Plasminogen and fibrinogen plasma levels in coronary artery disease

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The process of haemostasis ensures that following vascular damage blood remains confined to the circulatory system. This is not a single biological pathway, but rather a complex interplay of several distinct processes[1]. Injury to the endothelium causes the transition of endothelial surface from a non-thrombogenic state to one actively promoting thrombus formation. The process starts when injury causes a breach in the endothelium with exposure of subendothelial collagen and tissue factor. Collagen activates platelets and tissue factor exposure initiates the coagulation cascade – both processes lead to thrombus formation that is localised at the site of injury. While the end product is the generation of fibrin from fibrinogen, the composition of thrombi in the arterial and venous circulations is dissimilar. In the arterial system the thrombus predominantly comprises of platelets and fibrin whereas in the venous system fibrin together with red cells and white cells are the major components of the clot. Regardless of the site of clot, the formation of a stable fibrin network is the ultimate step in thrombus formation. The conversion of fibrinogen to fibrin is brought about by cleavage of fibrinogen. This process is undertaken by thrombin which cleaves fibrinogen into two smaller peptides, fibrinopeptide A and B. Fibrin monomers are then formed with subsequent polymerization. Finally, the clot is consolidated when factor XIII cross-links the fibrin monomers. Once the clot has formed and the fibrinolytic system begins the proteolytic removal of thrombi to ensure that vessel patency is restored. Plasminogen binds to fibrin and is activated by tissue plasminogen activator (tPA) to plasmin. Plasmin begins the dissolution of fibrin although; because of its broad specificity it causes degradation of fibrinogen as well. Just like the coagulation cascade, the fibrinolytic system is a complex interplay of activators and inhibitors to ensure optimal haemostasis. Obviously, in disease the fine balance of haemostasis is disturbed. Atherosclerosis is a multifactorial disease where vascular injury leads to lipid accumulation and deposition of platelets and fibrin. It is not surprising therefore, that disorders of different components of haemostasis can contribute to the pathogenesis of atherosclerosis.

The current study compared the level of fibrinogen and plasminogen in angiographically normal subjects and those with mild/moderate, and severe coronary artery disease[2]. A graded correlation was found between levels of fibrinogen and the severity of coronary artery disease. Elevated levels of plasma fibrinogen have been shown to be an independent risk factor for coronary artery disease[3,4]. Whether this is a direct effect of hyperfibrinogenemia is unclear, although some evidence exists to suggest that elevated fibrinogen may affect the process of atherogenesis by fibrin deposition within developing atherosclerotic lesions[5]. Because fibrinogen has also been associated with other traditional cardiovascular risk factors, an atherothrombotic effect mediated through a raised fibrinogen level would appear plausible. This would be indirectly supported by thrombotic association of dysfibrinogenemia[6], a condition which primarily produces a bleeding tendency but is well known to cause thrombotic events too.

There are several mechanisms by which fibrinogen may increase cardiovascular risk. It binds specifically to activated platelets via glycoprotein IIb/IIIa, contributing to platelet aggregation. Elevated fibrinogen levels increase plasma viscosity and promote fibrin formation. Chronic inflammatory conditions are known to result in accelerated atherosclerosis. That fibrinogen is an acute-phase reactant with levels rising significantly in inflammatory states may be pathogenetically relevant.

Like disorders of fibrinogen impaired fibrinolysis appears to have a role in thrombosis. Plasmin, which results from the cleavage of plasminogen by plasminogen activators (PAs), predominantly mediates the intravascular clearance of fibrin. The important role of plasminogen in fibrinolysis makes it an interesting parameter to evaluate in various diseases. It is recognized that a decreased plasminogen level may affect the fibrinolytic activity and result in thrombotic tendency[7]. It is therefore, not surprising that plasminogen levels were not found to be significantly elevated in patients with coronary artery disease. It is well known that increased levels of plasminogen activator inhibitor-1 (PAI-1) are found in myocardial infarction[8]. A raised PAI-1 level would inhibit fibrinolysis by inhibiting tissue plasminogen

activator and this may result in thrombotic tendency. It would have been interesting to look at PAI-1 levels as well and this aspect needs to be considered in future studies.

While this paper reaffirms the association of elevated fibrinogen with coronary artery disease, in view of the multifaceted nature of atherosclerosis, especially the emerging role of inflammation in its pathogenesis, information on inflammatory markers would have been valuable[9,10]. Further follow-up on the three cohorts with serial measurements of different parameters would give additional insight into correlating the progression of the disease with different haemostatic and fibrinolytic parameters.

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