Original Article

Relation of Plasma Fibrinogen Level With the Presence, Severity, and Complexity of Coronary Artery Disease

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Abstract

Background: Relation of plasma fibrinogen levels with extent, severity, and complexity of coronary artery disease (CAD) in patients with stable angina pectoris (SAP) has not been adequately investigated. The aim of this study was to evaluate whether plasma fibrinogen level is associated with coronary complexity, severity, and extent assessed by SYNTAX (Synergy between percutaneous coronary intervention with TAXUS and Cardiac Surgery) score (SS). **Methods:** We enrolled 134 consecutive patients with SAP who underwent coronary angiography. Baseline serum fibrinogen levels were measured, and SS was calculated from the study population. The patients were classified into 3 groups by tertiles of SS (SS, control group = 0; intermediate group < 22; and high group ≥ 22). **Results:** Plasma fibrinogen levels demonstrated a stepwise increase from control group to high SS group. There was a strong correlation between fibrinogen and the SS ($r = .535$, $P < .001$). Area under the receivers operating characteristic curve of fibrinogen was 0.72 (95% confidence interval [CI] 0.61-0.82; < .001) for predicting a high SS. Fibrinogen value higher than 411 mg/dL has a sensitivity of 75% and a specificity of 64% in prediction of high SS. In multivariate analyses, plasma fibrinogen was observed to be an independent predictor for high SS in patients with stable CAD (odds ratio [OR] 1.01; 95% CI, 1.01-1.02; $P < .001$). **Conclusion:** Plasma fibrinogen is a readily measurable systemic inflammatory marker and is independently associated coronary severity and complexity in patients with CAD.

Keywords

fibrinogen, syntax score, coronary, angina pectoris

Introduction

Coronary artery disease (CAD) occurs via complex pathophysiological mechanisms. Inflammatory process plays an important role in the onset and progression of the disease. In addition, recent evidences suggest that thrombosis and endothelial dysfunction are strongly associated with CAD.[1] It is known that raised levels of inflammatory markers are associated with increased rates of adverse cardiac events in patients with CAD.[2]

Fibrinogen, which is swiftly consumed, is a short half-life protein that is produced in the liver and is not only an indicator of procoagulant state but also a biomarker playing a role in inflammatory responses in various degrees. Although a few trials have shown evidence unlike most of the available data on the relationship between CAD and fibrinogen, numerous studies have suggested a relationship between plasma fibrinogen level and the severity of CAD. Moreover, few of them confirmed a correlation of high circulating plasma fibrinogen with adverse outcome in patients with CAD.[3]

The SYNTAX (Synergy between percutaneous coronary intervention with TAXUS and Cardiac Surgery) score (SS) is a comprehensive angiographic scoring system that is derived entirely from the coronary anatomy and coronary lesion characteristics.[4-6] It is used to quantify features of coronary lesion including severity, complexity, and morphology.[5-9] There are limited data about relation of serum fibrinogen levels and

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severity, extent as well as complexity of CAD in patients with stable angina pectoris (SAP). Therefore, we aimed to investigate the relationship between fibrinogen levels and CAD severity, complexity, and extent assessed with SS in patients presented with SAP.

Materials and Methods

Study Population

The present study was designed as a cross-sectional study. We enrolled 298 consecutive patients with SAP who underwent coronary angiography (CAG) for suspected CAD between February 2013 and April 2013. All patients recruited into the study had objective signs of ischemia (treadmill exercise or myocardial single photon emission computed tomography). Patients with history of previous myocardial infarction and coronary artery bypass grafting, clinically significant valvular heart disease and severe heart failure, hematological disease, cancer, severe renal or liver disease, chronic or current infections, chronic inflammatory disease, and autoimmune disease were excluded from the study.

Clinical risk factors for CAD such as age, sex, diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL), smoking, and family history of cardiovascular disease were recorded. Previous history of CAD was also recorded. Medications used prior to CAG were noted. For each participant, height and weight were measured. By dividing weight in kilograms by height in meters squared (kg/m^2), the body mass index was calculated. The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional ethics committee. All participants gave an informed consent.

Biochemical Measurements

Fasting venous blood samples were obtained 1 day before CAG from all patients. Blood samples to get serum and plasma collected into 5-mL serum separator tubes with clot activator and citrate-containing tubes (BD Vacutainer; Becton Dickinson, Meylan, France), respectively. Fasting blood glucose, creatinine, blood urea nitrogen, uric acid, low-density lipoprotein (LDL), high-density lipoprotein, total cholesterol, triglyceride, and C-reactive protein (CRP) levels were analyzed by colorimetric and enzymatic assays with use of an COBAS 8000 autoanalyzer (Roche Diagnostics GmbH, Mannheim, Germany). The quantitative fibrinogen levels in plasma were determined by the clotting method of Clauss[10] with Stago Compact (Diagnostica Stago, Asnieres sur Seine, France)

Coronary Angiography and SS

Coronary angiography was performed by the standard Judkins' technique. Coronary arteries were visualized in left and right oblique planes with cranial and caudal angles at a speed of 30 frames/s. An injection of contrast medium (iopromide; Ultravist-370 Schering AG, Berlin, Germany) was given manually at each position. SYNTAX score is an angiographic tool used in grading the complexity of CAD. From the baseline diagnostic angiogram, each coronary lesion producing $\geq$50% diameter stenosis in vessels $\geq$1.5 mm was scored separately and added together to provide the overall SS, which was calculated using the SS algorithm.[4-6] The online latest updated version was used in the calculation of the SSs (www.syntaxscore.com). All angiographic variables of the SS were computed by 2 experienced cardiologists who were blinded to the clinical data. In case of disagreement, the final decision was made by consensus. When evaluated according to the SS system, 35 patients were found to have a score of 0. These patients were considered as those without angiographic CAD and this group defined as control group. The remaining patients were divided according to the SS tertiles. Group 1 was defined as SS <22 (lower tertile) and group 2 was defined as SS $\geq$22 (upper 2 tertiles).[11]

Statistical Analysis

Statistical analysis was performed using the SPSS for Windows (version 19.0; SPSS Inc, Chicago, Illinois). The Kolmogorov-Smirnov test was used to determine whether the data were normally distributed. Levene test was used to assess data for variance homogeneity. If the P value in Levene test was >.05, we assumed that there was an equal variance, and the t test of equality of means was carried out and interpreted as usual. If the P value in Levene test was <.05, P values of Welch test were used. Continuous variables were expressed as mean $\pm$ standard deviation or median (interquartile range) values, whereas categorical variables were defined as number and percentages. The differences between normally distributed numeric variables were evaluated by Student t test or one way analysis of variance, while nonnormally distributed variables were analyzed by Mann-Whitney U test or Kruskal-Wallis variance analysis as appropriate. Chi-square test was employed for the comparison of categorical variables. Association between variables was tested using Spearman or Pearson correlation coefficient, when appropriate. In order to determine the independent predictors of high SS group, parameters that were found to have a significance ($P \leq .10$) in the univariate analysis were evaluated by stepwise forward logistic regression analysis; 95% confidence interval (CI) and odds ratios (OR) were presented together. The receiver-operating characteristic (ROC) analyses were used to detect the cutoff value of fibrinogen in prediction of high SS. All values are 2-tailed, and a P value < .05 was considered statistically significant.

Results

Baseline Characteristics

A total of 134 patients (mean age 60.8 $\pm$ 10.2 years) with SAP were included in the study. Ninety-five (71%) of the patients in the study population were male. The baseline demographic, clinical characteristics, and laboratory findings of the enrolled patients by the tertiles of SS (control group = 0, n = 35; low

Table 1. Comparison of Baseline, Clinical, and Laboratory Characteristics of the Study Population.[a,b]

Variables	Controls (n = 35)	SYNTAX Score < 22 (n = 63)	SYNTAX Score ≥ 22 (n = 36)	*P* Value[c]	*P* Value[d]
Clinical characteristics					
Age, years	56.4 ± 11.5	61.6 ± 9.8	63.5 ± 8.5	0.006	**.039**
Men	19 (54%)	46 (73%)	30 (83%)	0.023	**.055**
Hypertension	28 (80%)	58 (92%)	33 (92%)	0.157	.514
Diabetes	11 (18%)	31 (52%)	18 (30%)	0.181	.461
Current smoking	7 (20%)	16 (25%)	7 (19%)	0.732	.612
Hyperlipidemia	6 (17%)	51 (81%)	30 (83%)	<0.001	**.007**
Family history of CAD	21 (60%)	43 (68%)	27 (75%)	0.399	.287
Body mass index, kg/m^2	29.1 ± 5.5	28.3 ± 8.8	29.2 ± 6.2	0.538	.815
Biochemical parameters					
Total cholesterol, mg/dL	184.7 ± 39.7	199.9 ± 43.7	183.7 ± 54.6	0.143	.286
Triglyceride, mg/dL	112.0 ± 73.0	137.0 ± 77.0	125.5 ± 75.7	0.111	.729
HDL cholesterol, mg/dL	47.0 ± 12.0	45.0 ± 18.0	41.0 ± 15.5	0.171	**.066**
LDL cholesterol, mg/dL	113.9 ± 32.9	120.5 ± 41.7	116.7 ± 39.9	0.576	.486
Creatinine, mg/dL	0.80 ± 0.31	0.81 ± 0.23	0.93 ± 0.26	0.027	**.016**
BUN, mmol/L	15.0 ± 4.9	14.0 ± 7.0	15.5 ± 7.5	0.809	.519
Glucose, mg/dL	103.0 ± 29.0	108.0 ± 43.0	110.5 ± 40.1	0.429	.398
CRP, mg/dL	1.7 ± 2.6	3.3 ± 5.9	7.0 ± 11.2	<0.001	**<.001**
Fibrinogen, mg/dL	321.0 ± 72.1	391.9 ± 79.7	472.3 ± 79.7	<0.001	**<.001**
Uric acid, mg/dL	5.4 ± 1.8	5.9 ± 2.4	5.8 ± 1.7	0.201	.559
Previous medications					
ACE inhibitors	8 (23%)	33 (52%)	23 (64%)	0.002	**.023**
Angiotensin-receptor blockers	8 (23%)	13 (21%)	10 (28%)	0.719	.440
Beta-blockers	11 (31%)	32 (51%)	25 (70%)	0.006	**.009**
ASA	15 (43%)	38 (60%)	28 (78%)	0.011	**.013**
Ca-antagonists	1 (3%)	6 (10%)	9 251%)	0.011	**.005**
Statins	4 (11%)	22 (35%)	17 (47%)	0.004	**.023**
Clopidogrel	3 (9%)	24 (38%)	12 (33%)	0.007	.514
Insulin	4 (11%)	3 (5%)	6 (17%)	0.145	**.099**

Abbreviations: CAD, coronary artery disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; BUN, blood urea nitrogen; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, acetyl salicylic acid; SD, standard deviation; SS, SYNTAX score; SYNTAX, Synergy between percutaneous coronary intervention with TAXUS and Cardiac Surgery.
[a]Data are presented as the number (%) of patients, mean value ± SD or median value ± interquartile range.
[b]Bold face values are variables that analyzed in multivariate logistic regression.
[c]*P* value obtained from analysis of variance, Kruskal-Wallis test, or chi-square test.
[d]*P* values for high SS versus nonhigh (control and low) SS.

syntax group < 22, n = 63; high syntax group ≥ 22, n = 36) were summarized in Table 1.

The patients in the high SS group were older than patients in the other groups ($P = .039$). There were also significant differences between the groups in terms of frequency of male patients ($P = .021$); the number of male patients was less in the control group. Furthermore, the patients in the high SS group demonstrated higher HL frequency and higher creatinine when compared to the patients in the other groups. Nevertheless, there were no significant differences in the presence of HT, DM, current smoking, and previous history of CAD between groups (Table 1).

Serum CRP concentrations were significantly different assessed by both trend analysis for the 3 groups ($P < .001$) and comparison test for the high SS group and control—low SS group ($P < .001$). Plasma fibrinogen levels demonstrated significantly an increase from the control group to the high SS group. The low SS group had significantly higher fibrinogen levels compared with the control group (391.9 ± 79.7 vs 321.0 ± 72.1, $P < .001$); similarly, the fibrinogen levels were significantly higher in the high SS group than in the low SS group (472.3 ± 79.7 vs 391.9 ± 79.7, $P < .001$; Figure 1).

Association Between the Plasma Fibrinogen Levels and CRP and SS

To explore whether plasma fibrinogen levels were related to the SS and other biomarkers in patients with SAP, we performed a correlation evaluation. Spearman's correlation analysis revealed a significant association between plasma fibrinogen levels and SS ($r = .535$, $P < .001$; Figure 2). Similarly, there was a positive correlation between CRP and SS ($r = .473$, $P < .001$; Figure 3). In addition, an association between CRP and plasma fibrinogen levels was found ($r = .611$, $P < .001$).

Predictors of High SS

In order to determine the predictors of high SS, the variables found to be significantly different in the univariate analysis

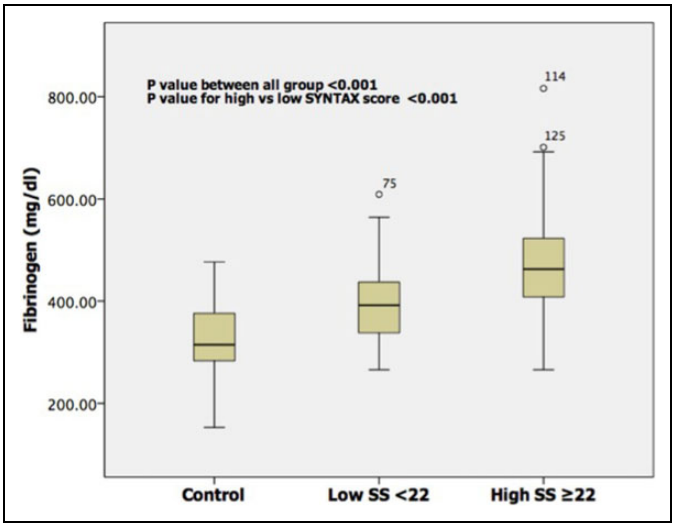

Figure 1. Fibrinogen values according to the SYNTAX score. SS indicates SYNTAX score; SYNTAX, Synergy between percutaneous coronary intervention with TAXUS and Cardiac Surgery.

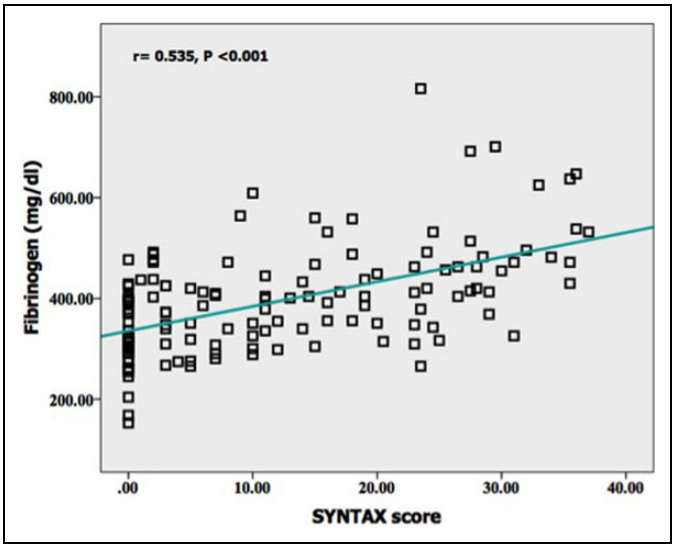

Figure 2. Correlation plot between the SYNTAX score and fibrinogen. SYNTAX indicates Synergy between percutaneous coronary intervention with TAXUS and Cardiac Surgery

were included in the multivariate logistic analysis. Accordingly, fibrinogen (OR, 1.01; 95% CI, 1.01-1.02; $P < .001$), male sex (OR, 5.60; 95% CI, 1.40-22.33; $P = .015$), acetylsalicylic acid use (OR, 3.45; 95% CI, 1.20-10.00; $P = .022$), and insulin use (OR, 1.10; 95% CI, 1.10-25.63; $P = .038$) were found to be the independent predictors of high SS (Table 2).

The area under the ROC curve of fibrinogen was 0.72 (0.61-0.82, $P < .001$) for predicting high SS (Figure 4). The optimal cutoff value of fibrinogen to predict high SS was 411 mg/dL (sensitivity of 75% and specificity of 64%). Any fibrinogen value higher than 411 mg/dL has a sensitivity of 75% and a specificity of 64%.

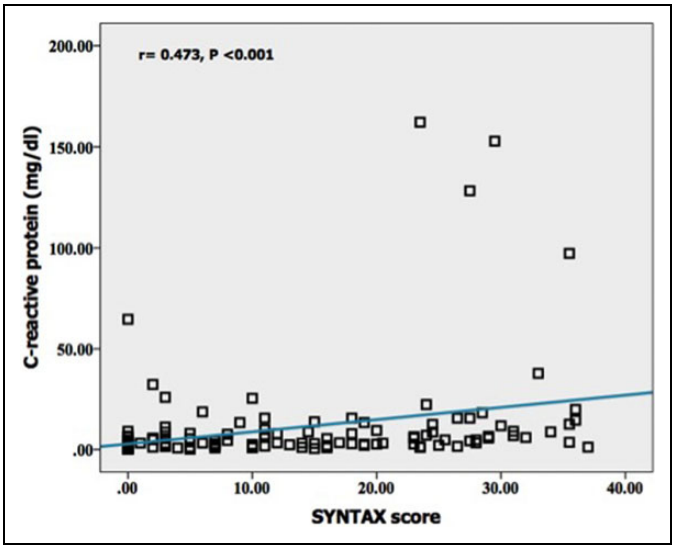

Figure 3. Correlation plot between the SYNTAX score and C-reactive protein. SYNTAX indicates Synergy between percutaneous coronary intervention with TAXUS and Cardiac Surgery.

Table 2. Effects of Various Variables on High SYNTAX Score in Univariate and Multivariate Logistic Regression Analyses.[a]

	Univariate			Multivariate		
Variable	*P*	OR	(95% CI)	*P*	OR	(95% CI)
Age	.042	1.04	1.00-1.08			
Gender (male)	.060	2.54	0.96-6.71	.015	5.60	1.40-22.33
Hyperlipidemia	.009	3.60	1.37-9.43			
Creatinine	.015	7.21	1.48-35.18			
C-reactive protein	.025	1.05	1.01-1.10			
Fibrinogen	<.001	1.01	1.01-1.02	<.001	1.01	1.01-1.02
HDL cholesterol	.221	0.98	0.95-1.01			
ASA	.015	2.97	1.23-7.17	.022	3.45	1.20-10.00
ACE inhibitor use	.025	2.46	1.12-5.42			
Beta-blocker use	.010	2.91	1.29-6.56			
Calcium antagonist use	.008	4.33	1.48-12.72			
Statin use	.025	2.48	1.12-5.48			
Insulin use	.108	2.60	0.81-8.34	.038	5.31	1.10-25.63

Abbreviations: ACE, angiotensin-converting enzyme; ASA, acetylsalicylic acid; CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio. SYNTAX, Synergy between percutaneous coronary intervention with TAXUS and Cardiac Surgery.

[a]Multivariate logistic regression model including all the variables are shown in univariate analysis.

Discussion

In the present study, our findings revealed that plasma fibrinogen levels were significantly higher in the patients with stable CAD exhibiting high SS; furthermore, we showed that a higher baseline fibrinogen value was independently

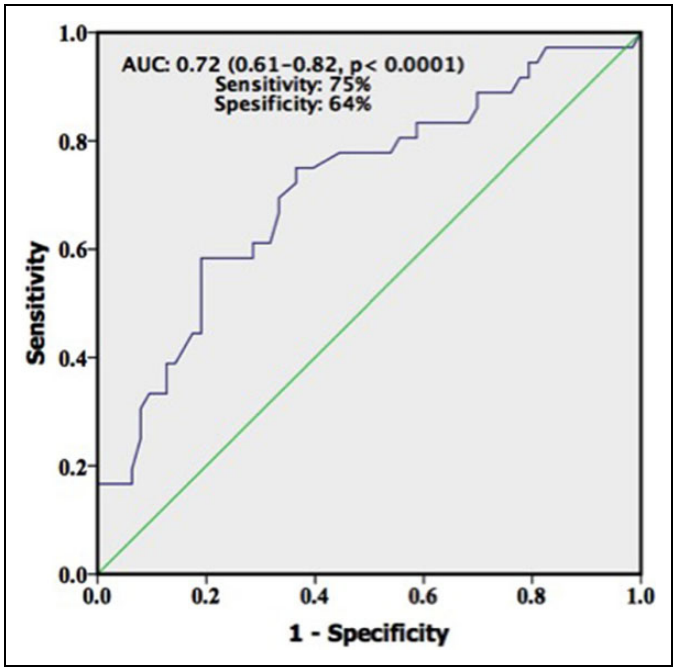

Figure 4. Receiver-operating characteristic curves for fibrinogen in prediction of high SYNTAX score (SS $\geq$ 22) with high sensitivity and specificity. SYNTAX indicates Synergy between percutaneous coronary intervention with TAXUS and Cardiac Surgery; SS, SYNTAX score.

associated with the severity and coronary complexity of CAD, as assessed by SS.

There are several scales for the evaluation of the extent and severity of CAD. However, SS does not only enable the assessment of CAD extent and severity but also differs from the other methods by allowing us to evaluate the coronary lesion complexity.[4] Moreover, the reproducibility of the SS has proven the feasibility of the method in clinical use.[12,13] In our study, we identified the association between the SS and fibrinogen levels and also found a significant positive correlation between the SS and fibrinogen levels. Additionally, plasma fibrinogen values were observed to be an independent predictor of high SS group.

To date, repeated meta-analyses and reviews have shown that increased concentrations of fibrinogen are associated with the development or presence of atherothrombotic disease.[14-17] Furthermore, many epidemiological studies also have examined the relationship between fibrinogen levels and the various processes of coronary atherosclerosis. Shojaie et al[18] and Pineda et al[19] introduced high levels of fibrinogen as a risk factor for premature CAD in patients <55 years. In the CARDIA study, Green et al[20] revealed that elevated levels of fibrinogen in middle-aged persons were associated with an increased prevalence of coronary artery calcification (CAC) after 13 years of follow-up. Opposite findings were observed in the study conducted by Taylor et al.[21] It did not show an association between fibrinogen and progression of CAC in a smaller population of 180 patients and a window of observation of only 4.2 years.

In the large ECAT study which recruited only patients with at least 1 coronary stenosis >50%, no relationship between extension of CAD with various inflammatory markers, including fibrinogen, was found.[22] Similarly, Hoffmeister et al[23] showed that the severity and extension of CAD are not related to levels of different biochemical markers. In contrast to the negative results of these 2 studies, some trials have suggested a relation of plasma fibrinogen to the severity of CAD. Early in 1989, Handa et al[24] indicated that the plasma fibrinogen level was an independent indicator of the severity of CAD in the Japanese population estimated both by the numbers of involved vessel and Gensini score. Similar relation was also detected among other races such as Italian population.[25] Additionally, recent study suggested that the elevated level of plasma fibrinogen was an independent indicator for the severity of CAD assessed by Gensini score in type 2 diabetic patients.[3]

SYNTAX score includes additional parameters in comparison to the Gensini score such as coronary artery dominance, thrombus, tortuosity, and bifurcation or trifurcation type lesions.[4,26,27] Therefore, SS, which contain these individual components, is associated with complexity of CAD as well as severity of coronary atherosclerosis. To the best of our knowledge, whether plasma fibrinogen was associated with complexity of CAD in patients with SAP is not clearly known. In agreement with above-mentioned studies, in the present study which was designed to elucidate these ambiguities, we demonstrated that plasma fibrinogen level was an independent indicator for presence, severity, and complexity of CAD, assessed by SS.

Fibrinogen and Atherosclerosis

Atherosclerosis is a complex process involving multiple, often interrelated pathophysiologic factors. A number of studies have validated the pivotal role of inflammation in the pathogenesis of atherosclerosis.[28] Furthermore, several inflammatory markers have been appraised as potential predictors of cardiovascular disease.[29-31] Among these inflammatory markers, plasma fibrinogen, which is an acute phase reactant, is a particularly attractive molecule in terms of the development and progression of coronary atherosclerosis. However, there are some uncertainties about the role of fibrinogen in pathogenesis of CAD such as whether fibrinogen is a causative or reactive agent in the inflammatory processes, and its increased plasma levels promote plaque formation or its level increase as a consequence of atherosclerosis. Nevertheless, several potential pathophysiological explanations may be mentioned to explain fibrinogen's role in atheromatous disease. Fibrinogen, which is a cofactor in plaque activation, may directly contribute to plaque formation, where it is converted to fibrin and fibrinogen degradation products.[32] Furthermore, fibrinogen and its metabolites may lead to endothelial dysfunction through various mechanisms. Fibrinogen binding to endothelial cells causes a release of vasoactive mediators and modulates endothelial permeability leading to fibrinogen deposition in the subendothelial space, which provides an adsorptive surface for an extracellular

accumulation of LDL and apolipoprotein a.[33] Fibrinogen also induces endothelial cell disorganization and migration, stimulates smooth muscle proliferation, and enhances the release of endothelial cell-derived growth factors.[34] Moreover, fibrinogen contributes to blood viscosity, platelet aggregation, fibrin formation, and modulates subsequent coagulation activation and fibrinolysis.[25] Coagulation activation and impaired fibrinolysis or oxidative fibrinogen may exacerbate pre-existing CAD and potentiate its evolution.[35] In addition to these, it has been shown that fibrinogen was independently correlated with atherosclerotic burden.[36] Taken together, these observations would suggest that fibrinogen is an important factor in the pathogenesis and progression of coronary atherosclerosis.

In summary, we showed the relationship between elevated baseline fibrinogen levels and coronary lesion complexity. We have demonstrated that plasma fibrinogen with an optimal cut-off value of 411 mg/dL predicts high SS with a sensitivity of 75% and a specificity of 64%. Knowing the association between fibrinogen and coronary atherosclerosis can give additional information about inflammatory process of atherosclerosis and potentially serve to establish new therapies directed against inflammation. Given that the assay for fibrinogen is considered simple and cost-effective, these findings should encourage the use of fibrinogen as a marker in the prediction of coronary lesion severity and complexity in patients with stable CAD. In addition, it may be used in risk stratification of patients with SAP before diagnostic CAG and coronary interventions.

Limitations

There are some limitations in our study. The first of these is the small number of patients in the study. Further studies of a larger scale are needed to clarify this subject. Second, the observational and cross-sectional design of our study makes it difficult to comment on the causal relationship of plasma fibrinogen and high SS. Finally, the use of intravascular ultrasound might have further expanded the results of the current study, yielding information on the composition of coronary artery plaques and the actual extent of atherosclerosis.

Conclusion

Plasma fibrinogen is a readily measurable systemic inflammatory marker and is independently associated with coronary severity and complexity in patients with stable CAD.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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