

Interaction of physical activity and diet: implications for haemostatic factors

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Abstract

Regular moderate intensity physical activity and habitual diet providing no more than one third of energy from fats have been recommended for the prevention of atherosclerotic diseases. The background for these guidelines is the key role of plasma lipids. However, the importance of thrombogenesis in acute myocardial infarction has become obvious during the last decade. Hyperlipidaemia and excess of adipose tissue increase platelet aggregability and blood coagulation, and decrease fibrinolysis. Both regular physical activity and dietary fat reduction decrease blood lipids and body fat thereby diminishing the risk of thrombosis. Currently, data on interactions between physical activity and diet on haemostasis are scarce, and the few studies available have not demonstrated additional effects when these two lifestyle modifications have been combined. This paper is restricted only to studies using controlled randomized design. Regular moderate intensity physical activity as well as diet rich in omega-3 fatty acids decrease platelet aggregability. The effects of regular physical activity on plasma fibrinogen remain contradictory, while the impact of diet is even less clear. Plasminogen activator inhibitor-1, a possible link between insulin resistance syndrome and coronary heart disease, may decrease due to physical training or low fat diet. It can be hypothesized that moderation in physical activity and diet carries a more powerful impact on blood coagulation and fibrinolysis than either lifestyle modification alone. Studies focusing on the interactions of regular moderate physical activity and fat-modified diet are needed in efforts to optimize the preventive actions by lifestyle changes.

Keywords
Regular physical activity
Diet
Platelets
Blood coagulation
Fibrinolysis

Key research topics

The following research topics are suggested for future clinical trials.

- Effects of regular mild to moderate intensity physical activity combined with low fat (30 E%) high carbohydrate diet on thrombogenesis involved in atherosclerosis with special reference to body composition.
- Effects of regular mild to moderate intensity physical activity combined with low fat (30 E%) high carbohydrate diet on thrombogenic profile in postmenopausal women.
- Effects of regular physical activity of different intensities combined with low fat (30 E%) high carbohydrate diet on haemostatic factors with special references to genetic variations in thrombogenic factors.

Introduction

The essential role that haemostatic factors play in the clinical events of atherosclerosis has been understood

only recently. Nowadays, it is well recognized that atherosclerosis is a chronic inflammatory condition¹, which turns into an acute clinical event as a consequence of plaque rupture with the ensuing thrombosis. The progression of an atherosclerotic lesion from a fatty streak to an atherosclerotic plaque is to a large extent dependent on the circulating level of low density lipoprotein cholesterol as well as other atherogenic lipoproteins and their susceptibility for oxidative modification. In the event of plaque rupture, the elements of circulating blood are exposed to tissue factor, the initiator of thrombosis². While moderation in both physical activity level and dietary fat intake have been shown to be effective in modifying the blood levels of atherogenic factors, very little data are available on the interactions of moderate regular exercise and diet on the haemostatic factors.

Haemostasis

Vascular haemostasis results from a regulated interaction of blood coagulation and fibrinolysis. In a normal situation these systems are in dynamic equilibrium, but

any imbalance between them leads to a tendency to bleeding or to an increased thrombogenesis². Platelets provide the key elements to haemostasis. They adhere to the damaged endothelium of vessel walls and to each other to form aggregates thereby stopping blood from leaving the vascular compartment. After reacting with foreign surfaces, platelets become activated and change their shape to irregular spheres by putting out pseudopods. These activated platelets adhere to the vessel wall and to each other to form aggregates. Blood coagulation is initiated by at least two different mechanisms (Fig. 1). The slower activation process of fibrin formation by the intrinsic mechanism is dependent on circulating coagulation factors. The more rapid activation process of the extrinsic system needs an extravascular factor, tissue factor, to initiate the coagulation process³. Factor VII (FVII) has a key role in the initiation of the extrinsic coagulation pathway by forming a complex with the tissue factor. Fibrinogen plays a

central role in the final phase of the blood coagulation cascade, and the binding of fibrinogen to platelet glycoprotein IIb/IIIa receptors is the principal mechanism for platelet aggregation⁴.

The fibrinolytic system regulates the formation and removal of thrombi and maintenance of vascular patency (Fig. 1). Plasminogen activators activate plasminogen to plasmin, which degrades fibrin into soluble fibrin degradation products. Activation of plasminogen to plasmin by tissue-type plasminogen activator (t-PA) is enhanced in the presence of fibrin or at the endothelial cell surface. Inhibition of fibrinolysis may occur at the level of plasminogen activation, plasminogen activator inhibitor type-1 (PAI-1) as the key inhibitor, or at the level of plasmin by α_2 -antiplasmin⁵. Increased PAI-1 and decreased t-PA levels lead to suppression of fibrinolytic activity and reduced plasmin generation favouring fibrin persistence and thrombosis⁶.

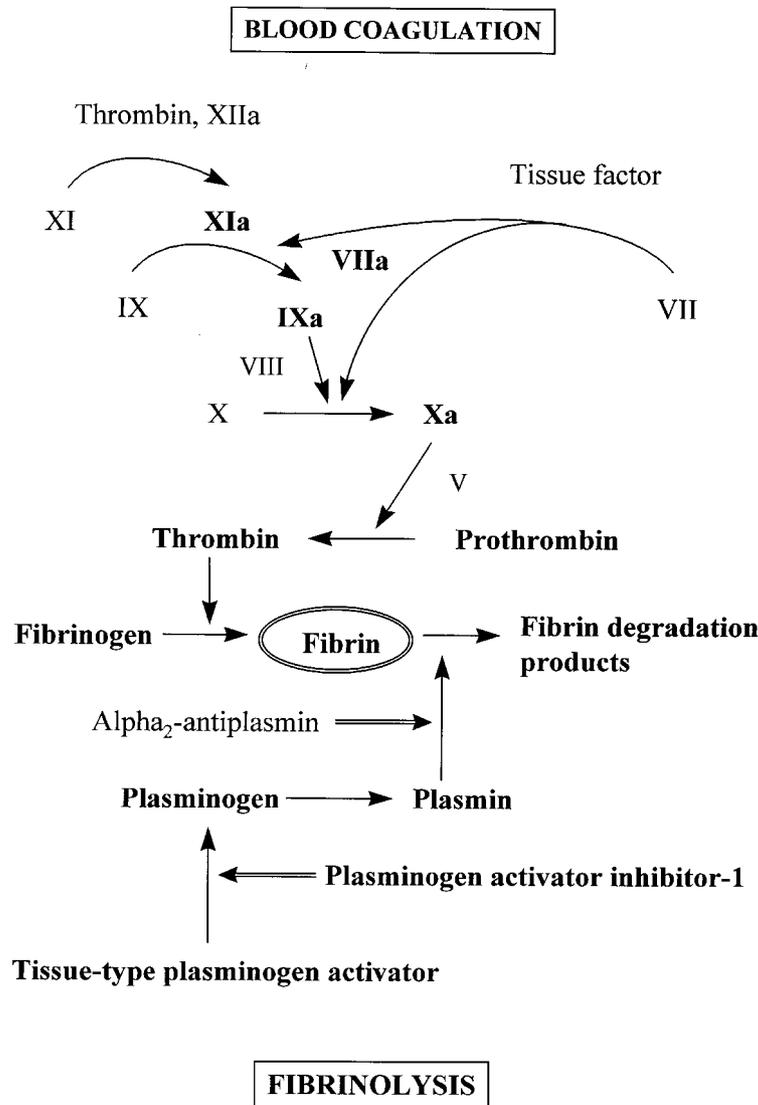


Fig. 1 A schematic presentation of factors participating in blood coagulation and fibrinolysis

Platelet aggregability

Increased platelet aggregability during the morning hours has been linked to the circadian fluctuation of acute cardiac events⁷. Strenuous exercise activates platelets acutely, while exercise training at moderate intensity suppresses platelet aggregation in overweight middle-aged men⁸, in young healthy men⁹ as well as in young women¹⁰. Physical activity can induce at least two different mechanisms, which affect platelet function. Regular physical activity increases serum high density lipoproteins, which can stimulate prostacyclin production¹¹ and thereby decrease platelet aggregation. In addition, physical activity increases release of nitric oxide, a potent mediator of antiplatelet effects for instance by elevating cGMP content in platelets, which in turn suppresses platelet reactivity⁹. However, the resting and exercise-induced reductions in platelet aggregation reverse back to the pretraining level after deconditioning^{9,10} indicating the importance of engaging in physical activity in a regular manner. Of the dietary components, fish intake, and particularly high intake of eicosapentaenoic acid (EPA) increases bleeding time and decreases platelet aggregability¹², and incorporating omega-3 fatty acids into a low rather than high fat diet appears to have especially beneficial effects on men at risk of CHD¹³.

Coagulation Factor VII

A positive association between increased factor VII coagulant activity (FVIIc) and risk of ischemic heart disease, especially for fatal events, was initially shown in the Northwick Park Heart Study¹⁴. Only few reports on the effects of physical exercise on FVII are available, and it seems that at least moderate exercise has no significant influence on FVII level^{15–17} or the effect is at the most only relatively short-lived¹⁸. Dietary fat intake associates positively with FVIIc both in the fasting and postprandial states^{19–25}. Blood lipids may have an essential role in the relationship between fat intake and FVII, since several cross-sectional and postprandial studies have shown a strong positive relation of triglyceride-rich lipoproteins to FVIIc or FVII antigen level (FVIIag)^{21,24,26,27}.

In the DNASCO study (DNA Polymorphism and Atherosclerosis: Controlled Randomized Clinical Trial on the Effects of Regular Physical Activity), we found that in subjects with low apolipoprotein B (apo B) level, FVIIc was raised only when fat intake was high (>38 E%), while FVIIc increased gradually with dietary fat in the middle apo B tertile. No association was seen in men with the highest serum apo B concentration. Dietary fat seems to be more important in the regulation of FVIIc in subjects with low to moderate serum apo B concentration than in those with higher apo B levels²⁸. In dietary interventions, FVIIc decreased after a low fat diet (fat intake 26–28 E%)^{29,30}, and also after a fat free

meal containing only carbohydrates²⁴. No difference in FVIIc was detected between two dietary periods, which differed moderately in fat content (39 E% vs. 31 E%)³¹, whereas FVIIc level was elevated after very high fat diets (62–63 E%) compared to a very low fat diet (<20 E%)³². Change in fat composition, when the total fat intake remained the same, had no effect on FVIIc in normolipidaemic subjects¹⁸, and FVIIc decreased similarly during low fat diets with different fatty acid compositions²⁹.

Cross-sectional studies revealed a positive correlation of FVIIag^{26,33} and FVIIc^{20,26,28} with triglyceride level. However, the relationship between FVIIc and triglycerides is not so evident during dietary interventions^{19,25,29,34}. When hypercholesterolaemic patients were treated with a lipid-lowering agent, FVIIag and FVIIc decreased concomitantly with the reduction in triglyceride level³⁵. Despite severe hypertriglyceridaemia in the chylomicron and VLDL fractions, neither FVIIag nor FVIIc were elevated in patients with homozygous familial lipoprotein lipase (LPL) deficiency³⁶ or in patients with myocardial infarction and decreased LPL activity²⁷. These observations suggest that lipolysis of the large lipoprotein particles has an important influence on the *in vivo* activation of FVII.

Genetic polymorphisms in the FVII gene contribute significantly to the FVII level^{37–41}. In Caucasians, an interaction between serum triglycerides and FVIIc was reported in subjects carrying the common ³⁵³Arg allele, which associates with higher FVIIc³⁸. However, Saha and coworkers³⁹ reported an opposite relationship in Dravidian Indians, in whom homozygotes for the ³⁵³Arg allele had a weaker relationship between triglycerides and FVIIc compared to the other genotypes. FVIIag responded to the oral fat load similarly in subjects homozygotes or heterozygotes for the ³⁵³Arg allele⁴¹. Weight loss by dietary modifications and physical activity induced reductions in FVIIc similarly in the carriers of the ³⁵³Gln allele and the homozygous for the ³⁵³Arg in moderately obese subjects. However, the absolute reduction in FVIIc was greater in the ³⁵³Arg homozygotes, who had initially higher FVIIc values⁴².

Fibrinogen

Fibrinogen is an independent risk factor for cardiovascular disease and mortality^{43,44} and the plasma level is elevated in inflammatory states, smokers, obesity, diabetes and hyperlipidaemia. Although an inverse relationship between fibrinogen and physical activity and/or cardiorespiratory fitness was found in several cross-sectional studies⁴⁵, the fibrinogen lowering effect of regular physical activity was reported in only a few exercise intervention studies ie, in an uncontrolled study in old men⁴⁶, in sedentary subjects with newly diagnosed NIDDM⁴⁷, and after 10 weeks of strenuous

Table 1 Summary table of the potential effects of regular physical exercise or diet (fat modified and/or energy restricted) on haemostatic factors in controlled randomized clinical trials

	Physical exercise	Diet
Platelet aggregability	↓	↓
Factor VII	no effect	↓
Fibrinogen	?	no effect
t-PA antigen	↓	↓
t-PA activity	↑	no effect
PAI-1 antigen and activity	↓	↓

and intensive training in young men⁴⁸. In contrast, moderate exercise did not change fibrinogen in overweight women⁴⁹ and an intensive exercise program increased plasma fibrinogen in elderly subjects⁵⁰.

Two recent studies have examined whether genetic polymorphisms in the fibrinogen genes can modulate the association between physical activity and plasma fibrinogen. We found an interaction between habitual physical activity and an α -fibrinogen polymorphism on fibrinogen level in postmenopausal women. The physically most active women, who were homozygous for the more frequent *Rsa I* allele, displayed a decreased plasma fibrinogen, while the association was not seen in other genotypes⁵¹. An acute phase response in fibrinogen level was reported in young men after an exhausting 2-day military exercise period. The subjects carrying the A allele of the G-453-A polymorphism in the β -fibrinogen gene had higher increase in plasma fibrinogen than in men with the GG genotype⁴⁸. Controlled exercise intervention studies are needed to further evaluate the effect of genetic variation at the fibrinogen gene loci on the relationship between physical activity and fibrinogen level in both genders.

As to the impact of diet on fibrinogen, very little data based on controlled randomized trials are available. In healthy middle-aged men, low dietary starch intake associated with increased levels of fibrinogen⁵², while reduction in dietary fat does not influence fibrinogen concentration^{18,49,53}.

Fibrinolysis

Elevated PAI-1 activity decreases fibrinolytic activity and increases the risk of coronary artery disease, venous thromboembolism and acute myocardial infarction^{54–56}. Most of the present data on thrombogenic profile, particularly in overweight or obese persons, relate to PAI-1, the primary inhibitor of the fibrinolytic system. Obese and NIDDM subjects have significantly higher plasma PAI-1 than control subjects⁵⁷, and waist/hip-ratio correlates strongly positively with coagulation factors and negatively with fibrinolytic factors in premenopausal women with abdominal obesity⁵⁸. Older women receiving postmenopausal hormone therapy have more favourable plasma levels of PAI-1 and fibrinogen than non-users⁵⁹.

It has been understood only very recently that adipose tissue has an active role in thrombogenesis⁶⁰. Elevated plasma PAI-1 activity in the obese may be caused by increased PAI-1 release from visceral adipose tissue⁶¹. Except for insulin⁶², at least two cytokines, tumour necrosis factor alpha (TNF- α) and transforming growth factor beta (TGF- β), induce PAI-1 gene expression in the adipose tissue^{62,63}. Although strenuous physical activity in young athletes increases acutely serum TNF- α ⁶⁴, it is not known how regular exercise training modulates cytokines chronically or acutely in a response to a single bout of physical exercise.

Fibrinolytic response to acute physical activity depends on exercise intensity⁶⁵. Increased plasma epinephrine during exercise is the primary stimulus for t-PA thereby reducing PAI-1 activity⁶⁶. However, this exercise-induced increase in fibrinolytic activity is short-lived⁶⁵. There is also suggestive evidence that regular exercise training decreases PAI-1 level at least in sedentary young men^{15,67} and in elderly men^{46,68}. Several preanalytical factors such as diurnal variation and difficulties in blood collection and handling have significant effects on fibrinolytic activity^{69,70}, and these confounding factors make it essential to include a reference group in a study design.

The 4G allele of the 4G/5G polymorphism in the PAI-1 promoter gene associates with an increased PAI-1 level and higher risk of cardiovascular diseases^{71–73}. Moreover, at least in diabetic patients^{73,74} and subjects who had suffered myocardial infarction⁷⁵, homozygotes for the 4G allele are particularly sensitive for the increasing effect of hypertriglyceridaemia on PAI-1 level. Diet rich in monounsaturated fatty acids decreases plasma PAI-1 in young healthy males⁷⁶, while in subjects with impaired glucose tolerance, fat-modified diet did not alter PAI-1⁷⁷. These observations raise the question whether the responses to physical activity or low fat diet in fibrinolysis vary between different 4G/5G genotypes. We observed in a three-year controlled randomized exercise intervention in a population based sample of middle-aged men that the 4G/4G subjects tend to have higher PAI-1 activity than other genotypes, but the 4G/4G men were also more sensitive to a PAI-1 lowering effect of physical activity⁷⁸. A change in waist circumference, although not identical to measurement of visceral fat, did not explain this finding.

Interactions between physical activity and diet on haemostatic factors

As reviewed above, both moderate physical activity and diet influence the individual's thrombogenic susceptibility in several ways. In the following we will consider only controlled randomized clinical trials, which respond to the current requirements for

Table 2 Controlled randomized clinical trials of interactions between physical activity and fat modified diets on haemostatic factors

Study design	Subjects (age, years)	Main results
A 14-week fish diet and exercise programme ⁷⁹ .	99 healthy female students (mean 22).	Platelet aggregation, thromboxane B ₂ and prostacyclin unchanged.
A 6-month aerobic exercise and/or fat modified diet ¹⁸ .	119 normolipidaemic men (51–53).	Modest decrease in saturated and/or increase in unsaturated fat intake did not modify FVIIc, FX activity, antithrombin III, fibrinogen, t-PA antigen or PAI-1 antigen either alone or in a combination with exercise.
A 12-week 4200 kJ/d diet and/or moderate exercise ⁴⁹ .	121 overweight women (54 ± 3).	Diet decreased PAI-1 activity and antigen, and t-PA antigen with no additional effect of physical activity. No effect on fibrinogen.
A 8-week moderate aerobic exercise and a low-fat diet with one daily fish meal ⁸⁰ .	55 sedentary type 2 diabetics with serum triglycerides >1.8 mmol/l and/or HDL-C <1.0 mmol/l (mean 53).	The fish diet and exercise as well as combined diet and exercise reduced t-PA antigen. The fish diet alone increased FVIIc, which was prevented by exercise. No effects on PAI-1 antigen or fibrinogen.

evidence based data in health sciences. Only four studies have dealt with diet and physical activity simultaneously with regard to changes in selected haemostatic factors as the outcome measure (Table 2). Such studies are very demanding (costs, study protocol, laboratory analyses etc.) to accomplish, particularly for any longer period of time. Sample size, compliance and adherence are the key issues, which determine whether the study will have power enough to detect the changes due to the intervention.

Controlled randomized clinical trials

Both physical activity and diet are natural components of human everyday life and therefore their impacts should be investigated together. Based on the review of the literature, one can expect to achieve a larger impact on the various outcome variables (blood lipids, coagulation and fibrinolytic factors) with simultaneous changes in habitual physical activity and diet. However, it may as well be the case that when two life-style interventions are combined, neither will work optimally. The functional nature of the haemostatic system is characterized by its rapid activation and inactivation and may well explain much of the controversies in the literature.

A 14-week exercise and fish diet intervention in a large group of young healthy females failed to induce any changes in platelet function and prostaglandins⁷⁹. In the diet and combined diet and exercise groups, proportion of omega-3 fatty acid increased in the platelets and erythrocytes suggesting compliance with diet. In contrast, the actual increase of exercise was only 1.3 times a week with no change in maximal oxygen uptake in the exercise groups indicating less than prescribed physical activity. Although the modest compliance with the intervention may explain to some

extent the lack of changes in outcome variables, one should keep in mind that the subjects were young, healthy girls with normal body weight.

In a controlled randomized clinical trial in men for six months¹⁸, we could not see any differences between reference and experimental groups in any coagulation or fibrinolytic parameters. The compliance of our clinically healthy subjects was good, the sample size was large and the age range was narrow (51 to 53 years). To avoid measuring the acute effects of exercise, blood samples were drawn one week after stopping the exercise programme. Our data indicate that the responses of thrombogenic and fibrinolytic parameters to aerobic exercise, if any, are a temporary phenomenon. Modest changes in dietary fat intake did not seem to have any influence on the haemostatic factors.

In a large group of overweight postmenopausal women, low energy diet (1000 kcal/d) decreased PAI-1 activity and antigen as well as t-PA antigen⁴⁹. Moderate intensity aerobic and resistance weight training did not induce any additional effect on PAI-1 or t-PA. Neither diet alone nor with exercise affected plasma fibrinogen. The main emphasis of the study was in the dietary energy restriction resulting in a substantial loss of fat tissue mass, while the exercise programme was modest with only three weekly exercise sessions.

In another recent fish diet and moderate aerobic exercise trial in dyslipidaemic type 2 diabetics⁸⁰, t-PA antigen concentration decreased in moderate exercise, diet and combined exercise and diet groups, while PAI-1 antigen and fibrinogen remained unchanged. Fish diet alone increased FVIIc, while concomitantly taken aerobic exercise prevented the elevation. The evaluation of the study results is hampered by the fact that the authors give no data on changes in diet (especially fat intake) or changes in physical activity or fitness.

Key issues

There have been several shortcomings in many studies investigating the impact of changes in physical activity patterns or in dietary habits in relations to blood coagulation and fibrinolysis. Generally, the requirement for adequate statistical power needs to be emphasized. Since haemostatic factors are characterized by high intraindividual variability, only with large enough sample size can one avoid false conclusions in clinical intervention trials. In order to find cause and effect relationships, only controlled randomized clinical trials represent appropriate study design. Using a representative sample of the study population as subjects, the results may be generalizable and thereby useful in the clinical practice for the prevention of thrombotic sequelae and complications.

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