Clinical Utility of the Ratio Between Circulating Fibrinogen and Fibrin (ogen) Degradation Products for Evaluating Coronary Artery Disease in Type 2 Diabetic Patients

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Abstract

Background: We investigated whether and to what extent the ratio between circulating fibrinogen (Fg) and its degradation products (FDP) reflects the severity of coronary artery disease (CAD) in type 2 diabetic patients.

Methods: Plasma levels of Fg and FDP were determined, and Fg/FDP ratio was calculated in 344 consecutive patients with type 2 diabetes and chest pain on exertion undergoing coronary angiography. The severity of CAD was evaluated by the number of significant CAD (>50% luminal diameter narrowing) and Gensini score.

Results: Plasma Fg was higher, but Fg/FDP ratio was lower in patients with significant CAD ($n = 255$) compared with those without ($n = 89$), due to a disproportionate increase in FDP. Fg and FDP correlated positively, while Fg/FDP ratio negatively, with the number of diseased coronary arteries and the tertile of Gensini score (all P values for trend < 0.01). After adjusting for age, sex, risk factors for CAD, lipid profiles, glycosylated hemoglobin A1c, creatinine, leukocyte count, and high-sensitivity C-reactive protein, Fg/FDP ratio remained an independent determinant for multivessel coronary disease (MVD) (odds ratio [OR], 0.869; 95% confidence interval [CI], 0.788–0.958, $P = 0.005$) and high tertile of Gensini score (OR, 0.797, 95% CI, 0.682–0.930, $P = 0.004$). The area under the curve of Fg/FDP ratio was larger than that of Fg for predicting the presence of MVD (0.647 vs. 0.563, $P = 0.048$) and Gensini score ≥ 30 (0.656 vs. 0.538, $P = 0.026$).

Conclusions: Elevated plasma Fg and FDP level and reduced Fg/FDP ratio are associated with presence of CAD, and Fg/FDP ratio is superior to Fg in reflecting severe coronary atherosclerosis for patients with type 2 diabetes.

Key words: Coronary Artery Disease; Diabetes Mellitus; Fibrin (ogen) Degradation Products; Fibrinogen

INTRODUCTION

It is well-recognized that diabetes mellitus represents a powerful independent risk factor for increased cardiovascular mortality associated with coronary artery disease (CAD).[1,2] A spectrum of researches attribute coronary atherosclerotic process in a diabetic setting, at least partly, to an imbalance of thrombotic and fibrinolytic system as well as augmented inflammation.[3,4] Fibrinogen (Fg) is a marker of activation of thrombotic system, and its plasma level has been shown to correlate, to certain extent, with the development of coronary atherosclerotic lesions, risk of myocardial injury after percutaneous coronary intervention, and cardiovascular events in diabetic patients, regardless of platelet aggregation.[5-9] Fibrin (ogen) degradation products (FDP), generated from an interaction between plasmin and fibrin (ogen),[10] have been considered as one of the determinants for future risk of death and diabetic vascular complications.[11-13] Currently, Ridker *et al.* indicated that elevated serum levels of D-dimer, induced by cleavage of plasmin at the fragment D site of fibrin polymers, were related to coronary artery occlusion.[14] Taken together, these observations support a notion that plasma Fg or FDP may serve as a mediator linking to thrombotic disease and clinical outcomes. However, it remains unknown whether or to what extent plasma Fg or FDP is associated with coronary atherosclerosis in patients with diabetes. Furthermore, it has been frequently reported that diabetic patients may be clinically asymptomatic even with severe coronary disease because of silent myocardial ischemia.[15] The methods for early detection of significant CAD in diabetic patients have been proven to be elusive, and as a result, prognostic improvement of these patients has not been successfully achieved.[16,17] Therefore, it is necessary to identify early diagnostic biomarkers to improve the clinical outcomes of

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diabetic patients with CAD. In this study, we hypothesized that Fg to FDP (Fg/FDP) ratio is superior to Fg or FDP alone in predicting severe coronary atherosclerosis in type 2 diabetic patients, defined by multivessel coronary disease (MVD) and high tertile of Gensini score.

METHODS

The research protocol was approved by the Institutional Review Board of Ruijin Hospital, Shanghai Jiaotong University School of Medicine, and was registered (NCT02089360). Informed consent was obtained in written form from all patients, and clinical investigation was conducted according to the principle of the *Declaration of Helsinki*.

Study population

A total of 627 consecutive patients with type 2 diabetes and chest pain on exertion referred for diagnostic coronary angiography in the Department of Cardiology, Shanghai Ruijin Hospital between April 2011 and November 2013, were enrolled. Baseline demographics, risk factors for coronary disease, and medications were recorded. The diagnosis of type 2 diabetes was made according to the criteria of the American Diabetes Association,[18] including a fasting blood glucose (FBG) level of ≥ 7.0 mmol/L or 2 h postprandial plasma glucose readings ≥ 11.1 mmol/L by multiple determinations or currently receiving insulin or oralhypoglycemic agents. Hypertension was considered as repeated (at least twice in different peaceful circumstances) blood pressure measurements ≥140/90 mmHg or currently taking antihypertensive drugs. Hyperlipidemia was defined as low-density lipoprotein cholesterol ≥160 mg/dl and/or triglyceride ≥200 mg/dl.

For the purpose of research, patients with acute coronary syndrome ($n = 116$) or a history of coronary artery bypass grafting ($n = 34$) were excluded. We also excluded patients with hepatic dysfunction and renal failure requiring hemodialysis ($n = 43$) and those who had chronic heart failure, pulmonary heart disease, malignant tumor or immune system disorders ($n = 78$). Patients with type 1 diabetes were excluded by measurement of C-peptide ($n = 12$). The remaining 344 eligible patients were included in the final analysis of this study.

Biochemical investigation

Peripheral venous blood was collected at the day of angiography in all patients after an overnight fasting. All samples were immediately refrigerated and transported to the Department of Clinical Laboratory for determining lipid profiles, FBG, glycosylated hemoglobin A1c (HbA1c), high-sensitive C-reactive protein (hs-CRP), blood urea nitrogen (BUN), creatinine, uric acid and a spectrum of hematological and liver functional tests by standard laboratory techniques on a Hitachi 912 Analyzer (Roche Diagnostics, Germany). Serum Fg level was determined using the Clauss method as previously reported,[19] and FDP level (including D and E fragments, D-dimer, and additional

intermediate cleavage products) was assessed by a sandwich immunoassay. The Fg/FDP ratio was then calculated.

Coronary angiography

Coronary angiography was performed through femoral or radial artery approach by the interventional cardiologists blinded to patients' biochemical status. Significant CAD was diagnosed as the presence of ≥50% luminal diameter narrowing in at least one major epicardial coronary artery; left main coronary artery stenosis ≥50% was considered as 2-vessel disease. MVD was defined as the presence of ≥50% luminal diameter stenosis involving two or three coronary arteries. Total Gensini score, which consists of individual scores for each separate lesion in the three major coronary arteries, was calculated as previously reported.[20]

Statistical analysis

Continuous and categorical variables are expressed as mean ± standard deviation (SD) and numbers or percentages, respectively. Differences between groups were analyzed by Student's *t*-test, Mann–Whitney *U*-test or Chi-squared test when appropriate. Association between variables was examined using the Spearman and Pearson correlation coefficient. Receivers operating characteristic curves were constructed at the most discriminating cut-off values to verify the predictive power of plasma Fg and FDP level and Fg/FDP ratio for the presence of significant CAD and severe coronary atherosclerosis defines as MVD or high tertile of Gensini score. The independent determinants for presence of significant CAD and severe coronary atherosclerosis were assessed by multivariate logistic regression analysis, and the covariates chosen to enter the multivariate analysis model included age, gender, body mass index (BMI), risk factors for CAD, hematological and glycemic measurements, and renal function. All *P* values were two-tailed, and a $P < 0.05$ was considered as statistically significant. Statistical analysis was performed with the SPSS software (version 16.0, SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics

Among overall 344 patients, there were 226 men and 118 women with an average age of 65.5 years. Significant CAD was detected in 255 patients. Diabetic patients with CAD were older and had higher HbA1c, BUN, creatinine, and lipoprotein (a) levels, but gender, BMI, blood pressure, and lipid profiles were similar compared with those without CAD [Table 1]. White blood cell count and serum levels of hs-CRP were significantly elevated in diabetic patients with CAD (all $P < 0.05$).

Fibrinogen and fibrin (ogen) degradation products levels and fibrinogen/fibrin (ogen) degradation products ratio

Plasma levels of Fg were higher but Fg/FDP ratio was lower in diabetic patients with CAD, due to a disproportionate increase in FDP [Table 1]. Fg and FDP increased whereas Fg/FDP ratio decreased stepwise from 1- to 3-vessel disease and from low to high tertile of Gensini score, with

significant difference between patients with 1- and 3-vessel disease and between low and high tertile of Gensini score (all *P* < 0.01) [Figure 1]. Fg and FDP correlated positively, while Fg/FDP ratio negatively, with the number of diseased coronary arteries and the tertile of Gensini score (all *P* values for trend < 0.01). In addition, plasma Fg was related to HbA1c ($r = 0.172$, $P < 0.01$) and hs-CRP ($r = 0.528$, $P < 0.01$). D-dimer levels were elevated in diabetic patients with CAD, and correlated significantly with Gensini score ($r = 0.133$, $P < 0.05$) and age ($r = 0.390$, $P < 0.01$).

Table 1: Baseline clinical characteristics and biochemical measurements of type 2 diabetic patients

Variables	DM only (*n* = 89)	DM with CAD (*n* = 255)	*P*
Age (years)	61.3 ± 9.5	65.9 ± 9.4	<0.001
Male, *n* (%)	57 (64.8)	169 (66.5)	0.763
BMI (kg/m²)	25.9 ± 3.6	25.5 ± 3.6	0.503
Smoking, *n* (%)	24 (27.0)	80 (31.4)	0.436
Hypertension, *n* (%)	71 (79.8)	195 (76.5)	0.521
Hyperlipidemia, *n* (%)	30 (33.7)	102 (40.0)	0.293
Leukocyte (10⁹/L)	6.5 ± 2.0	6.7 ± 1.8	0.042
Platelet (10⁹/L)	195.5 ± 64.0	184.8 ± 55.7	0.144
ALT (U/L)	28.1 ± 15.6	25.0 ± 14.1	0.053
AST (U/L)	23.8 ± 11.6	22.9 ± 10.5	0.566
AKP (U/L)	62.9 ± 18.3	65.6 ± 19.7	0.298
FBG (mmol/L)	6.2 ± 1.8	6.6 ± 2.3	0.126
2 h-PG (mmol/L)	11.8 ± 3.7	12.9 ± 5.4	0.163
HbA1c (%)	7.1 ± 1.3	7.7 ± 2.2	0.024
Blood urea nitrogen (mmol/L)	5.1 ± 1.4	5.8 ± 3.8	0.037
Creatinine (umol/L)	69.6 ± 15.3	77.3 ± 17.5	<0.001
Uric acid (mmol/L)	317.2 ± 93.9	324.4 ± 84.1	0.461
hs-CRP (mg/L)	2.6 ± 4.1	5.7 ± 15.0	<0.001
Triglyceride (mmol/L)	1.7 ± 1.1	1.8 ± 1.4	0.465
Total cholesterol (mmol/L)	3.9 ± 1.0	4.0 ± 1.2	0.857
HDL-cholesterol (mmol/L)	1.2 ± 0.7	1.1 ± 0.3	0.130
LDL-cholesterol (mmol/L)	2.3 ± 0.8	2.3 ± 0.9	0.679
Apolipoprotein A (g/L)	1.3 ± 0.2	1.2 ± 0.2	0.178
Apolipoprotein B (g/L)	0.8 ± 0.2	0.8 ± 0.3	0.908
Lipoprotein (a) (g/L)	0.3 ± 0.6	0.2 ± 0.3	0.039
LVEF (%)	66.0 ± 4.9	64.8 ± 6.6	0.203
Fg (g/L)	2.5 ± 0.6	2.8 ± 1.4	0.010
D-dimer (mg/dl)	0.3 ± 0.7	0.4 ± 0.8	0.001
FDP (mg/L)	1.2 ± 1.1	1.7 ± 1.7	0.001
Fg/FDP ratio	4.0 ± 3.2	2.9 ± 2.3	0.004
Medications, *n* (%)			
Anti-platelet	79 (88.8)	251 (98.4)	<0.001
Beta-blocker	60 (67.4)	205 (80.4)	0.012
ACE-I/ARB	61 (68.5)	162 (63.5)	0.394
Statin	63 (70.8)	221 (86.7)	0.001

ACE-I: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; AKP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CAD: Coronary artery disease; DM: Diabetes mellitus; FDP: Fibrin (ogen) degradation product; HbA1c: Glycosylated hemoglobin A1c; hs-CRP: High sensitivity C-reactive protein; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; LVEF: Left ventricular ejection fraction; 2 h-PG: 2 h-postprandial glucose; BMI: Body mass index; FBG: Fasting blood glucose.

Diagnostic value of fibrinogen and fibrinogen/fibrin (ogen) degradation products ratio for coronary artery disease

Multivariate logistic regression analysis revealed that after adjusting for age, sex, BMI, traditional risk factors of CAD, lipid profiles, leukocyte count, hs-CRP, renal function, and HbA1c, elevated Fg and reduced Fg/FDP ratio, but not FDP and D-dimer, were independently associated with the presence of significant CAD. Furthermore, Fg/FDP ratio still remained an independent determinant for severe coronary atherosclerosis defined as MVD (odds ratio [*OR*], 0.869; 95% confidence interval [*CI*], 0.788–0.958, *P* = 0.005) and Gensini score ≥ 30 (*OR*, 0.797, 95% *CI*, 0.682–0.930, *P* = 0.004) [Table 2].

Receivers operating characteristic curve analysis showed that the area under the curve (AUC) of Fg and Fg/FDP ratio was similar for predicting the presence of significant CAD (0.602 vs. 0.592). However, the AUC of Fg/FDP ratio was significantly larger than that of Fg for predicting severe coronary atherosclerosis defined by MVD (0.647 vs. 0.563, *P* = 0.048) and high tertile of Gensini score (0.656 vs. 0.538, *P* = 0.026) [Figure 2]. An optimal cut-off value of Fg/FDP ratio was 2.71. At this level, sensitivity and specificity were 70.0% and 55.2% for MVDs and 78.0% and 48.7% for Gensini score ≥ 30, respectively. The optimal cut-off value of Fg was 2.35 g/L, and the sensitivity and specificity at this level were 69.9% and 43.4% for MVDs and 71.8% and 35% for Gensini score ≥30.

DISCUSSION

To our knowledge, this is the first study to show that elevated plasma Fg and FDP level and reduced Fg/FDP ratio are

Table 2: Logistic regression analysis for presence of CAD and severe coronary atherosclerosis in patients with type 2 DM

Variables	*OR* (95% *CI*)	*P*
Presence of CAD		
Age	1.041 (1.011–1.072)	0.007
Creatinine	1.026 (1.010–1.043)	0.002
Fg	1.773 (1.143–2.748)	0.010
Fg/FDP ratio	0.887 (0.806–0.977)	0.015
Presence of MVD		
Age	1.041 (1.012–1.071)	0.006
BMI	0.898 (0.830–0.971)	0.007
HbA1c	1.438 (1.189–1.741)	<0.001
Creatinine	1.021 (1.006–1.036)	0.007
Fg/FDP ratio	0.869 (0.788–0.958)	0.005
Gensini score >30		
HDL-cholesterol	0.231 (0.084–0.637)	0.005
Fg/FDP ratio	0.797 (0.682–0.930)	0.004

BMI: Body mass index; CAD: Coronary artery disease; *CI*: Confidence interval; Fg: Fibrinogen; FDP: Fibrin (ogen) degradation product; HbA1c: Glycosylated hemoglobin A1c; MVD: Multivessel coronary disease; *OR*: Odds ratio; DM: Diabetes mellitus; HDL: High-density lipoprotein.
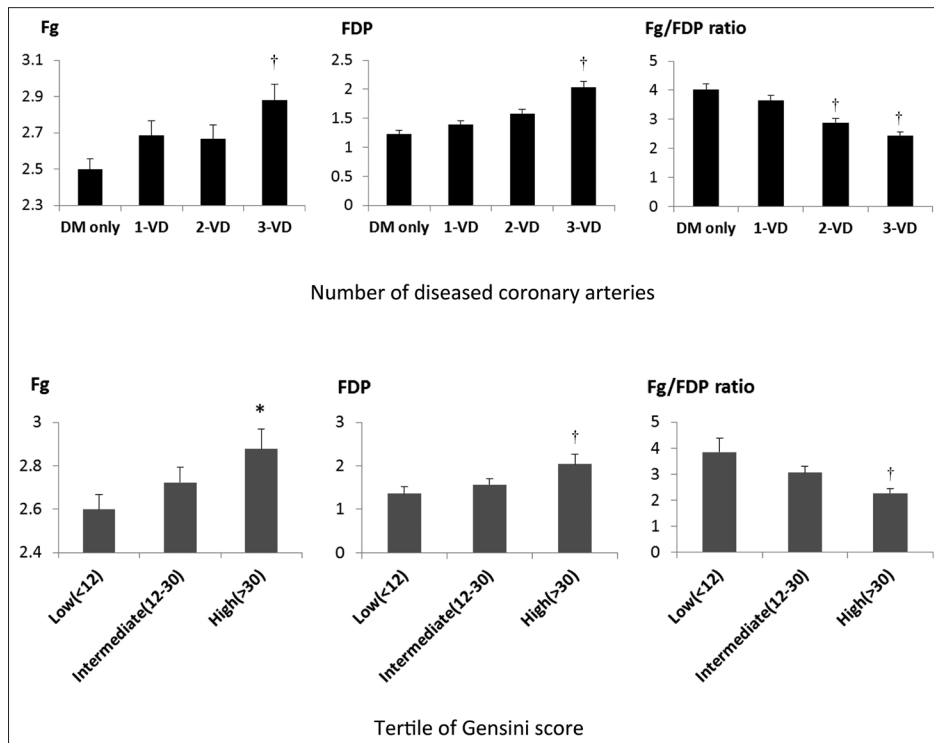
Figure 1: Association of plasma fibrinogen (Fg) and fibrin(ogen) degradation products (FDP) levels and Fg/FDP ration with number of diseased coronary arteries and Gensini score (*P < 0.05; †P < 0.01).
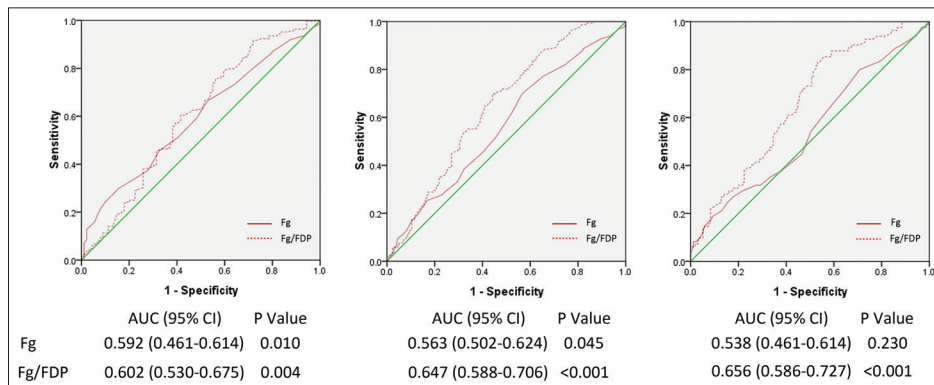

Figure 2: Receivers operating characteristic curves of fibrinogen (Fg) (solid line) and Fg/fibrin(ogen) degradation products ratio (dotted line) for detecting the presence of significant coronary artery disease (left), multivessel disease (middle) and Gensini score >30 (right) in type 2 diabetic patients (AUC: Area under curve; *CI*: Confidence interval).

associated with the presence of significant CAD, and Fg/FDP ratio is superior to Fg in predicting severe coronary atherosclerosis in patients with type 2 diabetes.

The mechanism of coronary atherosclerosis is likely to be complex especially in a diabetic setting, involving overactive thrombotic pathways,[3,4] reduced fibrinolysis, and chronic inflammatory response,[21] in addition to other abnormal biochemical and cellular alterations. Consistent with previous reports,[6,9,11] our results demonstrate a relationship of plasma Fg level with blood HbA1c concentration and the severity of coronary atherosclerosis expressed by number of significant diseased coronary arteries and Gensini score in patients with type 2 diabetes. This observation

substantiates a notion that increased plasma Fg level was implied with long-standing glycolipid metabolism, systemic inflammation as well as atherosclerotic plaque progression.[6] Recently, Rodrigues *et al*. found that an elevated circulating Fg could predict coronary artery calcification in diabetic patients independent of traditional risk factors for CAD.[22] Furthermore, the BARI 2D trial showed that elevated baseline plasma Fg level portends poor clinical outcomes with diabetic vasculopathy[20] and provides prognostic influence in unstable coronary disease.[23]

The main finding of this study is that despite elevated plasma Fg levels, Fg/FDP ratio was significantly lower in diabetic patients with significant CAD, predominantly due

to a disproportionate increase in FDP levels particularly for those with severe coronary atherosclerosis. Likewise, Fg/FDP ratio correlated inversely with the number of diseased coronary arteries and Gensini score, and remained an independent factor for MVD and high tertile of Gensini score after adjusting for conventional risk factors for CAD and inflammatory markers (leukocyte and hs-CRP). Interestingly, the optimal cut-off value of Fg/FDP ratio predicts the presence of severe coronary atherosclerosis in type 2 diabetic patients with good sensitivity and specificity. Although the reason behind this is still not clear, an elevation of circulating FDP may reflect, at least partly, a more rapid degradation of Fg given that it is a protein with short half-life. FDP including D-dimer are produced by clot degeneration.[24] In normal subjects, plasma FDP levels are below the detectable levels. In response to the fibrous deposition in the inflammatory area, the body produces more Fg and FDP, which counteract the thrombin. Therefore, plasma FDP has been used as an indicator of the procoagulant state and considered as a risk factor for coronary arterial and peripheral venous thrombosis.[6,25,26] In this study, although significant differences in plasma FDP and D-dimer levels existed between diabetic patients with and without significant CAD, both measurements were not independently associated with coronary disease. This suggests that FDP alone is not a reliable marker for assessing the degree of coronary atherosclerosis in diabetic patients.[27,28]

There are some limitations in our study. First, the study is cross-sectional for the point of coronary disease investigation, thereby allowing us to detect an association, but not to predict the outcome. Second, measurement of Fg and FDP in plasma mainly reflects atherosclerotic process of whole-body vasculature including peripheral artery disease, instead of coronary vessels solely. Data regarding other possible pertinent co-morbidities such as peripheral vascular disease would strengthen the linkage of Fg and FDP levels and Fg/FDP ratio to disease. Finally, the classification of significant CAD based on visual estimation of angiographic stenosis of coronary artery lesions at ≥50% is admittedly arbitrary. However, within the range of angiographically significant CAD, including lesions of ≥50% stenosis, this criterion of severity correlates well with physiological standards and is widely accepted clinical practice.[29]

In conclusion, the present study demonstrates that elevated plasma Fg and FDP level and reduced Fg/FDP ratio are associated with the presence of significant CAD, and Fg/FDP ratio is superior to Fg in predicting severe coronary atherosclerosis in patients with type 2 diabetes. Because diabetic patients may be clinically asymptomatic even at the presence of severe coronary disease partly due to silent myocardial ischemia, our findings on the use of Fg and FDP and their ratio as early diagnostic markers of coronary disease may have important clinical implications in improving the management strategy and outcome of these patients.

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