Fats, lipids and blood coagulation

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Saturated and n-3 fatty acids, postprandial lipaemia, and the combined effects of fatty acids and lipid-lowering drugs have been of principal interest in recent studies in the field of dietary fats, lipids and haemostasis. The sex-specific effect of individual saturated fatty acids on coagulation factor VII activity has been discovered, and the significant effect of factor VII *R353Q* polymorphism on the postprandial response has also been found. An increased intake of n-3 fatty acids or fat reduction when combined with intensive lifestyle interventions may lead to reduced thrombotic potential in type 2 diabetic patients and obese individuals. Furthermore, positive effects on haemostasis by combined treatment with long-chain n-3 fatty acids and simvastatin indicate that n-3 fatty acids may be of some relevance with lipid-lowering drugs. The possible unfavourable effect of n-3 fatty acids on plasminogen activator inhibitor-1 activity is still a matter of dispute, but recent studies suggest that n-3 fatty acids, including α-linolenic acid, may have antithrombotic effects by enhancing protein C activity. Curr Opin Lipidol 12:25–29.

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Abbreviations

ALA	α-linolenic acid
CHD	coronary heart disease
EPA	eicosapetaenoic acid
PAI-1	plasminogen activator inhibitor-1
tPA	tissue type plasminogen activator

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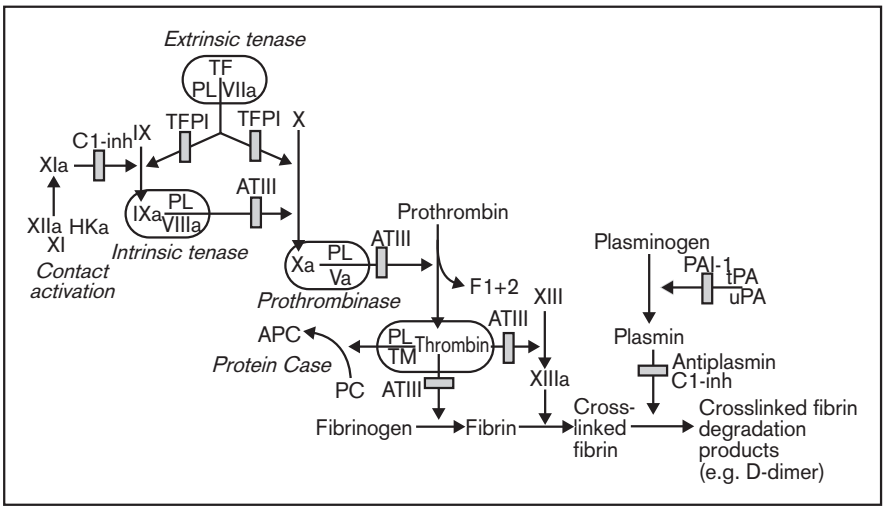
Introduction

A prothrombotic condition may arise in situations in which the balance between the three main parts of haemostasis, the coagulation system, fibrinolysis and platelet function, becomes disrupted [1]. Enhanced thrombotic tendency is of relevance because molecular markers of coagulation system activation and fibrin turnover suggest that there may be activation, even in individuals without overt thrombosis. Furthermore, a number of haemostatic components have been suggested to be associated with the risk of coronary heart disease (CHD). Among these are increased concentrations or activities of fibrinogen, factor VII and plasminogen activator inhibitor-1 (PAI-1), as well as enhanced platelet reactivity [2]. Several new risk marker candidates such as prothrombin fragments F_{1+2} or crosslinked fibrinogen degradation products (D-dimers) have also been postulated [3].

To be able to lower the risk of CHD at the population level, the environmental factors, including diet, responsible for prothrombotic alterations should be characterized. Considerable work has been carried out in the past few decades to understand how dietary fat, especially long-chain n-3 fatty acids, affect some markers of haemostasis in the fasting state. Those studies have recently been summarized [1,4,5], but only a few firm conclusions can be drawn. One of these is that the amount or quality of fat hardly affects the concentration of fibrinogen, the best CHD risk indicator among the markers of coagulation. Another established fact is that fasting factor VII coagulant activity and factor VII antigen can be reduced by low-fat diets regardless of the fatty acid composition [1]. Many recent studies have focused on the postprandial effects of dietary fatty acids, the effects of fat in different polymorphisms of coagulation factors [6], or the combined effect of dietary fat and lipid-lowering treatment on haemostasis. In dietary studies, changes in coagulation have often been determined using the concentrations of fibrinogen and prothrombin fragments F_{1+2}, as well as concentrations of the total antigen or activated factor or in-vitro activity of factor VII and other coagulation factors or antithrombin III. Tissue type plasminogen activator (tPA), its inhibitor PAI-1, and D-dimers have been measured as markers of fibrinolysis. An overview of the blood clotting and fibrinolytic systems is shown in Figure 1 [7,8].

Platelets participate in the coagulation system, e.g. by providing activated phospholipid surface for coagulation complexes [9]. Enhanced platelet activation may thus be

Figure 1. Blood coagulation and fibrinolysis (modified from Refs 7,8).



An extrinsic pathway of coagulation is initiated when tissue factor (TF) is exposed from damaged endothelial cells or activated monocytes. TF and activated factor VII (VIIa) on phospholipid (PL) surface form the extrinsic tenase complex, which activates both factors X and IX. Intrinsic tenase is formed by PL-bound activated factor VIII (VIIIa) and activated factor IX (IXa), which has been activated by the contact activation system or extrinsic tenase. Prothrombinase (Xa, Va on PL surface) catalyses thrombin activation. Thrombin cleaves fibrinogen to fibrin monomers, which are polymerized and crosslinked by activated factor XIII (XIIIa) to form insoluble fibrin. Thrombin in a complex with thrombomodulin (TM) also activates protein C (protein Case). Activated protein C (APC) inhibits factors Va and VIIIa. Antithrombin III (ATIII) is the major inhibitor of coagulation. Fibrinolysis is started with the activation of plasmin by tissue-type plasminogen activator (tPA). The major inhibitor of fibrinolysis is plasminogen activator inhibitor 1 (PAI-1). Plasmin catalyses fibrin degradation. F1+2, Prothrombin fragment 1+2; HKa, activated high-molecular weight kininogen; TFPI, tissue factor pathway inhibitor; uPA, urokinase-type plasminogen activator.

linked to hypercoagulability. The main method to assess platelet function in dietary studies has been the platelet aggregation *ex-vivo* test, although more specific markers of platelet activation have recently been used. Dietary fatty acids can modulate platelet aggregation, but interpretation of the results in terms of blood coagulability *in vivo* is difficult. No real progress has been made in this field recently, and thus a published review [1] is suggested for the interested reader.

Coagulation and fibrinolysis in the fasting state

After the discovery that all saturated fatty acids are not the same with respect to serum cholesterol levels, attention has also been paid to the effects of these fatty acids on haemostatic factors. Two recent studies have focused on this issue [10•,11]. When the effects of lauric (12 : 0) and palmitic acid (16 : 0) were compared with those of oleic acid (18 : 1 n-9) in a strictly controlled 6 week intervention [10•], a sex-specific effect was found in factor VII amidolytic activity, which reflects the total amount of factor VII. In female, but not in male subjects, both saturated fatty acids enhanced factor VII amidolytic activity significantly in comparison with oleic acid. PAI-1 activity was enhanced in the whole study group after the palmitic acid diet when compared with others. Other coagulation or fibrinolytic parameters measured did not show any differences between diets. In another study [11], a 4 week diet rich in stearic acid (18 : 0) did not affect fibrinogen levels or factor VII coagulant activity differently from a palmitic acid-rich diet in healthy men.

α-Linolenic acid (ALA; 18 : 3 n-3), an essential fatty acid and also a precursor for eicosapetaenoic acid (EPA; 20 : 5 n-3) is of interest as a possible antithrombotic fatty acid. Recent findings from the EURAMIC [12•] and Nurses' Health studies [13•] support the earlier assumptions that ALA may exert a protective role of its own with regard to myocardial infarction or coronary mortality. The haemostatic effects of ALA have recently been studied in two Australian human interventions. When the effects of ALA and linoleic acid (18 : 2 n-6) were compared in diets that differed only in the ALA : linoleic acid ratios (1 : 21 versus 1 : 1.2), no differences between the diets were seen in the coagulation and fibrinolytic markers measured [14•]. However, the activated protein C resistance ratio that illustrated the in-vitro anticoagulant activity of added activated protein C increased significantly within the high ALA group. This indicates that ALA may potentiate the activity of this important anticoagulant protein, thereby conferring a more antithrombotic environment. In vegetarian men, moderate or high ALA diets (n-3 : n-6 ratio 1 : 3 versus 1 : 1, respectively) had no effect on haemostatic markers [15•].

Long-chain n-3 fatty acids and especially fish oils have been the main focus in the field of diet and thrombosis. This is because of the findings from the 1960s showing a very low incidence of thrombosis among Greenland Eskimos. Even though the traditional Inuit diet contains approximately 8–9 g per day of n-3 fatty acids from the oil of seals, this oil has not been studied much with regard to cardiovascular risk factors. Among the large variety of coagulation or fibrinolytic markers measured,

only fibrinogen and protein C activity were reported to differ between 20 g per day of seal oil and evening primose oil (rich in n-6 fatty acids) in healthy normocholesterolaemic subjects [16]. The reported difference in fibrinogen may have been a time effect. However, the finding that protein C activity increased in the seal oil group is of interest because, in the few earlier studies, no diet effect on protein C was found [16].

In earlier studies, n-3 fatty acid supplementation, both long-chain fatty acids and ALA, has fairly constantly increased PAI-1 antigen and either increased or had no effect on PAI-1 activity. Because PAI-1 is a potent inhibitor of fibrinolysis, these changes may be harmful. To clarify further the possible adverse effect of n-3 fatty acids, a double-blind, placebo-controlled study was conducted among 224 middle-aged healthy men, who were supplemented either with 3.8 g per day of EPA or 3.6 g per day of docosahexaenoic acid (22 : 6 n-3) ethyl esters, or 4 g per day corn oil for 7 weeks [17•]. PAI-1 activity increased in all groups without significant differences between treatments. In their review of the literature, the authors stated that only two studies had been able to demonstrate a significant increase in PAI-1 attributable to n-3 fatty acid supplementation. They concluded that there is not strong evidence for an unfavourable, clinically relevant effect of n-3 fatty acids on PAI-1 activity in plasma [17•]. This conclusion is, however, contradicted by the results of another recent study with hypercholesterolaemic subjects [18], showing increased PAI-1 activity after 12 weeks' supplementation with 4 g per day EPA plus docosahexaenoic acid ethyl esters in comparison with corn oil.

Physical activity is one factor that may affect the results of dietary studies. An interesting approach has been taken in two recent studies [19••,20•] by combining dietary changes with increased physical exercise. The combined effects of n-3 fatty acids derived from one daily fish meal and a carefully controlled moderate or light aerobic exercise programme were studied in dyslipidaemic type 2 diabetic patients consuming a reduced-fat diet (30% of total energy) [19••]. The fish diet alone, moderate exercise alone, and a combination of the two treatments decreased tPA antigen concentration compared with controls. Fibrinogen and PAI-1 remained unaltered. The fish diet alone, however, significantly increased factor VII coagulant activity compared with controls. The increase was prevented by moderate exercise, indicating that in type 2 diabetic patients, an increased intake of n-3 fatty acids when combined with moderate exercise may lead to reduced thrombotic potential. In another study [20•], obese subjects with impaired glucose tolerance were randomly assigned either to an intervention group that participated in a one month intensive intervention including physical exercise and a low-fat high-fibre diet or to a control group that received one hour's counselling. Follow-up samples were taken after one year. PAI-1 activity and tPA antigen decreased significantly more in the intervention group than in the control group. There was also a significant 5.4 kg decrease in body weight in the intervention group compared with −0.5 kg in the control group. It is impossible to separate the effect of fat reduction *per se* on fibrinolytic potential in these subjects. However, the study clearly shows that an intense lifestyle programme may have sustained beneficial effects on fibrinolysis.

Coagulation and fibrinolysis in the postprandial state

It is fairly well established that factor VII activity is positively related to habitual fat intake and plasma triglyceride concentration, and that it increases after the consumption of a high-fat meal, usually irrespective of the fat type. Two studies have recently been carried out to investigate the effects of meal fatty acid saturation [21•], or chain length and *cis/trans* isomerization [22•] on factor VII coagulant activity and other haemostatic factors in the postprandial state. Tailored triglycerides, which contained mainly stearic acid, oleic acid, or linoleic acid (stearic–oleic–stearic, oleic–oleic–oleic, or linoleic–oleic–linoleic) were fed to healthy male subjects in amounts corresponding to a physiological fat load (44 g) [21•]. With these moderate fat doses, no significant alterations from fasted values were seen in factor VII coagulant activity or F_{1+2}, whereas the amount of activated factor VII increased during the postprandial phase. A difference between the meals was seen only when postprandial activated factor VII was expressed as a percentage of the fasted value (the linoleic–oleic–linoleic meal induced a lower response than the oleic–oleic–oleic meal) [21•]. Another study [22•] compared the effects of meals rich in palmitic acid, stearic acid, oleic acid, elaidic acid (18 : 1 n-9 *trans*), or medium-chain triglycerides (8 : 0 + 10 : 0) with a low-fat meal in healthy individuals. Factor VII coagulant activity increased after palmitic acid, oleic acid and elaidic acid meals, whereas all high-fat meals increased activated factor VII. The results show, for example, that 18 : 1 *cis/trans* isomers do not differ in their postprandial effects [22•].

The postprandial effects on fibrinolytic markers have been studied less than those on factor VII. Furthermore, interpretations from the earlier studies are complicated by the different methods used [23]. In the light of the published data, it seems, however, that fatty acid composition is not the main determinant of fibrinolysis. A recent study with meals high in oleic acid, butter-fat, or oleic acid plus medium-chain triglycerides [23] supports this, showing that there was no difference in PAI-1 activity, t-PA activity or D-dimer

concentrations between subjects consuming any of the three test fats.

Diet–gene interactions may have a greater effect on coagulation and fibrinolytic markers than is currently known. Approximately one-third of the variance in factor VII coagulant activity 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*). Approximately 20% of Europeans carry the *Q* allele [24]. Two studies related to the postprandial effect and factor VII *R353Q* polymorphism have recently been published [25••,26•], one of which reports a significant effect of *R353Q* polymorphism on postprandial response. High-fat test meals led to a significantly higher absolute and relative postprandial activated factor VII response in elderly healthy women homozygous for the R allele (*RR*) when compared with those carrying the Q allele (*RQ* or *QQ*) [25••]. Fasting activated factor VII was also significantly higher in women with the *RR* allele. The four test meals differing in their fatty acid composition (rich in palmitic acid, oleic acid, linoleic acid or ALA) did not differ between each other [25••]. A smaller study with men having moderately elevated plasma non-fasting triacylglycerol concentrations [26•] did not support the results obtained with women. Even though fasting factor VII coagulant activity and activated factor VII were also significantly lower in men carrying *RQ* than *RR*, genotypes did not differ in the postprandial responses to high-fat test meals.

Fatty acids and lipid lowering-treatment

Lipid-lowering drugs are used to reduce cardiovascular morbidity and mortality, and it has been suggested that the clinical benefits could be due to effects on both atherosclerotic and thrombogenetic processes. One way these drugs could affect thrombogenesis is by decreasing the contact surface for activation of clotting factors XII and IX and thus also the activation of factor VII. There is some evidence that long-chain saturated fatty acids might provide such a contact surface [27]. To address the hypothesis that hypertriglyceridaemia causes activation of the contact system, the changes in several markers of contact activation were studied in a group of men with severe hypertriglyceridaemia using either gemfibrozil or 4 g per day of n-3 fatty acids as lipid-lowering substances [28•]. Serum triglycerides and total cholesterol levels were decreased by both treatments. Gemfibrozil treatment significantly decreased prothrombin F_{1+2}, but at the same time increased antigen levels of factor XII, prekallikrein, and factor XI. n-3 Fatty acids had no effect on these parameters. Neither treatment had any effect on the activation markers of contact coagulation. It was thus assumed that contact activation is not likely to contribute to the hypercoagulability seen in this patient group.

Patients with combined hyperlipaemia commonly show changes in haemostatic variables, which may contribute to an increased risk of thrombosis. In one interesting study [29••], patients were first on simvastatin treatment for 10 weeks and then continued on simvastatin and received either 3.36 g per day of n-3 fatty acids or corn oil for 5 weeks. n-3 Fatty acid supplementation had some positive effects on haemostasis, not found in the placebo group. A reduction in the fasting antigen level of tissue factor pathway inhibitor and reduced activated factor VII concentrations in the postprandial state both indicate that n-3 fatty acid supplementation with simvastatin may be of relevance in this patient group.

A hot topic on the lipid-lowering side is plant sterols. Plant sterols are non-nutritive compounds that effectively prevent cholesterol absorption and thus lower LDL-cholesterol concentrations. In spite of a marked cholesterol-lowering effect of both vegetable oil-based and wood-based stanol ester mixtures, no effect on several markers for coagulation and fibrinolysis were found in a study consisting of 112 non-hypercholesterolaemic men and women [30•].

Conclusion

The results of recent publications are in line with earlier findings, which indicated that dietary fat quality as such is not a strong regulator of coagulation and fibrinolytic markers. One reason for this may be that the markers measured have not been sensitive enough. In the future, new sensitive markers for the three parts of haemostasis, the coagulation system, fibrinolysis, and platelet function, should be tested in well-controlled long-term dietary interventions. The interesting finding that links factor VII *R353Q* polymorphism with postprandial responses indicates that polymorphisms of several coagulation and fibrinolytic factors may also be of some interest.

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