Dietary Factor VII Activation Does Not Increase Plasma Concentrations of Prothrombin Fragment 1+2 in Patients With Stable Angina Pectoris and Coronary Atherosclerosis

Else Marie Bladbjerg, Anna-Marie Münster, Peter Marckmann, Niels Keller, Jørgen Jespersen

Abstract—Studies in healthy subjects showed that blood coagulation factor VII (FVII) is activated postprandially after consumption of high-fat meals, but accompanying thrombin formation has not been demonstrated. In patients with coronary atherosclerosis, the arterial intima is supposed to present more tissue factor, the cofactor of FVII, to circulating blood; therefore, thrombin formation in response to FVII activation is more likely to occur in such patients. This hypothesis was tested in a randomized crossover study of 30 patients (aged 43 to 70 years) with stable angina pectoris and angiographically verified coronary atherosclerosis. They were served a low-fat (5% of energy from fat) breakfast and lunch and a high-fat (40% of energy from fat) breakfast and lunch on 2 different days. Venous blood samples were collected at 8:15 AM (fasting), 12:30 PM, 2:00 PM, 3:30 PM, and 4:45 PM and analyzed for triglycerides, activated FVII (FVIIa), FVII protein concentration (FVII:Ag), prothrombin fragment 1+2 (F1+2), and soluble fibrin. Triglyceride levels increased from fasting levels on both diets, but they increased most markedly on the high-fat diet. FVIIa and FVIIa/FVII:Ag increased with the high-fat diet and decreased with the low-fat diet. For both diets, FVII:Ag and F1+2 decreased slightly. No postprandial changes were observed for soluble fibrin. Postprandial mean values of triglycerides, FVIIa, FVII:Ag, and FVIIa/FVII:Ag were significantly higher for the high-fat diet than for the low-fat diet. Our findings confirm that high-fat meals cause immediate activation of FVII. The clinical implication is debatable because FVII activation was not accompanied by an increase in plasma F1+2 concentrations in patients with severe atherosclerosis. However, a local thrombin generation on the plaque surface cannot be excluded. (Arterioscler Thromb Vasc Biol. 2000;20:2494-2499.)

Key Words: atherosclerosis ■ cardiovascular diseases ■ coagulation ■ diet ■ thrombosis

In large prospective epidemiological studies,1-2 the coagulant activity of blood coagulation factor VII (FVII:C) has been identified as a risk indicator of ischemic cardiac death, but other studies have been unable to confirm this observation.3-5 FVII:C is affected by genetics as well as environmental factors. In particular, it is well documented that diet has a remarkable effect on fasting and nonfasting plasma levels of FVII:C.6-18 Dietary changes in fasting levels of FVII:C seem to be due to changes in blood coagulation factor VII (FVII) protein concentrations,7,11,14 whereas changes in the nonfasting state are due to activation of circulating FVII protein.9,10,12,13,15,17,19

FVII is considered the “true” initiator of in vivo blood coagulation.20 This point of view is supported by the reported positive association between FVII:C and concentrations of prothrombin fragment 1+2 (F1+2), a marker of thrombin formation, in men at average and at high cardiovascular risk.21,22 Also, the reduction in FVII:C during anticoagulant therapy is accompanied by a decrease in concentrations of F1+2.23 Dietary modification of FVII:C levels may thus have an impact on in vivo thrombin generation. In 1 study, we observed that dietary-induced reductions in fasting FVII:C and FVII protein concentrations were indeed accompanied by a decrease in F1+2.14 However, postprandial FVII activation was not accompanied by any elevation of F1+2.15,24-26 Taken together, these observations suggest that thrombin generation is affected only by changes in FVII protein concentrations and not by an acute increase in concentrations of activated FVII (FVIIa).

Earlier studies on postprandial FVII activation and thrombin generation were conducted in apparently healthy subjects. Intimal exposure of tissue factor (TF), the cofactor of FVII, to circulating blood is probably very limited in such subjects. It is known that TF is present in high amounts in atherosclerotic plaques.27 Therefore, intimal TF expression is more likely to occur in highly atherosclerotic patients. We know from other studies that induction of TF expression by endotoxin promotes thrombin formation in healthy men.28 On the basis of

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these observations, we hypothesized that postprandial FVII activation increases thrombin formation in individuals with documented atherosclerotic arteries.

Methods

Study Population

Patients admitted to Ribe County Hospital, Esbjerg, Denmark, for coronary angiography between February 1998 and June 1998 were invited to participate in the present study (n = 113). The angiography showed coronary artery disease in 98 patients, who were informed about the study in more detail by an interview. Finally, 30 patients gave their informed consent to participate. Of these patients, 27 had severe atherosclerosis (>50% stenosis of the lumen) in 1 (n = 8), 2 (n = 2), or 3 (n = 1) of the major coronary arteries (left coronary artery, right coronary artery, left anterior descending coronary artery, and circumflex artery) or in 1 of their branches. Three patients had single-vessel disease with only 25% to 40% stenosis (in the left anterior descending coronary artery for 2 patients and the circumflex artery for 1 patient). All patients had stable angina pectoris and were treated with acetylsalicylic acid (75 to 150 mg/d). Other cardiac medications were as follows: β-blockers (n = 21), calcium antagonists (n = 14), long-lasting nitrates (n = 14), statins (n = 13), ACE inhibitors (n = 6), diuretics (n = 5), antiarrhythmics (n = 2), and other vasodilator therapy (n = 1). Two patients were treated for chronic obstructive pulmonary disease with inhaled therapy. Six patients had previously had a myocardial infarction. Four had undergone a coronary artery bypass operation, 3 had experienced a stenosis of the aortic valve, and 4 had hypertension. Exclusion criteria were as follows: anticoagulant therapy, diabetes, liver diseases, malignant disorders, coagulation defects, and simultaneous participation in other medical trials.

The study participants (25 men and 5 women) were aged 43 to 70 (mean age 59.8) years, with a mean ± SD body mass index of 28.5 ± 4.3 kg/m². Two patients were smokers, but they avoided smoking on the 2 study days. The study was approved by the regional ethics committee.

Study Design

The trial was a randomized crossover study. Two experimental diets (low fat and high fat) were served to the participants on 2 different days (Tuesday and Thursday). Meals were eaten under observation at the Staff Canteen at Ribe County Hospital. On both days, breakfast was served at 8:30 AM, and lunch was served at 11:00 AM. One glass (200 mL) of water was served with breakfast, and 2 glasses of water were served with lunch. The evening before (Monday and Wednesday), the patients consumed a low-fat asparagus soup with bread supplied by us to minimize preexperimental variation. On the 2 study days, the participants were allowed to leave the hospital between blood samplings, but they were not allowed to eat anything except the study meals or to perform any heavy physical activity. Tap water was allowed ad libitum but in equal amounts on both study days.

Experimental Diets

Low-fat meals (5% of energy from fat) and high-fat meals (40% of energy from fat) were served as described. The high-fat meals were low-fat rice dishes (rice, beef, onion, red pepper, corn, small amounts of spices, and bread) to which refined rapeseed oil was added. The main fatty acids of rapeseed oil are oleic acid (C18:1) and linoleic acid (C18:2).15 For breakfast, 13.5 g oil was added to a 135-g rice dish (1400 kJ), and for lunch, 49.5 g oil was added to a 495-g rice dish (5130 kJ). Refined rapeseed oil was chosen because it is almost tasteless. The low-fat meals were also low-fat rice dishes, but bread, bananas, and raisins were added instead of the rapeseed oil. The low-fat meals were isoenergetic with the high-fat meals. The meals were heated briefly in the oven before serving. All meals were prepared in 1 batch at the hospital kitchen, and all ingredients were precisely weighed out. Duplicate portions of the high-fat and the low-fat meals were chemically analyzed. The calculated and analyzed nutrient contents are presented in Table 1. Patients who could not eat the whole meal were instructed to eat identical amounts on both days. The breakfast meal was eaten in total by all participants.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Calculated</th>
<th>Analyzed</th>
<th>Calculated</th>
<th>Analyzed</th>
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<td>Fiber, E%</td>
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<td>2.5</td>
<td>1.1</td>
<td>1.3</td>
</tr>
</tbody>
</table>

E% indicates percent of energy from fat.

The lunch meal proved to be too large for most participants. Of the lunch, 2 individuals consumed it all, 7 consumed 75% of it, 14 consumed 50% of it, and 7 consumed only 25% of it.

Blood Sampling

Venous blood samples were drawn at 8:15 AM (fasting), 12:30 PM, 2:00 PM, 3:30 PM, and 4:45 PM after 10 minutes of standardized resting in a chair. Blood samples at 8:15 AM were drawn after at least 10 hours of fasting and nonsmoking and after 24 hours of abstenion from alcohol and strenuous physical activity.

Venous blood samples were collected with minimal stasis by use of siliconized tubes and 21-gauge needles. The first 5 mL was collected in tubes without additives and was used for triglyceride analyses. The following 4.5 mL of blood was collected in 0.5 mL (0.129 mol/L) trisodium citrate and was used for FVII analyses. Finally, 4.5 mL of blood for analysis of F1+2 and soluble fibrin was collected in 0.5 mL (0.47 mol/L) EDTA tubes on ice, to which immediately was added 10 μL Phe-Pro-Arg chromolyl ketone (2.63 mg/mL) to prevent any ex vivo generation of thrombin.

Tubes for triglyceride analysis were allowed to stand at room temperature for 1 hour before serum was separated by centrifugation at 20°C for 20 minutes at 2000g. Citrated tubes were centrifuged at 20°C for 20 minutes at 2000g. Tubes for analysis of F1+2 and soluble fibrin were centrifuged at 4°C for 20 minutes at 2000g. Plasma and serum were pipetted into plastic vials in aliquots of 400 μL and stored at −70°C until analysis. Blood cells from the citrated tubes were used for DNA analyses.

Blood Analyses

Plasma samples were rapidly thawed in a water bath at 37°C and analyzed in 1 series for each subject. Serum triglyceride levels (in millimoles per liter) were determined by a commercial enzymatic method (Boehringer-Mannheim GmbH). Plasma FVIIa was measured in a 1-stage clotting assay (STACLOT VIIa-ETF, Stago) by use of a recombinant truncated TF, which possesses cofactor activity for FVIIa but fails to support activation of single-chain FVII zymogen.29 Coagulation times were converted to FVIIa concentrations (in milliunits per milliliter) by interpolation on a calibration curve prepared from human recombinant FVIIa. FVII:Ag (percentage) was measured by ELISA with use of a rabbit anti-human FVII polyclonal IgG as first and second antibody (Stago). A commercial ELISA (Enzygnost-F1+2, Behringwerke AG) was used to measure concentrations of F1+2 (in millimoles per liter) in plasma. Rabbit anti-human F1+2 IgG was used as first and second antibody. Concentrations of soluble fibrin (in nanograms per milliliter) were assessed by ELISA (Fibrinostika Soluble Fibrin, Organon Teknika GmbH) with use of a murine anti-human monoclonal IgG as first and second antibody.

DNA was isolated from leukocytes by ammonium acetate precipitation and amplified in a polymerase chain reaction. The decanucleotide insertion in the FVII promoter at position −323 (FVII −323ins10 polymorphism) was analyzed as described by De Maat et al.30 In each polymerase chain reaction run, samples with known genotypes were included. As a quality control, we reanalyzed all heterozygotes and 10% of the homozygous samples, and the results were confirmed.
Statistical Analysis
We decided on a sample size of 30 individuals, \(N=[(C_0+C_b)^2] \times SD/D^2\), which was based on \(F1+2\) concentrations. We wanted sufficient power to detect a 0.25-nmol/L difference in \(F1+2\) between diets at a significance level of 5% and a power of 90%. According to a previous study, the population standard deviation of \(F1+2\) is 0.33 nmol/L.\(^3\) Variation over time was analyzed with repeated-measures ANOVA. When significant time effects were found, nonfasting levels were compared with fasting levels by a paired \(t\) test. The postprandial mean was selected as a summary measure, and results of the high-fat and the low-fat diets were compared by a paired \(t\) test. The Pearson correlation coefficient \((r)\) was calculated to describe the association between variables. The distribution of the \(F1+2\) results was skewed, and values were logarithmically transformed before analysis. When significant between-subject effects were observed in the ANOVA, the results were analyzed separately in groups based on FVII genotype or number of atherosclerotic coronary arteries by means of nonparametric statistics (Friedman ANOVA, Wilcoxon signed rank sum test, and Spearman rank correlation coefficient). A value of \(P<0.05\) was considered statistically significant. The SPSS program was used for all the statistical analyses.

Results
There was a marked increase in triglyceride concentrations on the high-fat diet \((P<0.001)\) and only a minor increase on the low-fat diet \((P<0.001)\). Concentrations of FVIIa and FVIIa/FVII:Ag, the specific activity of the FVII protein, increased from fasting levels on the high-fat diet \((P=0.001\) and \(P<0.001\), respectively) and decreased on the low-fat diet \((P<0.01\) and \(P<0.05\), respectively). On both diets, there was a postprandial decrease in FVII:Ag (high-fat diet, \(P=0.06\); low-fat diet, \(P<0.01\)) and \(F1+2\) (high-fat diet, \(P<0.01\), low-fat diet, \(P<0.05\)). No postprandial variation was observed in concentrations of soluble fibrin. Results for triglycerides, FVIIa, and \(F1+2\) are presented in the Figure.

Table 2 presents fasting and postprandial mean values for the variables measured. There were no significant differences in fasting values between diets. Postprandial mean values for triglycerides, FVIIa, FVII:Ag, and FVIIa/FVII:Ag were significantly higher on the high-fat diet than on the low-fat diet. There was no difference between diets for \(F1+2\) and soluble fibrin.

An effect of the FVII genotype was observed for FVIIa and FVII:Ag but not for \(F1+2\) and soluble fibrin. Among our participants, we found 7 carriers and 23 noncarriers of the rare allele of the FVII genotype (P0P0 and P0P10, respectively). Concentrations of FVIIa and FVIIa/FVII:Ag varied during the day as described above for both genotypes, but fasting and nonfasting FVII levels were significantly higher for the P0P0 genotype than for the P0P10 genotype. Fasting FVIIa was 51.9 \(\mu\)mol/mL for P0P0 and 35.5 \(\mu\)mol/mL for P0P10. Fasting FVII:Ag was 124% for P0P10 and 98% for P0P0.

FVII, \(F1+2\), and soluble fibrin concentrations did not differ between patients with atherosclerosis in 1 (n=11) or more (n=19) coronary arteries.

For both diets, there was a highly significant positive association between FVIIa and FVII:Ag for fasting and postprandial mean values. No other significant associations were observed in the whole group of patients. In subgroup analyses, significant associations were observed between postprandial mean values of FVIIa and \(F1+2\) after consumption of the high-fat diet in patients with the P0P0 genotype

\[\text{Fasting (8:15 AM [8.15 hours]) and nonfasting (12:30 PM, 2:00 PM, 3:30 PM, and 4:45 PM [12.30, 14.00, 15.30, and 16.45 hours, respectively]) concentrations of triglycerides, FVIIa, and F1+2 on the low-fat diet (E) and the high-fat diet (O). Values are mean±SEM for triglycerides and FVIIa and geometric mean±SEM for F1+2 (n=30). M indicates meals. Postprandial mean values of triglycerides and FVIIa were significantly higher for the high-fat diet than for the low-fat diet (see Table 2).}\n
\[r^2<0.05, *r^2<0.01, ***r^2<0.001 \text{ compared with fasting values.}\]

Discussion
We have demonstrated that in patients with severe atherosclerosis in \(\geq 2\) coronary arteries, there is a significant postprandial increase in FVIIa after ingestion of a high-fat meal and a significant decrease in FVIIa after ingestion of a low-fat meal. The postprandial increase in FVIIa is not accompanied...
by a detectable increase in thrombin generation (as assessed by F1+2) or fibrin formation (as assessed by soluble fibrin).

Several earlier studies demonstrated postprandial FVII activation after high-fat meals but unchanged or minor decreases in F1+2 in venous blood. These studies have all been conducted in apparently healthy subjects. We hypothesized that FVII activation is more likely to cause detectable thrombin and fibrin formation in individuals with severely atherosclerotic vessels and augmented intimal TF expression.

However, we were unable to confirm our hypothesis. Several explanations can be proposed. First, F1+2 and soluble fibrin are generated locally at the site of TF expression, and these peptides have been strongly diluted at the time they appear in a peripheral venous blood sample. Excessively sensitive methods are thus required unless very extensive coagulation activation is taking place, as seen in certain populations of cancer patients. However, it has been demonstrated that fasting concentrations of F1+2 in venous blood are increased in patients with unstable conditions while possibly did not present TF in adequate amounts for efficient downstream in the coagulation system because of effective inhibition by the TF pathway inhibitor and antithrombin. It is known that patients with ischemic heart disease have increased concentrations of TF pathway inhibitor and that oral fat loads do not seem to affect postprandial TF pathway inhibitor or antithrombin concentrations. Perhaps the postprandial FVII activation did not exceed the inhibitory threshold of the anticoagulant mechanisms in our patients. On the other hand, earlier studies demonstrated that infusion of recombinant FVIIa does lead to higher F1+2 concentrations and that this increase can be prevented by simultaneous infusion of anti-TF antibodies.

Our patients had verified coronary atherosclerosis, but they were in a stable phase of their coronary disease and therefore possibly did not present TF in adequate amounts for efficient formation of active TF-FVIIa complexes. Dietary FVII activation more likely leads to systemically detectable thrombin generation in patients with acute coronary syndromes, eg, unstable angina pectoris and myocardial infarction. These patients have significantly higher concentrations of TF in atherosclerotic plaques, in monocytes, and in plasma, and they also have more coronary lesions, suggesting higher availability of TF for FVII-mediated thrombin formation. This possibility is supported by the finding that patients with unstable coronary artery disease have significantly higher fasting plasma concentrations of F1+2 than do patients with stable coronary artery disease. Therefore, it would be interesting to test the impact of a high-fat meal on F1+2 formation in patients with unstable conditions while withdrawing their heparin treatment. However, for ethical reasons, this seems impossible.

| Table 2: Plasma Levels Before and After Consumption of High-Fat and Low-Fat Meals |
|-----------------------------------------------|------------------|-------------------|
| Variable                                     | High-Fat Meals   | Low-Fat Meals     | P*          |
| Triglycerides, mmol/L                        |                  |                   |
| Fasting                                      | 1.50 (1.32–1.68) | 1.53 (1.31–1.74)  | NS          |
| Postprandial mean                            | 1.80 (1.54–2.06) | 1.55 (1.35–1.75)  | <0.001      |
| FVIIa, nM/mL                                 |                  |                   |
| Fasting                                      | 48.6 (42.7–54.5) | 47.6 (41.9–53.2)  | NS          |
| Postprandial mean                            | 61.0 (53.4–68.6) | 42.9 (38.3–47.4)  | <0.001      |
| FVII:Ag, %                                   |                  |                   |
| Fasting                                      | 117 (100–131)    | 117 (101–133)     | NS          |
| Postprandial mean                            | 114 (97–133)     | 112 (93–130)      | <0.05       |
| FVIIa/FVII:Ag                                |                  |                   |
| Fasting                                      | 0.41 (0.37–0.45) | 0.41 (0.36–0.45)  | NS          |
| Postprandial mean                            | 0.54 (0.48–0.60) | 0.39 (0.35–0.42)  | <0.001      |
| Soluble fibrin, ng/mL                        |                  |                   |
| Fasting                                      | 23.87 (21.39–26.35) | 23.27 (20.94–25.59) | NS          |
| Postprandial mean                            | 23.22 (20.66–25.77) | 22.79 (20.69–24.90) | NS          |
| F1+2, nmol/L                                 |                  |                   |
| Fasting                                      | 1.53 (1.34–1.74) | 1.45 (1.26–1.67)  | NS          |
| Postprandial mean                            | 1.39 (1.23–1.57) | 1.37 (1.21–1.55)  | NS          |

Values are mean (95% CIs) (n=30).

*Difference between response for high-fat and low-fat meals.
†P<0.001 and †P<0.01 vs fasting levels.
§Geometric means and CIs (n=30).

Finally, fat consumption may cause FVII activation but have no effect further downstream in the coagulation system because of effective inhibition by the TF pathway inhibitor and antithrombin. It is known that patients with ischemic heart disease have increased concentrations of TF pathway inhibitor and that oral fat loads do not seem to affect postprandial TF pathway inhibitor or antithrombin concentrations. Perhaps the postprandial FVII activation did not exceed the inhibitory threshold of the anticoagulant mechanisms in our patients. On the other hand, earlier studies demonstrated that infusion of recombinant FVIIa does lead to higher F1+2 concentrations and that this increase can be prevented by simultaneous infusion of anti-TF antibodies. Our patients had verified coronary atherosclerosis, but they were in a stable phase of their coronary disease and therefore possibly did not present TF in adequate amounts for efficient formation of active TF-FVIIa complexes. Dietary FVII activation more likely leads to systemically detectable thrombin generation in patients with acute coronary syndromes, eg, unstable angina pectoris and myocardial infarction. These patients have significantly higher concentrations of TF in atherosclerotic plaques, in monocytes, and in plasma, and they also have more coronary lesions, suggesting higher availability of TF for FVII-mediated thrombin formation. This possibility is supported by the finding that patients with unstable coronary artery disease have significantly higher fasting plasma concentrations of F1+2 than do patients with stable coronary artery disease. Therefore, it would be interesting to test the impact of a high-fat meal on F1+2 formation in patients with unstable conditions while withdrawing their heparin treatment. However, for ethical reasons, this seems impossible.
In the present study, we measured FVIIa with a clot assay, as was the case in all other dietary studies on FVIIa. Recently, an ELISA for FVIIa was developed, and samples from the present study were kindly analyzed by Dr Philippu (Department of Haematology, Imperial College School of Medicine, London, UK). Unfortunately, for some unknown reason, only 9 individuals had FVIIa values above the detection limit of the ELISA (0.01 ng/mL). Therefore, we decided to include only the FVIIa results measured with the clot assay in this presentation. Future studies should investigate the difference between the 2 methods of FVIIa determination.

Kapur et al have suggested that postprandial concentrations of F1+2 are determined by fasting concentrations of FVII:Ag. They found a positive correlation between fasting concentrations of FVII:Ag and nonfasting concentrations of F1+2 in 30 healthy individuals eating a high-fat meal. We could not confirm this positive correlation, and the fact that FVII:Ag, but not F1+2, was significantly affected by the FVII genotype does not speak in favor of such an association.

We observed a positive correlation between postprandial mean values of FVIIa and F1+2 after consumption of the high-fat meals in patients with atherosclerosis in ≥2 coronary arteries. A similar correlation was observed in patients homozygous for the common P0 allele of the FVII −323ins10 polymorphism. This is an interesting observation inasmuch as patients with atherosclerosis in ≥2 arteries are assumed to have the highest TF expression, and patients with the P0P0 genotype have the highest FVII level. However, because postprandial FVII activation in these subgroups is accompanied by a decrease in F1+2, the importance of these observations is doubtful.

In conclusion, we observed that FVII is activated postprandially after high-fat meals in patients with stable angina pectoris and severe atherosclerosis in their coronary arteries. We were unable to demonstrate any accompanying effect on thrombin and fibrin generation in venous blood. These observations seem to challenge the opinion that single high-fat meals are prothrombotic and should be avoided by patients with coronary atherosclerosis. However, it is not possible at this stage to conclude that postprandial FVII activation has no adverse clinical impact, because there may be a local effect at the site of the plaque rupture, particularly in patients with unstable conditions. Therefore, knowing the central biochemical role of FVII in the coagulation system, we still find that coronary patients (in particular those with unstable conditions) should be advised to avoid very high-fat meals to minimize their risk of fatal thrombosis. It should be noted that the present study investigated the immediate effect of single high-fat meals on coagulation activation. Earlier studies demonstrated that longer-term intake of high-fat diets increases FVII:C, FVIIa, and FVII:Ag as well as the risk of reinfarction in patients with a previous myocardial infarction.

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References


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