

Invited Commentary

Obesity and thrombotic risk

The link between obesity and thrombotic risk represents an important issue since the prevalence of obesity in adults has increased rapidly in the last decades, especially in Western countries although this is an emerging health issue elsewhere too. Estimates from the WHO indicate that globally there are more than 300 million obese adults.

From a physiological point of view, adipose tissue is the major site of storage of TAG. An increase in adipose tissue mass, however, often triggers pathophysiological events, such as inflammation, insulin resistance, hypertension and dyslipidaemia, all involved in promoting the development of atherosclerosis. Besides these metabolic disorders, obesity is associated with abnormalities of haemostasis, potentially leading to a pro-thrombotic state. Tendency to form thrombi, either arterial or venous, is increased 1.5- to 2.5-fold in obese compared with lean subjects^(1,2) and may thus play a key role in the higher risk of CVD in obese individuals.

Dysfunctional adipose tissue secretes adipokines, such as leptin and adiponectin⁽³⁾, along with pro-inflammatory cytokines. These influence the production of clotting factors (fibrinogen and factor VII) by the liver and directly contribute to an enhanced pro-thrombotic state.

Fibrinogen, the final actor in the coagulation cascade, is the substrate for thrombin and is also essential for platelet aggregation. Elevated fibrinogen levels are strongly, consistently and independently related to cardiovascular risk⁽⁴⁾, although synthesis by adipocytes has not been described so far. In addition, elevated fibrinogen levels could reflect a pro-inflammatory state, a hallmark of obesity. The factor VII coagulant activity (FVII:c) has been shown to be specifically linked to elevated concentrations of TAG-rich chylomicrons and VLDL⁽⁵⁾, lipid abnormalities often seen in obesity. Obesity, and in particular an abdominal type of body fat distribution, is associated with elevated levels of plasminogen activator inhibitor (PAI)-1 antigen and activity. PAI-1, the main inhibitor of fibrinolysis, is expressed in adipose tissue⁽⁶⁾ and the greater the fat cell size and adipose tissue mass, the larger is the adipose contribution to circulating PAI-1. Reduced fibrinolysis is potentially very harmful because it may facilitate fibrin deposition, even without preceding enhanced coagulation. A number of studies have associated the up-regulation of PAI-1 to a state of low-grade inflammation. PAI-1 synthesis is, indeed, stimulated by TNF- α , a pro-inflammatory cytokine produced by adipose tissue, and chronically elevated in obese states⁽⁷⁾. Besides TNF- α , the multifunctional cytokine transforming growth factor- β can also raise PAI-1 activity in plasma⁽⁷⁾. Of note, and similarly to TNF- α , production of this latter cytokine is increased in obese adipose tissue. Additionally, a recent hypothesis suggests hypoxia in adipose tissue as a major factor eliciting low-grade inflammation and

its sequelae⁽⁸⁾; with the increase of adipose tissue mass, the existing capacity of fat tissue vasculature will be insufficient to ensure normoxia.

Obesity is in part characterised by increased platelet function, possibly involving leptin, the adipokine produced by adipocytes that acts as a regulator of food intake and energy expenditure. Elevated leptin concentrations are an independent risk factor for CVD⁽⁹⁾. Importantly, the leptin receptor has been found in platelets⁽¹⁰⁾ and its activation may potentiate aggregation in response to agonists. Additionally, globular adiponectin, a circulating cleavage product of adiponectin, induces platelet aggregation and exhibits pro-inflammatory properties^(11,12).

Besides platelet activation, a procoagulant state is characteristic of obese individuals. This involves major plasma proteins, as already mentioned, as well as tissue factor that can be synthesised by adipocytes and mononuclear cells upon exposure to leptin and pro-inflammatory cytokines^(13,14). Tissue factor, in complex with factor VIIa, catalyses the conversion of factors IX and X into their activated forms, leading to the generation of thrombin. Increased tissue factor levels have been detected in atherosclerotic conditions⁽¹⁵⁾ and in obese individuals⁽¹⁶⁾, providing further evidence that a pro-thrombotic state accompanies obesity.

Among intervention strategies, either diets (low-fat, high-fibre) or lifestyle (physical activity) can be effective in improving obesity-associated pro-thrombotic risk⁽¹⁷⁾. In an article published in this issue of the *British Journal of Nutrition*, Bladbjerg *et al.*⁽¹⁸⁾ compared the long-term (6 months) effect of three different diets (control, low-fat and high-MUFA) on haemostatic variables in healthy obese subjects after weight loss. Notably, the study was carried out based on a highly controlled and validated supermarket model. Results are of definite interest since the low-fat and control diets, but not the high-MUFA diet, reduced fibrinogen concentration without affecting clotting variables (FVII:c and prothrombin fragment F1 + 2). The lack of effect of the high-MUFA diet might be possibly attributed to the higher BMI of patients assigned to this dietary intervention. It should be noted that MUFA-rich diets exert a favourable effect on platelet function in high-risk patients⁽¹⁹⁾.

Rather unexpectedly, reductions in concentrations of fibrinogen and D-dimer occurred in the low-fat and control diet groups, in spite of a significant increase in body weight. As suggested by the authors, lowered D-dimer may, in turn, reduce liver fibrinogen synthesis by an IL-6-mediated effect.

PAI-1 levels increased markedly during the 6-month intervention, irrespective of the diet, possibly due to increased BMI (detected in all treatment groups) or to seasonal variations, as suggested by the authors.

An acceptable conclusion is that the dietary intervention protocol reduces low-grade inflammation rather than the pro-thrombotic profile in obese individuals, although a potentially favourable effect on clotting might be obscured by the 3-month standardisation period that resulted in weight loss. Of note, results from the study support the notion that duration and rate of weight reduction may be critical when assessing the beneficial effect of fat loss. Indeed, a previous study from the same group, carried out in obese subjects who underwent a 20-week controlled intervention with a low-energy diet for weight loss and maintenance, failed to detect fibrinogen reduction in spite of a significant weight loss⁽²⁰⁾.

Overall, from this study it emerges that fibrinogen reduction by a low-fat-diet could be considered of potential significance for reducing the low-grade inflammatory status in obesity, rather than for the control of cardiovascular risk.

There are no conflicts of interest.

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