Assessment between Plasma Follistatin-like Protein 1 Levels and the Presence and Severity of Coronary Artery Disease

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Summary
Follistatin-like protein 1 (FSTL1) is a secreted glycoprotein known for its role in inflammation. However, plasma FSTL1 levels in patients with coronary artery disease (CAD) have not been fully elucidated. Thus, in this study, we investigated the plasma FSTL1 levels of 350 patients who underwent elective coronary angiography. The severity of CAD was represented as the numbers of > 50% stenotic vessels and segments and the severity score. CAD was detected in 196 patients, of whom 84 had 1-vessel disease (1-VD), 62 had 2-VD, and 50 had 3-VD. Plasma high-sensitivity C-reactive protein (hsCRP) levels were higher in patients with CAD than in those without CAD (median 0.56 versus 0.44 mg/L, P < 0.01). Notably, plasma FSTL1 levels were higher in patients with CAD than in those without CAD (median 4.05 versus 3.47 ng/mL, P < 0.02). A stepwise increase in FSTL1 levels was found depending on the number of > 50% stenotic vessels: 3.47 in CAD(−), 3.74 in 1-VD, 4.42 in 2-VD, and 4.65 ng/mL in 3-VD (P < 0.05). FSTL1 levels also correlated with the number of > 50% stenotic segments and the severity score (r = 0.14 and r = 0.15, respectively, P < 0.005) and hsCRP levels (r = 0.10, P < 0.05). In the multivariate analysis, FSTL1 levels were an independent factor associated with CAD. The odds ratio for CAD was 1.61 (95% CI = 1.01-2.58) for high FSTL1 level of > 3.6 ng/mL (P < 0.05). In conclusion, plasma FSTL1 levels in patients with CAD were found to be high and associated with the presence and severity of CAD, thus, suggesting that FSTL1 may play a role in the progression of coronary atherosclerosis.

Key words: Atherosclerosis, Biomarker, Inflammation

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Methods

Study patients: We prospectively collected blood samples and clinical data from patients undergoing coronary angiography. This study was approved by institutional ethics committee (R15-056). After written informed consent was obtained, overnight-fasting blood samples were taken on the morning of the day of angiography. In total, 350 consecutive patients who underwent elective coronary angiography at Tokyo Medical Center for suspected CAD because of chest discomfort or dyspnea on exertion and/or abnormalities on electrocardiography, exercise testing, or myocardial scintigraphy were enrolled in this study to measure plasma FSTL1 levels. Patients with a history of percutaneous coronary intervention (PCI) or cardiac surgery were excluded. Patients with ACS, such as acute MI and unstable angina, were excluded. Because serum FSTL1 levels were high in patients with heart failure (HF) and cardiac FSTL1 gene expression was increased in HF,12,13,14 patients with HF were also excluded. Moreover, patients with severe valvular heart disease, peripheral artery disease, aortic disease, or inflammatory diseases were excluded. Hypertension was defined as blood pressures of ≥ 140/90 mmHg or on drugs, wherein 204 (58%) patients were determined to be taking anti-hypertensive drugs. Hyperlipidemia was defined as LDL-cholesterol level of > 140 mg/dL or on drugs, wherein 138 (39%) patients were found to be taking statin. Diabetes mellitus (DM) (a fasting plasma glucose level of ≥ 126 mg/dL or on treatment) was detected in 101 (29%) patients, while 131 (37%) patients with HF were also excluded. Moreover, patients with severe valvular heart disease, peripheral artery disease, aortic disease, or inflammatory diseases were excluded. Hypertension was defined as blood pressures of ≥ 140/90 mmHg or on drugs, wherein 204 (58%) patients were determined to be taking anti-hypertensive drugs. Hyperlipidemia was defined as LDL-cholesterol level of > 140 mg/dL or on drugs, wherein 138 (39%) patients were found to be taking statin. Diabetes mellitus (DM) (a fasting plasma glucose level of ≥ 126 mg/dL or on treatment) was detected in 101 (29%) patients, while 131 (37%) patients were determined to be smokers (≥ 10 pack-years).

Measurements of plasma FSTL1 and C-reactive protein (CRP) levels: Blood samples were collected in EDTA-containing tubes and were centrifuged at 2000 g for 15 minutes at 4°C. Plasma was frozen and stored at −80°C until analysis. Plasma FSTL1 levels were measured using an enzyme-linked immunosorbent assay (ELISA) with a commercially available kit (ELISA Kit for Follistatin-Like Protein 1, Cloud-Clone, Katy, TX, USA) according to the manufacturer’s instructions. According to the data supplied by the manufacturer, the range of values detected by this assay was from 1.56 to 100 ng/mL. The intra- and inter-assay coefficients of variation were < 10% and < 12%, respectively. Plasma high-sensitivity CRP (hsCRP) levels were also measured using a BNII nephelometer (Dade Behring, Tokyo, Japan).

Coronary angiography: Angiograms were recorded on a cineangiogram system (Philips Electronics Japan, Tokyo, Japan). CAD was defined as at least one coronary artery having > 50% luminal diameter stenosis on angiograms. The severity of CAD was represented as the numbers of > 50% stenotic coronary vessels and > 50% and > 25% stenotic segments and the severity score of stenosis. The degree of stenosis in each segment was scored from visual assessment from 0 to 4 points (0, ≤ 25%; 1, 26%-50%; 2, 51%-75%; 3, 76%-90%; 4, > 90% stenosis), and then the severity score was defined as the sum of scores of all segments. Coronary artery segments were defined as 29 segments according to the Coronary Artery Surgery Study classification. All angiograms were evaluated by a single cardiologist (Y.M.), who had been blinded to clinical and laboratory data.

Statistical analysis: Any differences between the 2 groups were evaluated by using unpaired t-test for parametric variables, by Mann-Whitney U test for nonparametric variables, and by chi-squared test for categorical variables. Differences among ≥ 3 groups were evaluated by an analysis of variance with Scheffe’s test for parametric variables, by Kruskal-Wallis test together with the Steel-Dwass test for nonparametric variables, and by chi-squared test for categorical variables. Since the distributions of measured FSTL1 and hsCRP levels were considered to be highly skewed and to be nonparametric variables by Shapiro-Wilk test, results were presented as the median value and interquartile range. Correlations between FSTL1 levels and hsCRP levels or the severity of CAD were evaluated using Spearman’s rank correlation test. To determine the cut-off point of FSTL1 levels for CAD, a receiver operating characteristic (ROC) curve was created, and then the optimal cut-off point was determined to be 3.6 ng/mL, which is the point where the Youden index was the highest. The optimal cut-off points of age and serum creatine level were also determined to be 70 years and 0.9 mg/dL, respectively. Regarding the cut-off point of hsCRP levels, the previously reported cut-off point of 1.0 mg/L for CAD was used.14,15 The areas under ROC curves (AUC) were measured to compare the diagnostic abilities of FSTL1 and hsCRP levels to predict CAD. A forward stepwise multiple logistic regression analysis was performed to determine the independent association between FSTL1 levels and CAD. All statistical analyses were performed using the SPSS software package (IBM SPSS version 25, Tokyo, Japan). A P-value of < 0.05 was considered to be statistically significant. The results are presented as the mean ± SD or the median value.

Results

Among the 350 study patients, CAD was detected in 196 patients (56%) (1-vessel disease [1-VD], n = 84; 2-vessel disease [2-VD], n = 62; 3-vessel disease [3-VD], n = 50). Compared with 154 patients without CAD, 196 patients with CAD were older and had a male predominance; higher prevalence of hypertension, DM, and hyperlipidemia; and lower HDL-cholesterol and higher creatinine levels (Table I). Plasma hsCRP levels were noted to be higher in patients with CAD than in those without CAD (median 0.56 versus 0.44 mg/L, P < 0.01). A stepwise increase in hsCRP levels was determined, depending on the number of > 50% stenotic coronary vessels: 0.44 in CAD(−), 0.52 in 1-VD, 0.56 in 2-VD, and 0.62 mg/L in 3-VD (P < 0.02) (Table I).

Notably, plasma FSTL1 levels were significantly higher in patients with CAD than in those without CAD (median 4.05 versus 3.47 ng/mL, P < 0.02) (Figure 1). A stepwise increase in FSTL1 levels was also noted, depending on the number of > 50% stenotic vessels, that is, 3.47 in CAD(−), 3.74 in 1-VD, 4.42 in 2-VD, and 4.65 ng/mL in 3-VD (P < 0.05); moreover, FSTL1 levels were highest in 3-VD (P < 0.05) (Figure 1). FSTL1 levels significantly correlated with hsCRP (r = 0.10, P < 0.05) and creatinine (r = 0.16, P < 0.01) levels but not with body...
and the severity score (numbers of > 50% and > 25% stenotic coronary segments mass index (BMI). FSTL1 levels also correlated with the numbers of > 50% and > 25% stenotic coronary segments and the severity score ($r = 0.14$, $r = 0.15$, and $r = 0.15$, respectively, $P < 0.005$) (Figure 2).

The sensitivity and specificity to predict CAD were 61% and 54% for FSTL1 level of > 3.6 ng/mL and 29% and 77% for hsCRP level of > 1.0 mg/L, respectively (Table I). The AUC for FSTL1 levels was 0.576 (95% CI = 0.516-0.636), which did not differ from the AUC for hsCRP levels (0.583; 95%CI = 0.522-0.644) (Figure 3).

**Table 1.** Clinical Characteristics and Plasma FSTL1 Levels of Patients with and Without CAD

|                     | CAD (−) (n = 154) | P-value CAD (−) versus CAD (n = 196) | CAD (n = 84) | 1-VD (n = 62) | 3-VD (n = 50) | P-value among 4 groups |
|---------------------|-------------------|-------------------------------------|--------------|---------------|---------------|------------------------|
| Age (years)         | 64 ± 12           | > 0.05                              | 69 ± 9       | 70 ± 10       | 72 ± 9        | 0.15                   |
| Gender (male)       | 88 (57%)          | < 0.001                             | 149 (76%)    | 46 (74%)      | 39 (78%)      | 0.003                  |
| BMI (kg/m²)         | 24.6 ± 4.6        | 0.126                               | 23.9 ± 3.5   | 24.3 ± 3.9    | 24.4 ± 3.0    | 0.038                  |
| Hypertension        | 91 (59%)          | 0.009                               | 152 (78%)    | 64 (76%)      | 45 (73%)      | < 0.001                |
| SBP (mmHg)          | 130 ± 21          | > 0.05                              | 133 ± 19     | 131 ± 18      | 137 ± 19      | 0.12                   |
| Diabetes mellitus   | 25 (16%)          | > 0.001                             | 76 (39%)     | 26 (31%)      | 31 (50%)      | < 0.001                |
| HbA1c (%)           | 5.9 ± 0.6         | > 0.001                             | 6.3 ± 1.0    | 6.2 ± 0.9     | 6.5 ± 1.0     | < 0.001                |
| Smoking             | 49 (32%)          | > 0.001                             | 82 (42%)     | 37 (44%)      | 26 (42%)      | 0.24                   |
| Hyperlipidemia      | 63 (41%)          | < 0.001                             | 119 (61%)    | 51 (61%)      | 38 (61%)      | 0.002                  |
| Statin              | 41 (27%)          | > 0.001                             | 97 (49%)     | 43 (51%)      | 31 (50%)      | < 0.001                |
| LDL-C (mg/dL)       | 112 ± 30          | > 0.001                             | 107 ± 28     | 113 ± 32      | 121 ± 30      | 0.063                  |
| HbCRP (mg/dL)       | 5.9 ± 15          | > 0.001                             | 52 ± 13      | 56 ± 15       | 51 ± 12       | < 0.001                |
| Creatinine (mg/dL)  | 0.80 ± 0.19       | > 0.001                             | 0.90 ± 0.23  | 0.92 ± 0.24   | 0.87 ± 0.22   | < 0.001                |
| > 0.9 mg/dL         | 42 (27%)          | < 0.001                             | 87 (44%)     | 44 (52%)      | 22 (35%)      | 0.002                  |
| hsCRP (mg/dL)       | 0.44              | > 0.001                             | 0.56         | 0.52         | 0.56         | 0.14                   |
| > 1.0 mg/L          | 0.281             | > 0.001                             | 0.57         | 0.19         | 0.18         | 0.24                   |
| FSTL1 levels (ng/mL)| 3.47              | 0.015                               | 4.05         | 3.74         | 4.42         | 0.032                  |
| > 3.6 ng/mL         | 71 (46%)          | 0.009                               | 119 (61%)    | 49 (58%)      | 36 (58%)      | 0.031                  |

Data represent the mean ± SD or the number (%) of patients, except for hsCRP, and FSTL1 levels which are presented as the median value and interquartile range. BMI indicates body mass index; SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol; and HDL-C, high-density lipoprotein cholesterol.

**Figure 1.** Plasma FSTL1 levels and the presence of CAD or the number of stenotic coronary vessels. Plasma FSTL1 levels were significantly higher in CAD than in CAD (−) (left). Moreover, FSTL1 levels in the 4 groups of CAD (−), 1-VD, 2-VD, and 3-VD were 3.47, 3.74, 4.42, and 4.65 ng/mL, respectively, and FSTL1 level was found to be the highest in 3-VD (P < 0.05 by Kruskal–Wallis test) (right). The central line represents the median, and the box represents the twenty-fifth to seventy-fifth percentiles. The whiskers represent the lowest and highest value in the twenty-fifth percentile minus 1.5 IQR and seventy-fifth percentile plus 1.5 IQR, respectively.
To elucidate the independent association between FSTL1 levels and CAD, variables (age, gender, BMI, hypertension, DM, smoking, hyperlipidemia, statin use, and HDL-cholesterol, creatinine, hsCRP, and FSTL1 levels) were entered into a multiple logistic regression model. FSTL1 levels were considered to be a significant factor associated with CAD independent of atherosclerotic risk factors and creatinine and hsCRP levels. The odds ratio for CAD was 1.61 (95% CI = 1.01-2.58) for a high FSTL1 level of > 3.6 ng/mL (P < 0.05) (Table II).

Discussion

In this present study, plasma FSTL1 levels in patients with CAD were found to be high and to be positively correlated with the severity of CAD, defined as the numbers of stenotic vessels and segments and the severity score. FSTL1 levels also significantly, but weakly, correlated with hsCRP levels. However, FSTL1 level was a significant factor associated with CAD independent of atherosclerotic risk factors and hsCRP level.

Atherosclerotic disease, including CAD, is recognized to be a chronic inflammatory disease. As shown in patients with inflammatory diseases, such as RA and ulcerative colitis, serum FSTL1 levels were reportedly higher in 216 patients with ACS than in 120 healthy controls. The production of FSTL1 in infarcted myocardium was reported in patients with acute MI, but no significant difference was noted in terms of the serum FSTL1 levels among 62 patients with unstable angina, 68 with non-ST-elevation MI, and 86 with ST-elevation MI. Regarding the associations between blood FSTL1 levels and stable CAD or coronary atherosclerosis, only one small study reported that serum FSTL1 levels tended to be higher in 28 subjects with coronary artery plaque detected by computed tomography than in 38 without plaque, but this difference did not reach statistical significance, probably due to the small number of study subjects. We then investigated the plasma FSTL1 levels in 350 patients who underwent elective coronary angiography. In this study, patients with ACS were excluded. This study reported for the first time that FSTL1 levels were significantly higher in 196 patients with stable CAD than in 154 without
CAD and that FSTL1 levels correlated with the severity of CAD. These findings suggest that plasma FSTL1 levels are associated with the presence and severity of stable CAD and that FSTL1 may play a role in the progression of coronary atherosclerosis. However, the correlation between plasma FSTL1 levels and the severity of CAD, defined as the number of stenotic segments and the severity score, was noted to be significant but weak ($r = 0.14$ and $r = 0.15$) (Figure 2). In this study, patients with inflammatory diseases were excluded. As shown in Figure 1, a substantial overlap was determined in the FSTL1 levels between patients with and without CAD. Therefore, FSTL1 levels in patients with CAD may reflect not only the degrees of atherosclerosis and inflammation in coronary arteries but also those in other vascular beds.

The positive correlation between FSTL1 levels and hsCRP levels was reported in patients undergoing PCI, those with ACS, and healthy subjects. We also found that FSTL1 levels significantly but weakly correlated with hsCRP levels ($r = 0.10$). FSTL1 levels were also reported to correlate with serum creatinine levels in patients undergoing PCI. However, Hayakawa, et al. reported no correlation between FSTL1 levels and creatine levels among the healthy subjects. As per the findings of this present study, it was determined that FSTL1 levels significantly correlated with creatine levels ($r = 0.16$). Moreover, one study reported the positive correlation between FSTL1 levels and BMI, but another did not. We found no correlation between FSTL1 levels and BMI. In this present study, we demonstrated that FSTL1 levels were a significant factor associated with CAD independent of hsCRP and creatinine levels and BMI. However, the sensitivity and specificity to predict CAD were 61% and 54% for FSTL1 level (> 3.6 ng/mL), respectively. The AUC for FSTL1 levels was 0.58, which did not differ from that of hsCRP levels. Therefore, FSTL1 levels as well as hsCRP levels are unlikely to be a good biomarker reflecting the presence or severity of CAD. However, to determine the diagnostic ability of FSTL1 levels for CAD, a further prospective study is needed.

Although most studies in vitro and in vivo reported that FSTL1 promotes inflammation, some studies suggested the anti-inflammatory effect of FSTL1. This discrepancy may be explained by differences in experimental models and FSTL1 target organs. Moreover, Murakami, et al. proposed that two signaling pathways of FSTL1 might explain the pro- and anti-inflammatory effects of FSTL1. They suggested that FSTL1 may exert its pro-inflammatory effect through CD14 and Toll-like receptor 4 pathway, whereas the anti-inflammatory effect involves the disco-interacting protein 2 homolog A (DIP2A) pathway. Further studies are still needed to completely understand the role of FSTL1 in inflammation and atherosclerosis. In this present study, we demonstrated that plasma FSTL1 levels were associated with the presence and severity of CAD. Recently, Aikawa, et al. evaluated plasma FSTL1 levels in 410 patients undergoing PCI with drug-eluting stents. They showed that FSTL1 levels before PCI were higher in patients who developed cardiovascular events than in those who did not and that FSTL1 level may be a predictor of cardiovascular events in patients undergoing PCI. This, as well as our own findings, suggests that high FSTL1 levels play a role in promoting the progression of coronary atherosclerosis, probably due to the proinflammatory effect of FSTL1. However, a further study is needed in a prospective manner to elucidate the prognostic value of FSTL1 levels in patients with stable CAD.

This study has several limitations. First, in this study, coronary angiography was used to evaluate coronary atherosclerosis. Angiography cannot visualize plaques and only shows the lumen characteristics. However, intravascular ultrasound (IVUS) or optical coherence tomography, which can visualize coronary plaques, was not always performed in our patients. Furthermore, the degree of stenosis was not evaluated using quantitative coronary angiography, but it was scored by visual assessment with a single cardiologist, as in our previous study. These may have confounded our results. Second, FSTL1 was reportedly secreted by various cells, including cardiomyocytes, fibroblasts, and endothelial cells. However, since we did not measure FSTL1 levels in the coronary sinus, our study did not provide any information about the main sources of FSTL1 in patients with CAD. Third, our study was cross-sectional in nature and was unable to establish causality, since it only depicted some associations and proposed some hypotheses. To elucidate the role and its mechanism of high FSTL1 levels in the progression of coronary atherosclerosis, further studies are needed. Finally, like other studies examining patients undergoing coronary angiography, we compared patients with and without CAD and had no healthy controls. Our study population was limited to Japanese patients undergoing coronary angiography, who are generally considered to be a highly select population at high risk for CAD. Our results may not be applica-

### Table II. Factors Associated with CAD (Multiple Logistic Regression Analysis of the 350 Study Patients)

| Factor                  | Odds ratio (95% CI) | P-value |
|-------------------------|---------------------|---------|
| Age ( > 70 years)       | 2.37 (1.47–3.83)    | <0.001  |
| Male gender             | 3.03 (1.77–5.17)    | <0.001  |
| Statin use              | 2.77 (1.66–4.63)    | <0.001  |
| DM                      | 2.38 (1.36–4.15)    | 0.002   |
| High FSTL1 level ( > 3.6 ng/mL) | 1.61 (1.01–2.58) | 0.048   |

The dependent variable was the presence of CAD. The analysis included age ( > 70 years), gender, BMI, hypertension, DM, smoking, hyperlipidemia, statin use, low HDL-cholesterol ( < 40 mg/dL), high creatinine ( > 0.90 mg/dL), high hsCRP ( > 1.0 mg/L), and high FSTL1 ( > 3.6 ng/mL) levels.
ble to the general or other ethnic populations.

In conclusion, plasma FSTL1 levels in patients with CAD were found to be high and positively correlated with the severity of coronary atherosclerosis. FSTL1 levels also correlated with hsCRP levels. However, FSTL1 levels were identified to be a significant factor for CAD independent of atherosclerotic risk factors and hsCRP levels. High FSTL1 levels in patients with CAD may play a role in the progression of coronary atherosclerosis.

Disclosure

Conflicts of interest: This study was supported in part by a grant from Tanuma Green House Foundation. Financial funding was also provided by Bayer Yakuhin Ltd., Daiichi Sankyo Co., and Pfizer Japan Inc.; however, these sponsors had no role in the design, analysis, or interpretation of the study.

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