Review article

Diet and haemostasis: time for nutrition science to get more involved

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Abnormal haemostasis, and specifically a pre-thrombotic state characterized by hypercoagulability, increased platelet aggregation and impaired fibrinolysis, is associated with increased atheroma and thrombosis. The recent literature clearly indicates that diet may prevent or be used to treat some abnormal haemostatic states. There are reports on effects of energy intake and expenditure, alcohol consumption, intakes of total fat, different fatty acids, fish oil, NSP and vitamins on markers of coagulation, platelet function and fibrinolysis. Some of the confusion and controversy in this field has arisen because the wrong markers of haemostasis have been measured in dietary trials. Moreover, many of the studies have lacked good dietary control. It is suggested that more sensitive, functional markers of the balance between the different facets of the haemostatic system should be measured. It is also important to test hypotheses developed from known observations and to propose mechanisms of action of the various dietary factors, based on our improved understanding of the haemostatic system.

Haemostasis: Factor VII: Cardiovascular disease

The term ‘haemostasis’ describes the combined processes of vascular smooth-muscle-cell contraction, platelet aggregation or plug formation, and blood (plasma) coagulation, aimed at preventing bleeding from injured smaller blood vessels. Blood coagulates or turns into a solidified mass when plasma fibrinogen is converted by thrombin (generated by the coagulation enzyme cascade) into monomers which polymerize into a fibrin network. This network entraps blood cells and aggregated platelets to form a clot. As illustrated in Fig. 1, the clot is eventually dissolved by plasmin, generated from plasminogen by tissue plasminogen activator (tPA) which is part of the fibrinolytic system. Plasminogen activator inhibitor (PAI-1) inhibits this process. The term ‘thrombus’ refers to an intravascular blood clot. A pre-thrombotic state (Miller, 1993) is characterized by hypercoagulability of plasma, hyperaggregability of platelets, increased viscosity of whole blood, reduced blood flow with vortices, impaired fibrinolysis and a loss of the natural anticoagulant properties of cell surfaces in contact with blood. Hypercoagulability (Miller, 1992) is defined as ‘an increased reactivity of blood plasma to thrombogenic surfaces’.

There is now convincing epidemiological and clinical evidence, supported by plausible underlying molecular mechanisms, that the pre-thrombotic state is an important predictor of cardiovascular disease. Known risk factors are increased plasma fibrinogen and factor VII coagulant activity (factor VIIc), increased platelet aggregability, as well as impaired fibrinolysis because of decreased tPA and increased PAI-1. This knowledge has led to a
Growing perception that dietary factors or patterns which are associated with an increased risk of cardiovascular disease (Marckmann, 1995; Simon et al. 1995) or which protect against these diseases (Anderson, 1995) may operate through effects on haemostatic function. For example, the positive correlation between dietary intake of saturated fatty acids and negative association of the \( n-3 \) polyunsaturated fatty acids with CHD still remain after adjustment for effects on blood lipid levels (Simon et al. 1995).

Despite agreement that diet is strongly associated with risk of cardiovascular disease, the effects of dietary patterns, specific foods or nutrients on haemostasis, and especially on the many facets of the pre-thrombotic state are not well understood. The purpose of the present contribution is to review briefly what is known about dietary effects on haemostasis, and to provide possible explanations for existing controversies in recent literature. Further research needed to make recommendations to the public for preventing cardiovascular disease through dietary interventions on the haemostatic system, will be suggested.

**ENERGY: INTAKE AND EXPENDITURE**

*Effects of obesity*

Obesity or increased BMI (\( > 30 \text{ kg/m}^2 \)) is associated with increased plasma concentrations of fibrinogen (Vorster et al. 1989; Iso et al. 1993b), increased PAI-1 (Iso et al. 1993a; Urano et al. 1993), impaired fibrinolytic capacity (Cepelak et al. 1991) and increased
plasma viscosity (Fanari et al. 1993). These observations were made in both men and women, from Caucasian (Iso et al. 1993a), Japanese (Iso et al. 1993a), and African (Venter et al. 1992) populations. The distribution of body fat may be an important determinant of fibrinogen concentration. Krobot et al. (1992), examining 4940 subjects in the second multinational monitoring of trends and determinants in cardiovascular disease (MONICA) trial, found a positive relationship between waist:hip ratio and fibrinogen in men and women.

**Effects of reduced energy intake and weight loss**

Little is known about the effects of weight loss on haemostasis, and there is some controversy regarding effects on fibrinogen. Poggi et al. (1994) found that a very-low-energy diet (VLCD) followed for 3 months by fifty-two subjects with BMI > 30 kg/m², significantly reduced packed cell volume, blood viscosity, erythrocyte aggregation, globulin levels and leukocyte count. Albumin levels increased but no effect on fibrinogen concentration was seen. Slabber et al. (1992) found that a similar VLCD followed for 7 d by nine obese subjects, increased fibrinogen non-significantly from 4.22 (SD 0.66) to 4.64 (SD 1.06) g/l, but significantly reduced factor VIIc. Fanari et al. (1993) showed a reduction in erythrocyte aggregation index with reduced energy intake. Although these authors demonstrated a reduction of fibrinogen, whole-blood viscosity of their subjects did not change on the reducing diet. A low-energy diet improved the fibrinolytic profile of 50% of patients with deep-vein thrombosis (Cepelak et al. 1991). The conflicting effects of reduced energy intake and weight loss on fibrinogen may be explained by effects on free fatty acids (FFA). Vorster et al. (1989) showed that during an 8-week period of diet-induced weight loss, fibrinogen levels fluctuated in a similar manner to that of circulating FFA. During periods of rapid weight loss, fibrinogen and FFA rose, and both decreased during periods of slower weight loss. It is known that FFA stimulate hepatic fibrinogen production and that increased FFA levels are associated with increased fibrinogen (Pilgeram & Pickart, 1968).

**Effects of activity level and exercise**

Comparison of inactive with more active or very active subjects in different studies has shown that active women have significantly lower PAI-1 and tPA antigen levels (Stevenson et al. 1995) and active men have lower fibrinogen and factor X levels (Rankinen et al. 1994). Stevenson et al. (1995) could not find differences in fibrinogen levels related to activity in women, but Vanninen et al. (1994) showed a linear inverse correlation between fibrinogen and \( \text{O}_2 \text{uptake (V}\text{O}_2) \) of patients with non-insulin-dependent diabetes mellitus. Increased exercise in healthy subjects or sedentary diabetic subjects led to a decrease in fibrinogen concentration of the diabetics accompanied by improvement in glycaemic control (Vanninen et al. 1994) and an improvement in fibrinolytic profiles of the healthy subjects (Boman et al. 1994). These changes were thought to be related to improvements in insulin sensitivity during exercise. The mechanism by which insulin sensitivity may influence haemostasis is not clear. We have hypothesized that it could be mediated through effects on FFA (Venter et al. 1990).

Thus, high energy intake and inactivity, leading to obesity, are associated with increased coagulation factors and decreased fibrinolytic capacities in the majority of studies. More importantly decreases in energy intake, weight loss, and increased exercise, are associated with improvement in many haemostatic variables.
Alcohol is not strictly regarded as a nutrient. However, it does provide energy, and alcoholic beverages form an important part of the diet and social life of many people. Moreover, moderate alcohol consumption is known to be protective against heart disease (Doll et al. 1994). Epidemiological surveys have indicated that alcohol intake is positively associated with increased tPA levels in men and women (Iso et al. 1993a; Ridker et al. 1994) but also with raised PAI-1 levels in men (Iso et al. 1993a). In a 3-month intervention study, Struck et al. (1994) showed that both red and white wine have antithrombotic effects by reducing thrombin-initiated platelet aggregation. Renaud et al. (1992) examined the relationship between alcohol intake and platelet aggregation in the Caerphilly prospective heart disease study. They found an increased sensitivity of platelets to thrombin stimulation, but a decreased aggregation response to ADP and collagen stimulation with increased alcohol consumption. Based on these results, Renaud & De Logeril (1992) hypothesized that the high alcohol (wine) intakes in France may be responsible for the low CHD mortality (despite high saturated fat intakes and HDL levels comparable with other populations) because of these effects of alcohol on platelet aggregation.

Many studies have shown an inverse relationship between alcohol intake and fibrinogen level. Meade et al. (1979) showed that drinkers had 5–7% lower fibrinogen concentrations and increased fibrinolytic activity, compared with non-drinkers. Krobot et al. (1992) described a U-shaped relationship between alcohol intake and fibrinogen, suggesting that maximal beneficial effects on fibrinogen will be seen at moderate levels of alcohol consumption. This is supported by the results of Lippi et al. (1992) who indicated that fibrinogen concentrations of alcoholics, with or without liver damage, were raised, possibly as an acute-phase response.

The acute, postprandial effects of alcohol taken with meals have also been examined. Veenstra et al. (1990) found that 30 g alcohol as port and red wine taken with an evening meal tended to increase platelet aggregation and PAI-1 activity, while decreasing tPA activity. Similar results were reported by Hendriks et al. (1994) when 40 g alcohol as beer, spirits or wine was taken with a meal. However, both groups found that these adverse effects were temporary and that fasting haemostatic profiles on the following morning were consistent with a decrease in CHD risk.

The mechanisms through which the effects of alcohol are mediated are not clear. Basista et al. (1994) thought that the fact that ethanal (acetaldehyde), a metabolic product of alcohol, reacts with proteins and alters their function, could explain the prolonged clotting times they observed in vitro when clotting proteins were incubated with ethanal. They concluded that ethanal may be responsible for some of the deranged coagulation seen in alcoholics. Spertini et al. (1992) also demonstrated that ethanal forms adducts with human platelets which may interfere with platelet activation and aggregation.

The protective effect of moderate alcohol consumption on CHD may therefore be mediated in part through effects on haemostasis. A possibility that deserves to be examined is that acetate, the major metabolic product of alcohol, could, through its lowering of FFA (Crouse et al. 1978) influence fibrinogen synthesis, secretion or function, and therefore be responsible for some of the effects of alcohol. Veldman (1996) recently showed that acetate influenced fibrin network formation in in vitro as well as in vivo circumstances.

Dietary Fats and Oils

Because total fat and different fatty acids have such profound effects on serum lipoproteins and risk of cardiovascular disease, the relationship of total fat and different fatty acid...
intakes with haemostatic variables has received relatively more attention than that of other
nutrients. Several types of long-term or short-term studies in healthy subjects,
hyperlipidaemic or diabetic patients, some with conflicting results, have been reported.

Effects of total fat

There is general agreement that a high fat intake is associated with increased factor VIIc
(Miller, 1992; Bladbjerg et al. 1994; Vaisanen et al. 1995) and that low intakes correlate
with low factor VIIc (Vaisanen et al. 1995). There is also evidence that increasing fat intake
impairs fibrinolytic activity (Ho et al. 1995). These authors found that twenty-eight
Chinese volunteers who increased their fat intake to 50% of total energy for 3 d, showed
smaller rises in tPA after the venous occlusion test. However, Ferlito & Di Mauro (1990)
could not show any adverse effect of an oral fat load (1 g butter/kg body weight) on
postprandial haemostatic variables associated with the pre-thrombotic state such as tPA, D-
dimer and β-thromboglobulin. Freese & Mutanen (1995) confirmed increases in factor VIIc
after fat intake. Habitual high fat intakes are also related to other coagulation factors.
Rankinen et al. (1994) demonstrated positive correlations between fat intake and factor X,
PAI-1 and tPA. However, there is little evidence that total fat intake influences fibrinogen
levels. The fatty acid profile of the diet may be a more important determinant of fibrinogen
level. Comparing two groups of Africans, Vorster et al. (1987) found higher fibrinogen
values in the group who had a higher fat intake; but this group also had higher cholesterol
and animal protein and lower fibre intakes. Other variables known to influence fibrinogen
concentration such as BMI, smoking habit and activity levels, were similar in the two
groups.

It can, therefore, be expected that lowering fat intake should improve haemostatic
profiles. Lopez-Segura (1996) showed that a low-fat diet, rich in monounsaturated fatty
acids, decreased PAI-1 level, accompanied by parallel decreases in plasma insulin. Sundell
et al. (1991) also demonstrated reductions in PAI-1 when fat intake was lowered. However,
Marckmann et al. (1992) found that a reduction of fat intake from 39 to 31% of total
energy by healthy subjects, had no effect on coagulation or fibrinolytic profiles. This
reduction also did not influence blood lipid levels, suggesting that only substantial
reductions will have beneficial effects.

Total fat intake may theoretically influence haemostasis indirectly through effects on
blood lipoproteins. Serum or plasma triacylglycerol concentration is positively associated
with factor VIIc (Miller, 1993), bleeding times (Mundal et al. 1994) and with tPA and PAI-
1 concentrations (Iso et al. 1993a). Factor VIIc also correlates with apolipoprotein B levels
(Vaisanen et al. 1995). HDL are negatively associated with fibrinogen (Iso et al. 1993b)
while lipoprotein (a) showed a positive association with fibrinogen in a large cross-
sectional study involving 4125 subjects aged 25–55 years (Howard et al. 1994). Miller
(1993) is of the opinion that hyperlipidaemia leads to a sustained activation of the extrinsic
pathway, resulting in an increased generation of thrombin (and possibly of other
zymogens) which will stimulate the hepatic production of the vitamin K-dependent clotting
factors.

In addition to increased levels of factor VII being an accepted risk factor for CHD, the
relationship between fat intake, hyperlipidaemia and haemostasis may also be important at
an acute, clinical level. Altomare et al. (1993) have shown that the infusion of a lipid
emulsion used as a standard component of parenteral nutrition, significantly reduced tPA
and had no effect on PAI-1 release after 10 min of venous occlusion. This haemostatic
profile is associated with an increased thrombotic risk.


Effects of different types of fatty acids

In an earlier review on dietary factors involved in cardiovascular disease, Ulbricht & Southgate (1991) suggested that the atherogenic or hyperlipidaemic saturated fatty acids are lauric (12:0) myristic (14:0) and palmitic (16:0) acids, while the thrombogenic fatty acids are myristic, palmitic and stearic (18:0) acids. The long-chain unsaturated n-6 (linoleic) and n-3 fatty acids from fish oils are thought to be anti-atherogenic and anti-thrombogenic.

The effects of individual fatty acids will be influenced by which fats they replace in the diet. Incubation of citrated plasma with micellar stearate activates the contact system of coagulation (factors XII and IX to XIIa and IXa), with resultant increases in factor VII (Mitropoulos et al. 1994). These authors believe that dietary fat induces changes in activation of factor VII through effects on plasma free-stearic-acid concentration. However, in an in vivo study, Tholstrup et al. (1994) showed that a diet rich in stearic acid, when compared with diets rich in palmitic acid and myristic plus lauric acid lowered not only serum lipoproteins (12-26 %) but also factor VIIc by 13 %. Mustad et al. (1993) also compared a diet rich in stearic acid with one rich in myristic plus lauric acids and could not demonstrate any effects on prostacyclin and thromboxane production, the two prostaglandins involved in platelet function.

Not only do different experiments with the same fatty acid show different effects, but effects of a particular fatty acid or diet on different coagulation variables may also differ. Bladbjerg et al. (1995) showed that a diet rich in stearic acid compared with one rich in myristic plus lauric acids significantly decreased factor VIIc and other vitamin K-dependent proteins, but increased fibrinogen. Cigolini et al. (1994) however, found no relationship between plasma fibrinogen and fatty acid profiles of adipose tissue. The latter should reflect dietary intakes. In a comparison of diets containing monounsaturated fatty acids with those containing polyunsaturated fatty acids in hyperlipidaemic patients, Gustafsson et al. (1992) could not demonstrate any effects on fibrinogen, despite significant reductions of 12 and 15 % in total cholesterol concentration. In non-insulin-dependent diabetic patients, a similar study demonstrated that the diet containing monounsaturated fatty acids lowered Von Willebrand factor but had no effect on fibrinogen, fibronectin or α-2-macroglobulin (Thomsen et al. 1995).

These different effects of a particular diet or fatty acid on haemostatic variables were also described by Freese & Mutanen (1995). They showed that collagen-induced platelet aggregation was decreased 5 h after fat intake while factor VIIc was increased. In another study Mutanen et al. (1995) found that platelets from subjects on a high-saturated-fat diet were less sensitive to aggregating agents than those from subjects on an unsaturated-fat diet.

The relationship of intakes of fish, fish oils, eicosapentaenoic acid and docosahexaenoic acid with haemostatic variables have been studied in more detail, but again with some conflicting results. Their inhibitory effects on platelet aggregation with resultant prolonged bleeding times through effects on prostaglandin metabolism are well known (Dyerberg, 1986; Hansen et al. 1993). But fish intake also affects clotting factors and fibrinolytic enzymes. High intakes are associated with lower plasma levels of fibrinogen, factor VIII and Von Willebrand factor (Iso et al. 1993b; Shahar et al. 1993). However, studies which examined the effect of supplementation of diets with fish oil on plasma fibrinogen, gave conflicting results. Some studies showed a lowering of fibrinogen (Höstmark et al. 1988; Radack et al. 1989), others found no effect (Haglund et al. 1990; Brown & Roberts, 1991) while some even demonstrated increases (Haines et al. 1986; Schmidt et al. 1992). Haglund et al. (1991) showed that fish oil lowered fibrinogen levels.
only when it contained 1.1 α-tocopherol equivalents (1.5 IU) vitamin E per g fish oil but not when it contained 0.2 α-tocopherol equivalents (0.3 IU)/g. Oosthuizen et al. (1994) showed that a vitamin E-rich fish oil lowered plasma fibrinogen level in women who had relatively high initial values (from 3.23 (SD 0.96) to 2.64 (SD 0.55) g/l) but not in men who had low baseline values (2.03 (SD 0.62) g/l). The latter study also reported decreases in factors Vc, VIIc and Xc in the women during intakes of fish oil.

The increases in fibrinogen seen with fish-oil supplementation in some studies, especially in diabetic patients (Haines et al. 1986; Silvis et al. 1990), question the ‘safety’ of these supplements. In several studies it was also reported that increases in PAI-1 occurred, despite decreases in triacylglycerol levels with fish-oil supplementation, both in diabetic (Boberg et al. 1992) and healthy subjects (Fumeron et al. 1991; Oosthuizen et al. 1994). In addition, Herrmann et al. (1995) reported decreases in tPA with a supplement of 12 g fish oil in CHD patients.

From these studies one might conclude that although fish oil may inhibit platelet aggregability and lower some coagulation factors, it may also impair fibrinolytic potential by lowering tPA and raising PAI-1 in some circumstances. Marckmann (1995) also is of the opinion that the anti-fibrinolytic effect of the fish-oil fatty acids might counteract their anti-thrombotic influence on platelet function.

**DIETARY CARBOHYDRATES**

Diets high in carbohydrate (CHO) including fibre (NSP) are usually low in fat and relatively higher in plant than animal protein. Studies looking at the effect of CHO on haemostasis should therefore control for amounts and types of fat and protein. Because soluble and insoluble NSP have different physiological effects on gastrointestinal function and lipid metabolism, it can furthermore be expected that effects of different types of NSP on haemostasis will also differ.

Some of the first observations that diets high in ‘fibre’ may protect against thrombosis were made by British physicians who reported that incidences of post-operative deep-vein thrombosis could be lowered by feeding patients with high-fibre diets (Frohn, 1976; Latto, 1976). Fehily et al. (1982) then provided epidemiological evidence that high cereal-fibre intakes correlated negatively with plasma fibrinogen. However, in a follow-up study, Fehily et al. (1986) could not demonstrate decreases in fibrinogen when healthy subjects increased their cereal-fibre intake.

Simpson et al. (1982) also could not demonstrate a change in fibrinogen level with an increase in NSP intake by diabetic patients. But they found that coagulant activities of factors VII and X decreased on the higher fibre intake in non-insulin-dependent diabetic patients, and factor VIII antigen decreased in patients with insulin-dependent diabetes.

If fibre intake influences plasma fibrinogen level, it is probably due to the soluble NSP components. Koepp & Hegewisch (1981) found that supplementing the diet of ten diabetic children with 0.45 g guar gum/kg for 4 weeks reduced fibrinogen level in seven of the children from a mean of 3.13 to 2.63 g/l. Another soluble NSP, konjac-glucomannan, significantly lowered plasma fibrinogen in an obese baboon model (Venter et al. 1990) and the obese Zucker rat (Venter et al. 1991). Soluble NSP do not seem to affect platelet function. Challen et al. (1983) found no effects on platelet aggregation, platelet fatty acid composition, bleeding times or dilute blood-clot lysis time in healthy volunteers who were given 36 g pectin daily for 3 weeks.

Low fibre intakes are also associated with impaired fibrinolysis and this situation may be rectified by increasing fibre intake. Sundell & Ranby (1993) found that oat husk fibre,
and Landin et al. (1992) that guar gum, significantly reduced PAI-1 levels. Marckmann et al. (1993) also showed that a low-fat, high-fibre diet followed for 8 months by healthy volunteers improved fibrinolytic potential by increasing tPA activity. This study did not show changes in fibrinogen or PAI-1. Mehrabian et al. (1990) demonstrated, however, that a ‘high-complex-CHO, low-fat’ diet followed for 3 weeks significantly reduced plasminogen, tPA and PAI-1 levels, while fibrinogen level tended to decrease ($P=0.07$). It is however, difficult to dissect effects of fibre from those of fat in these studies.

In the past, much has been learned about the effects of NSP by analysing diets and disease risk profiles of vegetarians. Haines et al. (1980) showed that concentrations of factors VII and II were lower in vegetarians, while the only haemostatic difference between Chinese Buddhist vegetarians and omnivores that Pan et al. (1993) could find was increased levels of anti-thrombin III in the vegetarians.

These studies show that high-fibre diets have beneficial effects on coagulation and fibrinolysis. The effects of starch, resistant starch and other carbohydrates such as the oligosaccharides have not been examined.

**VITAMINS**

Very few studies have reported effects of vitamins on coagulation. Kruger et al. (1994) observed in healthy elderly women that those who took micronutrient supplements and who had significantly higher levels of serum vitamin A, retinol binding protein, pyridoxal and pyridoxal phosphate, also had significantly lower plasma fibrinogen levels. Eliasson et al. (1995) found in the Swedish MONICA study that high plasma retinol levels were associated with lower plasma fibrinogen but also with low tPA levels and therefore with impaired fibrinolytic activity. Haglund et al. (1991) showed, as already mentioned, that fish oil had a fibrinogen lowering effect only when it contained high levels of vitamin E.

Kiserud et al. (1995) supported these observations in their studies on the effects of various fatty acids, alone or in combination with vitamin E on fibrinogen secretion by human hepatoma (HepG2) cells. These authors showed that polyunsaturated fatty acids increased fibrinogen release by HepG2 cells. Vitamin E alone decreased the amount of fibrinogen in the medium in a dose-dependent manner. When vitamin E was added to the polyunsaturated fatty acids, fibrinogen in the cell medium was lowered. The monounsaturated oleic acid, and the saturated palmitic acid, decreased fibrinogen secretion, both alone and in combination with vitamin E. The authors hypothesized that vitamin E may have these effects by preventing oxidation of the polyunsaturated fatty acids.

**SPECIFIC FOODS**

There is some evidence that specific foods or substances in foods such as the flavonoids or polyphenols may influence haemostasis. Strongly flavoured foods such as onions (Menon et al. 1968), chillies (Glatzel & Rüberg-Schweer, 1965), spices (Glatzel & Rüberg-Schweer, 1967), capsicum (Visudhiphan et al. 1982) or green tea (Ali & Afzal, 1987) may increase fibrinolytic activity. However, Vorster et al. (1996) found no evidence that fibrinogen, tPA or PAI-1 levels were influenced by tea drinking. Vorster et al. (1992) also reported that an increased egg intake from two to seven and fourteen per week in young healthy men over a period of 5 months, did not influence coagulation or fibrinolytic (plasminogen) profiles.
COMMENT

Despite all the reported controversies, it is clear that many dietary factors influence different variables of haemostasis. But it is also clear that we do not know enough about the relationship between diet and haemostasis and particularly the mechanisms involved to give detailed and specific advice to patients or the public, other than that the 'prudent', low-fat, high-CHO, high-NSP diet known to protect against development of chronic diseases of lifestyle, will probably have beneficial effects, as indicated by numerous epidemiological surveys.

There are many possible reasons for the existing conflicting findings. They include differences in study design, choice of subjects or patients and their baseline values, total dietary composition, and duration of studies. A major reason is that the most important variables have not been measured in dietary studies. Normal haemostasis is a result of a complex regulatory process involving the interaction of zymogens, activators, inhibitors and activated enzymes in plasma with blood cells, and the secretions of the endothelial lining of blood vessels. To measure the balance amongst these molecules and their actions, appropriate markers of hypercoagulability, inhibition of coagulation, fibrin formation and deposition, activation of fibrinolysis and fibrinolytic products should be measured. These should include inter alia, prothrombin fragment 1+2, fibrinopeptide A, thrombin–antithrombin III complexes, fibrin monomer, active PAI-1 antigen, tPA–PAI-1 complex, plasminogen, α-2-plasmin inhibitor, plasin–α-2 plasmin inhibitor complex and D-dimer, as well as fibrinogen and factor VIIc (Kario & Matsuo, 1993; Tripodi et al. 1993; Hansson et al. 1994). Measurement of these variables will give more information on the processes of fibrin formation and dissolution.

Measurement of fibrinogen concentration alone will only give limited information. Nieuwenhuizen (1994) mentions that the term ‘fibrinogen’ covers a large, heterogeneous family of closely related molecules whose functional properties may differ. Measurement of polymerization of fibrin monomers, as reflected in fibrin network structure and properties (Nair & Dhall, 1991) will give information on plasma factors which affect clot formation, the thrombogenicity of the clot (Collet et al. 1993) as well as its potential to influence the conversion of plasminogen to plasmin by tPA and therefore to be digested (Carr & Alving, 1995).

It could also be worthwhile to measure the macromolecular protein complex described by Lipinski et al. (1995). Macromolecular protein complex is known to form complexes with fibrin in the clot, increasing its mass and making it resistant to fibrinolysis. It therefore increases risk of thrombosis. There is no information on the effects of diet on macromolecular protein complex level.

The determinants of the different haemostatic factors or markers in different population groups, should be studied in more detail. Jerling et al. (1994) found that a group of rural Venda men had lower PAI-1 but higher fibrinogen levels than a matched control group of white men, indicating that the determinants of fibrinogen and PAI-1 may differ or that there are ethnic (genetic) differences in these variables. It is also not known to what extent compensatory increases or decreases in haemostatic variables are possible in an attempt to maintain balance between and within the coagulation and fibrinolytic systems.

In conclusion, there may be several different hypercoagulable states (Miller, 1993) depending on which variables are abnormal. We need to know much more about the effects of specific foods and nutrients, as well as the total diet on a broader range of sensitive markers of the total haemostatic system, before these different conditions can be prevented or treated by diet. With a better understanding of the complexities of the haemostatic
system, and with our existing knowledge of effects of specific dietary substances, we believe it is possible to develop working hypotheses that could be tested in controlled dietary trials. The challenge is there: it is now time for nutritional scientists to accept it! The reward will be improved dietary prevention and treatment of many chronic diseases of lifestyle in which abnormal haemostasis plays a role.

REFERENCES


