

Diet and haemostatic processes

Hester H. Vorster¹, John H. Cummings² and Johann C. Jerling¹

¹ Department of Nutrition, Potchefstroom University for Christian Higher Education, Potchefstroom, 2520 South Africa; ² MRC Dunn Clinical Nutrition Centre, Cambridge, CB2 2DH, UK.

Abstract

Diet plays an important role in the primary and secondary prevention of cardiovascular disease. The growing perception that abnormal haemostatic processes of coagulation, platelet aggregation and fibrinolysis contribute to cardiovascular disease aetiology motivated this review on the relationships of diet, specific foods and nutrients with haemostatic function. Functional endpoints that reflect the function and status of some of these processes and which can be measured in dietary trials are identified. The effects of energy intake and expenditure, alcohol, total fat and specific fatty acids, non-starch polysaccharides (dietary fibre), antioxidant nutrients and some foods on a variety of haemostatic markers are reviewed. The results indicate that the prudent low-fat, high-fibre diet and maintenance of ideal body weight recommended to protect against and treat hyperlipidaemia and coronary heart disease will also benefit haemostatic profiles. It is concluded that more research on specific effects is needed for improved recommendations on a population level for prevention of cardiovascular disease.

Introduction

The term haemostasis means prevention of blood loss (Guyton, 1991). In this review the term is used collectively to describe the processes of coagulation, platelet aggregation, fibrinolysis and secretion of substances by vascular endothelium which influence these functions. Abnormal haemostasis, characterized by an imbalance in procoagulant and anticoagulant activities, is now accepted as a major risk factor for atherosclerosis, thrombosis and resultant cardiovascular disease (reviewed by Tanaka & Sueishi, 1993; Vorster & Venter, 1994). It is also accepted that diet, *inter alia* through its effects on lipid metabolism and antioxidant properties, plays an important role in the primary and secondary prevention of cardiovascular disease (Ulbricht & Southgate, 1991). In this review the relationship between diet and haemostasis is explored to test the hypothesis that the protective effects of diet are also mediated through the haemostatic system. A better understanding of this relationship could lead to improved dietary guidelines for prevention and treatment of cardiovascular disease.

The notion that diet influences haemostasis is not new. However, despite many reports and reviews (Marckmann, 1995; Vorster *et al.* 1997) the relationships of the total diet, as well as specific foods and nutrients, with the different variables of haemostasis are far from clear. One

reason is that scientists are only now beginning to understand the complexities of the different components of the haemostatic system, with its highly specific and intricate mechanisms of regulation and control. Furthermore, it has been suspected for over a century that thrombotic elements in blood must influence atherosclerosis, but only during the past decade have the powerful relationships of components of the haemostatic system with atherosclerosis and thrombosis and with other risk factors of cardiovascular disease been firmly established. Other reasons are the limitation of dietary epidemiology, the difficulties with dietary placebos, dietary control and compliance in clinical trials with free-living subjects, as well as our inability to draw valid conclusions from results of studies with different and sometimes inappropriate designs.

In the following sections, the components of the haemostatic system will be briefly outlined, and functional endpoints that could be measured in dietary trials identified. The known effects of diet, specific nutrients and foods will then be summarized, possible mechanisms of actions delineated, and directions for future research and practical applications suggested.

Haemostasis

Components and interrelationships

The haemostatic system protects the integrity of the vascular system by preventing haemorrhage and promoting tissue defence and repair after injury. Haemostasis is the culmination of a series of precisely controlled and interrelated actions involving the clotting factors, fibrinolytic enzymes, platelets and the vascular endothelium (Takada *et al.* 1994).

The balance between procoagulant and anticoagulant activities in the system is carefully controlled by the specificity and interaction of molecules from the different components of the system, regulated by positive and negative feedback mechanisms. This balance ensures sufficient blood flow to all tissues and organs under normal circumstances. The interaction of the molecules from the different components of the system also ensures that when the system is triggered by injury, the coagulant activities and subsequent fibrinolysis are localized within the area of injury. Disturbance of haemostatic balance may lead either to thrombosis (clot formation inside a blood vessel) and atherosclerosis, or a bleeding tendency.

Some of the interrelationships of the different components of the haemostatic system are illustrated in Fig. 1. The figure shows how thrombin, generated in the coagulation component of the system, also influences events in the fibrinolytic, platelet and endothelial cell components (Bertina *et al.* 1992; Esmon, 1993).

Understanding of these interrelationships, and the compensatory control mechanisms in all parts of the system to maintain haemostatic balance, is important for understanding and evaluating the effects of diet on the system.

Coagulation

Blood coagulation is an autocatalytic, self-limiting process which is triggered by tissue injury. It requires the sequential 'cascade' activation of a series of proteinase zymogens of which some combine with a protein cofactor on membrane surfaces for further activation, culminating in the formation of thrombin from prothrombin, with release of prothrombin fragments 1+2. Thrombin formation must be in sufficient quantities to overcome the effect of antithrombins

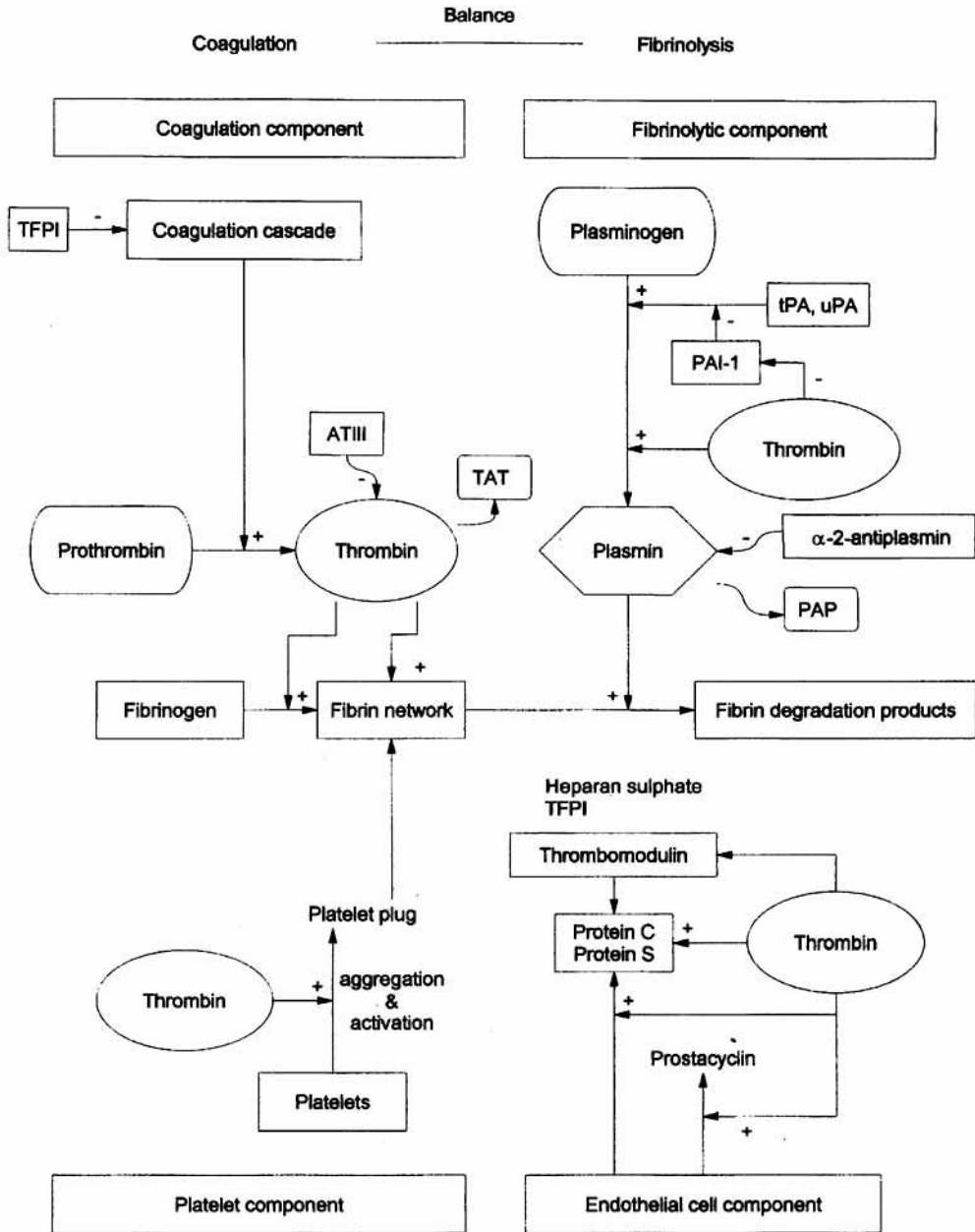


Fig 1. Interrelationships between the coagulation, fibrinolytic, platelet and endothelial cell components of the haemostatic system. Thrombin generated in the coagulation component influences events in other components. AT III, antithrombin III; PAI-1, plasminogen activator inhibitor 1; PAP, plasmin–antiplasmin complex (marker of plasmin generation); TAT, thrombin–antithrombin complex (marker of thrombin generation); TFPI, tissue factor pathway inhibitor; tPA, tissue type plasminogen activator; uPA, urokinase type plasminogen activator.

and proteinase inhibitors (antithrombin III, protein C, protein S, thrombomodulin and tissue factor pathway inhibitor). Thrombin cleaves four peptide bonds in fibrinogen, forming soluble monomers and the two negatively charged fibrinogen peptides A and B. The monomers polymerize linearly and laterally to form an insoluble fibrin network or white clot (reviewed by Verstraete, 1991). The coagulation mechanism is normally active at a low level, even without tissue injury. Small elevations in coagulation factor activities and concentrations give rise to a hypercoagulable (Miller, 1992) and therefore also probably to a prethrombotic (Rosenberg & Bauer, 1992) state, associated with increased atherosclerosis and thrombosis. Raised fibrinogen concentration and factor VII coagulant activity (VII_c) are the two clotting factors that have been identified in epidemiological and clinical studies as risk factors for cardiovascular disease (reviewed by Vorster & Venter, 1994; Mennen *et al.* 1996) and which may be influenced by diet (Vorster *et al.* 1997).

Fibrinolysis

The fibrinolytic system, through the proteolytic action of a blood component, plasmin, degrades the fibrin network by digesting fibrin and clotting factors associated with the clot. Two types of plasminogen activators, tissue type (t-PA) and urokinase type (u-PA) are responsible for the conversion of inactive plasminogen to active plasmin. The fibrinolytic process is further regulated and influenced by the concentrations and activities of α -2-antiplasmin, plasminogen activator inhibitors (PAI-1 and PAI-2) as well as thrombin and fibrin itself (reviewed by Van der Bom *et al.* 1996).

The fibrinolytic system is not only responsible for the dissolution of blood clots. It is involved in cell migration and wound healing. Its role in tumour invasion and metastasis, atherosclerosis, thrombosis, embolism and bleeding makes the modulation of fibrinolytic function likely to become an important approach in the prevention of many diseases (Hamsten & Eriksson, 1995).

The fibrinolytic capacity of an individual is the ability to react to fibrin formation. Increased concentration and/or activity of PAI-1 is probably the main cause of impaired fibrinolytic capacity. PAI-1 is the major plasminogen activator inhibitor. High concentrations and activities of PAI-1, possibly because of increased insulin secretion (Vague *et al.* 1986) or insulin resistance (Juhan-Vague *et al.* 1993) have been shown repeatedly in epidemiological and clinical studies to be a risk factor for atherosclerosis and thrombosis (Aznar & Estelles, 1994). PAI-1 is a protein which is highly regulated at a transcriptional level. Because of both up and down regulation of PAI-1 synthesis and secretion, a large number of cellular functions and circulating molecules could influence PAI-1 concentrations.

Platelet aggregation

Platelet aggregation and the formation of a platelet plug is part of the haemostatic mechanism to prevent blood loss from injured vessels. Aggregating platelets participate in fibrin network formation, clot retraction and tissue repair. Damaged endothelium exposes collagen. Platelets adhere to the collagen, form platelet aggregates and release their granule contents, which activate further platelet aggregation and the coagulation cascade. In addition to exposure to collagen, many other factors such as thrombin, thromboxane A, fibrinogen (Mikhailidis *et al.* 1985) and also oxidized low density lipoprotein cholesterol (Weidtmann *et al.* 1995) may

activate platelets. Increased platelet aggregation plays an important role in the development of atherosclerosis and thrombosis (Packham & Mustard, 1986).

Endothelial cell participation

Endothelial cells line blood vessels and passively separate the circulating blood from tissues. One of their major functions is to maintain a nonadhesive antithrombotic luminal surface which contributes to the fluidity of blood. They have also the ability to respond to their physical, chemical and humoral environment by producing numerous substances which influence vascular smooth muscle tone, haemostasis, cellular proliferation and inflammatory and immune responses (Rubanyi, 1993).

The antithrombotic properties of the endothelium are maintained by the synthesis and secretion of anticoagulant and profibrinolytic substances such as prostacyclin, proteins C and S, thrombomodulin, tissue factor pathway inhibitor, glycosaminoglycans (including heparan sulphate) and plasminogen activators tPA and uPA (Dittman & Majerus, 1990).

When endothelial cells are injured or stimulated by substances such as thrombin, or inflammatory and pathological agents, their anticoagulant products are downregulated, and they acquire procoagulant properties by secreting *inter alia* coagulation factors, PAI-1, and tissue factor (Tanaka & Sueishi, 1993), which contribute to the development of atherosclerosis and thrombosis.

Functional endpoints to measure

To diagnose hypercoagulable and prethrombotic states and to monitor effects of dietary or other interventions, it is important that sensitive endpoints or markers that reflect disturbances in the haemostatic balance and which correlate with atherosclerosis and thrombosis should be identified and measured. Unfortunately, few really sensitive markers are available.

In the past, clinical tests have been developed and standardized to monitor bleeding tendencies rather than hypercoagulability. However, recent advances in our understanding of the regulation of haemostatic balance have led to the development of assays which can evaluate aspects of the *in vivo* function and status of the system.

Haemostatic balance can be shifted towards a procoagulant, profibrinolytic, anticoagulant or antifibrinolytic direction, depending on where changes in the system occur. For example, the balance will be shifted towards a procoagulant state during hypercoagulability of plasma and/or impaired fibrinolysis, hyperaggregability of platelets, loss of the anticoagulant properties of vascular endothelial cells, as well as increased blood viscosity and reduced flow with vortices (Rosenberg & Bauer, 1992). Miller (1993) points out that the time is approaching when the hypercoagulant state of plasma, like the hyperlipidaemic states, will be quantified and separated into different types. However, for a proper diagnosis and classification, much more information is needed on the normal ranges of the different markers, their distribution in different age and gender groups, and the compensatory adjustments and adaptations in the different components of the system in an attempt to maintain haemostatic balance.

Other complicating factors are the short plasma half-life of some markers, differences in fasting and postprandial plasma samples, effects of blood sampling methods e.g. stasis which activates endothelium to secrete antithrombotic products *v.* nonstasis, circadian fluctuations of many of the variables, relationships of *in vitro* measurements with *in vivo* events, as well as the

assay method. For example, fibrinogen concentration measured by functional methods based on coagulation time will differ from those measured by immunological, precipitation or gravimetric methods (Palareti *et al.* 1992). Also, more information could be obtained by measuring the different molecular weight variants of fibrinogen (Nieuwenhuizen, 1994).

Table 1 summarizes some of the more sensitive markers of the functions of the coagulation, fibrinolytic, platelet and endothelial cell components of the haemostatic system, and the information they provide. In addition to measurement of the concentration and activity of many coagulation and fibrinolytic factors and enzymes, measurement of factor and enzyme fragments and complexes will give information on *in vivo* coagulation and fibrinolytic processes and turnover. Measurement of fibrin network characteristics is not widely done but can give indications of thrombogenicity, atherogenicity and the potential of the network to be digested by plasmin (Veldman, 1996). Measurements of the concentration and activity of the inhibitors of coagulation will give information on the ability of vascular endothelial cells to respond to stimuli affecting coagulation.

Diet and haemostasis

Effects of energy intake and expenditure

The relationships of energy intake and expenditure with some haemostatic variables have been examined in baseline epidemiological surveys, during energy restricted (weight loss) dietary interventions, during increases in energy expenditure (activity, exercise) and combinations of diet and exercise.

Energy intake and obesity

There is agreement that obesity is associated with a prethrombotic and hypercoagulable state characterized by increased plasma fibrinogen (Vorster *et al.* 1989), increased PAI-1 (Iso *et al.* 1993*b*), decreased tPA secretion after venous occlusion (Licata *et al.* 1995), impaired fibrinolytic capacity (Cepelak *et al.* 1991), and increased plasma viscosity (Fanari *et al.* 1993). Subjects with abdominal (android) obesity may have a more adverse haemostatic profile than those with peripheral (gynoid) obesity. Krobot *et al.* (1992) found a positive correlation between waist-hip ratio and fibrinogen in the second MONICA trial. The same correlation was observed by Avellone *et al.* (1994) in premenopausal women. These authors also found higher factor VII and PAI-1 activities and lower tPA antigen levels after the venous occlusion test in women with abdominal obesity. However, Oosthuizen *et al.* (1996) could not demonstrate significant differences in fibrinogen concentrations in the blood of android and gynoid obese African women and concluded that in these women the putative 'healthy' obesity state was associated with normal lipoprotein profiles but increased plasma fibrinogen.

Energy restricted diets

Energy restricted diets which result in weight loss improve haemostatic profiles. Decreases have been reported in blood viscosity (Poggi *et al.* 1994), factor VII_c (Slabber *et al.* 1992), PAI-1 concentration and activity (Huisveld *et al.* 1990; Peternel *et al.* 1994) and in the tPA/PAI-1 complex (Calles-Escandon *et al.* 1996). Improvement in fibrinolytic activity during weight loss has been reported (Peternel *et al.* 1994) while Calles-Escandon *et al.* (1996) also showed increases in the plasmin-antiplasmin complex. In some studies (Folsom *et al.* 1993; Calles-Escandon *et al.* 1996) the decreases in PAI-1 and improvement in fibrinolytic capacity

correlated with decreases in serum triacylglycerols. However, Peternel *et al.* (1994) reported that improvements in fibrinolytic activity were not accompanied by changes in blood lipids.

The effect of low energy diets and weight loss on plasma fibrinogen is more controversial. Fanari *et al.* (1993) reported a reduction while Gelmini *et al.* (1989) also found that a low energy, salt restricted diet decreased fibrinogen in elderly obese women with hypertension. However, Palareti *et al.* (1994) could demonstrate no effect of weight loss on fibrinogen, while Slabber *et al.* (1992) even found an increase in obese subjects following a very low energy diet. These conflicting results may be explained by effects of weight loss on increasing circulating free fatty acids, which is known to stimulate hepatic fibrinogen production (Pilgeram & Pickart, 1968). Vorster *et al.* (1989) showed that during an 8 week period of diet induced weight loss, fibrinogen levels fluctuated in a similar manner to free fatty acids. During periods of rapid loss, fibrinogen and free fatty acids rose and both decreased during periods of slower weight loss.

Energy expenditure: exercise

Exercise (physical activity or training) protects against coronary heart disease (CHD) (Morris, 1994). It is hypothesized that part of this protection is mediated through effects on haemostasis (Connelly *et al.* 1992). From the available literature it is difficult to gather which haemostatic effects of exercise are caused by increased energy expenditure, usually coupled with increased intake, which by improved energy balance, and which by exercise and physical fitness *per se*. Studies with different intensity and duration of exercise and uncertainties in defining optimal exercise further complicate comparison and interpretation of results.

Nevertheless, there is agreement that fibrinolytic capacity is increased by exercise (Boman *et al.* 1994) especially because of effects on PAI-1 and tPA. One study on patients who had myocardial infarction (Suzuki *et al.* 1992) found that exercise decreased plasminogen, tPA antigen, α -2-antiplasmin, PAI-1 and the plasmin-antiplasmin complex, indicating decreased fibrinolysis. However, the same study found decreases in fibrinogen, factor VIII coagulant activity, thrombin-antithrombin complex, and activities of antithrombin III and plasminogen, indicating a decrease in hypercoagulability. The authors concluded that the decreased fibrinolysis was a result of the decrease in coagulability.

Effects on plasma fibrinogen are less clear. Rankinen *et al.* (1994) reported lower fibrinogen concentrations in active than in inactive men, while Connelly *et al.* (1992) showed in a large group of 3967 men 45–69 years old that strenuous exercise was associated with lower fibrinogen than mild exercise. Factors X and VII were also lowered by exercise in these two studies respectively. However, El-Sayed & Davies (1995) could not demonstrate a lowering of fibrinogen with increased exercise. But their two groups of young healthy subjects had relatively low fibrinogen concentrations of 2.43 and 2.47 g/l. Vanninen *et al.* (1994) reported that the increased fibrinogen found in diabetic subjects could be lowered by exercise accompanied by improved glycaemic control, while Suzuki *et al.* (1992) also showed that exercise training lowered fibrinogen during the recovery phase of patients who had had myocardial infarction. The inference is that it would be difficult to lower a 'normal' fibrinogen level in healthy subjects.

Acute and long term exercise may have separate effects on haemostasis. Acute bouts of dynamic exercise increased tPA activity and decreased PAI-1 activity, but values returned to pre-exercise values after 24 h (Rankinen *et al.* 1995). Wang *et al.* (1995) showed that acute bouts of strenuous exercise transiently increased platelet adhesiveness and aggregability, but that long term endurance training suppressed it.

Little is known about the combined effect of dietary energy restriction and increased expenditure (exercise). Svendsen *et al.* (1996) found that exercise conferred no additional

Table 1. Markers of haemostatic function

Component of the system	Marker	Information provided	Reference
Coagulation			
Coagulation factor concentration	Fibrinogen	Blood viscosity; risk CHD, MI, stroke	Reviewed by Vorster & Venter (1994)
Coagulation factor activity	Factor VII _c	'Upstream', hypercoagulability, risk of CHD, MI	Reviewed by Miller (1993)
Coagulation factor fragments	Prothrombin fragment 1 + 2	Thrombin generation	Tripodi <i>et al.</i> (1993)
	Factor IX activation peptide	'Upstream' hypercoagulability	Reviewed by Miller (1993)
	Factor X activation peptide	Midstream hypercoagulability	Van der Bom <i>et al.</i> (1996)
Coagulation factor complexes	Fibrinopeptides A, B	Fibrin formation: thrombin-catalysed conversion of fibrinogen	
	Thrombin-antithrombin III complex	Thrombin generation, latent activation of coagulation	Uno <i>et al.</i> (1989); Merlini <i>et al.</i> (1995)
	Macromolecular protein complex	Protein complexes in fibrin clot; thrombogenicity	Lipinski <i>et al.</i> (1995)
Fibrin network characteristics	Compaction	Polymerization conditions in plasma	Nair & Dhall (1991)
	Fibre mass-length ratio (diameter)	Thrombogenicity	Collett <i>et al.</i> (1993)
	Permeability	Atherogenicity	Fatah <i>et al.</i> (1992)
	Fibrin content	Potential of clot to be lysed	Carr & Alving (1995)
Fibrinolysis			
Fibrinolytic proenzymes, enzymes (serine proteinases), activators and inhibitors: concentration and activation; complexes	α -2-antiplasmin	Fibrinolytic potential and function; atherogenic and thrombotic risk	Aznar & Estelles (1994)
	tPA antigen		Van der Bom <i>et al.</i> (1996)
	tPA activation (activity)		
	PAI-1 antigen	Inhibition of fibrinolysis	
	PAI-1 activation (activity)	Fibrinolytic activity	
	tPA-PAI-1 complex		
Fibrin degradation products	plasmin-antiplasmin complex		
	D-dimer	<i>In vivo</i> fibrinolysis	Herren <i>et al.</i> (1994)

Platelet aggregation

Aggregation

Activation and aggregation response

β -Thromboglobulin, platelet factor 4, thromboxane β_2 , serotonin
Physical and biochemical changes at activated platelet surface, using monoclonal antiplatelet antibodies

Extent of platelet activation

Extent of platelet activation and thrombotic risk
Conversion of GP IIb/IIIa into receptor
Exposure of membrane protein and expression of binding sites; surface binding of protein: development of platelet procoagulant activity

Shattil (1992)

Shattil (1992)

Shattil (1992)

Activated platelets: whole blood flow cytometry

Endothelial cell function

Synthesis/secretion of anticoagulants

Antithrombin III

AT III forms complexes with coagulation factors that move away from growing clot: may reflect response to coagulation

Rubanyi (1993)
Tanaka & Sueishi (1993)
Dittman & Majerus (1990)
Walker & Fay (1992)

Protein C (antigen)

Protein S

Heparin cofactor III (heparan sulphate)

Thrombomodulin

Natural anticoagulant

AT III, antithrombin III; CHD, coronary heart disease; MI, myocardial infarction; PAI-1, plasminogen activator inhibitor 1; tPA, tissue type plasminogen activator.

benefit to the improvement in fibrinolytic profiles observed in obese post-menopausal women following energy restricted diets.

Therefore, high energy intake and inactivity leading to obesity are associated with hypercoagulability and decreased fibrinolytic capacity, while decreases in energy intake and increases in physical activity are associated with improvement of many haemostatic variables. The mechanisms through which these effects are mediated are not known. Reduced energy intake, weight loss and increased exercise are known to increase insulin sensitivity, which may be related to some haemostatic variables (Juhan-Vague *et al.* 1993).

Effects of alcohol intake

Although alcohol (ethanol) is not strictly regarded as a nutrient, it does provide dietary energy and forms an important part of the diet and social life of many people. Moderate alcohol consumption is known to protect against CHD (Doll *et al.* 1994). This characteristic has been ascribed to beneficial effects on high density lipoprotein cholesterol levels, but new evidence indicates that effects on haemostasis may also contribute. Renaud & De Logeril (1992) hypothesize that the 'French paradox for CHD' (low mortality despite high intakes of saturated fat, and HDL cholesterol levels that are similar to those in other populations with high CHD mortality) may be a result of effects of the high wine consumption of the French population on platelet aggregation.

There is consensus from epidemiological surveys that moderate alcohol consumption is associated with lower plasma fibrinogen (Krobot *et al.* 1992) and with increased fibrinolytic activity (Meade *et al.* 1979), mainly because of increases in tPA (Lee *et al.* 1995). Paradoxically, alcohol consumption increases PAI-1 activity (Marques-Vidal, 1995). An increase in PAI-1 activity was also seen one hour after a meal containing alcohol and persisted after an overnight fast (Veenstra *et al.* 1993). The short term or acute studies also showed decreases in tPA antigen levels and varying effects on platelet aggregation (Veenstra *et al.* 1993; Hendriks *et al.* 1994). However, these postprandial effects were mostly temporary and fasting haemostatic profiles on the following morning were consistent with a lower CHD risk.

Part of the long term antithrombotic effects of moderate alcohol consumption can be ascribed to beneficial effects on platelet aggregation. Struck *et al.* (1994) showed that both red and white wine reduced thrombin initiated platelet aggregation. Renaud *et al.* (1992) found in the Caerphilly prospective heart disease study that alcohol consumption was associated with an increased sensitivity of platelets to thrombin induced aggregation but a decreased aggregation response to ADP and collagen stimulation. The type of fat intake may modulate response of platelets to aggregation stimuli (Renaud *et al.* 1992).

There is some speculation on mechanisms through which alcohol consumption may affect haemostasis. Acetaldehyde, one of the products of alcohol metabolism, could react with coagulation proteins to alter their function (Basista *et al.* 1994) or form adducts with platelets which may interfere with their activation and aggregation (Spertini *et al.* 1992). Another possibility is that ethanol inhibits secretion of phospholipase A₂ (EC 3.1.1.4) with resultant suppressed arachidonic acid release from platelet membranes, and decreased prostanoid formation and aggregation responses (Stubbs & Rubin, 1992). The differences in acute (postprandial) and long term effects suggest that ethanol and its metabolic products may have different and even opposing effects on haemostatic variables.

Effects of dietary fats and oils

The relationships of dietary fat content and type with haemostatic variables have received more attention than those of other nutrients, probably because of the established association of fat intake with CHD, and the early recognition of the powerful effects of the n-3 fatty acids (Eskimo or fish diet) on platelet function.

Total fat intake

There is agreement from results of epidemiological surveys as well as both acute and long term dietary studies that high total dietary fat intakes, rather than type of fat, are associated with increased factor VII_c during fasting or postprandial states (Bladbjerg *et al.* 1994; Mennen *et al.* 1996). Low fat intake correlates with low factor VII_c (Vaisanen *et al.* 1995). There is some evidence that high fat intake may impair fibrinolytic activity. Rankinen *et al.* (1994) reported positive correlations with PAI-1 and tPA. Ho *et al.* (1995) found after a 3-day increase in fat intake that the tPA response to venous occlusion was suppressed, while Kozima *et al.* (1993) showed that PAI-1 was increased and clot lysis time prolonged 8 h after intake of 100 g butter. Ferlito & Di Mauro (1990), however, could not show any adverse effect of an oral fat load on tPA, β -thrombomodulin or D-dimer, a degradation product of cross-linked fibrin. The latter is regarded by many as an indicator of an activated fibrinolytic system and is increased during many pathological states such as deep vein thrombosis.

Little is known about effects of total fat intake on other haemostatic variables. Rankinen *et al.* (1994) reported a positive correlation with factor X, while Vorster *et al.* (1987) found higher fibrinogen and factor IX levels in subjects who habitually followed a diet high in fat, cholesterol, and animal protein and low in fibre compared to a control group on a low fat, high fibre diet.

There is some speculation on the mechanisms whereby total fat intake may influence haemostasis, and especially factor VII concentration and activation (reviewed by Mennen *et al.* 1996). Briefly, it is thought that factor VII may bind with triacylglycerols with a resultant prolonged half-life; that triacylglycerol-rich lipoprotein metabolism may lead to the formation of negatively charged micelles capable of activating factor XII which then activates factor VII; and that the increased activation of the extrinsic pathway will lead to increased prothrombin fragment 1 + 2 and thrombin formation, which will stimulate synthesis of all vitamin K dependent coagulation factors.

Theoretically, fat intake may therefore influence haemostasis indirectly through effects on blood lipoproteins. This is supported by correlations between blood lipids and haemostatic variables. Serum triglycerides are positively associated with factor VII_c (Assmann & Schulte, 1992), bleeding times (Mundal *et al.* 1994) and with tPA and PAI-1 (Iso *et al.* 1993a). Apo B levels also correlate with factor VII_c (Vaisanen *et al.* 1995) while high density lipoprotein cholesterol has a negative correlation with fibrinogen (Iso *et al.* 1993b) and Lp (a) a positive one (Howard *et al.* 1994).

It can therefore be expected that lowering fat intake should improve haemostatic profiles. Miller (1993) reviewed the evidence that treatment of hypertriglyceridaemia leads to lowering of factor VII_c, and concluded that some lipid lowering drugs protect against CHD by reducing coagulability of blood. There is also some evidence that lower fat intakes decrease PAI-1 (Sundell *et al.* 1991). The absence of effects reported by Marckmann *et al.* (1992) and Velthuis- Wierik *et al.* (1996) who had relatively modest fat intake reductions in their study designs, and also the studies of Vorster *et al.* (1987) and Marckmann *et al.* (1993) suggest that only

substantial reductions in fat intake, or concomitant changes in type of fat and other nutrient intakes, will have significant beneficial effects on haemostasis.

In addition to increased levels of factor VII_c 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 venous occlusion. This haemostatic profile is associated with an increased risk of thrombosis.

Type of fatty acid

There is an increasing perception and growing evidence that the relationships between CHD and intakes of fatty acids with different chain lengths and degree of saturation are mediated not only through effects on serum lipids, but also through effects on haemostatic variables (Dupont *et al.* 1996). Ulbricht & Southgate (1991) suggested that the atherogenic or hyperlipidaemic fatty acids are lauric (C12:0), myristic (C14:0) and palmitic (C16:0) acids, while myristic, palmitic and stearic (C18:0) acids are the thrombogenic fatty acids. The long chain polyunsaturated n-6 (linoleic, C18:2) and the n-3 fatty acids from fish oils are thought to be antiatherogenic and antithrombotic.

The above is an oversimplification. Unfortunately, the relationships of the different fatty acids with haemostatic variables are much more complex. For example, stearic acid, compared with lauric and myristic acids, decreased fasting factor VII_c in long term dietary interventions (Bladbjerg *et al.* 1995) but increased factor VII_c postprandially (Tholstrup *et al.* 1996). Also, a particular fatty acid may have both procoagulant and anticoagulant activities. Bladbjerg *et al.* (1995) showed that while stearic acid compared with lauric and myristic acid diets decreased factor VII concentration and activity as well as factors II, X, protein C and prothrombin fragment 1 + 2, it increased plasma fibrinogen. From the available literature it is difficult to conclude what the effect of the habitual, long term intake of a particular fatty acid on haemostatic balance will be.

Nevertheless, there are indications that increased intake of the monounsaturated fatty acids lowers von Willebrand factor in non-insulin dependent diabetes mellitus patients (Thomsen *et al.* 1995), and that it decreases PAI-1 levels and activity in healthy young men (Lopez-Segura *et al.* 1996). None of these studies showed any effects of monounsaturated fatty acids on a variety of other haemostatic parameters, including fibrinogen, thrombin-antithrombin complex, prothrombin fragment 1 + 2, plasminogen, α -2-antiplasmin and tPA.

The effects of different fatty acids on platelet function are intriguing. Mutanen *et al.* (1995) showed that platelets are less sensitive to aggregating agents in subjects following diets with highly saturated fat than in those on unsaturated fat. Renaud *et al.* (1986) found that reduction in saturated fat intake from 16.2% to 9.9% of dietary energy over a period of one year decreased thrombin stimulated platelet aggregation by 81% but increased ADP stimulated aggregation by 54%. Freese & Mutanen (1995) further showed that while fat intake increased factor VII_c postprandially, it decreased collagen induced platelet aggregation.

Effects of fish and fish oil intakes

Although fish intake does not grant a population immunity from CHD (Katan, 1995) protective effects of moderate intakes have been demonstrated (Kromhout *et al.* 1985). These could be mediated through effects of the long chain, highly unsaturated n-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid in fish on haemostatic variables.

The relationships of intakes of fish, fish oils, eicosapentaenoic acid and docosahexaenoic acid with haemostatic variables have been studied extensively. Their inhibitory effects on platelet aggregation with resultant prolonged bleeding times through effects on prostanoid metabolism are well known (Dyerberg, 1986). But fish intake also affects coagulating factors and fibrinolytic enzymes. High intakes are associated with lower plasma levels of fibrinogen, factor VIII and von Willebrand factor (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 (Høstmark *et al.* 1988), others found no effect (Brown & Roberts, 1991) while some even demonstrated increases (Schmidt *et al.* 1992). Haglund *et al.* (1991) showed that fish oil lowered fibrinogen levels only when it contained 1.5 IU vitamin E/g and not when it contained 0.3 IU/g. Oosthuizen *et al.* (1994) showed that a vitamin E-rich fish oil lowered plasma fibrinogen in women who had relatively high initial values (from 3.23 ± 0.96 to 2.64 ± 0.55 g/l) but not in men who had low baseline values (2.03 ± 0.62 g/l). Vitamin E is known to protect unsaturated fatty acids from oxidation. The possibility that oxidized fatty acids are responsible for the observed increases in fibrinogen should therefore be examined.

Although the safety of fish oil *re* bleeding episodes and haemostasis in patients with CHD has been demonstrated (Eritsland *et al.* 1995), the increases in fibrinogen seen in some studies, especially in diabetic patients (Haines *et al.* 1986) question the safety of these supplements. In several studies it was also reported that increases in PAI-1 occurred, despite decreases in triglyceride levels with fish oil supplementation, in both diabetic (Boberg *et al.* 1992) and healthy (Oosthuizen *et al.* 1994) subjects. In addition, Herrmann *et al.* (1995) reported decreases in tPA with a supplement of 12 g fish oil in CHD patients. However, fish oil supplementation has other anticoagulant effects. Oosthuizen *et al.* (1994) reported decreases in factors V_c, VII_c and X_c in women with initial high levels, while Osterud *et al.* (1995) showed a decrease in prothrombin fragment 1 + 2 with supplements containing whale oil.

From these studies one might conclude that fish oil inhibits platelet aggregability and lowers some coagulation factors and thrombin generation, but also that it impairs fibrinolytic potential by lowering tPA and raising PAI-1 in some circumstances. Marckmann (1995) is of the opinion that the antifibrinolytic effect of the fish oil fatty acids might counteract their antithrombotic influence on platelet function.

Effects of dietary carbohydrates

The prudent diet, recommended to lower risk of developing chronic diseases of lifestyle, is high in carbohydrate, including fibre or nonstarch polysaccharides (NSP), low in fat, and relatively higher in plant than animal protein. Studies looking at the independent effect of dietary carbohydrate on haemostasis should therefore control for amounts and types of fat and protein. Because different types of NSP have different physiological effects on gastrointestinal function and lipid metabolism, it can be expected that effects on haemostasis will also differ. Fehily *et al.* (1982) 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 with increased NSP intake by diabetic patients, but they found that factors VII_c and X_c decreased on the higher fibre intake in non-insulin dependent patients, and factor VIII antigen decreased in the insulin-dependent ones. If fibre intake influences plasma fibrinogen, it is probably owing to the gel-

forming NSP components. Koepf & Hegewisch (1981) found that supplementing the daily diet of 10 diabetic children with 0.45 g guar gum/kg for 4 weeks reduced fibrinogen level in 7 of the children from a mean of 3.13 to 2.63 g/l. Another NSP, konjacglucomannan, significantly lowered plasma fibrinogen in an obese baboon model (Venter *et al.* 1990) and the obese Zucker rat (Venter *et al.* 1991).

NSP probably do not 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 given 36 g pectin daily for 3 weeks. Sanders & Roshanai (1992) also found no effect on platelet function of a vegetarian diet which contained no n-3 fatty acids.

Much can be learned about the effects of NSP by analysing the diets and disease risk profiles of vegetarians. Haines *et al.* (1980) showed that 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 antithrombin III.

High fibre intakes are associated with increased fibrinolysis. Sundell & Ranby (1993) demonstrated 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) reported that a 'high complex CHO, low-fat' diet followed for 3 weeks significantly reduced plasminogen, tPA and PAI-1, while fibrinogen tended to decrease ($P=0.07$). It is however difficult to dissect effects of NSP from those of fat or other factors in these studies.

High NSP diets, therefore, affect coagulation and fibrinolysis. The effects of starch, resistant starch and other carbohydrates such as the oligosaccharides have not been examined. Nor have the possible mechanisms, through which haemostatic effects of NSP may be mediated, received much attention. Venter & Vorster (1989) hypothesized that the colonic production of short chain fatty acids may contribute. The recent work of Veldman (1996) supports this concept. He reported that pectin intakes of 15 g/d increased blood acetate levels, decreased free fatty acid concentrations and improved blood viscosity, fibrin network compaction, fibre diameter, permeability, fibrin content, and lysis of the clot in hypercholesterolaemic subjects.

Effects of micronutrients

Very few studies have reported effects of vitamins and minerals on coagulation and no clear mechanisms are established. 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 and high PAI-1 levels, and therefore with impaired fibrinolytic activity. Hankey *et al.* (1996) also found positive associations between plasma retinol concentration that had been standardized for total plasma lipids and PAI-1 activity and factor VII_c in patients with angina. In contrast, Van Giezen *et al.* (1993), using a rat model, showed that retinoic acid increased fibrinolysis by selectively increasing tPA without affecting PAI-1, uPA, plasminogen or α -2-antiplasmin. Their results were confirmed by Van Bennekum *et al.* (1993) in a vitamin A deficient rat model. *In vitro* work by Kiserud *et al.* (1995) showed that vitamin E prevented hyperfibrinogenaeamic

effects of some polyunsaturated fatty acids, probably by preventing oxidation of these fatty acids.

The effects of some micronutrients on platelet function have been studied. Chen *et al.* (1994) found that rats who were vitamin E deficient showed a prothrombotic state which could be rectified with vitamin E supplementation. Nadler *et al.* (1992) found that intravenous and oral magnesium supplementation of non-insulin dependent diabetic subjects reduced platelet aggregability.

It is possible that vitamins affecting homocysteine metabolism could also be indirectly involved in haemostasis. Stamler & Slivka (1996) reviewed the evidence which shows that homocysteine induces activation of factors V and XII, and that it is associated with inhibition of protein C because it acts as a competitive inhibitor for thrombin binding to thrombomodulin. Therefore, a detailed investigation of the relationship between homocysteine metabolism and haemostasis may reveal the importance of folate and vitamin B₆ for normal haemostasis.

Effects of specific foods

There is some evidence that specific foods or substances in foods such as the flavonoids or polyphenols may influence haemostasis. Petroni *et al.* (1995) showed for example that 2-(3,4-dihydroxyphenyl-1)-ethanol, a phenolic component with potent antioxidant properties isolated from virgin olive oil, inhibited *in vitro* platelet aggregation and thromboxane formation. Strongly flavoured foods such as onions (Menon *et al.* 1968), garlic (Resch & Ernst, 1995), 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 were influenced by tea drinking. Vorster *et al.* (1992) also reported that an increased egg intake from 2 to 7 and 14 per week in young healthy men over a period of 5 months did not influence coagulation or fibrinolytic (plasminogen) profiles. The association of high intakes of fruits, vegetables and root vegetables with lower PAI-1 activity reported by Nilsson *et al.* (1990) could possibly be related to the fibre and/or vitamin C content of these products.

Comments, conclusions and recommendations

There is no doubt that many dietary substances influence the haemostatic system. There is enough evidence to conclude that some of the protective effects of diet against the development of atherosclerosis, thrombosis and resultant CHD are mediated through effects on haemostasis. Other than the function of vitamin K in the synthesis of some coagulation factors, it is too early to reach conclusions regarding the *essentiality* of nutrients for haemostasis. However, with the exception of platelet function which seems to be separately affected, it is clear that both procoagulant and anticoagulant events may be influenced by the same food or nutrient. This is probably the result of the interrelationships between different components of the system, and the compensatory adjustments in one part when another is affected, in an attempt to maintain haemostatic balance. Therefore, to shift this balance, substantial dietary adjustments would probably be needed.

There is not enough evidence to recommend a diet at a population level to protect against hypercoagulability and risk of atherogenesis and thrombogenesis. Much more research is needed. Nevertheless, it seems that the prudent low fat, high fibre diet, rich in antioxidants from

fruits and vegetables, low in salt, which contains fatty fish and moderate amounts of alcohol, and which would balance energy requirements to maintain ideal body weight, is not only hypolipidaemic but will also protect against hypercoagulability.

The physiological and pathological mechanisms through which diet, as well as other lifestyle factors, influence the different components of the haemostatic system need more clarification before different types of hypercoagulability can be identified, prevented or treated. In this research, measurement of appropriate functional endpoints or markers which reflect the balance in the system (see Table), as well as good dietary control and careful selection of subjects suffering from hypercoagulability, would be necessary. These subjects will probably also have other risk factors for CHD (Mitropoulos, 1994; Genest & Cohn, 1995) or suffer from diabetes (Simpson *et al.* 1982) or syndrome X (Dae *et al.* 1993). The latter is a cluster of metabolic abnormalities associated with resistance to insulin mediated glucose uptake, which includes hypertension and high plasma concentrations of triacylglycerols and insulin.

Much has been learned about the determinants of variances in serum lipoproteins by comparing different ethnic groups. Comparisons of fibrinogen levels between Japanese and Europeans (Iso *et al.* 1993b), Europeans and Afro-Americans (Folsom *et al.* 1991) and South Africans of African, Indian, and European origins (Venter *et al.* 1992) and fibrinolytic activity in Europeans and Africans (Jerling *et al.* 1994) indicate that this is an area in which more research will contribute to a better understanding of factors which influence haemostasis. Future research on genetic determinants of haemostatic variables and genetic–environmental interactions will also contribute. A better understanding of these may lead to dietary treatments of individual patients suffering from hypercoagulability, and improved recommendations on a population level for the prevention of chronic diseases

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