Association of low serum level of secreted frizzled-related protein 5 (SFRP5) with the presence and severity of coronary artery disease

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Abstract

Introduction: Secreted frizzled-related protein 5 (SFRP5), an anti-inflammatory adipokine, is excreted by adipose tissue and may have protective effects on cardiovascular system. In the present study, the relationships of serum level of SFRP5 with the presence and severity of coronary artery disease (CAD) was investigated.

Materials and methods: In the current study, 40 control subjects, 40 stable and 40 unstable CAD patients were included. Serum level of SFRP5 in all subjects in the study was determined by immunoassay method. The severity of CAD (based on Gensini score) was assigned by angiography examination. The status of conventional risk factors was also determined. Then, the association of SFRP5 with CAD severity and traditional CAD risk factors was explored.

Results: Serum level of SFRP5 was lowest in unstable CAD, followed by stable CAD patients and then control subjects ($P < 0.001$). The correlation of SFRP5 with Gensini score was significant only in unstable CAD patients ($P < 0.01$). However, the correlation of SFRP5 with the traditional CAD risk factors was relatively significant and negative in all patients ($P<0.05$). SFRP5 had a reverse association with the presence of CAD.

Conclusion: Decreased level of serum SFRP5 is associated with the presence and severity of CAD, highlighting its usefulness as a potential clinical biomarker.

Keywords: SFRP5, Unstable CAD, Coronary artery diseases

Introduction

Secreted frizzled-related protein 5 (SFRP5), a recently known anti-inflammatory adipokine, is secreted from adipose tissue and ameliorates adverse effects of metabolic dysregulation and inflammation (1). We previously demonstrated that serum level of SFRP5 is inversely associated with CAD and could differentiate CAD patients from control subjects (2). CAD is naturally a low-grade and chronic inflammatory disorder, therefore, the anti-inflammatory factors such as SFRP5 may alleviates or protects against the low-grade inflammatory-related inflammatory comorbidities, especially cardiovascular diseases (3). It has been shown that SFRP5 inhibits Wnt5a signaling (4). On the other hand, it has been revealed that Wnt5a promotes inflammation in endothelial cells of veins (5) and is highly expressed in atherosclerotic lesions of mouse and

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human (6).

Although, until now there are some data on the cardioprotctive effects of SFRP5, the clinical significance of serum SFRP5 levels in the context of stable and unstable CAD has not been delineated. Therefore, we determined the serum levels of SFRP5 in stable and unstable CAD patients compared to control subjects.

Materials and methods

For the this prospective, observational study, from January 2016 to July 2018, 80 CAD (40 stable and 40 unstable CAD) patients and 40 control subjects who consecutively underwent coronary angiography evaluation for treatment purposes at the Shahid Mostafa Khomeini Hospital in Ilam were participated. All angiograms were strictly and blindly examined by two independent cardiologists to determine patients' specifications. On angiography, subjects with coronary artery narrowing ≥ 50% were considered CAD and those with narrowing < 50% regarded as controls. The severity of CAD in the afflicted coronary arteries was assigned using Gensini scoring system (7). Briefly, according to the scoring system, the scores 1, 2, 4, 8, 16, and 32, are devoted to the coronary artery obstructions 25%, 50%, 75%, 90%, 99%, and 100%, respectively. Furthermore, in the scoring system the importance and location of diseased segment of every coronary artery is also calculated. Stable CAD patient were differentiated from stable CAD according to their specific clinical features and symptoms.

Subjects with any inflammatory-related diseases such as stroke, heart failure disease, and recent myocardial infarction and surgery operations were not included in the study.

Clinical and demographic information of the enrolled subjects was acquired by clinical examination and refereeing to medical documents of the patients. Subjects with systolic/diastolic blood pressure >140/90 mmHg or consuming antihypertensive medications were considered as hypertensive. In terms of the family history of CAD, patients with an evidence of CAD in their first degree relatives (at age < 60 years) were suspected as having family history of the disease.

Individuals with serum glucose ≥ 126 mg/dl, or consuming hypoglycemic medications were assumed as type 2 diabetes. Smoking of any form of cigarette or tobacco was supposed as smoking status. Subjects with the following criteria were put into the hyperlipidemic groups: 1) circulating total cholesterol and triglyceride levels ≥ 200 mg/dl and > 150 mg/dl, respectively, and 3) consumption of lipid lowering drugs.

Institutional approval for the study was given by the ethics committee of the Payame Noor University and a written informed consent was signed by every participant.

Serum sample was prepared from overnight fasting blood of all subjects and was kept as multiple aliquots at -80 ºC until biochemical assays. Serum SFRP5, oxidized low density lipoprotein (Ox-LDL) and high-sensitivity C-reactive protein (hsCRP) levels were measured by commercial ELISA kits (USCN Life Science Inc, Wuhan, China for SFRP5 and Mercodia, Uppsala, Sweden for Ox-LDL, and Pars Azmoon Laboratories Ltd., Tehran, Iran for hsCRP) according to their manufacturers' instructions. The coefficients of variation for intra- and inter-assay precisions of the assays were

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7.2 and 10.5% for SFRP5, 4.2 and 7.1% for Ox-LDL, and 4.1% and 5.7% for hsCRP, respectively. Serum lipid profile was assayed by enzymatic methods on a Hitachi 902 autoanalyzer (Hitachi, Tokyo, Japan).

Statistical analysis

All data of the study were depicted as mean ± SD, median (interquartile range), and number/percent (categorical data). The differences between continuous variables were examined by Kruskal–Wallis test or ANOVA t-test. Categorical variables were compared by Chi-squared test. The association of serum SFRP5 levels with other clinical characteristics was evaluated by Spearman's correlations test. The association between serum SFRP5 and CAD was examined by a multivariate logistic regression analysis (after log transformation), adjusting for other confounding variables. All statistical analyses were performed using the statistical software SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) and a P value < 0.05 was defined as significant.

Results

Clinical and demographic characteristics of the subjects enrolled in the study are presented in Table 1. The differences between CAD patients and control subjects were not significant for some clinical characteristics including age, gender, body mass index (BMI), diabetes mellitus, hyperlipidemia, and smoking. Ox-LDL and hsCRP were higher in the CAD patients (stable and unstable CAD) as compared with the control subjects (P < 0.001 and P=0.04, respectively). However, the values were similar between the stable and unstable CAD patients and (P = 0.61 and P = 0.74, respectively). Serum SFRP5 level was lower in the unstable CAD patients, as compared with the stable CAD patients and control subjects (25.12[25.33-32.76] in unstable CAD patients *vs* 28.76[25.88-33.92]), and 39.85[39.02-50.21] in stable CAD patients and control subjects, respectively P < 0.001).

Table 1. Baseline characteristics of the subjects participated in the study.

Variable	Control subjects (n=40)	Stable CAD patients (n = 40)	Unstable CAD patients (n = 40)	P value
Age (years)	55.83 ± 210.01	56.07 ± 7.15	55.91 ± 6.36	0.41
Male sex	22(55)	23(57.5)	24(60)	0.67
BMI (kg/m^2)	27.51 ± 3.05	27.63 ± 4.12	28.03 ± 2.32	0.52
Cholesterol (mg/dL)	170.16 ± 25.91	171.18 ± 27.20	169.97 ± 26.22	0.16
Triglycerides (mg/dL)	129.17 (117.34-213.64)	128.41 (114.02-220.33)	127.77 (111.51-219.66)	0.42
LDL (mg/dL)	109.91 ± 14.58	110.65 ± 17.43	112.37 ± 15.92	0.21
HDL (mg/dL)	46.74 ± 8.54	44.89 ± 7.17	45.09 ± 5.50	0.38
hsCRP (mg/L)	2.28(1.90-2.89)	2.89(2.21-3.85)	3.71(2.35-4.07)	0.04
Ox-LDL (ng/mL)	57.01(51.38-64.29)	83.97(78.77-89.21)	86.12(80.34-88.07)	<0.001
SFRP5 (ng/mL)	39.85(39.02-50.21)	28.76(25.88-33.92)	25.12(25.33-32.76)	<0.001
Diabetes mellitus	6(15)	10(25)	8(20)	0.18
Smoking	8(20)	12(30)	10(25)	0.24
Hypertension	8(20)	14(35)	12(30)	0.20
Family history of CAD	6(15)	8(20)	10(25)	0.09
Aspirin	0(0)	29(72.5)	31(77.5)	<0.001
Lipid-lowering agents	12(30)	26(65)	28(70)	0.001

Data are expressed as mean ± SD, median (interquartile range) or number (%); CAD, coronary artery disease; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hsCRP, high sensitive C-Reactive Protein; Ox-LDL, oxidized LDL; SFRP5, Secreted frizzled-related protein 5.

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Correlations between SFRP5 and dependent clinical risk factors are displayed in Table 2. The correlation of SFRP5 with Ox-LDL and hsCRP was found in stable and unstable CAD patients (r = 0.25, P = 0.039 and r = 0.25, P = 0.039, respectively), which was absent in control subjects (r = 0.25, P = 0.039).

Table 2. Correlations of SFRP4 with other clinical variables in all subjects under study.

Variable	ρ	P value
Age	-0.08	0.73
BMI	-0.34	0.02
Total cholesterol	-0.21	0.07
Triglycerides	-0.18	0.18
LDL	-0.21	0.08
HDL	0.41	0.31
hsCRP	-0.39	0.001
Ox-LDL	-0.46	0.01
Gensini score	-0.33	0.01

BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hs-CRP, high sensitive C-Reactive Protein; Ox-LDL, oxidized LDL; SFRP5, Secreted frizzled-related protein 5.

Table 3. Logistic regression analysis to identify the independent predictors of CAD.

Variable	OR(95%CI	P value
Age	1.72(1.25-3.12)	0.47
Male sex	1.19(1.04-1.98)	0.31
BMI	2.14(1.65-3.54)	0.04
Total cholesterol	2.37(1.21-2.33)	0.26
Triglycerides	2.16(1.48-3.55)	0.17
LDL	1.84(1.23-2.99)	0.16
HDL	0.47(0.08-0.83)	0.22
hsCRP	2.11(1.61-2.42)	0.03
Ox-LDL	2.83(1.96-3.29)	0.02
SFRP5	0.18(0.12-0.48)	0.01
Hypertension	1.78(1.45-3.44)	0.14
Diabetes mellitus	2.72(1.34-3.19)	0.09
Familial CAD	1.77(1.52-2.40)	0.31
Smoking	1.87(1.48-2.17)	0.12

OR, odds ratio; CI, confidence intervals; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hsCRP, high sensitive C-Reactive Protein; Ox-LDL, oxidized LDL; SFRP5, Secreted frizzled-related protein 5.
SFRP5, Ox-LDL, triglycerides and hsCRP were log transformed before the analysis.

Independent prediction value of serum SFRP5 for CAD was analyzed by a multiple logistic regression analysis, controlling for the other potential confounding risk factors (Table 3). Among the analyzed covariates, BMI, hsCRP, Ox-LDL and SFRP5 (as a negative predictor) were identified as independent predictors of CAD. Likewise, in another multiple logistic regression analysis conducting to find the predictors of CAD severity (based on the Gensini scores), only the serum level of SFRP5 was appeared as an independent predictor of CAD severity (Odds ratio [95%CI]: 0.48[0.14-0.79], P=037).

Discussion

Results of the current study demonstrated that the values of serum SFRP5 were significantly decreased in unstable CAD patients as compared to those in stable CAD patients and control subjects, being also lower in stable CAD patients as compared to those in subjects without CAD. Furthermore, decreased level of SFRP5 was associated with the presence and severity of CAD.

The anti-inflammatory and protective effects of SFRP5 in the context of cardiovascular diseases and many obesity-related disorders has been demonstrated (8, 9). Therefore, the clinical significance of SFRP5 with regarding to its anti-inflammatory property may be useful. In this regard, Miyoshi et al. (10) reported that serum levels of SFRP5 are significantly decreased in patients with CAD compared to non-CAD patients and the decreased levels of SFRP5 were negatively correlated with the presence and severity of CAD. Accordingly, the trend of SFRP5 decrement from control subjects to stable CAD and then unstable CAD patients in the current study are in concordant with the previous studies. Given that the unstable CAD is a sever condition, the lower levels of SFRP5 in the patients (compared to stable CAD patients and controls) may be conceived in context of the anti-inflammatory impact of SFRP5. Notably, in supporting the notion, the concentrations of other inflammatory related biomarkers such as hsCRP and Ox-

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LDL had inverse trends in comparison with SFRP5.

More importantly, SFRP5 suppress the production of inflammatory mediators in macrophages and/or adipocytes (8). In addition, it has been shown that Sfrp5 is correlated with oxidative stress in human (11) and inhibits inflammation in rheumatoid arthritis fibroblast-like synoviocytes (12). Collectively, these studies along with results of the current study imply that decreased SFRP5 state are accompanied with enhanced production of inflammatory mediators and oxidative stress agents that lead to chronic inflammatory related disorders such as CAD.

We inferred that the inverse relations between serum SFRP5 and hsCRP/Ox-LDL in the present study is compatible with the anti-inflammatory, as well as the anti-oxidative effects of SFRP5 in CAD. Especially, the risk factors, hsCRP and Ox-LDL, have a strict link with low-grade inflammatory and oxidative state in CAD (13, 14). In this way, the lower the concentration of SFRP5, the more severe CAD, as observed in the unstable CAD patients in the study.

The control subjects in the study may not be considered as an exact candidate of healthy subjects of general population, because they underwent to angiography examination for diagnostic purposes. Therefore, some clinical parameters may be influenced by their conditions. The relatively small number subjects may be another concern that should be considered. Despite these limitations, significant and robust contribution of sfrp5 in unstable and stable CAD was attained in the study.

Conclusion

Our results highlighted that serum SFRP5 is decreased in unstable CAD patients as compared to stable CAD patients and control subjects. Moreover, the serum SFRP5 level was inversely and profoundly associated with the presence and severity of CAD and seems to differentiate between unstable and stable CAD patients as well as the control subjects.

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Conflict of interests

There is no conflict of interest.

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