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The influence of dietary fat on postprandial lipaemia and factor VII coagulant activity in human subjects

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Factor VII coagulant activity (FVIIc) is a potent risk factor for heart disease. The Northwick Park Heart Study (NPHS) found that elevated levels of FVIIc are associated with increased risk of fatal IHD, particularly in men over the age of 55 years and this association was stronger than that for plasma cholesterol (Meade *et al.* 1986). Subsequent studies have confirmed this association (Meade *et al.* 1993).

Factor VII is a key factor in the coagulation cascade. The coagulant glycoprotein factor VII circulates as a single-chain zymogen at a concentration of about 450 ng/ml with about 4 ng/ml present in normal plasma as an activated two-chain form, factor VIIa (FVIIa; Broze, 1994). The coagulation cascade can be initiated when FVIIa forms a complex with its cofactor, tissue factor (TF). The FVIIa–TF complex then cleaves factors IX and X to their active enzymes (IXa and Xa respectively), thereby inducing the conversion of prothrombin (Davie, 1995). In the presence of TF and a physiological concentration of Ca^{2+}, factor Xa can activate the single-chain factor VII, thus accelerating the generation of prothrombin. FVIIa can also be generated in the absence of TF by enzymes involved in the contact system of coagulation, factors XIIa or IXa. The contact system can be activated *in vitro* when citrated plasma is incubated in the presence of a negatively-charged surface such as glass. During incubation of citrated plasma in the presence of a contact surface, the activation of factor XII and the sequential activation of factors XI and IX results in activation of factor VII (Thomson, 1980). There are several measurements of factor VII which need describing. Plasma FVIIc can be measured in the presence of TF and an appropriate factor VII-deficient substrate such that the test plasma's FVIIa is rate-limiting, and related to the recorded clotting time. FVIIc and FVIIa are not synonymous. FVIIa is quantitative, whereas FVIIc is qualitative and is influenced also by the concentration of factor VII zymogen. In practice, most studies have measured FVIIc.

A striking feature of FVIIc is its positive association with plasma triacylglycerol (TAG) concentration (Table 1). Treatment of hypertriacylglycerolaemia leads to a fall in FVIIc (Elkeles *et al.* 1980; Simpson *et al.* 1983; Andersen *et al.* 1990). This suggests that the relationship is causal. Thus, a fat-rich meal is frequently followed by transient increases in the levels of plasma TAG and FVIIa without any change in the factor VII zymogen concentration (Sanders *et al.* 1996). However, when the diet is habitually rich in fat, an increase in the fasting level of factor VII zymogen also occurs (Miller *et al.* 1986, 1989).

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Table 1. *Relationships between levels of factor VII coagulant activity (FVIIc), factor VII antigen (FVIIag), factor VII–phospholipid (FVII-PL) complex, plasma triacylglycerol and total cholesterol concentrations*

Reference	No. of men	No. of women	Mean age (years)	Entry status	Triacylglycerols			Cholesterol		
					FVIIc	FVIIag	FVII–PL	FVIIc	FVIIag	FVII-PL
Dalaker *et al.* (1985)	36	–	40	Healthy	NS	–	Pos***	NS	–	Pos*
Balleisan *et al.* (1985)	2880	1306	38	Healthy	Pos***	–	–	Pos***	–	–
Miller *et al.* (1986)†	24	16	Young and middle-aged	Healthy	Pos***	–	–	Pos***	–	–
Meade *et al.* (1986)†	1511	–	43	No previous IHD event	–	–	–	Pos***	–	–
Dalaker *et al.* (1987)	100	–	58	Survivors of MI	Pos***	–	Pos***	NS	–	Pos*
Bruckert *et al.* (1989)	90 (men and women)		> 20	Type IIa hyperlipidaemia	Pos*	Pos*	–	NS	NS	–
Miller *et al.* (1989)	170	–	50	Healthy	Pos**	–	–	Pos**	–	–
Nordøy *et al.* (1990)	73	90	48	Healthy	Pos**	–	–	Pos**	–	–
Markmann *et al.* (1992)	74 (men and women)		25	Healthy	Pos*	–	–	NS	–	–
Hoffman *et al.* (1992)	132	65	35	Healthy	NS	Pos**	–	Pos***	Pos***	–
Negri *et al.* (1993)	74	28	52	Healthy	Pos***	Pos***	Pos***	–	–	–
Hoffman *et al.* (1994)	216	81	23	Healthy	Pos*	Pos***	–	Pos***	Pos***	–
Väisänen *et al.* (1995)	119	–	55	Healthy and positive history of CVD	Pos***	–	–	Pos***	–	–

MI, myocardial infarction; CVD, cardiovascular disease; Pos, positive relationship.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
†Non-fasting blood samples; all other studies used fasting blood samples.

Table 2. *Comparison of feeding trials on factor VII levels*

Study	Subjects	Diets	Duration	Results
Miller *et al.* (1986)	Six healthy men and women	Two diets consisted of low-fat diet (13 % energy from fat; 9·3 MJ) and high-fat diet (62 % energy from fat; 12·0 MJ)	Each diet was consumed for 2 weeks	Plasma FVIIc and plasma factor VII concentration were on average 8 and 19 % higher respectively on the high-fat diet than on the low-fat diet
Markmann *et al.* (1990)	Eleven healthy men and women	Two diets consisted of 32 % energy from fat, with a low or high polyunsaturated:saturated fatty acid ratio (0·28 and 0·89 respectively) with total energy of 10·7 MJ	Each diet was consumed for 2 weeks	The state of activation of factor VII was not affected by the change in the dietary fat following both diets
Miller *et al.* (1991)	Nine healthy adults (five men, four women)	Two diets consisted of about 40 % energy from fat, with a low or high polyunsaturated: saturated fatty acids ratio ($< 0·3$ and $> 0·3$ respectively) with total energy of 8·5 MJ	Each diet was consumed for 1 week	Dietary fat composition did not influence FVIIc or FVIIag levels
Tholstrup *et al.* (1994)	Fifteen young healthy men	Three isoenergetic diets: shea butter (42 % energy from fat, was rich in stearic acid), palm oil (43 % energy from fat, was rich in palmitic acid), or palm-kernel oil with high-oleic sunflower oil (35 % energy from fat, was rich in myristic and lauric acids; 10 and 30 g/100 g fatty acids respectively) with total energy of 14·4 MJ	Each diet was consumed for 3 weeks	The diet enriched with stearic acid resulted in 13 % lower FVIIc levels
Markmann *et al.* (1994)	Twenty-one healthy middle-aged individuals (ten men, eleven women)	Two diets consisted of low-fat diet (28 % of energy and 3·3 g fibre/MJ, 10·4 MJ/d) and Danish diet (39 % of energy and 2·1 g fibre/MJ, 10·5 MJ/d)	Each diet was consumed for 2 weeks	The low-fat diet lowered plasma FVIIc activity level by 8 % (88 % on low-fat diet *v.* 96 % on high-fat diet) and FVIIag by 4 %.

FVIIc, factor VII coagulant activity; FVIIag, factor VII antigen.

INFLUENCE OF DIETARY FAT CONTENT OR POLYUNSATURATED FATTY ACIDS:SATURATED FATTY ACIDS ON POSTPRANDIAL LIPAEMIA AND FACTOR VII

A summary of the studies on the influence of dietary fat composition on factor VII is presented in Table 2. The main finding from most of these studies is that factor VII levels are not affected by polyunsaturated fatty acids:saturated fatty acids *per se*.

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Table 3. *Influence of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish and fish oil supplementations on factor VIIc*

Study	No. of men		No. of women		Mean age (years)	Entry status	Duration of test period	EPA + DHA dose (g)	Effects on FVIIc
	T	C	T	C					
Sanders *et al.* (1981)	12		-		23	Healthy	6 weeks	3	NS
Haines *et al.* (1986)	14	5	16	6	42	Diabetic	6 weeks	4·6	NS
Sanders (1987)	12	12	-		-	Healthy	6 weeks	4	NS
Muller *et al.* (1989)*	40	42	-		28	Healthy	6 weeks	4·7	NS
Schmidt *et al.* (1989)	9		8		45	Hyperlipidaemia	6 weeks	6	NS
Schmidt *et al.* (1990)	10		-		34	Healthy	6 weeks	1·3	NS
	10		-		34	Healthy	6 weeks	4	NS
	10		-		34	Healthy	6 weeks	9	NS
Hendra *et al.* (1990)	30	25	10	15	55·9	Diabetic	6 weeks	3	+ 19·3 %
Markmann *et al.* (1991)*	12		-		-	Healthy	10 d	3·4	NS
Møller *et al.* (1992)	10	10	10	10	34·5	Healthy	Single dose	13·6	NS
Boberg *et al.* (1992)	12		2		65	Diabetic	8 weeks	3	NS
Schmidt *et al.* (1992)	10		14		39·5	Healthy	9 months	3·2	NS
Sanders *et al.* (1997)	26		-		23	Healthy	3 weeks	5	+ 7 %

T, treatment group; C, control group.
*Fish-diet trials; the rest were fish-oil trials.

INFLUENCE OF *n*-3 FATTY ACIDS ON POSTPRANDIAL ACTIVATION OF FACTOR VII

It has been suggested that the consumption of fatty-fish or fish-oil supplements may affect blood coagulation factors. Most studies have not had sufficient statistical power to detect a change and failed to demonstrate any effect of fish oils on FVIIc (Table 3). However, two studies (Hendra *et al.* 1990; Sanders *et al.* 1997) using the NPHS assay have found an increase in FVIIc. These observations are unexpected since long-chain *n*-3 fatty acids decrease plasma TAG concentrations.

We have also examined the acute effects of fish oil (MaxEPA; Seven Seas Ltd) on postprandial activation of factor VII (Yahia & Sanders, 1996). Four isoenergetic test meals were administered to twelve subjects in a randomized block design. The test meals consisted of 90 g olive oil, 75 g olive oil + 15 g MaxEPA, 15 g olive oil or 15 g MaxEPA. In this study, plasma TAG concentration was significantly elevated by the test meal with 90 g olive oil but not by the test meal with the admixture of olive oil and fish oil (Table 4). The low-fat test meals did not lead to an increase in postprandial lipaemia, and there were no differences between the test meals with olive oil and fish oil. FVIIc was significantly elevated by 90 g fat loads but not by 15 g test meals at 3 and 7 h. Despite the lower degree of postprandial lipaemia following the test meal with the admixture of olive oil and fish oil, the degree of factor VII activity was similar to that of the test meal with olive oil. This elevation of FVIIc by *n*-3 fatty acids with decreased lipaemia might be due to an increase in the rate of lipolysis which acts as a catalyst for activation of factor VII.

In this study, despite the lower degree of postprandial lipaemia following *n*-3 fatty acids, factor VII activity levels were not reduced. It is proposed that *n*-3 fatty acids increase the rate of lipolysis, thus leading to the generation of remnant particles, which expose a large contact surface that may activate factor VII.

Table 4. *Plasma triacylglycerol (TAG) concentrations and factor VII coagulant activity (FVIIc) at 0, 3 and 7 h following the test meals*

(Mean values with their standard errors)

Test meal....	90 g olive oil		75 g olive oil + 15 g MaxEPA*		15 g olive oil		15 g MaxEPA*	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
FVIIc (% reference plasma)								
0 h	81	5·6	85	6·6	82	7·4	81	5·9
3 h	93[a]	5·6	94[ab]	7·5	85[cb]	8·4	82[c]	5·4
7 h	93[a]	6·5	94[b]	8·1	83[c]	8·8	83[c]	7·8
TAG								
AUC	9·92[a]	1·7	6·91[b]	1·4	1·66[c]	0·5	2·17[c]	0·8

[a,b,c] Mean values in the same row with unlike superscript letters were significantly different ($P < 0·05$).
AUC, total area under the curve described by plasma TAG concentrations *v.* time to 7 h.
*Seven Seas Ltd.

Table 5. *Postprandial triacylglycerol concentrations and postprandial activation of factor VII following the test meals*

Test meal...	90 g olive oil		90 g MCT	
	Mean	SE	Mean	SE
Change from fasting triacylglycerol at 3 h (mmol/l)	1·58[a]	0·63	−0·14	0·07
Change from fasting FVIIc at 7 h (% reference plasma)	11·2[b]	3·28	−0·6	7·38

[a,b] Mean values in the same column with unlike superscript letters were significantly different ($P < 0·05$).
MCT, medium-chain triacylglycerol; FVIIc, factor VII coagulant activity.

DOES THE CHAIN LENGTH OF DIETARY FATTY ACIDS INFLUENCE POSTPRANDIAL LIPAEMIA AND FACTOR VII COAGULANT ACTIVITY?

Only a few studies have examined the effect of fatty-acid chain length on FVIIc. Tholstrup *et al.* (1994), found that dietary stearic acid led to lower levels of FVIIc compared with palmitate or a mixture of myristic and lauric acids. We have found that medium-chain TAG (MCT) do not lead to activation of FVIIc (Yahia *et al.* 1995). In this study we compared two test meals containing either 90 g olive oil or 90 g MCT providing 5·6 MJ. Results showed that the plasma TAG concentration was significantly elevated during the test meal with olive oil, whereas such an effect was not noticed during the MCT test meal (Table 5). FVIIc was elevated at 7 h for the test meal with olive oil but not for the test meal with MCT. Thus, the activation of factor VII by the test meal with olive oil but not by the test meal with MCT would suggest that long-chain fatty acids which lead to chylomicron formation are able to activate factor VII in the postprandial state (Sanders *et al.* 1996).

DOES THE PATTERN OF FAT INTAKE AFFECT FACTOR VII COAGULANT ACTIVITY LEVELS?

It would be predicted that one very-high-fat meal would cause greater postprandial lipaemia and, thus, be more likely to increase FVIIc to a greater extent than if the fat was consumed in divided amounts. To investigate this hypothesis, the effect of a low fat intake

and that of a high fat intake (120 g) consumed in a single meal or in three meals on plasma TAG concentration and FVIIc were compared. Results suggested that the pattern of fat intake might be as important as the total intake itself (Yahia *et al.* 1996).

CONCLUSION

FVIIc can be elevated in healthy subjects following consumption of relatively-large intakes of long-chain TAG, providing lipaemia is induced. Although postprandial lipaemia is reduced following the consumption of *n*-3 fatty acids, the degree of factor VII activation is not reduced. However, there are also a number of factors that influence postprandial lipaemia such as obesity, physical activity, age, gender and genotype (polymorphism in the factor VII gene). A common polymorphism in the factor VII gene has been found to affect FVIIc (Green *et al.* 1991). The base gene that causes polymorphism is G-to-A substitution in the second position of the codon for amino acid 353, which leads to the replacement of arginine by glutamine. This suggests that possession of the factor VII-Gln_{353} allele is likely to confer protection by reducing the amount of FVIIa produced in response to fat intake. Future studies are needed to consider the influence of these factors on the postprandial activation of factor VII.

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