The association of dietary fat and fiber with coagulation factor VII in the elderly: The Rotterdam Study¹⁻³

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ABSTRACT  Considerable evidence suggests that a high concentration of coagulation factor VII is a risk factor for ischemic heart disease. Factor VII is known to be influenced by dietary fat and probably by dietary fiber in young and middle-aged people. There are no data available in elderly people and the effects of different types of fat are unclear. This study examines the relation of factor VII activity (factor VIIc) with dietary fat and fiber in The Rotterdam Study. The Rotterdam Study is a population-based study among 7983 men and women aged 55 y. Factor VIIc was measured in 5007 subjects (1730 women and 1277 men aged 67.3 ± 7.8 and 66.3 ± 7.0 y, respectively). Measurements included cardiovascular risk factors and habitual diet was assessed by a semiquantitative food-frequency questionnaire. Associations that were significant or nearly significant differed for some nutrients between men and women. Total fat intake showed a direct association with factor VIIc only in women (β = 0.1%/g; 95% CI: 0.01, 0.20). Saturated fat intake was associated with factor VIIc in women (β = 0.18%/g; 95% CI: 0.001, 0.36) and in men (β = 0.11%/g; 95% CI: −0.6, 0.27). Monounsaturated fat was positively related to factor VIIc in women (β = 0.17%/g; 95% CI: −0.05, 0.39) and polyunsaturated fat was inversely associated with factor VIIc in men (β = −0.15%/g; 95% CI: −0.33, 0.03). Fiber intake was inversely associated with factor VIIc in both men (β = −0.31%/g; 95% CI: −0.57, −0.06) and women (β = −0.36%/g; 95% CI: −0.63, −0.09). No associations were found for energy intake. In elderly persons, factor VIIc is associated with fat and fiber intake. This suggests that factor VIIc is influenced by nutritional factors, even in old age. Am J Clin Nutr 1997; 65:732-6.

KEY WORDS  Factor VII, dietary fat, dietary fiber, elderly persons, thrombosis, atherosclerosis, coagulation, cardiovascular disease

INTRODUCTION

Factor VII is one of the coagulation factors of the extrinsic pathway of the coagulation cascade. This pathway is activated during vascular injury, which results in the rapid formation of a blood clot. A high concentration of factor VII contributes to a high thrombotic tendency. In the presence of atherosclerosis, this tendency may be a trigger for a cardiovascular event. Atherosclerosis is common in elderly people, reflecting development over many years. The effects of thrombosis, however, are acute and subject to change even at older ages. Increased thrombotic tendency in elderly persons constitutes an elevated risk for cardiovascular disease and considerable evidence indeed suggests that factor VII coagulant activity (factor VIIc) is a major contributor (1, 2). In the Northwick Park Heart Study (n = 1511) factor VII was found to be a risk factor for ischemic heart disease (1), and in the PROCAM study (n = 10 581) this seemed to be the case only when fatal events were taken into account (2).

Two nutritional factors, dietary fat and fiber, are considered major environmental determinants of factor VIIc. From several intervention studies among young adults it is known that factor VIIc depends on dietary fat intake (3–8). A high-fat diet results in high factor VIIc concentrations and after a fatty meal postprandial factor VIIc rises concomitantly with the rise in triacylglycerols (3–5, 8). These changes in factor VIIc are believed to be independent of the type of fat consumed (6, 7). The results from three observational studies among middle-aged men, however, are inconsistent (6, 9, 10). Connelly et al (10) and Miller et al (6) observed an association between factor VIIc and dietary fat whereas Rankinen et al (9) did not.

Three crossover trials in young and middle-aged subjects showed a decrease in factor VIIc after a high-fiber diet (11–13). An association between dietary fiber and factor VIIc was also observed in one cross-sectional study (9). No other nutrients have been consistently found to be associated with factor VIIc (6, 8).

To our knowledge, there are no published data on factor VIIc and dietary factors in elderly people. It is important to know whether the association of factor VIIc with dietary factors also exists at an age when most cardiovascular events occur. Because the level of factor VIIc directly influences the thrombotic
tendency, in the presence of atherosclerosis it may determine whether a cardiovascular event is triggered. We studied the relation between factor VIIc and dietary fat and fiber in The Rotterdam Study.

SUBJECTS AND METHODS

Population
The Rotterdam Study is a single-center, population-based prospective cohort study of 793 persons. All inhabitants ≥ 55 years from a suburb of Rotterdam were asked to participate in the study, which resulted in a response rate of 78%. In short, the objective of the study is to clarify the determinants of occurrence of chronic disabling cardiovascular, neurorefractory, locomotor, and ophthalmologic diseases. The rationale and design of The Rotterdam Study were published elsewhere (14).

Dietary data were collected for 5435 persons and study subjects were excluded for the following reasons: myocardial infarction in the year before the investigation (n = 574), diabetes mellitus (n = 779), use of anticoagulants (n = 1349), stasis during venipuncture (n = 1513), and no blood sample available (n = 933). Because some subjects were excluded for multiple reasons, a total of 4976 were not eligible for this study. The present analysis is thus based on cross-sectionally obtained data for 3007 subjects.

Examination procedures
The participants came to the research center at varying times during the day. At the research center a brief clinical examination was performed and height and weight were measured. Body mass index was determined by dividing the weight (kg) by height (m) squared. Blood pressure, with the subject in a sitting position, was measured on the right arm by using a random zero sphygmomanometer. The participants were not asked to refrain from smoking or physical exercise and nonfasting blood samples were taken by using a 21-gauge butterfly needle after no or minimal stasis.

Dietary assessment
The habitual diet was assessed by a semiquantitative food-frequency questionnaire. The questionnaire was a modification of a validated self-administered mailed semiquantitative food-frequency questionnaire that was used previously in a large-scale prospective cohort study involving a younger population. Measures of the validity and repeatability of the original questionnaire for several nutrients have been reported (15, 16). The questionnaire was adapted to allow an easy and time-efficient dietary assessment in an older population. Modification consisted mainly of inclusion of additional items (ice cream, corn flakes, and linseed); collection of more detailed information on vegetable, fruit, and meat consumption; and a different mode of administration, which was undertaken in two consecutive phases. The modified questionnaire contains 170 food items in 13 food groups and general questions about dietary habits. Its aim is to assess habitual food intake during the past year.

In the first phase a self-administered questionnaire was handed out and explained to each participant by trained research assistants during a home visit. Participants had to mark the foods that they consumed at least once a month. Also, the amounts of several foods they used were weighed and the content of cups and bowls was measured. In the second phase a dietary interview was conducted by trained dietitians on the basis of the already completed dietary questionnaire. During the dietary interview the dietitians concentrated on obtaining accurate information on amount and frequency of food items noted by participants as being consumed at least once a month. General questions to check the consistency of the completed dietary questionnaire were asked. The modified questionnaire was validated by comparison with multiple food records. The correlation coefficients were corrected for within-person variation in food records and adjusted for age, sex, and energy intake. For the different types of fat and fiber they varied between 0.50 and 0.65 (Klipstein et al, unpublished observations, 1994).

All data were entered into a self-made interactive computer program, which included automatic checks for inconsistencies in the answers of the participant. A computer application was developed to calculate the frequency and amounts of foods consumed. Questionnaires were checked for completeness by an interactive data entry program and automatically coded for later conversion into nutrients. The program checked further for consistency, range, and other response errors. The conversion from foods to energy and nutrient intakes was done with a computerized version of the Dutch Food Composition Table (17) and percentages of total energy delivered by macronutrients were calculated.

Laboratory measurements
Samples were collected into siliconized evacuated tubes containing 0.129 mol sodium citrate/L (Becton Dickinson, Meylan, France). Samples were centrifuged for 10 min at 1600 × g and 4 °C. Citrated plasma was snap frozen and stored at −80 °C until analyzed. Factor VIIc was measured with a one-stage clotting assay by using human thromboplastin (Tromborel S. Behringwerke, Germany) and factor VII-deficient plasma (Ortho Diagnostic System, Beersel, Belgium). This assay measures the activity of the sample to correct the clotting time of human factor VII-deficient plasma. The plasma concentrations were then expressed as percentage activity by relating the clotting time to a calibration curve constructed of a standardized control plasma. As a control, the pooled plasma of 50 healthy middle-aged persons was used and three control samples were run with each batch of study samples. The CV is 7.3% for this method. Serum total cholesterol was determined by using an automated enzymatic procedure (16). High-density-lipoprotein (HDL)-cholesterol concentration was measured similarly after precipitation.

Data analysis
The association of factor VIIc with dietary factors was examined by multiple-linear-regression analysis, using the BMDP statistical package (19). In the analysis, both total weight and percentage of energy of macronutrients were used. Adjustments were made for age and when nutrients in grams were used in the analysis, adjustment for energy intake was made by including total kilojoules as an independent variable in the regression model. In some models we included additional nutrients when appropriate.
RESULTS

General characteristics of the study population are presented in Table 1. Mean age was 66.3 y in men and 67.3 y in women. Mean factor VIIc was 108.0% in men and 120.4% in women. Energy and nutrient intakes from the subjects’ habitual diet are shown in Table 2. Mean energy intake was 9546 KJ in men and 7515 KJ in women.

The coefficients and 95% CIs of regression analysis with factor VIIc as the dependent variable and nutrient intake as the independent variable are shown in Table 3. Total fat intake showed a direct association with factor VIIc only in women. Saturated fat intake was associated with factor VIIc in women; in men the association was smaller. Monounsaturated fat was positively related to factor VIIc in women and polyunsaturated fat was inversely associated with factor VIIc in men. In general, the results were the same when calculated for the percentage of energy delivered by the nutrient as for the absolute intake.

Furthermore, total cholesterol intake was associated with factor VIIc in men and women, but when saturated fat was included in the regression model the regression coefficients of cholesterol were smaller. Fiber intake was inversely associated with factor VIIc in both men and women. When this association was adjusted for total, saturated, or polyunsaturated fat the results did not change. No associations were found with energy intake.

DISCUSSION

We investigated associations of several nutrients with factor VIIc among 3007 elderly persons. Associations that were significant or nearly significant differed for some nutrients between men and women. Plasma factor VIIc levels were associated with cholesterol and fiber intake in both women and men. Also, an association was observed between factor VIIc and saturated fat intake, which was stronger in women than in men. Furthermore, factor VIIc was related to total and monounsaturated fat in women and to polyunsaturated fat in men. Energy intake was not associated with factor VIIc.

Factor VII activation was determined by a one-stage clotting assay, a method that is commonly used in other studies (1, 2). Although determination of factor VII with an improved method (factor VIIa; 20) may have been preferable, this measurement was not in use at the start of our study in 1991. Furthermore, in this study, blood samples were collected from subjects in a nonfasting state. However, when we adjusted the associations for the time since the last meal, the results did not change.

There have been several intervention studies that compared the effect of saturated and unsaturated fat on factor VIIc (4, 7, 21, 22). In a crossover trial among 21 male and 17 female subjects a diet rich in mono- or polyunsaturated fat was consumed for 23 d, and no change in factor VIIc was found for either diet (21). Another crossover trial among 11 young adults, in which two low-fat diets were given, showed a similar decrease in factor VIIc after a diet with mainly saturated fat compared with a diet with mainly unsaturated fat (7). Also, there was no difference in postprandial levels of factor VIIc after a meal with high saturated fat or a meal with high polyunsaturated fat (4, 22). The results of these studies suggest that factor VIIc decreases with a low-fat diet, irrespective of the type of fat.

In two cross-sectional studies in middle-aged men, a positive association of factor VIIc with dietary fat was also observed (6, 8, 10), but nothing was reported for associations of factor VIIc with different types of fat.

The results of the trials mentioned above showed positive associations of factor VIIc with all fat types. This is not in line with the results of our study. In those trials however, saturated and unsaturated fats were fully exchanged in the different diets to get a high contrast between the fat types. This results in an unnaturally high intake of unsaturated fat; the intake of unsaturated fat in an ordinary Western diet is much lower (21, 7). Because data on habitual diet were used in our study, the intake of unsaturated fat may have been too low to uncover a positive association with factor VIIc.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Women (n = 1730)</th>
<th>Men (n = 1277)</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td>67.3 ± 7.8</td>
<td>66.3 ± 7.0</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>6.9 ± 1.2</td>
<td>6.4 ± 1.2</td>
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<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.5 ± 0.4</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>137.6 ± 21.6</td>
<td>137.5 ± 21.1</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>72.9 ± 10.8</td>
<td>75.3 ± 11.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.6 ± 4.0</td>
<td>25.8 ± 2.8</td>
</tr>
<tr>
<td>Factor VIIc (% of standard)</td>
<td>120.4 ± 24.3</td>
<td>108.0 ± 22.5</td>
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<tr>
<td>Smoking (%)</td>
<td></td>
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<tr>
<td>Current</td>
<td>19.1</td>
<td>24.6</td>
</tr>
<tr>
<td>Former</td>
<td>28.8</td>
<td>58.6</td>
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<tr>
<td>Never</td>
<td>52.1</td>
<td>16.8</td>
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\( \bar{x} \pm SD \).
The results of our study showed some differences between men and women, but this was mainly restricted to mono- and polyunsaturated fats. The lack of association between factor VIIc and total fat in men may be a consequence of the inverse association of polyunsaturated fat with factor VIIc in men, whereas in women monounsaturated fat was positively associated with factor VIIc. We have no other explanations for the differences in men and women.

In agreement with three intervention studies and one cross-sectional study in middle-aged subjects, our cross-sectional study (9, 11–13) showed an inverse association of factor VIIc with fiber intake in elderly people; an increase of fiber intake of 10 g would result in a decrease of factor VIIc of 3.6% in women and 3.1% in men. Such an increase would raise the mean fiber intake toward that recommended by the Dutch Nutrition Council (23).

The study conducted here was cross-sectional. The results show an association between factor VIIc and dietary factors, but no definite conclusions can be made on a causal relation. Two mechanisms have been proposed to explain a causal relation between factor VIIc and dietary fat (24, 25). One mechanism is based on decreased catabolism of factor VII through binding of factor VII protein to triacylglycerol-rich lipoproteins (24). The second is based on activation of factor VII by negatively charged surfaces, which occurs during lipolysis of lipoproteins (25).

The mechanism to explain an association of factor VIIc with fiber is unknown so far. A high fiber intake may be a marker of a healthy diet or even of a healthy lifestyle. Another option is the lowering effect of fiber on blood cholesterol (26), which in turn might have an effect on factor VII (27). Intervention studies that confirm the specific effect of fiber intake on factor VII are needed to disentangle direct and indirect effects.

A high factor VII concentration increases the thrombotic tendency, which may be a trigger for cardiovascular events. If factor VII can be lowered, a cardiovascular event might be postponed or even prevented. Because factor VII influences the thrombotic tendency directly, even at older ages, lowering of factor VIIc may be of public health importance. The results from this study suggest that factor VIIc may be affected by a low-fat or high-fiber diet, or both at older ages. Intervention studies are needed to further support the preventive potential of changes in diet through this mechanism.

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