, thus elevated serum salusin-β levels can be used as a promising biomarker of CSF.

CSF is defined as sluggish coronary artery flow despite absence of significant coronary artery stenosis. The misdiagnosis of CSF in the CAG can be made due to coronary artery ectasia, coronary spasm, myocardial dysfunction, valvular disease, connective tissue diseases that may affect the coronary vascular bed, coronary air embolism, pain-related vagotonia during the femoral or radial procedure, or an overlooked ostial lesion (19). Considering these reasons, the flow should be determined by the TFC method in detail. We, therefore, have used TFC to settle

Table 2. Correlations between salusin β - mean TFC and other clinical characteristics

	Correlations between salusin-β and clinical characteristics		Correlations between mean TFC and clinical characteristics	
Variables	**Correlation coefficient**	***P* value**	**Correlation coefficient**	***P* value**
Age, year	0.067	0.551	0.144	0.202
Body mass index	0.116	0.301	0.306	0.006
Systolic blood pressure	0.196	0.081	0.130	0.251
Diastolic blood pressure	0.113	0.320	0.101	0.371
Fasting glucose	-0.104	0.357	0.056	0.623
Total cholesterol	0.128	0.256	0.111	0.331
Triglycerides	-0.107	0.343	0.173	0.125
HDL-cholesterol	-0.066	0.556	-0.130	0.251
LDL-cholesterol	0.058	0.607	0.093	0.413
Uric acid	-0.187	0.095	0.161	0.153
Creatinine	0.055	0.627	0.115	0.312
Hemoglobin	-0.038	0.735	0.142	0.210
Hs-CRP	0.184	0.103	0.196	0.081
Corrected LAD TFC	0.438	<0.001	0.708	<0.001
CX TFC	0.282	0.011	0.617	<0.001
RCA TFC	0.474	<0.001	0.644	<0.001
Mean TFC	0.564	<0.001	1	<0.001

LAD - left anterior descending artery; CX - circumflex artery; RCA - right coronary artery; Hs-CRP - high sensitive C-reactive protein; HDL - high-density lipoprotein; LDL - low-density lipoprotein; TFC - thrombolysis in myocardial infarction frame count

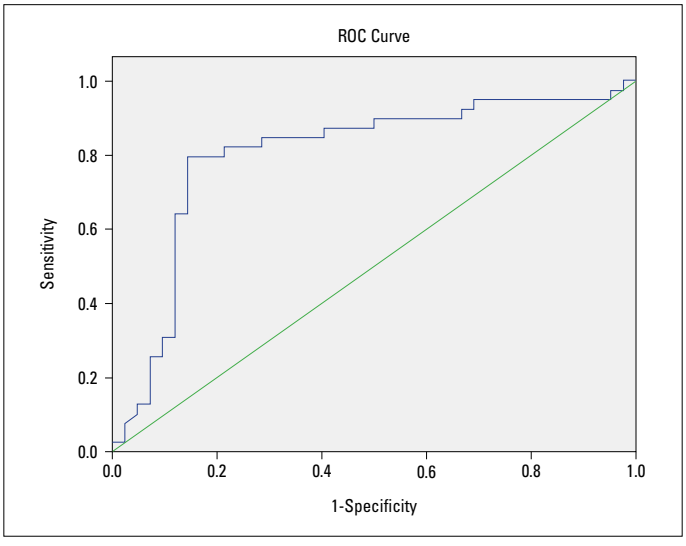

Figure 3. ROC analysis curve for the specificity and sensitivity of serum salusin-β

the diagnosis of CSF. It may exist in patients with reduced flow-mediated dilatation even in the absence of major cardiovascular risk factors such as diabetes, smoking, hyperlipidemia, and smoking (20). Therefore, CSF is considered as a preliminary vascular disease that affects both resistive intramyocardial small and epicardial coronary arteries (3). In previous studies, it was also found that there might be concomitant slow flow in the cerebral circulation in patients with CSF. This suggests that slow flow is not a specific disease to myocardium, and it is also a systemic disease (21).

In our study, CRP was found not to be associated with mean TFC and salusin-β. The lack of correlation of TFC with hs-CRP may potentially suggest that the CRP acts as a bystander in CSF phenomenon. Although hs-CRP level was higher in the CSF group, it was not found as a predictive variable in the regression analyses. This was an interesting finding in this study. CRP is an established marker of inflammation that reduces endothelial nitric oxide bioavailability (22). Although the important role of CRP has been well established in CAD, its relation to CSF is controversial. Publications exist not only in favor of a relationship between CRP and CSF (23-25) but also against (5, 26-28) in the literature. Previous studies that suggest a correlation between CRP and CSF are limited mainly by inclusion of patients with CAD with obstructive atherosclerotic lesions and confounding risk factors that are not controlled in the study population. Because most patients in previous studies were CSF patients with obstructive CAD, an expected yet indirect relationship between CRP and CSF was detected. The patients

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Table 3. Univariate and multivariate logistic regression for the analysis of predictor variables of coronary slow flow

Dependent variable: Coronary slow flow presence			
Univariate	**Unstandardized Beta±SE**	**OR 95% confidence interval**	***P* value**
Gender	1.304±1.03	3.68 (0.48-28)	0.206
Body mass index	0.185±0.09	1.73(1.38-2.79)	0.021
Diastolic blood pressure	0.05±0.06	1.05 (0.93-1.2)	0.478
Hypertension	-0.391±1.106	0.68 (0.07-5.9)	0.724
Hyperlipidemia	-1.464±1.07	0.23 (0.028-1.89)	0.172
Smoking	-0.073±1.21	0.93 (0.087-9.89)	0.952
Salusin-β	0.005±0.001	1.75 (1.19-2.55)	<0.001
High sensitive C-reactive protein	-2.41±1.75	0.98 (0.87-1.49)	0.074
Multivariate			
Body mass index	0.178±0.08	1.71 (1.31-2.32)	0.005
Salusin-β	0.653±0.157	1.92 (1.43-2.69)	<0.001

with CSF with obstructive atherosclerotic stenoses, however, were excluded in our study providing data on CSF irrespective of severe coronary atherosclerosis. We, therefore, have not demonstrated an association between CRP and CSF in our study. Numerous similar studies are in parallel with our finding that CRP has no influence on the CSF (23, 26-28).

In our study, smoking rates were statistically similar between the two groups. In the study of Xia et al. (25), which reported an association with CRP and CSF, the rate of smoking of the CSF group was higher than the control group. It is well defined in the literature that cigarette smoking significantly increases systemic inflammation and serum CRP values (29, 30). In our study, the similarity of age, BMI, systolic blood pressure, diabetes, and hyperlipidemia rates between the two groups made the result of our study more valuable by limiting the possible confounding factors. Although male sex was more common in the CSF group, statistical regression analysis demonstrated that male gender was not a predictor of CSF. Therefore, we did not think that this was a limitation for the study. In the literature, there is research showing the relationship of both male sex and obesity with CSF (31). However, the only increased BMI was found to be the risk factor associated with CSF as well as salusin-β in our study. Increased BMI is related to decreased plasma adiponectin level, which yields to insulin resistance, dyslipidemia, endothelial dysfunction, and increased risk of cardiovascular disease (32). Our finding is highly compatible with previous studies (31-33). Because insulin has a vasodilator effect, there is a decreased myocardial vasoreactivity in young individuals with increased BMI, which is associated with insulin resistance (34).

Salusin-β, which exists in large quantities in atheroma plaques, is known as a vasoactive peptide released from fibroblasts and smooth muscles in the arterial media layer (35), accelerates macrophage foam cell formation (12), and causes inflammation in endothelial cells, which leads to endothelial dysfunction (36). It is well known that endothelial dysfunction and microvascular atherosclerosis play a fundamental role in the pathogenesis of CSF (37). In our study, the correlation of serum salusin-β with the mean TFC indicates that there is a high-grade relationship between salusin-β and slow flow. Salusin-β was one of the main predictors of CSF in regression analyses. Except for this study, there is only one study that addressed possible relationship between CSF and salusin β; in which Wang et al. (13) documented a positive correlation between salusin-β and TFC. Their study is now complemented by our study.

Salusin-β triggers the inflammation pathway (NF-KB). Besides, inflammatory cytokines such as bacterial, viral, fungal infections, interleukin-1, tumor necrosis factor, pentraxin, some oxidative stress products such as free radicals can also trigger the proatherogenic NF-KB pathway. When this pathway is triggered, CRP, pentraxin 3, vascular growth and adhesion molecules, some metalloproteinases are secreted from inflammatory cells (38, 39). Salusin-β accelerates monocyte adhesion to endothelial cells via the NF-KB pathway (36), and it also induces acyl-coenzyme A cholesterol transferase-1 that accelerates the formation of cholesterol ester and LDL-cholesterol from free cholesterol (40). In our study, however, there was no correlation between salusin-β and CRP. Although CRP was higher in the CSF group, it had borderline significance in univariate analyses regarding the presence of CSF and it was found to be not related to CSF when salusin-β was added to the analyses. We think that CRP is related to the presence of nonobstructive atherosclerosis but not CSF. CSF seems to develop through distinct mechanisms different from atherosclerosis. In our study, salusin-β was not correlated with BMI that further supports the findings of multivariate analyses and suggests that salusin contributes to CSF through different mechanisms than that of BMI. Apart from these mechanisms, salusin-β may have different effects that calls for additional studies to clarify its effects.

We excluded patients with obstructive CAD, concomitant coronary ectasia, or aneurysm from the study. Nevertheless, we did not exclude patients with nonobstructive coronary atherosclerotic plaques. Although this may be proposed as a limitation, intravascular ultrasound studies revealed that most visually normal coronary artery segments on angiogram had atherosclerosis including various plaque types (41, 42). Moreover, literature has evidence of diffuse microvascular atherosclerosis in CSF phenomenon (43, 44). We, therefore, considered it as futile attempt to exclude patients with nonobstructive coronary lesions.

Salusin-β is a marker that is related to atheroma formation; therefore, CSF mainly reflects microvascular atheromatous. Salusin-β is a marker that is related to both micro- and macrovascular atheroma formation. This study demonstrated its further association to CSF in patients with nonobstructive CAD, which makes it a potential biomarker in CSF. Yet, in a patient with angina pectoris and suspected CAD, CAG will always be top priority for settling the diagnosis of CSF

Our findings potentially suggest that the patients with CSF can be followed by salusin-β in serum as well as lifestyle changes, such as smoking cessation, walking, and weight loss. At the same time, salusin-β levels may be used to evaluate whether there is a decrease in the severity of CSF after proper cardiovascular medical treatment.

Study limitations

The main limitation of this study was its size. We specifically excluded patients with acute coronary syndromes even if they had CSF. We also excluded patients with CSFs concomitant with coronary ectasia or stenosis that limited the number of patients in the study. Nevertheless, exclusion of patients with CSF with obstructive CAD (≥50% stenosis in an epicardial coronary artery) was important for the validity of the study. Secondly, to confirm the presence of CAD, the collection of blood samples from the patients referred to CAG may partially affect the selection of patients. Thirdly, our data would be more valuable if we have analyzed cytokines, such as TNF, interleukin-6, or pentraxin 3.

Conclusion

In conclusion, we found that serum salusin-β level is a biochemical marker indicating the presence of CSF. Therefore, our findings suggest that serum salusin-β plays a key role in the pathophysiology of CSF. This study, which can be a reference to further studies, showed that high serum salusin-β levels might be helpful in suspected CSF prior to CAG. We think that salusin-β can be used in the follow-up and treatment strategies of CSF.

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Anatol J Cardiol 2019; 22: 177-84
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