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Original Article

Decreased plasma levels of sestrin-1 and sestrin-2 in patients with coronary artery disease and their association with the disease severity

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Abstract

Background: Oxidative stress has been well established to participate in the pathology of coronary artery disease (CAD). Sestrin family of proteins have recently emerged as important suppressors of oxidative stress. However, only few studies have reported the levels of sestrins and their clinical significance in CAD patients.

Methods: Participants were ninety patients referred to the cardiac angiography unit for cardiac angiography. Thirty-two subjects were diagnosed as having stable CAD, twenty patients had unstable CAD and thirty-eight subjects had no CAD. All patients underwent angiography and the severity of coronary stenosis was calculated by modified Gensini score. The levels of glucose, triglyceride, total cholesterol, HDL, LDL, hs-CRP and hematological parameters were determined in the fasting blood samples by routine methods. Plasma levels of sestrin-1 and sestrin-2 were measured by ELISA.

Results: Although the plasma levels of sestrin-1 were significantly lower in both case groups compared with the control group (P<0.001), there were no significant differences in sestrin-1 levels between the two patient groups. The levels of sestrin-2 were also significantly lower in both CAD groups than in controls (P=0.001), but no significant difference was found between stable and unstable patients. In the whole study subjects, plasma sestrin-1 and sestrin-2 showed negative correlation with the coronary artery score. By multivariate analysis only sestrin-2 levels were significantly related to CAD severity.

Conclusion: Our findings showed a negative association of sestrin levels and the coronary stenosis severity.

Keywords: Coronary artery disease, Sestrins, Sesn1 protein, Sesn3 protein, Coronary stenosis.

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Coronary artery disease (CAD) is one of the most prevalent causes of mortality in developing and developed countries. Atherosclerosis is the leading cause of CAD and it is a multifactorial process causing an excessive inflammatory response to numerous damaging stimuli in the arteries leading to vessel injury, which slowly lead to narrowing of the arteries, thrombosis and acute coronary syndrome (1). Several inflammatory factors such as C-reactive protein (CRP), platelet-activating factors, cytokines as well as factors involved in the oxidative stress and angiogenic growth factors cause instability of atherosclerotic plaques, disease progression and acute phase of disease (2-4). Oxidative stress through the oxidation of lipids, especially low-density lipoproteins (LDL) particles, is an important factor in promoting atherosclerosis (5). Antioxidants are very important in maintaining normal cell function through protecting cells against oxidative stress and oxygen free radicals. Antioxidants are very structurally diverse and range from simple structural compounds such as vitamin C to complex compounds such as several antioxidant proteins (6).

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In recent years, a family of proteins with antioxidant properties called sestrins have been identified which are highly conserved and induced by oxidative stress. Sestrins, proteins with a molecular weight of 57-52 KDa, have three isoforms: sestrin-1, sestrin-2, and sestrin-3 (7). Members of this family are involved in various diseases by regulating oxidative stress, inflammatory responses, and cellular apoptosis (8). Among members of this family, sestrin-2 plays an important role in reducing hydroperoxide radicals due to its terminal domain oxidoreductase motif. Studies have shown that sesterins can have significant effects on the pathogenesis of cardiovascular diseases through the effects on oxidative stress. Lack of sestrins leads to several age-related injuries including accumulation of triglycerides, mitochondrial dysfunction, muscle dystrophy, and impaired heart function (9, 10).

Yang et al. (11) provided evidence of the involvement of sestrins in mice models with heart disease. They showed that decreased sestrin-2 expression led to the blood hypertension in mice with silenced dopamine 2 receptor (D2R). D2R reduces the ROS production in kidney tissue and regulates blood pressure, which is partly due to its positive effect on paraoxonase-2 (PON2) and sestrin-2. Moreover, other evidence indicated that sestrin-2 protects myocardial tissue against induced damage. A recent investigation demonstrated that myocardial damage and fibrosis in the respective mouse models were worsened after the mutation eliminating sestrin-2. Sun et al., showed that sestrin-1 regulates fibroblast cell proliferation in heart tissue by reducing oxidative stress (12). In addition, research shows that sestrin-2 gene expression increases in heart failure (13). Although plasma levels of sestrins have been reported in animal models of heart disease and also in some human cardiovascular diseases, to our knowledge, only two studies have examined the plasma levels of sestrins in CAD patients (14, 15). Therefore, we decided to measure the plasma concentration of sestrins 1 and 2 and investigate their relationship with the CAD severity.

Methods

Study participants and their characteristics: Participants were ninety consecutive patients admitted to the Cardiac Angiography Unit (Shahid Beheshti Hospital, Kashan, and Iran) for cardiac angiography. All patients performed coronary angiography and thirty-two subjects were diagnosed as having stable CAD, twenty patients had unstable CAD and thirty-eight subjects had no CAD.

Unstable CAD patients had irregular chest pain at rest and an abnormal electrocardiogram but a negative troponin test result. Stable patients had a regular and predictable chest pain during exercise or times of stress which was alleviated by medication and rest. Age and sex matching was done among the study groups. Data about patient's drug use and CAD risk factors was collected by a structured questionnaire. Patients who had a history of recent myocardial infarction (MI), blood disorders, metabolic or hormonal disorders, inflammatory diseases, or malignancy were excluded from the study. Hypertension and hyperlipidemia were defined as previously described (16). The study was done based on the Declaration of Helsinki and written informed consents were obtained from all participants.

Angiographic analysis: Coronary angiography was done for all the patients using the Judkins technique. Two blinded cardiac surgeons analysed all angiograms and calculated the modified Gensini score (17).

Biochemical analysis: Blood glucose and lipid profile including, triglyceride, total cholesterol, LDL and HDL were determined using routine colorimetric methods. The measurement of hs-CRP was carried out through an immunoturbidometric method. All routine parameters were measured using a clinical biochemistry analyzer (BT-3500, Italy) and commercially available kits (Pishtazteb, Iran). Sestrin-1 and sestrin-2 levels in plasma samples were assessed by ELISA, following the manufacturer's guidelines (ZellBio, Germany).

Statistical analysis: Data analysis was done by SPSS statistical software (Version 20). Qualitative data were reported as percentages. After checking the normality of data distribution by Kolmogorov-Smirnov test, the normally distributed parameters were represented as mean plus and minus standard deviation (SD). For quantitative data whose distribution was not normal, the median and interquartile ranges were used. The ANOVA test was used to check the difference in the mean values of variables with normal distribution among studied groups. For qualitative variables, chi-square test was used for inter-group comparisons. Multivariable linear regression was applied to assess the association between sestrins levels, CAD score and cardiovascular risk factors.

Results

Demographics and clinical characteristics of participants: Table 1 shows the clinical and demographic characteristics of the study groups. No significant differences were found in sex, age, demographic measures, the percentage of hypertensive patients and the number of smokers among the study groups. Except for the number of

nitrate users, there was no difference in the type of medications used among the studied groups.

The number of nitrate users was significantly lower in the unstable patients than controls. The serum concentration of total cholesterol, LDL and HDL was higher in stable patients than unstable patients. Unstable patients had significantly lower levels of serum HDL-C than stable patients. Also, they had significantly higher levels of erythrocyte sedimentation rate (ESR) than those in stable patients and controls.

Comparison of plasma sestrin-1 and sestrin-2 levels in three groups: As shown in figure 1, although the plasma levels of sestrin-1 were significantly lower in both case groups compared with the control group, there were no significant differences in sestrin-1 levels between two patient groups. Plasma levels of sestrin-2 were also significantly lower in both unstable and stable patients when compared to that of non-CAD patients. No significant difference was observed in sestrin-2 levels between two groups of patients (figure 2). Also, as shown in figure 3, there was a direct relationship between plasma levels of sestrin-1 and sestrin-2 in all subjects.

The relationship between laboratory parameters and coronary stenosis severity: Figure 4 and 5 show the relationship between plasma levels of sestrin-1 and sestrin-2 with the Gensini score, respectively. There was an inverse relationship between the plasma concentration of these two proteins and the severity of coronary artery occlusion (measured by the Gensini score). A positive relationship ($r = 0.390$, $P = 0.01$) was observed between plasma sestrin-1 and HDL levels in all subjects. Also, a significant positive relationship was found between plasma sestrin-2 and HDL levels ($r = 0.349$, $P = 0.01$) (not shown). By multivariate analysis, it was found that only the relationship between sestrin-2 levels and the severity of coronary artery stenosis is significant (table 2).

Table 1. Demographic, anthropometric, biochemical, and clinical data in participant

Variable measured	Unstable (n = 20)	Stable (n = 32)	Controls (n = 38)	P-value		
				S vs.C	U vs.C	S vs.U
Demographic data						
Age (years)	64.6±15.2	64.4±10.4	59.4±11.1	0.21	0.32	0.90
Men/women (n)	9/11	15/17	16/22	0.38	0.16	0.52
BMI (kg/m^2)	25.7±3.9	26.1±4.0	27.1±5.0	0.62	0.32	0.87
WHR	0.90±0.03	0.91±0.05	0.88±0.03	0.46	0.34	0.97
Systolic pressure (mm Hg)	126.3±15.2	131.2±14.8	127.8±17.2	0.67	0.90	0.43
Diastolic pressure (mm Hg)	79.1±12.7	79.5±7.3	79.1±9.7	0.97	0.99	0.97
Risk factors						
Hypertensive, n (%)	10 (50)	18 (56.2)	20 (52.6)	0.51	0.52	0.32
Hyperlipidemic, n (%)	7 (35.0)	11 (34.4)	18 (47.4)	0.11	0.27	0.92
Family history of CAD, n (%)	4 (20)	6 (18.7)	13 (34.2)	0.15	0.26	0.86
Smokers, n (%)	2 (10)	5 (15.6)	3 (7.9)	0.32	0.21	0.22
Medications						
Aspirin, n (%)	12 (60.0)	21 (65.6)	31 (81.6)	0.27	0.06	0.49
Nitrates, n (%)	7 (35.0)	19 (59.4)	18 (47.4)	0.27	0.20	0.02†
ACE inhibitors	5 (25.0)	11 (34.4)	16 (42.10)	0.68	0.11	0.27
Clopidogrel, n (%)	4 (20.0)	11 (34.4)	12 (31.5)	0.92	0.35	0.43
Statins, n (%)	9 (45.0)	18 (56.2)	26 (68.4)	0.14	0.06	0.69

Variable measured	Unstable (n = 20)	Stable (n = 32)	Controls (n = 38)	P-value		
				S vs.C	U vs.C	S vs.U
Biochemistry						
Fasting blood glucose (mg/dl)	95.7±15.5	90.7±19.3	95.2±14.2	0.50	0.91	0.61
Triglycerides (mg/dl)	149.6±50.9	164.1±55.8	142.8±40.7	0.21	0.92	0.62
Cholesterol (mg/dl)	158.7±44.5	189.2±43	183.3±36.3	0.80	0.11	0.04*
LDL (mg/dl)	85.1±25.7	107.8±22.9	97.9±20.9	0.12	0.22	0.04*
HDL (mg/dl)	49.± 11.4	60.1±10.1	59.1±11.3	0.90	0.005*	0.009*
hs-CRP mg/L	1 (0.1-4.7)	1.4 (0.3-9.6)	1.4 (1.9-3)	0.81	0.07	0.09

*For ANOVA test; †for chi-square test. BMI: Body mass index; HDL: High density lipoprotein; hs-CRP: High-sensitivity C-reactive protein; LDL: Low density lipoprotein; S vs.C: Stable patients versus controls; S vs.U: Stable patients versus unstable patients; U vs.C: Unstable patients versus controls; WHR; Waist-hip ratio.

Table. 2. Evaluation of multivariate linear regression between CAD risk factors, sestrin-1 and -2 levels and severity of coronary artery stenosis in the subjects

Variabl	β	t	P-value
Age	0.012	0.103	0.918
Gender	0.036	0.309	0.758
BMI	-0.056	-0.479	0.634
WHR	0.150	1.283	0.203
Smoking	-0.085	-0.738	0.463
Hypertension	0.087	0.825	0.412
Cholesterol	0.141	0.463	0.644
LDL	-0.029	-0.097	0.923
HDL	0.156	1.349	0.181
Sestrin-1	-0.166	-1.192	0.237
Sestrin-2	-0.417	-2.993	0.004
Significance (ANOVA)			0.002

ANOVA: Analysis of variance; BMI: Body mass index; HDL: High density lipoprotein; hs-CRP: High-sensitivity C-reactive protein; LDL: Low density lipoprotein; WHR; Waist-hip ratio.

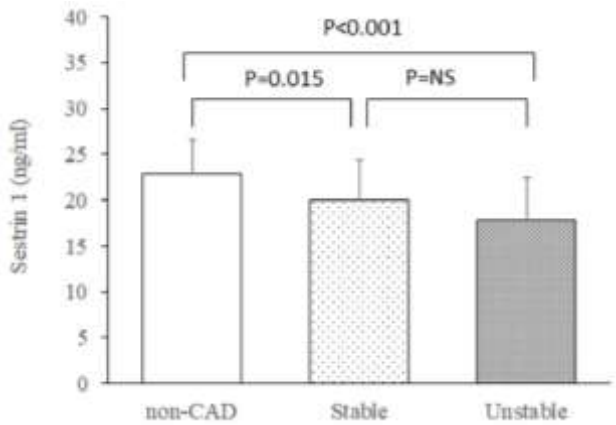

Figure 1. Plasma sestrin-1 concentrations in CAD patients and controls

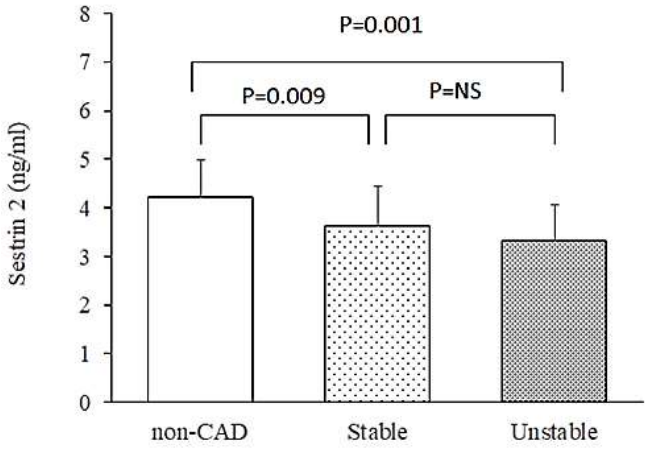

Figure 2. Plasma sestrin-2 concentrations in CAD patients and controls

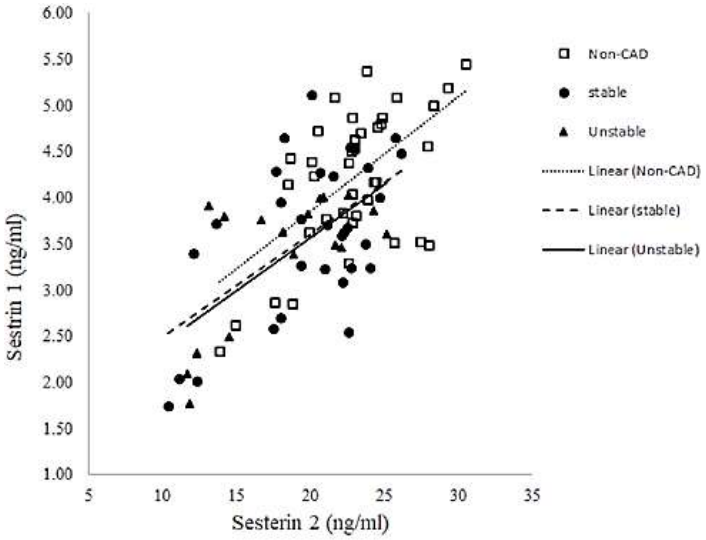

Figure 3. Correlation between plasma levels of sestrin-1 and sestrin-2 in all study participants

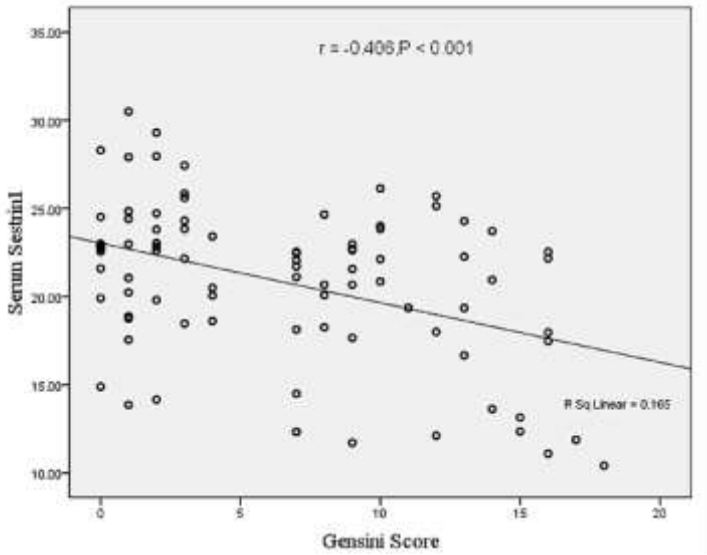

Figure 4. Correlation of coronary stenosis scores with sestrin-1

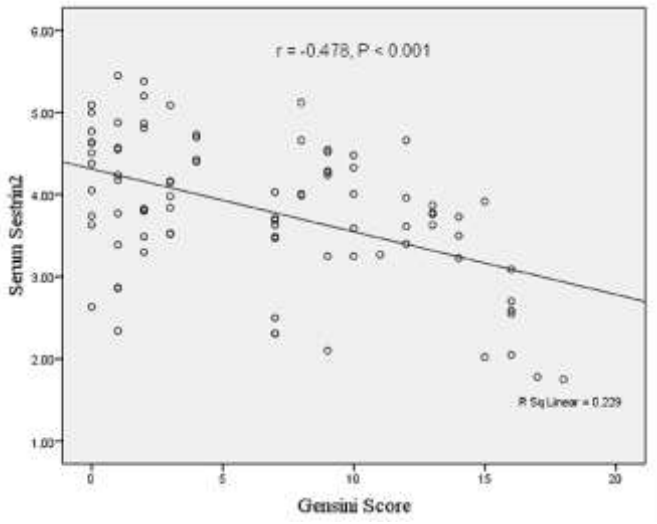

Figure 5. Correlation of coronary stenosis scores with sestrin-2

Discussion

In this study, we found that the plasma levels of sestrin-1 and sestrin-2 were decreased significantly in CAD patients and showed a negative correlation with the coronary stenosis severity. This correlation remained significantly for sestrin-2 (but not sestrin-1), after multivariate adjustment for traditional CAD risk factors. In contrast to our result, two previous studies reported higher plasma levels of sestrin-2 in CAD patients than controls (14, 15). This difference could be due to study design as neither of these two studies considered diabetes as an exclusion criterion. According to in vitro and animal models, several studies have shown that diabetes could alter the sestrins expression (18).

Furthermore, although sestrins, like other antioxidant proteins, are overexpressed during acute stress conditions, the translation of these proteins could be suppressed in chronic conditions. So, in the present study, decreased levels of sestrins may be due to the prolonged duration of CAD in our study population. In line with our result, Sundararajan et al. found that decreased sestrin levels may activate monocytes and consequently stimulate atherogenesis (19). We also found a significant positive relationship between plasma sestrins and HDL in the present study. Nourbakhsh et al., showed that the lower levels of HDL were related to lower levels of sestrin (20). Sesterins, especially sestrin-2, activate AMP-activated protein kinase (AMPK) and thereby have profound impacts on lipid metabolism. AMPK inactivates key lipid biosynthesis enzymes such as acetyl coacarboxylase and b-hydroxy-b-methylglutaryl-CoA (HMG-COA) in the synthesis of fatty acids and cholesterol biosynthesis, respectively. Thus, decreased sestrin-2 levels can affect on lipid profile by decreasing AMPK activity (21). In this study, we also found that the ESR was higher in unstable patients than the two other groups. ESR indicates the rate of sedimentation of erythrocytes in one hour, measured in millimeters per hour, and its elevation shows inflammation (22). Numerous studies have examined the association of ESR with CAD and have identified this factor as an indicator for the diagnosis of CAD disease and the risk of mortality due to this disorder (23, 24). We also found an increase in ESR levels in unstable patients compared to both stable-CAD and non-CAD groups, which confirms the involvement of inflammatory responses in atherosclerosis. Andresdottir et al. examined the association of ESR with other CAD risk factors in a large study (24). They reported that ESR could be considered as a prognostic marker based on the inflammatory process of atherosclerosis in CAD. A large number of studies have also shown an increase in ESR as a risk factor for CAD (25, 26).

Therefore, an increase in ESR may indicate the extent and severity of atherosclerosis as well as increased risk of thrombosis. The present study faces several limitations that must be addressed. First, we have studied a relatively small population, and as a result, our results must be validated in a larger statistical population. Second, the study has conducted on a population of Iranian nationality, and therefore its results cannot be generalized to other societies. Finally, despite the fact that the intravascular ultrasound (IVUS) is more accurate than angiography, we could not use IVUS because of affordability issues. Overall, the present study showed that sestrin-1 and sestrin-2 were reduced and negatively associated with the disease severity in CAD patients. Moreover, a significant correlation between sestrin levels and HDL-cholesterol showing that sestrins may play a cardio-protective role in the cardiovascular system by increasing the amount of HDL.

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Ethics approval: Ethics Committee of KAUMS approved the study with ethics code IR.KAUMS.MEDNT.REC.1398.025.

Conflict of interests: None.

Authors' contribution: Designing the study and preparing the manuscript: SHB, PA, MA and GN; Blood sample collection and processing: AM and RS; angiographic analysis: FR; biochemical parameters detection and ELISA assay: SH and GN. The final version of manuscript was approved by all authors.

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