Dietary oleic and palmitic acids and postprandial factor VII in middle-aged men heterozygous and homozygous for factor VII *R353Q* polymorphism[1–3]

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ABSTRACT

Background: The *R353Q* genotype is a major determinant of factor VII coagulant (FVIIc) activity, which is associated with an increased risk of ischemic heart disease (IHD) and elevated plasma triacylglycerol concentrations.

Objective: The objectives were to *1*) compare the effects of meals rich in palmitate or oleate with those of a meal low in fat on FVIIc in subjects with moderately elevated plasma nonfasting triacylglycerol concentrations and *2*) determine whether the postprandial increase in FVIIc induced by dietary oleate differs in carriers of the *Q* allele.

Design: Fifty-two men aged >52 y with nonfasting plasma triacylglycerol concentrations between 2 and 5.5 mmol/L were randomly assigned to receive isoenergetic (5.1 MJ) meals providing 50 g high-oleate or high-palmitate oils or a low-fat meal providing 15 g high-oleate oil. In a second study, 17 men aged >52 y who were heterozygous for factor VII *R353Q* polymorphism were age-matched with subjects homozygous for the *R* allele and their responses to a 50-g, high-oleate meal were measured.

Results: FVIIc decreased by 11% after the low-fat meal. FVIIc increased by 9% and FVIIa (the activated form of FVII) increased by 55% after the high-oleate meal, whereas FVIIc did not change but FVIIa increased by 25% after the high-palmitate meal. Fasting FVIIc and FVIIa concentrations were 24% and 48% lower, respectively, in men with the *RQ* genotype than in men with the *RR* genotype but increased postprandially in both groups with no evidence of a genotype interaction.

Conclusions: A high-fat meal rich in oleate increases FVIIa, whereas a low-fat meal does not, in men at high risk of IHD, independent of *R353Q* genotype. *Am J Clin Nutr* 1999;69:220–5.

KEY WORDS Factor VII, palmitic acid**,** postprandial lipemia, *R353Q*, oleic acid, men, Northwick Park Heart Study, ischemic heart disease, coagulation

INTRODUCTION

Elevated factor VII coagulant (FVIIc) activity is believed to indicate a hypercoagulable state predisposing to coronary thrombosis in subjects with extensive atherosclerosis (1, 2). FVIIc is a functional assay of factor VII activity that depends on the concentration of the proenzyme, which can be measured as antigen (FVIIag), and the proportion of FVII circulating in the activated form (FVIIa). FVIIc is positively associated with plasma triacylglycerol concentrations (3, 4) and habitual dietary fat intakes (5, 6) and was shown to rise 3–7 h after the consumption of a meal rich in long-chain fatty acids (7–16). Acute feeding studies have generally found no clear difference between the effects of saturated and monounsaturated fatty acids on postprandial activation of factor VII. However, oils rich in oleic acid lead to a reproducible increase in FVIIc and FVIIa in subjects with normal plasma triacylglycerol concentrations (12, 16). The importance of dietary fat intakes in determining FVIIc is questionable because most acute feeding studies used very high intakes of fat to induce changes in FVIIc and most were carried out in healthy, young subjects at low risk of coronary thrombosis. Some studies suggest that genetic variation may have a greater effect on FVIIc than does dietary fat intake (17, 18). About one-third of the variance in FVIIc can be explained by *R353Q* polymorphism, a guanine-to-adenine substitution in the codon for amino acid 353 resulting in the replacement of arginine (*R*) by glutamine (*Q*) in the FVII protein. About 20% of Europeans are carriers for the allele coding the Q353 protein (19). It is uncertain whether subjects with the *Q* allele differ with regard to their response to dietary fat.

FVIIc increases with age (20) and may be related to the age-related increase (21) in nonfasting plasma triacylglycerol concentrations. Older individuals with elevated nonfasting triacylglycerol concentrations may, therefore, be more sensitive to the acute effects of dietary fat on FVIIc. To test this hypothesis, the postprandial effects of meals containing moderate amounts of fat, provided either by an oil enriched with palmitic acid or one

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enriched with oleic acid, were compared with the effects of a low-fat meal on FVIIc and FVIIa in healthy, older men with moderately elevated nonfasting triacylglycerol concentrations. Because it is uncertain whether *R353Q* polymorphism influences the response to dietary fat, postprandial responses were compared according to *R353Q* genotype. A second study was subsequently carried out to compare the postprandial responses to a high-oleate test meal in subjects heterozygous for the *Q* allele and age-matched subjects homozygous for the *R* allele.

SUBJECTS AND METHODS

Subjects

The protocol was reviewed and approved by the Human Experimentation Committees of King's College London and the Hertfordshire Health Authority and all participants gave informed written consent before the study began. All subjects were men and had been recruited into the ongoing second Northwick Park Heart Study (NPHS-II) (1). Exclusion criteria for the NPHS-II are clinical history of myocardial infarction, unstable angina, stroke, cardiac surgery, life-threatening malignancy or other disease, aspirin or anticoagulant therapy, any known condition that would make blood sample handling more hazardous (eg, HIV infection or hepatitis), or inability to give informed consent or attend for annual reexamination. Subjects in the NPHS-II are examined annually. Those with morning appointments are requested to avoid a cooked breakfast and more than one cup of tea or coffee beforehand. Those with a later appointment are asked to defer their main meal until after the examination and, if needed, to eat only a light meal beforehand with no more than one cup of tea or coffee.

In the first study, men were selected on the basis of their nonfasting plasma triacylglycerol concentrations (2.0–5.5 mmol/L) and had to be > 52 y of age; subjects who were known to consume a high amount of alcohol were excluded. Nonfasting plasma triacylglycerol concentrations were extracted from annual screening records of the NPHS-II. In the second study, subjects were selected on the basis of their FVII *R353Q* genotype. All subjects enrolled in the NPHS-II in the general practice (ie, the subjects' primary health care center) used in the first study were screened for *R353Q* genotype. Subjects > 52 y of age with the *RQ* genotype were aged-matched to subjects with the *RR* genotype. Background medication, blood pressure, nonfasting plasma triacylglycerol and cholesterol concentrations, and body mass index (BMI; in kg/m^2) were extracted from records of the subjects' annual examination in the NPHS-II. No attempt was made to control for aspirin use; however, it has been shown that aspirin consumption does not affect the postprandial increase in FVIIc induced by dietary fat (21). Mean (±SD) systolic and diastolic blood pressures of the entire NPHS-II cohort at the time of the present study were 138.2 ± 19.2 and 84.5 ± 11.4 mm Hg, respectively; mean values of the subjects in the present study at their annual examination were comparable: 137.4 ± 21.1 and 84.9 ± 11.6 mm Hg, respectively. Subjects were invited by letter to take part in the study and received no remuneration.

Subjects were advised to avoid consumption of foods high in fat from 2200 on the day preceding the test meal because studies have shown that a high fat content in preceding meals can influence the composition of triacylglycerol-rich lipoproteins after a test meal (22). Subjects were given a list of foods to avoid. The morning after the fast, a venous blood sample was taken in the clinic of the general practice for determination of clotting factors and plasma triacylglycerol concentrations. The subjects then consumed the test meal within 20 min. Additional venous blood samples were obtained 3 and 6 h postprandially. After the 3-h postprandial venous sample was taken, the subjects were given a low-fat lunch: a fat-free yogurt and a piece of fruit. Subjects were advised to avoid any strenuous activity throughout the study period, but were allowed to leave the clinic to return home or to work between blood samplings.

Pilot study

A pilot study was carried out to determine a suitable and realistic fat load and the acceptability of the proposed test meal in a community setting. Nine men were randomly allocated into 3 groups to receive a 40-, 50-, or 60-g fat load in isoenergetic meals (5.1 MJ, 38 g protein, and 8 g fiber) that consisted of a muffin and a milkshake. The fat was provided by a high–oleic acid sunflower oil, and a polydextrose solution (Polycal; Cow & Gate, Trowbridge, Wiltshire, United Kingdom) was used to replace the energy provided by fat. All meals were well tolerated by the subjects. Plasma triacylglycerol concentrations increased significantly ($P < 0.01$) from fasting by 65%, 124%, and 139% 3 h after the 40-, 50-, and 60-g fat meals. FVIIa increased significantly ($P < 0.01$) from the fasting value from an average 1.5 μg/L to 2.2 μg/L 3 h after and to 2.4 μg/L 6 h after the test meals ($P < 0.01$), FVIIc increased from 114% to 117% 3 h after and 118% 6 h (NS) after the test meal. Consequently, a 50-g test meal was selected for further studies because it had led to significant lipemia, is an amount typically found in many main meals, and is similar to the proportion of energy found in the typical British diet (23). No attempt to adjust meal size according to body weight and estimated energy expenditure was made because, in practice, individuals consume standard portions, not carefully titrated amounts, of food.

Test meals

In the first study, the effects of high-palmitate and high-oleate meals were compared with the effects of a low-fat meal in subjects randomly allocated into 3 groups of 18 subjects. Subjects were recruited into the study so that a similar number of subjects in each treatment group was studied concurrently. A crossover design would have had greater statistical power; however, our experience suggested that working subjects would be unwilling to take several days off for the study, so a randomized controlled study was chosen instead. In the second study, subjects identified as having the *RQ* genotype and their *RR* age-matched control subjects received the high-oleate test meal.

The test meals were isoenergetic and details of their composition are shown in **Table 1**. The test meal ingredients were vegetable oil, wheat flour, wheat bran, sugar, skim milk, pasteurized egg whites, vanilla essence, baking powder, and polydextrose solution. The nutrient composition of the meal was calculated from information provided by the manufacturers of the ingredients or from food tables. The fatty acid composition of the test meals was confirmed by gas-liquid chromatography of the fatty acid methyl esters (13). The high-fat test meals used for this purpose were designed to be similar in all respects, except for the saturated and monounsaturated fatty acid contents. Particular care was taken to ensure that the proportion of linoleic acid was similar. The oils used in this study had high–oleic acid sunflower

TABLE 1
Nutrient composition of the test meals

	Test meal		
	Low-fat	High-oleate	High-palmitate
Energy (MJ)	5.1	5.1	5.1
Protein (% of energy)	12	12	12
Carbohydrate (% of energy)	77	51	51
Fat (% of energy)	11	37	37
Fiber (g)	8	8	8
Fat (g)	15	50	50
Palmitic acid (g)	0.6	2	22
Stearic acid (g)	0.6	2	2
Oleic acid (g)	11.9	40	20
Linoleic acid (g)	1.4	5	5

oil and high palm oil contents and were supplied by Unilever (Vlaardingen, Holland). The oil in the low-fat meal was supplied by the high–oleic acid sunflower oil, and the polydextrose solution was used to replace the energy provided by fat. Palm oil was used as a source of palmitic acid because it is the richest dietary source of this fatty acid.

Blood sampling and analytic methods

Venous blood samples were collected into evacuated tubes with as minimal compression as necessary to display the vein. The first 4.5 mL blood was drawn into a tube containing EDTA, and plasma was separated by centrifugation at 4 °C for 15 min and stored at 4 °C for determination of triacylglycerols within 48 h. For determination of FVII, blood was collected into 0.5 mL of 38 g trisodium citrate solution/L at room temperature and centrifuged at 20 °C at 1000 × *g* for 15 min. The plasma was portioned into sealable polypropylene tubes and stored at −40 °C until transferred to the laboratory.

DNA was isolated from white blood cells and amplified by polymerase chain reaction, and *R353Q* genotype was determined as described previously (17). Plasma triacylglycerol was determined by enzymatic assay (GPO-PAP; Boehringer Mannheim, Lewes, United Kingdom). FVIIc activity was measured by a one-stage, semiautomated bioassay by using rabbit-brain thromboplastin (Diagen; Thame, Oxon, United Kingdom) and an FVII-deficient substrate plasma prepared as described elsewhere (24). FVIIa was measured according to the bioassay method described by Morrissey et al (25). All hemostatic assays were carried out on samples stored at −70 °C by the coagulation laboratory at the MRC Epidemiology and Medical Care Unit. Samples for each subject were analyzed in the same run to minimize between-assay variation. The within-run and between-run CVs were 3.2% and 5.6% for FVIIc and 11.3% and 17.7% for FVIIa, respectively. The standard used for FVIIc was a human, frozen, plasma pool calibrated in terms of the 1st International Standard for Blood Coagulation Factors II, VII, IX, and X in Plasma (code no. 84/665). The standard used for FVIIa was one supplied by J Morrissey from the Oklahoma Medical Research Foundation. This standard was calibrated against active site-titrated FVIIa to determine the actual FVIIa concentration and against the 1st British Standard for Blood Coagulation Factor VIIa Concentrate, Human (5.130 IU/ampoule, code no. 89/688).

TABLE 2
Age, BMI, nonfasting plasma cholesterol and triacylglycerol concentrations, and *R353Q* genotype of the subjects given different test meals[1]

	Test meal		
	Low-fat (n = 16)	High-oleate (n = 18)	High-palmitate (n = 18)
Age (y)	59 ± 3.7	59 ± 3.7	61 ± 4
Plasma triacylglycerol (mmol/L)	2.7 ± 0.7	2.7 ± 0.9	3.1 ± 1.1
BMI (kg/m^2)	27.4 ± 3.6	26.7 ± 3.6	27.4 ± 2.7
Plasma cholesterol (mmol/L)	6.2 ± 1.2	6.1 ± 1	6.5 ± 0.8
R353Q genotype (n)			
RR	13	14	14
RQ	3	2	3
QQ	0	2	1

[1]There were no significant differences between groups.
[2]$\bar{x}$ ± SD.

Statistical analyses

In the first study, results were obtained for 16 men after the low-fat meal, 18 after the high-oleate meal, and 18 after the high-palmitate meal. In the second study, results were obtained for 17 subjects with the *RQ* genotype and 17 age-matched control subjects with the *RR* genotype after the high-oleate meal. Data were analyzed by repeated-measures analysis of variance with the SPSS/PC package 7.5 (SPSS Inc, Chicago) with meal type and genotype as between-subject factors. When the overall F test for the times effect or meal × times interaction was significant ($P < 0.05$), comparisons between meals were made with a two-sample t test with Bonferroni's correction for multiple comparisons. Comparisons between different time points were made by using the repeated-measures analysis of variance and Bonferroni's multiple comparison test using PRISM version 2.01 (GraphPad Software, San Diego). Both studies had statistical power to detect a change of 1 SD unit in the variables under consideration at $P < 0.05$ with 80% power.

RESULTS

The 3 test groups were well matched with regard to age, BMI, nonfasting plasma cholesterol and triacylglycerol concentrations, and *R353Q* genotype (**Table 2**). Fasting plasma triacylglycerol concentrations were similar in all 3 groups (**Table 3**). Analysis of variance revealed a significant meal × time interaction for plasma triacylglycerol ($P < 0.001$). Plasma triacylglycerol concentrations increased 3 h after the high-oleate and high-palmitate meals and then declined between 3 and 6 h postprandially ($P < 0.001$), the 6-h value being higher than the fasting value after the high-oleate meal ($P < 0.01$). The percentage increase from fasting in plasma triacylglycerol at 3 h was similar after both the high-oleate and high-palmitate meals and was significantly different from the low-fat meal.

There was a significant meal × time interaction for FVIIc ($P = 0.001$); when the *R353Q* genotype was entered as an additional factor into the analysis, this effect was reduced to $P = 0.006$. Although fasting FVIIc was slightly lower in the high-oleate group, there was no significant difference in fasting values between groups. To confirm that the differences between meals were significant, a repeated-measure analysis of variance using the fasting value as the covariate was conducted. This gave a significant meal effect ($P < 0.002$) with no significant effect of postprandial times; when *R353Q* genotype was entered as a factor in the analysis, the meal effect was still highly significant ($P < 0.005$). FVIIc fell from the fasting value after the low-fat

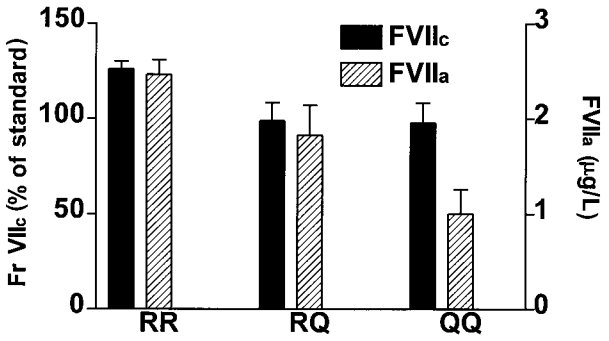

FIGURE 1. Mean (±SEM) fasting factor VII coagulant (FVIIc) activity and activated FVII (FVIIa) concentrations in moderately hypertriglyceridemic men according to *R353Q* polymorphism (*RR* genotype: $n = 41$; *RQ* genotype: $n = 8$; *QQ* genotype: $n = 3$).

meal, increased after the high-oleate meal, but remained stable after the high-palmitate meal (Table 3). The 6-h value was significantly lower ($P < 0.01$) than the fasting value after the low-fat meal. After the high-oleate meal, the 6-h value was significantly greater ($P < 0.05$) than the fasting value. The percentage change in FVIIc from fasting was calculated 3 and 6 h postprandially and compared between groups. The change in FVIIc 3 and 6 h after the high-oleate meal ($P = 0.006$ and $P < 0.001$) and 6 h after the high-palmitate meal was significantly different ($P = 0.045$) from corresponding values after the low-fat meal. The statistical analyses for FVIIa showed a strong time effect ($P = 0.001$) and a time × meal interaction ($P = 0.045$). Fasting FVIIa concentrations did not differ significantly between meals or with time after the low-fat meal. FVIIa rose by 55% and 48% 3 and 6 h after the high-oleate meal, respectively (both $P < 0.001$). FVIIa rose by 25% 3 h after ($P < 0.05$) and by 18% 6 h after (NS) the high-palmitate meal. The increase in FVIIa 3 h after the low-fat meal was significantly different from that after the high-oleate meal ($P = 0.009$).

TABLE 3
Plasma triacylglycerol concentration, factor VII coagulant (FVIIc) activity, and activated FVII (FVIIa) concentration in moderately hypertriglyceridemic men after different test meals[1]

	Test meal		
	Low-fat ($n = 16$)	High-oleate ($n = 18$)	High-palmitate ($n = 18$)
Plasma triacylglycerol (mmol/L)			
Fasting	1.71 ± 0.169	1.91 ± 0.138[a]	2.15 ± 0.117[a]
3 h Postprandial	1.86 ± 0.176	3.46 ± 0.215[c,2]	3.62 ± 0.220[b,2]
6 h Postprandial	1.96 ± 0.194	2.37 ± 0.222[b]	2.45 ± 0.129[a]
Percentage change at 3 h (%)	10.9 ± 4.4	88.9 ± 12.8[2]	70.2 ± 7.2[2]
Percentage change at 6 h (%)	19.7 ± 8.4	22.9 ± 5.5	16.1 ± 5.0
FVIIc (% of standard)			
Fasting	123 ± 7.6[a]	116 ± 5.8[a]	123 ± 6.7
3 h Postprandial	117 ± 7.9[a,b]	124 ± 5.8[a,b]	123 ± 7.1
6 h Postprandial	112 ± 7.3[b]	126 ± 7.6[b]	122 ± 6.5
Percentage change from fasting at 3h (%)	−5.5 ± 2.3	8.4 ± 3.2[2]	0.7 ± 3.3
Percentage change from fasting at 6h (%)	−9.2 ± 3.1	8.8 ± 3.4[2]	0.3 ± 2.1[3]
FVIIa (μg/L)			
Fasting	2.1 ± 0.24	2.3 ± 0.24[a]	2.4 ± 0.26[a]
3 h Postprandial	2.3 ± 0.34	3.4 ± 0.26[b]	3.0 ± 0.35[b]
6 h Postprandial	2.4 ± 0.43	3.3 ± 0.30[b]	2.8 ± 0.33[a,b]
Percentage change from fasting at 3 h (%)	11.7 ± 9.55	54.7 ± 9.30[2]	25.4 ± 8.91
Percentage change from fasting at 6 h (%)	13.4 ± 12.34	48.2 ± 10.54	18.3 ± 9.21

[1] $\bar{x}$ ± SEM. Values in the same column with different superscript letters are significantly different, $P < 0.05$.
[2, 3] Significantly different from the low-fat meal: [2] $P < 0.01$, [3] $P < 0.05$.

TABLE 4
Age, BMI, and nonfasting plasma cholesterol and triacylglycerol concentrations in 17 subjects with the *RQ* genotype for factor VII *R353Q* polymorphism and aged-matched control subjects with the *RR* genotype[1]

	R353Q genotype	
	RR ($n = 17$)	*RQ* ($n = 17$)
Age (y)	57 ± 2.4	57 ± 2.9
BMI (kg/m^2)	24.5 ± 2.82	25.8 ± 3.15
Plasma cholesterol (mmol/L)	5.9 ± 0.74	5.8 ± 1.04
Plasma triacylglycerol (mmol/L)	1.5 ± 0.69	1.6 ± 0.89

[1] $\bar{x}$ ± SD. There were no significant differences between groups.

Of the 52 subjects in the first study, 41, 8, and 3 subjects had *RR*, *RQ*, and *QQ* genotypes, respectively. Fasting FVIIc activity and FVIIa concentrations were much lower ($P = 0.002$ and $P = 0.013$) in subjects carrying the *Q* allele, being lowest in the group with the *QQ* genotype (**Figure 1**). FVIIa increased by 54% and 51%, respectively, 3 and 6 h after the high-oleate meal in the 14 subjects with the *RR* genotype and by 59% and 38%, respectively, in the 4 subjects with one or more *Q* allele; these differences were not significant. To test whether the *R353Q* genotype influenced the postprandial response of FVIIc and FVIIa to dietary fat, 17 men with the *RQ* genotype and 17 age-matched subjects with the *RR* genotype were recruited and given a 50-g oleate test meal. The ages, BMIs, and nonfasting plasma cholesterol and triacylglycerol concentrations of the subjects are shown in **Table 4**. As expected, overall plasma triacylglycerol concentrations increased from fasting values but there was no significant difference in this pattern between genotypes (**Table 5**). There were time ($P = 0.056$) and genotype ($P = 0.004$) effects on FVIIc but no genotype × time interaction ($P = 0.98$). FVIIc was significantly lower in men with the *RQ* genotype at all time points ($P < 0.01$). There was a significant time ($P < 0.001$) and genotype ($P < 0.01$) effect on FVIIa, which was significantly lower in the heterozygotes at all times. FVIIa increased significantly from fasting values 3 and 6 h after the high-oleate meal (both $P < 0.001$).

DISCUSSION

The aims of this study were to *1*) test the hypothesis that older men with moderately elevated nonfasting triacylglycerol concentrations would be more sensitive to the effects of dietary fat on FVIIc and FVIIa and *2*) test whether this was influenced by *R353Q* genotype. The subjects in the present study were older, had a higher BMI, and had a higher plasma cholesterol concentration than subjects in the previous controlled feeding studies and they belonged to a group with a substantial risk of fatal myocardial infarction. Furthermore, the study was conducted in a community setting on a randomly selected sample from a cohort of the NPHS-II. Previous studies describing the effect of

TABLE 5
Plasma triacylglycerol concentration, factor VII coagulant (FVIIc) activity and activated FVII concentration (FVIIa) after following a high-oleate test meal in men with the *RQ* genotype compared with age-matched control subjects with the *RR* genotype[1]

	RQ (n = 17)	RR (n = 17)
Plasma triacylglycerol (mmol/L)		
Fasting	1.5 ± 0.16[a]	1.3 ± 0.15[a]
3 h Postprandial	2.3 ± 0.23[c]	2.3 ± 0.28[b]
6 h Postprandial	1.9 ± 0.19[b]	1.5 ± 0.14[a,b]
Percentage change at 3 h(%)	66 ± 12.0	72 ± 14.9
Percentage change at 6 h (%)	38 ± 10.1	23 ± 7.4
FVIIc (% of standard)		
Fasting	93 ± 7.2[2]	123 ± 5.3
3 h Postprandial	99 ± 8.1[2]	127 ± 5.6
6 h Postprandial	98 ± 8.7[2]	127 ± 5.8
Percentage change from fasting at 3 h(%)	6 ± 4.4	4 ± 2.3
Percentage change from fasting at 6 h (%)	5 ± 4.9	4 ± 2.8
FVIIa (μg/L)		
Fasting	1.5 ± 0.21[a,2]	2.9 ± 0.39[a]
3 h Postprandial	2.1 ± 0.32[b,2]	3.8 ± 0.47[b]
6 h Postprandial	2.3 ± 0.26[b,2]	4.0 ± 0.54[b]
Percentage change from fasting at 3 h (%)	45 ± 8.9	33 ± 7.1
Percentage change from fasting at 6 h (%)	64 ± 16.2	43 ± 7.7

[1]Values in the same column with different superscript letters in the same column are significantly different $P < 0.05$.
[2]Significantly different from *RR*, $P < 0.01$.

varying dietary fat composition on postprandial changes in FVII have usually been conducted on healthy, young volunteers with an average BMI < 25 (7–10, 12, 14–16) or in patients in a metabolic ward (9, 11) and generally have used extremely high fat intakes. The present study used a fat intake (50 g) that supplied 37% of the dietary energy, an amount similar to that in the typical British diet.

In the first study, men were selected on the basis of an elevated nonfasting plasma triacylglycerol concentration. (Approximately two-fifths of the men within the NPHS-II cohort have nonfasting triacylglycerol concentrations between 2 and 5.5 mmol/L.) The postprandial increase in triacylglycerol after the high-palmitate and high-oleate test meals was greater than that in younger subject given higher intakes of fat (12, 13, 16). Furthermore, the increase in plasma triacylglycerol was greater than that in the second study, in which subjects were selected on the basis of *R353Q* genotype, most of whom did not have elevated nonfasting triacylglycerol concentrations. This confirms the view that older men with elevated nonfasting plasma triacylglycerol concentrations are more sensitive to the effects of dietary fat on plasma triacylglycerol concentrations.

FVIIc increased by 8% and 4% in the first and second studies, respectively, 6 h after the test meal supplying 50 g fat rich in oleate. FVIIc increased by 10–12% 7 h after the high-oleate test meal containing 90 g fat in younger, normotriglyceridemic subjects (12, 13, 16). These findings indicate that lower intakes of fat in men with moderately elevated nonfasting triacylglycerol concentrations result in an increase in FVIIc of similar magnitude to that in young men with high fat intakes.

It was surprising that the high-palmitate meal, despite leading to the same degree of postprandial lipemia, did not lead to any postprandial change in FVIIc. FVIIa concentrations increased after the high-palmitate meal, but this increase was half that seen after the high-oleate meal, but was not significant. Larsen et al (15) found similar increases in FVIIc and FVIIa after their subjects consumed test meals providing 70 g olive oil and palm oil. Mennen et al (26) conducted a crossover study in 91 elderly women to compare four 50-g-fat test meals enriched with palmitate, stearate, linoleate, or linoleate+linolenate with a low-fat meal. They found that all high-fat meals increased FVIIa. However, all 4 high-fat meals provided ≈20 g oleic acid—an amount similar to that provided by the high-palmitate meal in the present study. They found that FVIIa increased by 18–24% after the high-palmitate meal, which is similar to the 25% increase observed after the high-palmitate meal in the present study. Although the increase in FVIIa was twice as high after the high-oleate meal than after the high-palmitate meal, a larger sample size than that used in the present study and a crossover design would be needed to verify that there really was a difference between the effects of oleate and palmitate.

FVIIc fell after the low-fat meal, in agreement with studies carried out in younger subjects (12, 15, 16). Mennen et al (26) reported a modest decline of ≈8% in FVIIa after a very-low-fat meal (≈2 g fat) in elderly women. However, the intake of fat in our low-fat meal was greater than this and there was no evidence of a fall in FVIIa after the low-fat meal. It is possible, therefore, that the fall in FVIIc may have been a consequence of a fall in FVIIag. FVIIc was 18% lower 7 h after the low-fat meal than after the high-oleate meal.

R353Q polymorphism exerted a large effect on FVIIc, with values being lowest in the *Q* homozygotes. FVIIc was ≈27% lower in men with the *RQ* genotype than in those with the *RR* genotype, in agreement with previous reports (17, 18, 27, 28). Possession of the *Q* allele might offer protection against fatal ischemic heart disease (IHD). One recent study (27) reported a lower risk of myocardial infarction in subjects carrying the *Q* allele but a similar study failed to find any significant difference in risk (28). Much of the variation in FVIIc with *R353Q* polymorphism appears to be due to differences in FVIIag concentrations, whereas the postprandial increase in FVIIc with dietary fat appears to be due to an increase in FVIIa concentration. No significant differences between *R353Q* genotype groups in the response of FVIIa to the high-oleate meal were found, which agrees with the findings of an earlier study (29) of 8 subjects with the *RQ* genotype given larger amounts of fat. Although the increase in FVIIa after the high-oleate meal tended to be proportionally greater in the men with the *RQ* genotype (64% compared with 43% with the *RR* genotype), the absolute increase was 0.8 μg/L compared with 1.1 μg/L in the men with the *RR* genotype. This suggests that the effects of dietary fat and genotype act independently on FVIIc, but that the FVIIa concentration is greater, both in the fasting state and after a high-fat meal, in those with the more prevalent *RR* genotype. Subjects with the *RR* genotype had FVIIa concentrations (2.6 μg/L) after the low-fat meal similar to those of subjects with the *RQ* genotype after the high-oleate meal (2.3 μg/L), whereas FVIIa was almost twice these values (4 μg/L) in subjects with the *RR* genotype after the high-oleate meal. This suggests that subjects with the *RR* genotype would be most likely to benefit from a low fat intake.

The finding that oleate acutely increases FVIIc is important because diets supplying ≈40% energy from fat, mainly in the form of oleic acid, have been recommended (30) as an alternative to the lower-fat diet (25–30% of energy from fat) currently

advocated for the prevention of IHD. Whereas such an approach may well be justified for young adults and premenopausal women in energy balance, it may not be appropriate for those groups most at risk of fatal IHD, who will have extensive atherosclerosis. Although a major limitation of the present study is that it reports the response to a single meal rather than the response to many meals, the results suggest that moderate intakes of fat rich in oleic acid induce activation of FVII in older men and therefore may increase the risk of fatal IHD, particularly in those homozygous for the *R* allele. Consequently, we remain skeptical about the benefits of advocating meals high in fat for this high-risk group.

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