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Review Article

The Prothrombotic Predominance in Metabolic Syndrome: A Complex Pathomechanism

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ABSTRACT

Patients with metabolic syndrome (MS) have many cardiovascular complications related to atherothrombotic complications. MS contributes premature atherosclerosis, increases platelet activation, promotes coagulation factors, and reduces fibrinolytic activity. The last step in the atherothrombotic cascade is blood clot formation, and altered clot structure is a key role to determine cardiovascular complications. The MS, caused in part by an excess of atherosclerosis and in part by fibrinolytic dysfunction, is profoundly related to an excess of CVD. These combinations of factors involved in MS parameters contribute the increased propensity of people with MS to develop atherothrombosis and fibrinolysis. Awareness and preventive measures are important to improve outcomes in patients with MS.

1. Introduction

The incidence of cardiovascular disease (CVD) is increased in people with metabolic syndrome (MS), including abdominal adiposity, elevated triglycerides, hypertension, low high-density lipoprotein (HDL) cholesterol level, and glucose intolerance. In the past decade, most patients with MS have accelerated thrombosis events due to premature atherosclerosis. Atherosclerosis is increased, and fibrinolytic function is abnormal in this population. Several studies stated that plasminogen activator inhibitor-1 (PAI-1) was increased and predicted myocardial infarction among patients with hyperglycemia.[1]

Other findings, including elevated endogenous tissue-type plasminogen activator (tPA), also predict myocardial infarction and high mortality.[1] Therefore, it is likely that MS reveals an imbalance of hemostasis due to high PAI-1 and tPA. Arterial thrombosis leading to increase CVD in people with metabolic syndrome has been accelerated due to fibrinolytic disturbances. This stetting is supported by Grundy et al. and Tsai et al., showing that abdominal obesity and diabetes are risk predictors of thrombosis in arteries and veins.[2,3]

This review highlights the understanding of the relationship between MS and fibrinolysis. It could elaborate how the impact of MS on the clinical outcome of patients with myocardial infarction.

2. Discussion

2.1 The Hemostatic Balance

Hemostasis imbalance directing to a procoagulant state induces the risk of thrombosis. Tissue factor (TF) is a cornerstone of blood coagulation activation.[4] TF is a transmembrane glycoprotein mostly found in monocytes and subendothelial cells. The TF pathway of blood coagulation will be activated by acting as a receptor for factor VIIa (FVIIa) after TF is exposed to blood. This coagulation pathway generates thrombin when the prothrombinase complex converts the proenzyme prothrombin. Then, thrombin cleaves fibrinopeptide and converts fibrinogen into fibrin polymers. Activated factor XIII (FXIIIa) forms cross-linked fibrin mesh into an insoluble fibrin clot.[5,6]

Fibrinolytic enzymes are responsible for anticoagulation effects, and the endothelial-derived protein t-PA is the main component in this pathway. It activates plasminogen into plasmin on the fibrin clot surface, cleaving soluble fibrin degradation products. PAI-1 inhibits t-PA, so that fibrin clearance is impaired.[6,7] Figure 1 presents a simplified overview of coagulation and fibrinolysis. There are complex mechanisms of enhancing the prothrombotic state and reducing fibrinolytic activity.

2.1.1. Obesity enhances prothrombotic factors

Several reviews focus on the association between biomarkers of hemostatic balance and obesity. Adipose tissue secretes the proinflammatory cytokines contributing to promoting a prothrombotic state. Interleukin-6 (IL-6), tumor necrosing factor-a (TNF-a), and leptin

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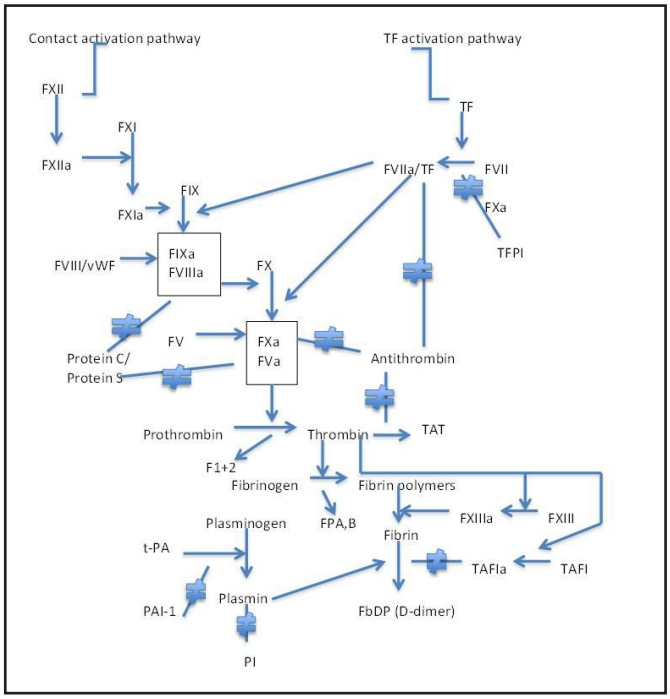

Figure 1. Overview of coagulation and fibrinolysis.[5]
F = coagultion factor (e.g. FVII); FbDP = fibrin degradation product; PAI-1 = plasminogen activator inhibitor type 1; PI = plasmin inhibitor; TF = tissue factor; TFPI = tissue factor pathway inhibitor; TAT = thrombin-antithrombin complexes; F1+2 = prothrombin fragment 1+2; FPA,B = fibrinopeptide A or B; TAFI = thrombin activatable fibrinolysis inhibitor; t-PA = tissue plasminogen activator.

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increased because of the increased synthesis of these proteins in adipose tissue.[8,9]

Many hemostatic biomarkers in people with average weight and obesity have been studied. Enhanced biomarkers of hemostatic

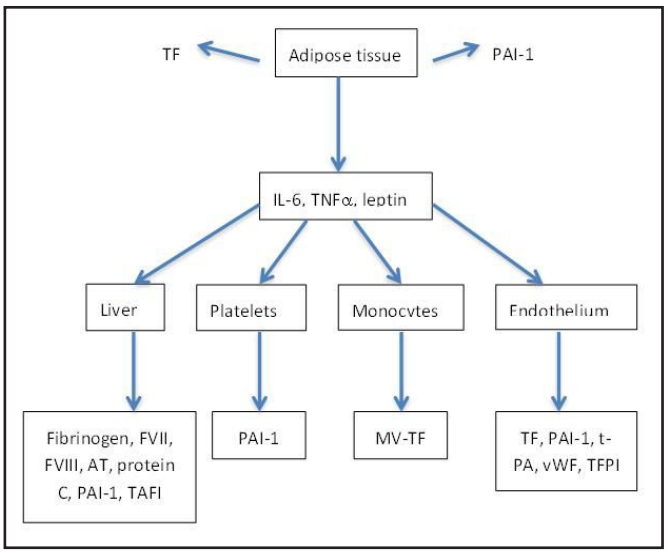

Figure 2. Hemostatic consequences of low-grade inflammation in obesity.[5]
AT = antithrombin; FVII = coagulation factor VII; FVIII = coagulation factor VIII; IL-6 = interleukin-6; MV-TF = microvesicle tissue factor; PAI-1 = plasminogn activator inhibitor type 1; TNF- = tumor necrosis factor- ; t-PA = tissue plasminogen activator; TF = tissue factor; TFPI = tissue fator pathway inhibitor.

dysfunction are seen in obesity, e.g., von Willebrand factor (vWF), t-PA, D-dimer, and impaired fibrinolysis.[10,11] Interestingly, elevated concentrations of coagulation inhibitors have been suggested in patients with obesity. However, an increased thrombin level is the most commonly seen as the net effect. Chronic low-grade inflammation-inducing endothelial dysfunction, platelet activation, impaired fibrinolysis, and hypercoagulability are the consequences of obesity (see figure 2). Therefore, this shifts the hemostatic balance to the prothrombotic predominance, especially PAI-1 and TF, which inhibit fibrinolysis and activate the coagulation pathway, respectively.[12]

2.1.2. Hypertriglyceridemia reduces fibrinolytic activity

Increased coagulation factors have been commonly found in high blood lipid levels. Increased coagulation factor VII is found in high fat intake conditions. This evidence supported that lipid-lowering drugs (statins) reduce hypercoagulability. Patients with high triglyceride levels (200 mg/dL) revealed profoundly shorter prothrombin time (PT) values than normal levels.[13]

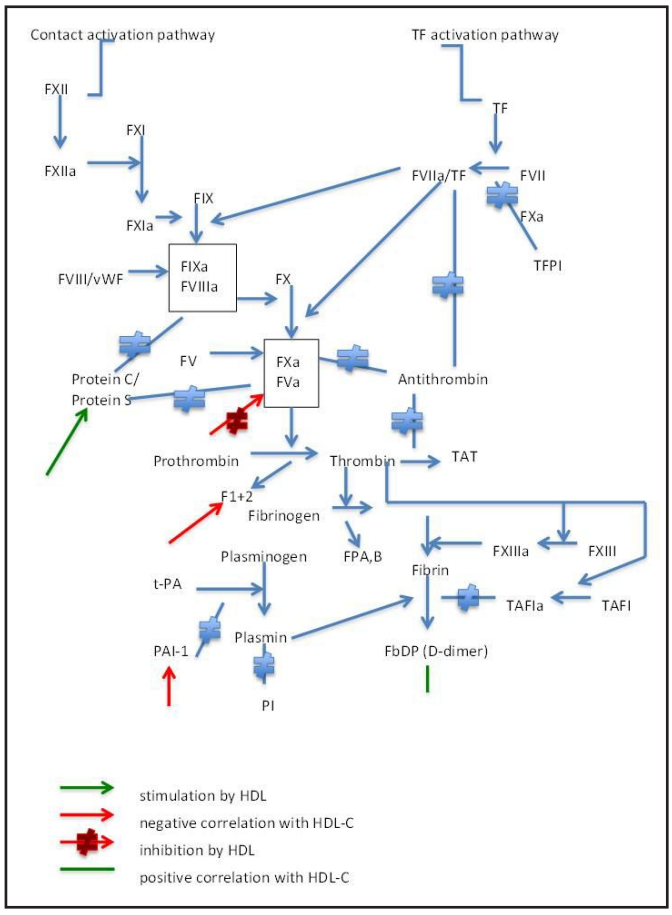

Figure 3. HDL modulation in coagulation cascade pathway.[5,17]
F = coagultion factor (e.g. FVII); FbDP = fibrin degradation product; PAI-1 = plasminogen activator inhibitor type 1; PI = plasmin inhibitor; TF = tissue factor; TFPI = tissue factor pathway inhibitor; TAT = thrombin-antithrombin complexes; F1+2 = prothrombin fragment 1+2; FPA,B = fibrinopeptide A or B; TAFI = thrombin activatable fibrinolysis inhibitor; t-PA = tissue plasminogen activator; and HDL-C = high density lipoprotein cholesterol.

Interestingly, postprandial triglycerides contribute to blood coagulation and are closely associated with coronary heart disease. Several studies investigated the acute postprandial effect of dietary fat on postprandial factor VII levels. The fat contents of the meal are significantly related to the postprandial increase in VIIa. The higher the fat contents of the meal, the greater the factor VII activation. Additionally, very-low-density lipoprotein (VLDL) triglyceride is associated with PAI-1. Experimental studies revealed that VLDL enhanced PAI-1 secretion from endothelial cells.[14] Reduced fibrinolytic capacity is also associated with hypertriglyceridemia. In addition to hypercoagulability (increased factor VII, VIII, X, and fibrinogen), Simpson et al. found significantly lower fibrinolytic activity in patients with severe hypertriglyceridemia than with severe hypertriglyceridemia controls.[15]

2.1.3. HDL cholesterol (HDL-C) modulates the coagulation cascade

A higher incidence of CVD is generally related to low levels of circulating HDL particles. HDL is well-known recognized as a multifunctions component in the cardiovascular system. HDL exhibits anti-inflammatory, immunomodulatory, antioxidative, antiapoptotic, and antithrombotic effects.[16] HDL modulates the coagulation pathway at different levels (see figure 3). Plasma apolipoprotein A-I (apoA-I) levels are positively related to anticoagulant effects, and HDL is inversely associated with prothrombin fragments F1+2. The formation of the prothrombinase complex is prevented by cleaving apoA-I into anionic vesicles because FVa could not bind to the vesicles.[17,18]

HDL enhances anticoagulant effects by activating the protein C pathway. This pathway generates the proteolytically active vitamin K-dependent zymogen protein C (APC) form, which can inactivate FVa and FVIIIa. As a cofactor of APC, protein S (vitamin K-dependent protein) is needed in this pathway. Purified HDL, but not low-density lipoprotein (LDL), increases protein S, which act to inhibit FVa.[16,19]

Enhanced fibrin clot permeability and decreased clot lysis time are found in elevated HDL-C. Moreover, the levels of PAI-I are inversely related to both HDL size and HDL-C, suggesting that HDL particles diminish the prothrombotic state by activating plasmin generation and thus fibrinolysis. In addition, D-dimer levels associated with HDL size and HDL-C.[20]

On the other hand, HDL is known to be more susceptible than LDL to oxidation. However, the relevance of blood ox-HDL levels remains unclear. HDL-C and ox-HDL levels are shown to be associated with D-dimer.[21] Ebara et al. Stated that ox-HDL was associated with thrombin-antithrombin complex (TAT) and plasmin-a2 plasmin inhibitor complex (PIC). Low CVD risk is thought to be related to high ox-HDL level.[16]

2.1.4. Hypertension: prothrombotic paradox

Hypertension is considered the main contributor to increased CVD, including circulating lipoprotein levels, homocysteine, and fibrinogen.[22] Thrombotic events represent a significant complication, even though hypertension increases pulsatile stress to the vessel wall. This setting is known as the thrombotic paradox of hypertension or “Birmingham paradox”.[23] Increased plasma concentrations of C-reactive protein (CRP) are found in hypertensive patients. CRP may enhance inflammation as well as coagulation. Proinflammatory cytokines potentially stimulate vascular endothelial cells to generate PAI-1 and TF. The balance between PAI-1 and t-PA modulates the fibrinolytic system.[24]

In hypertensive patients, vessel walls are exposed to cyclic strain and shear stress. Transmural pressure induces cyclic strain leading to augmented wall stress and dilated vessel. Endothelium-derived nitric oxide synthase (eNOS) expression and nitric oxide (NO)