Dietary treatment of thrombogenic disorders related to the metabolic syndrome

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The increased risk of coronary heart disease associated with the metabolic syndrome may be partially explained by prothrombotic deviations of the haemostatic system. Individuals with insulin resistance, dyslipidaemia and obesity are characterized by elevated plasma fibrinogen and factor VII coagulant activity levels and raised concentrations of plasminogen-activator inhibitor, the main inhibitor of endogenous fibrinolysis. These haemostatic abnormalities may be corrected with dietary treatment of the underlying clinical disorder. Dietary trials of diseased and healthy volunteers suggest that the optimal antithrombotic diet is a low-fat diet with a high content of foods rich in complex carbohydrates and dietary fibre. The dietary fatty acid composition has a profound effect on blood lipids, but seems of minor importance for the haemostatic system.

Coronary heart disease: Factor VII: Fibrinolysis: Diet: Lipids: Dietary fibre

The metabolic syndrome represents a cluster of metabolic abnormalities associated with increased risk of CHD and centred around insulin resistance (Reaven, 1988). In addition to insulin resistance and hyperinsulinaemia, classical components of the metabolic syndrome are dyslipidaemia with elevated triglycerides and/or low HDL cholesterol plasma levels and obesity. According to what is known about CHD pathogenesis, the increased risk of CHD seen in patients with the metabolic syndrome must be explained by an increased tendency to the formation of vulnerable atherosclerotic plaques, a prothrombotic imbalance of the haemostatic system, or – maybe most likely – a combination of the two (Fuster *et al*. 1992*a*, *b*). This presentation focuses on evidence demonstrating that the haemostatic balance, i.e. the delicate balance between procoagulant and fibrinolytic factors, is shifted in the direction of augmented thrombogenicity in subjects with the metabolic syndrome. Also, findings are discussed which suggest that the haemostatic imbalance of such patients can be corrected or even normalized by a change of diet.

The concept of haemostatic balance

The tendency of an individual to form a coronary thrombus in response to plaque rupture depends on the balance between procoagulant and fibrinolytic forces at the site of intimal injury (Astrup, 1958). Platelets and coagulation factors are the primary determinants of blood coagulability, whereas the fibrinolytic system represents the sole endogenous system capable of resolving fibrin and thrombi (Fig. 1). Epidemiological observations indicate that elevated plasma levels of factor VII coagulant activity and fibrinogen are both associated with increased risk of coronary thrombosis, suggesting that these variables are particularly important in the coagulation process (Meade *et al*. 1986; Thompson *et al*. 1995). This may be explained by the fact that both hold key positions in the coagulation system: coagulation factor VII as the *in vivo* trigger of the coagulation cascade when ruptured plaques expose their tissue factor content, and fibrinogen as the final substrate of the coagulation system (Marckmann, 1995; Marckmann *et al*. 1998*a*). On the other side of the balance, the activity of the tissue-type plasminogen activator (tPA) is the main determinant of the fibrinolytic capacity because tPA is capable of effectively cleaving fibrin-bound plasminogen (present in excess in plasma) to plasmin, the fibrin degrader (Jespersen, 1988). The main inhibitor of intravascular tPA activity is the plasminogen activator inhibitor PAI-1. According to this understanding and interpretation of the extremely complex haemostatic system, shifts in the haemostatic balance may be assessed by simultaneous measurements of plasma factor VII activity, fibrinogen concentrations and tPA activity or PAI-1 levels. The assessment is probably not fully reliable in the case of major changes in platelet count and function, but this is seldom seen in response to dietary changes (consumption of several grams of very long-chain *n*-3 polyunsaturated fatty acids is the only well known example of marked diet-induced changes in platelet function).

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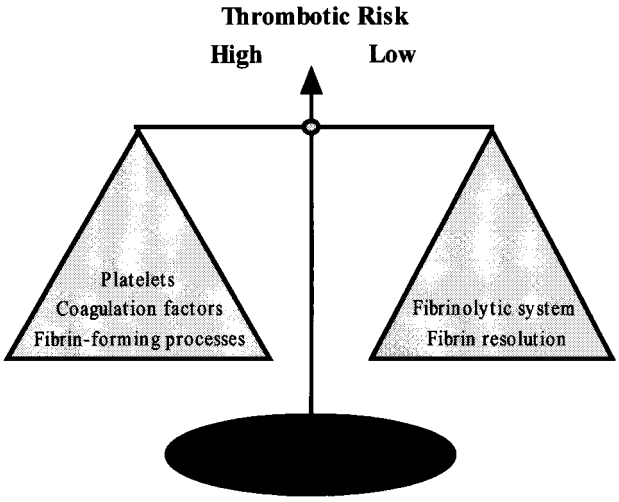

Fig. 1. The haemostatic balance between processes leading to fibrin formation on the one side and the process of fibrin resolution (fibrinolysis) on the other side determines the risk of thrombosis in the case of rupture of atherosclerotic plaques.

Haemostatic abnormalities in hyperinsulinaemic, hypertriglyceridaemic and obese subjects

Numerous cross-sectional epidemiological studies have investigated the association between characteristics of the metabolic syndrome and plasma levels of haemostatic factors. In essence, their findings are unequivocal: hyperinsulinaemia, hypertriglyceridaemia and obesity are all associated with prothrombotic deviations in the haemostatic balance. The primary abnormality observed in patients with insulin resistance/hyperinsulinaemia is an elevation of plasma PAI-1 concentrations (Table 1) (Juhan-Vague *et al*. 1991, 1993, 1996). Due to the elevated PAI-1 levels, the circulating concentration of tPA-PAI-1 complexes and tPA antigen (counting both free and complex-bound tPA molecules) are also high in such patients. The physiological result is a decline in tPA activity shifting the haemostatic balance in the direction of increased thrombogenicity (cf. Fig. 1). This imbalance is augmented by minor procoagulant increases in factor VII and fibrinogen in hyperinsulinaemia.

Hypertriglyceridaemia is primarily characterized by elevated plasma factor VII antigen and activity levels, whereas the association between triglycerides and fibrinogen is weaker and more inconsistent (reviewed by Miller, 1993; Marckmann, 1995). The coexistence of high triglycerides and increased factor VII activity is particularly obvious in postprandial blood samples. High-fat meals leading to postprandial triglyceride spikes also cause postprandial activation of factor VII zymogen, and consequently increased factor VII coagulant activity is observed under these circumstances (Larsen *et al*. 1997). Many studies also found a positive correlation between plasma triglycerides and PAI-1 levels (Marckmann *et al*. 1992*a*).

Table 1. Haemostatic abnormalities associated with main components of metabolic syndrome

Components	Coagulation system	Fibronolytic system	Haemostatic balance
Insulin resistance, hyperinsulinaemia	FVIIc (↑) Fibrinogen (↑)	PAI-1 ↑↑	Prothrombotic
Hypertriglyceridaemia	FVIIc ↑↑ Fibrinogen (↑)	PAI-1 ↑	Prothrombotic
Obesity	FVIIc ↑↑↑ Fibrinogen ↑	PAI-1 ↑↑↑	Prothrombotic

In moderate and severe obesity, procoagulant and antifibrinolytic deviations of the haemostatic system are both marked (Meade *et al*. 1979; Folsom *et al*. 1991). In a study of 36 subjects weighing around 100 kg and having an average BMI of 35.5 kg/m^2, plasma levels of factor VII coagulant activity were almost twice the normal, fibrinogen concentrations were 10–20 % higher than in healthy subjects, and PAI-1 concentrations were elevated two- to threefold (Marckmann *et al*. 1998*b*). Accordingly, obesity appears to be an important determinant of increased blood thrombogenicity, which could partly explain the increased CHD morbidity and mortality in obese individuals, including those suffering from the metabolic syndrome.

Dietary management of prothrombotic states

The prothrombotic state seen in patients with hyperinsulinaemia, hypertriglyceridaemia and/or obesity can be

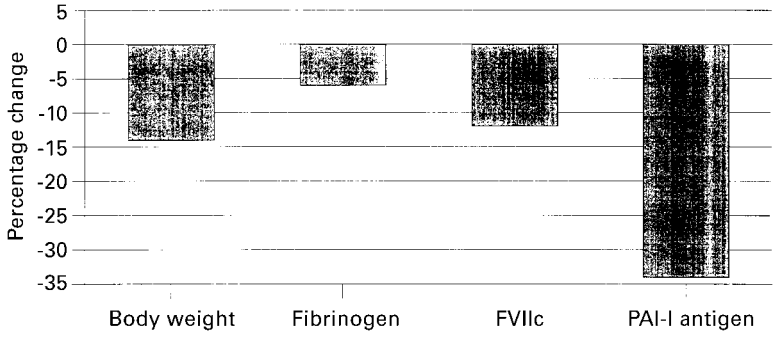

Fig. 2. Average changes (%) from baseline in body weight, plasma fibrinogen, factor VII coagulant activity and PAI-1 antigen in 36 obese subjects with an initial average body weight of 98 kg. Blood samples were collected at baseline and after 24 weeks' weight maintenance at reduced body weight (Marckmann *et al.* 1998*b*). All changes were highly significant.

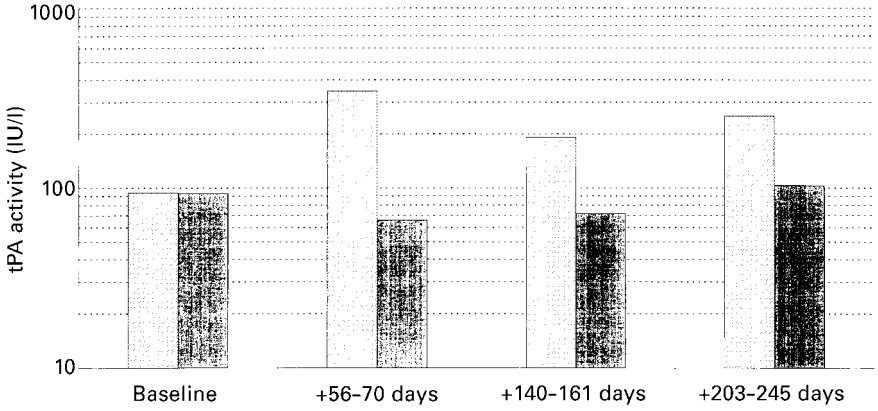

Fig. 3. Median plasma tPA activity (IU/litre) of 16 young healthy males at baseline and during 8 months on a low-fat, high-fibre experimental diet (light bars). Dark bars represent median tPA activity in a parallel control group of another 16 young healthy males (Marckmann *et al.* 1993). The increase in the intervention group was highly significant.

corrected by a change in diet (Simpson *et al*. 1983; Folsom *et al*. 1993; Lindahl *et al*. 1998, 1999; Järvi *et al*. 1999). We studied 36 obese individuals, mostly females, who were slimmed on low-calorie diets over 4–8 weeks and who were then weight maintained on diets moderately low in total fat (Marckmann *et al*. 1998*b*). After an average weight loss of 14 kg and 24 weeks' subsequent weight maintenance we found remarkable improvements in their haemostatic profile along with desirable changes in blood lipids. Plasma factor VII coagulant activity fell by 12 %, fibrinogen was 6 % lowered, and a 34 % decline in PAI-1 as compared with baseline was also observed (Fig. 2). These changes might – when combined – account for a 20–40 % reduction in risk of coronary thrombosis according to risk estimates obtained from epidemiological studies. Our findings are in good agreement with observations from other slimming trials and confirm that the beneficial impact on the haemostatic profile of weight loss is maintained as long as weight regain is prevented (Folsom *et al*. 1993; Mavri *et al*. 1999). Dietary-induced weight loss is accompanied by decreases in plasma triglyceride and insulin levels and *vice versa*, and it is difficult to identify the true train of causation. However, multivariate analyses tend to show that body fatness has an independent and dominant role with respect to PAI-1 levels (Charles *et al*. 1998; Mavri *et al*. 1999).

In the classical study by Simpson *et al*. (1983), the impact on haemostatic variables of dietary treatment of patients with hypertriglyceridaemia was investigated. The dietary treatment included calorie and fat restriction (maximum 35 E% fat), fat modification (P/S ratio 0.8), and increased dietary fibre intake from cereals and vegetables, and lasted 6 months. It led to the desired reduction in triglycerides (from 6.8 to 3.1 mmol/litre). The haemostatic changes were very marked. There was a 20 % decline in factor VII coagulant activity, an insignificant 10 % fall in fibrinogen, and a 50 % increase in fibrinolytic activity as assessed from the method available at that time (clot lysis time). Body weight changes were also seen, however (10 kg average weight loss), and therefore no conclusions about the independent impact of triglyceride lowering on haemostatic variables can be drawn from this or similar studies. Other observations suggest that the plasma triglyceride concentration itself has a very limited influence on haemostatic variables (Mitropoulos *et al*. 1992; Marckmann *et al*. 1994, 1997; Miller *et al*. 1998). The common coexistence of hypertriglyceridaemia and prothrombotic deviations of the haemostatic system therefore seems to be explained by an underlying confounding mechanism. Maybe the 24 h total flux of products derived from lipoprotein lipase digestion of triglyceride-rich lipoproteins is the common denominator linking not only hypertriglyceridaemia, but also hyperinsulinaemia and obesity with increased coagulability and impaired endogenos fibrinolysis.

Additional benefits of choosing the optimal diet

Whatever the mechanism, dietary correction of hyperinsulinaemia, hypertriglyceridaemia and obesity is associated with desirable effects on the haemostatic balance in most cases. Studies of non-obese, healthy individuals have demonstrated that it is possible to influence blood thrombogenicity further by diet modification, even in the absence of any metabolic abnormality related to the metabolic syndrome (Miller *et al*. 1986; Brace *et al*. 1994; Avellone *et al*. 1998). We found that diets with a fat content around 30 E%, a saturated fat content below 10 E%, and rich in mixed dietary fibre derived from grains, vegetables, and fruit (more than 3 g/MJ in total) led to important 5–10 % lowerings of factor VII coagulant activity and enhanced fibrinolytic capacity as compared with more fatty diets (around 35–40 E%) with low fibre contents (around 2 g/MJ) (Marckmann *et al*. 1993, 1994) (Fig. 3). It is important to focus not only on total fat, but also on dietary fibre in order to compose the optimal anti-thrombotic diet. In one randomized cross-over study we found that reducing total fat from 40 to 30 E% and replacing fat with very low-fibre carbohydrate foods (sucrose-rich foods) had no impact on the haemostatic variables of interest (Marckmann *et al*. 1992*b*). In another very recent study, we confirmed in a direct comparison that starchy foods have a more favourable impact than sucrose on factor VII coagulant activity (Marckmann *et al*. 1999). Correspondingly, Järvi *et al*. (1999)

recently reported that diets varying in glycaemic index but otherwise identical affected PAI-1 activity of type 2 diabetics differentially. In contrast to the high glycaemic index version of the diet, the low glycaemic index version caused a 50 % decline and normalization of PAI-1 activity among the study subjects. Based on observations such as these, it seems justified to conclude that the optimal anti-thrombotic diet for individuals suffering from the metabolic syndrome is not just a diet leading to weight loss, or reduced plasma levels of triglycerides and insulin. The optimal anti-thrombotic diet also has to have a low fat content and to be rich in dietary fibre of mixed origin (Marckmann & Jespersen, 1996).

The impact of dietary fat quality

Dietary fat quality is a very important and dominant regulator of the metabolism and plasma concentration of lipoproteins. Unsaturated fats are associated with more favourable plasma lipid profiles than saturated fats. However the evidence accumulating during recent years indicates that the impact of the dietary fatty acid composition (saturated, monounsaturated, *trans* or *n*-6 polyunsaturated) on haemostatic factors is quite limited (Heinrich *et al*. 1990; Miller *et al*. 1991; Marckmann *et al*. 1992*c*; Almendingen *et al*. 1996; Larsen *et al*. 1997; Mutanen & Aro, 1997; Mennen *et al*. 1998; Allman-Farinelli *et al*. 1999). Neither acute nor longer-term effects have been reported. The only exceptions reported so far are from studies in which very special and uncommon edible fats were eaten in large quantities (high-stearic acid shea fat from an African nut, or medium-chain fatty acids) (Tholstrup *et al*. 1994; Sanders *et al*. 1996). The very long-chain polyunsaturated *n*-3 fatty acids (*n*-3 VLCPUFA) constitute another important exception: if eaten in large amounts (more than 2–3 g daily as compared with common intakes of 0.2–0.4 g daily in most societies) they may raise the plasma concentration of the plasminogen activator inhibitor, PAI-1 (reviewed by Schmidt, 1997). The *n*-3 fatty acids seem to have no significant effects on the coagulation system, including factor VII, however.

Most recently, the first reports have been published demonstrating an impact of the fatty acid composition of background diet on meal responses with respect to factor VII activation. Volunteers living on a diet based on olive oil or oleic acid-rich milk fat during the preceding weeks were found to exhibit a somewhat attenuated postprandial factor VII activation in response to a standard fat load, as compared with what was seen after diets based on saturated fat (Roche *et al*. 1998), rapeseed or sunflower oil (Larsen *et al*. 1999), or conventional milk fat (Tholstrup *et al*. 1999). The clinical implication of this finding is not known.

Conclusions

The metabolic syndrome and its main components (insulin resistance, hypertriglyceridaemia and obesity) are associated with a prothrombotic imbalance of the haemostatic balance. Blood coagulation factor VII activity and fibrinogen concentrations are raised and endogenous fibrinolysis suppressed. Almost any dietary therapy will correct the haemostatic abnormalities to some extent. The optimal anti-thrombotic dietary therapy should focus on normalization of body weight and ensure a dietary fat content around 30 E% or less, and a dietary fibre content of 3 g/MJ or more. The dietary fatty acid composition is of little importance for the thrombogenicity of blood, but has a very essential impact on blood lipids and atherosclerosis. Individuals with the metabolic syndrome will therefore also benefit importantly from a reduction of dietary saturated fat to less than 10 E% (preferably 5–8 E%).

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