

# Fibrinogen and Coronary Artery Disease – A Review

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## Introduction:

Plasma fibrinogen is an important component of the coagulation cascade, as well as a major determinant of blood viscosity and blood flow. Increasing evidence from epidemiological studies suggests that elevated plasma fibrinogen levels are associated with an increased risk of cardiovascular disorders, including ischaemic heart disease (IHD), stroke and other thromboembolism.<sup>1,2</sup> This increase in plasma fibrinogen levels may promote a prothrombotic or hypercoagulable state, and may in part explain the risk of stroke and thromboembolism in conditions such as atrial fibrillation (AF). Nevertheless, the relationship between hyperfibrinogenemia, atherosclerosis and thrombosis is complicated. As the process of thrombogenesis is very closely related to atheroma formation (atherogenesis), it follows that specific thrombogenic factors such as fibrinogen may play key roles in the process of atherosclerotic lesion formation, with subsequent effects on cardiovascular diseases.

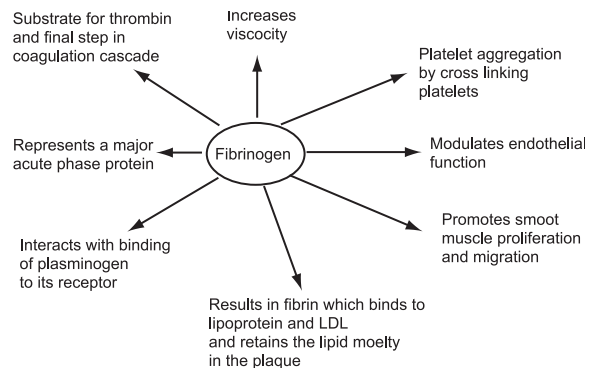
## Pathophysiology:

Fibrinogen is a soluble glycoprotein found in the plasma, with a molecular weight of 340 kDa.<sup>3</sup> It comprises of three pairs of non-identical polypeptide chains (alpha, beta and gamma chains)<sup>4</sup> linked to each other by disulphide bonds. Fibrinogen has a biological half-life of about 100 h and is synthesized predominantly in the liver.<sup>5</sup> Fibrinogen plays a vital role in a number of physiopathological processes in the body, including inflammation, atherogenesis and thrombogenesis (Figure 1). Proposed mechanisms include the infiltration of the vessel wall by fibrinogen, haemorrhheological effects due to increase in blood viscosity, increased platelet aggregation and thrombus formation. Furthermore, plasma fibrinogen is also a prominent acute-phase reactant. It augments the degranulation of platelets in response to adenosine diphosphate (ADP), when taken up by the granules. Thus, elevated concentrations of fibrinogen, perhaps secondary to inflammation or infection (*Chlamydia pneumoniae* or

*Helicobacter pylori*) implicated in cardiovascular risk may operate, in part, by increasing the reactivity of platelets.<sup>6</sup>

## • Fibrinogen and inflammation

The process of inflammation is primarily mediated by its interaction with leucocytes through the surface receptors of the latter termed 'integrins'. The 2 main receptors for fibrinogen on the surface of leukocytes include Mac-1 (CD11b/CD18, alpha M beta 2) and alpha X beta 2 (CD11c/CD18, p150, 95). Leukocytes (both monocytes and myelocytes) can specifically induce MAC-1 receptor to bind fibrinogen.<sup>7,8</sup> Fibrinogen is also a ligand for Intercellular Adhesion Molecule-1 (ICAM-1), and enhances monocyte-endothelial cell interaction by bridging the Mac-1 on monocytes to ICAM-1 on endothelial cells.<sup>9,10</sup> Thus, ICAM-1 behaves as a cell surface ligand for alpha L beta 2 and alpha M beta 2 (MAC-1) integrins, and has a key role in leukocyte



**Fig.-1:** Plasma fibrinogen thrombogenesis and atherogenesis.

adhesion to the vascular endothelium. Furthermore, fibrinogen upregulates and increases the concentration of ICAM-1 proteins on the surface of endothelial cells, resulting in increased adhesion of leukocytes on the surface of endothelial cells,<sup>11</sup> even at high shear rates in flow conditions.<sup>12</sup> Moreover, the fibrinogen binding to ICAM-1 on the endothelial cells also mediates the adhesion of platelets. The interaction of fibrinogen and cells expressing

ICAM-1 is associated with cellular proliferation.<sup>13</sup> Fibrinogen, on binding to its integrin receptor on the surface of leukocytes also facilitates a chemotactic response, thus playing a vital role in the process of inflammation.<sup>14</sup>

- Fibrinogen and atherogenesis

Fibrinogen has several effects that may facilitate the development of atherosclerosis:<sup>15,16,17</sup>

- It can infiltrate into the arterial wall where it bonds LDL and other clotting factors
- It can be a precursor of mural thrombi
- Fibrin (ogen) degradation products stimulate smooth muscle cell proliferation and cholesterol loading of macrophages

Elevated blood and plasma viscosity — The high molecular weight and asymmetry of fibrinogen make this molecule the primary determinant of plasma viscosity. Fibrinogen also binds to red cells, which promotes red cell aggregation and further increases blood viscosity.

Increased platelet aggregability — Fibrinogen binds to the platelet glycoprotein IIb/IIIa receptor, and serves to bridge platelets into aggregates which serve as the primary hemostatic mechanism following vascular injury. In addition, fibrinogen may increase platelet reactivity independent of the glycoprotein IIb/IIIa receptor.

- Fibrinogen and thrombogenesis

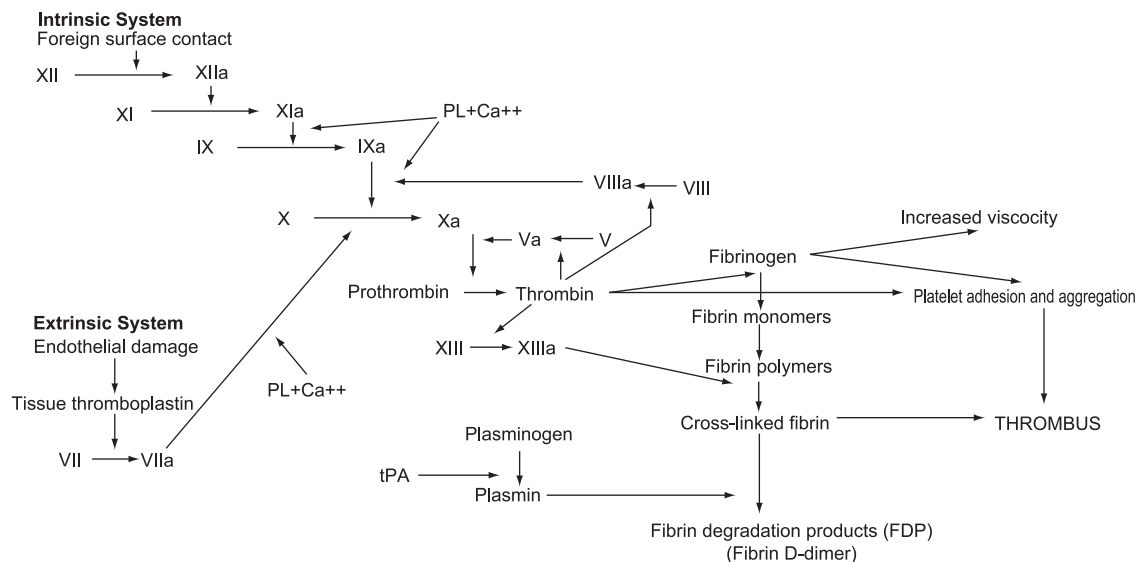
Thrombogenesis is regulated by a fine balance between the coagulation and fibrinolytic pathways (Figure 2). Subsequent to vessel wall trauma, tissue thromboplastin

is released from the sub-endothelium. Tissue thromboplastin in turn triggers the extrinsic pathway of coagulation by activating factor VII to VIIa. Contact of blood with the foreign surface initiates the intrinsic pathway of coagulation, by activating factor XII to XIIa, as well as platelets. The final common pathway of the coagulation cascade involves the activation of factor X to Xa, and the subsequent activation of prothrombin to thrombin. Thrombin, which is a protease enzyme, facilitates the cleavage of fibrinogen into fibrin monomers, which link to each other both sideways and end-to-end to form fibrin polymers. Activated factor XIII facilitates the cross linkage of fibrin polymers to form a stable fibrin clot.

**Association of fibrinogen with cardiovascular disease:**

Multiple prospective studies have identified an association between plasma fibrinogen concentrations and coronary heart disease. This relationship can be illustrated by the following observations:

- In prospective studies of patients who were free of coronary heart disease (CHD) at baseline, those who subsequently developed CHD had higher plasma fibrinogen concentrations (usually by 8 to 16 percent, but as much as 31 percent) than patients who remained free of detectable CHD.<sup>18-25</sup> As an example, the PRIME study was a prospective cohort study of 10,500 men initially free of cardiovascular disease<sup>25</sup>. An association was noted between the plasma fibrinogen concentration and cardiovascular disease; the odds ratio was 1.26 for each rise of one standard deviation of plasma fibrinogen after adjusting for other



**Fig.-2:** Interaction(s) between the coagulation system and fibrinolytic system PL, phospholipid.

cardiovascular risk factors.<sup>25</sup> In the Physicians Health Study of 14,916 subjects, the fibrinogen levels of 199 subjects who had a myocardial infarction were compared to 199 age- and smoking-matched controls; even after adjusting for lipid and other coronary risk factors and aspirin therapy, those with high fibrinogen levels (343 mg/dL) had a twofold increase in the risk of a myocardial infarction.<sup>21</sup>

- Plasma viscosity, which is predominantly determined by the fibrinogen level, is also an independent risk factor for CHD and the incidence of CHD is increased with increasing fibrinogen levels at every level of viscosity and vice versa.<sup>24</sup> In men, but not women, blood and plasma viscosity, hematocrit, and fibrinogen levels are also associated with increased carotid intima-media thickness, a marker for the early stages of atherosclerosis.<sup>26</sup>
- Fibrinogen levels have been positively correlated with the number of diseased vessels and the severity of coronary stenoses.<sup>27,28</sup>
- In prospective studies of patients with CHD, those patients who had recurrent CHD had higher fibrinogen concentrations (by 6.2 to 10.4 percent) than those who did not have recurrent disease.<sup>29-31</sup> Higher fibrinogen concentrations, particularly in patients with elevated systolic blood pressure, is associated with an increased stroke risk.<sup>29</sup>
- Plasma fibrinogen concentrations predict recurrent cardiovascular death and myocardial infarction in stroke survivors and all-cause mortality in patients with myocardial infarction.<sup>30</sup>
- In patients with stable angina pectoris and normal serum cholesterol concentrations (mean 203 mg/dL [5.26 mmol/L]), fibrinogen was the strongest predictor of global coronary score, and the number and severity of stenoses.<sup>28</sup>
- Fibrinogen levels predict occlusion of femoropopliteal bypass grafts and carotid stenoses.<sup>32</sup>
- Fibrinogen levels are an independent marker for the presence and relative severity of thoracic aortic plaques.<sup>33</sup>
- Hyperfibrinogenemia was an independent predictor of plaque rupture, decreased cap thickness, macrophage foam cell infiltration of the cap, and thrombosis (odds ratio 5.83 compared with other risk factors) in 71 patients undergoing carotid endarterectomy after a first transient ischemic attack.<sup>34</sup>

Evidence suggests that thrombosis, endothelial dysfunction and inflammation are strongly associated with coronary artery disease (CAD). Inflammation plays a crucial role in characterizing the formation of atheromatous plaque, as well as its progress.<sup>36-39</sup> The secretion of proinflammatory cytokines from the vascular endothelium as well as from macrophages induces the production of inflammatory molecules that are measured in the circulation, such as C-reactive protein (CRP), serum amyloid A and fibrinogen.<sup>36,38</sup> Several studies have focused on fibrinogen, demonstrating a strong association with the presence of CAD, while others failed to show a significant association. Although most of the available data favor the involvement of fibrinogen in CAD, there is still evidence against this hypothesis.

- Link between inflammation and CAD: a role for fibrinogen

Fibrinogen and its metabolites may lead to endothelial dysfunction through various mechanisms.<sup>40</sup> Several atherosclerotic lesions contain large amounts of fibrin, either in the form of wall thrombus in the intact surface of the plaque or scattered diffusely all over the plaque. This phenomenon is associated with a decrease in fibrinolytic activity and plasminogen concentrations, states that are observed in CAD.<sup>41</sup> It has been found that fibrin (intima) triggers cell proliferation, contributing to cell migration, and bonds fibronectin, which triggers cell migration and adhesion.<sup>42</sup> Fibrinogen and products of its decomposition mediate the transportation of adhesion molecules in the surface of endothelium and their further migration to the intima.<sup>11</sup> The decomposition products located in the inner layer can trigger mitogenesis and synthesis of collagen, attract leukocytes, and enhance permeability as well as vascular tone. In advanced atherosclerotic plaques fibrin participates in the close linkage of lowdensity lipoprotein (LDL) and lipid accumulation, leading to the creation of the lipid nucleus of atherosclerotic lesions.<sup>41</sup> In addition, proinflammatory cytokines, such as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF- $\alpha$ ), are produced from the vasculature, adipose tissue and myocardium; these increase the synthesis of nitric oxide (NO) and favor leukocyte migration in the sub-endothelial space. These cytokines also have a further regulatory role, inducing liver synthesis of acute phase proteins, such as fibrinogen, and consequently inflammatory and prothrombotic reactions.<sup>43</sup> Thus, fibrinogen participates in the formation of atherosclerotic plaque during the first stages of CAD, suggesting that it is a causative factor rather than a result.

- Evidence supporting the association between fibrinogen and CAD

Early evidence from previous decades pointed to a strong association between fibrinogen levels and CAD manifestation (Table 1). The Gothenburg Study<sup>44</sup> reported that plasma fibrinogen levels represent an independent risk factor for myocardial infarction (MI) and stroke in univariate analysis. Similarly, the Framingham study<sup>45</sup> demonstrated that the risk for MI and stroke increased progressively along with fibrinogen levels. The effect of fibrinogen levels on cardiovascular risk was even greater in young individuals and was similar to the effect of known risk factors such as hypertension, diabetes mellitus, and smoking. Novel data from the EPIC-Norfolk study<sup>46</sup> showed prospectively that fibrinogen levels were

significantly higher in patients presenting with fatal or non-fatal coronary heart disease, than in those remaining free of any cardiovascular disease during follow up, while Acevedo et al<sup>47</sup> reported that fibrinogen was directly associated with the presence of MI and was revealed to be an independent short-term predictor of mortality. Interestingly, increased levels of fibrinogen have been correlated with adverse cardiac events after intracoronary stenting, suggesting a potential role of fibrinogen levels in the outcomes following percutaneous coronary interventions.<sup>48</sup> Despite the data supporting a role of fibrinogen as a marker of CAD and its manifestations, several studies have investigated the role of fibrinogen as a risk factor mediator of CAD. Fibrinogen levels have been found to be independently related to cardiovascular mortality, extent, as well as the severity of disease.<sup>49</sup>

**Table-I**  
*Studies focusing on the association between fibrinogen and coronary artery disease.*

Study	Population	Number	Years	Comments on fibrinogen and CAD	Level of significance
Wilhelmsen et al <sup>2</sup>	General population	792	13.5	Fibrinogen levels strongly associated with stroke and MI.	—
Kannel et al <sup>45</sup>	Healthy	1315	12	Fibrinogen is a predictor of CVD.	—
Thompson et al <sup>29</sup>	Angina pectoris	3043	2	Increased incidence of MI or sudden death with higher fibrinogen levels.	p=0.01
Rana et al <sup>46</sup>	Healthy	2550	6	Fibrinogen levels were significantly higher in subjects with CAD	p<0.001
Acevedo et al <sup>47</sup>	CAD vs. Healthy	2126	—	Fibrinogen directly associated with MI. Independent predictor of mortality.	p=0.001 (HR=1.81, 0.001)
Robinson et al <sup>20</sup>	FH of MI vs. Healthy	170	—	Subjects with a dual parental and sibling history of MI had higher fibrinogen levels.	p<0.05
Germing et al <sup>48</sup>	CAD	228	—	Significantly higher level of fibrinogen in the group with adverse cardiac events compared with controls.	p=0.028
Rizzo et al <sup>45</sup>	HT (PM) women	127	5	Fibrinogen levels were associated with the extension of carotid atherosclerosis. Elevated fibrinogen was an independent predictor of subclinical atherosclerosis.	p<0.0001 p=0.0298
Espinola-Klein et al <sup>49</sup>	Undergoing coronary angiography	719	6.5	Greater mortality in those with high fibrinogen levels. Predictive value of fibrinogen for mortality	p<0.0001 p<0.01
Gil et al <sup>42</sup>	ACS vs. stable angina	101	—	Plasma fibrinogen levels were significantly higher in patients presenting with unstable angina. Significant correlation between fibrinogen and troponin I levels in unstable patients.	p=0.002 p=0.0015

Moreover, fibrinogen levels were significantly higher in patients presenting with unstable than in those with stable angina, suggesting a role for fibrinogen in the pathophysiology of acute coronary syndromes.<sup>49</sup>

### Determinants of plasma fibrinogen levels

Plasma fibrinogen level is dependent upon both genetic and environmental factors.

#### • Genetic influences

The evidence suggests that plasma fibrinogen levels are probably under substantial genetic control, as genetic polymorphisms account for some 20–51% of variations in plasma fibrinogen levels.<sup>50</sup> The fibrinogen locus comprises three genes coding for fibrinogen gamma (FGG), fibrinogen alpha (FGA), and fibrinogen beta (FGB), clustered in a region of approximately 50 kb on the long arm of chromosome 4q23-q32, the direction of transcription of the b gene being in the opposite direction to that of the other two. There is a single copy of each gene; the a gene in the middle flanked by the b gene on one side and the g gene on the other. Variation in the fibrinogen locus contributes to the individual differences in plasma fibrinogen levels.<sup>51</sup> The genetic influence on the fibrinogen betachain gene has been more extensively studied, because b-chain synthesis is the limiting step in the production of mature fibrinogen. In recent years, several polymorphisms have been identified in the fibrinogen chain genes that determine plasma levels of fibrinogen, mainly by restriction fragment length polymorphism (RFLP) and single-stranded conformation polymorphism (SSCP) analyses.<sup>50-52</sup>

#### • Extrinsic influences

There is evidence that plasma fibrinogen level and its associated cardiovascular risk may be dependent upon an interaction between environmental and intrinsic (genetic) factors (Table 2).<sup>53</sup> For example, there is a dose-response effect between the number of cigarettes smoked and plasma fibrinogen level, as well as an inverse relationship with time since cessation of smoking. Moderate drinking may lower plasma fibrinogen concentration, and if fibrinogen is a causal risk factor for cardiovascular disease, it may be one of the variables that explain the protective effect of moderate alcohol consumption on cardiovascular disease. The observation of extrinsic influences on plasma fibrinogen levels suggests that elevated plasma fibrinogen levels may be modifiable through appropriate lifestyle changes.

**Table-II**

### *Factors influencing plasma fibrinogen levels*

Factors associated with raised fibrinogen	Factors associated with lower fibrinogen
Advancing age	Young age
Female sex	Male sex
Black race	Caucasians
Smoking	Cessation of smoking
Obesity	Weight reduction
Physical inactivity	Regular exercise
Elevated cholesterol	Moderate alcohol consumption
Menopause	Hormone replacement therapy
Oral contraception	
Low socio-economic status	
Stress	

### Measurements of plasma fibrinogen:

There are several methods available for measurement of the plasma fibrinogen concentration. Clotting methods use thrombin to convert fibrinogen to fibrin which can be quantified by the time-to-clot formation (eg, the Clauss method), photometry, or gravimetry. The Clauss method is the most widely used.

Immunologic methods use antifibrin antibodies. The fibrinogen concentration is quantified by immunoprecipitation, radial immunodiffusion, or enzyme-linked immunoassay. Precipitation methods use a chemical to precipitate fibrinogen which is generated by nephelometry, turbidometry or weighed after centrifugation.

Normal values- The PROCAM study defined the following limits for plasma fibrinogen levels<sup>21</sup>

- Low — <2.36 g/L (236 mg/dL)
- Moderate — 2.36 to 2.77 g/L
- High — >2.77 g/L

The peak elevation in fibrinogen during the acute phase occurs by three to five days. Fibrinogen levels gradually return to baseline following resolution of the inflammation.<sup>35</sup>

### Conclusion:

Fibrinogen represents an inflammatory marker that appears to be implicated in the pathophysiology and prognosis of CAD. Its presence contributes to the formation of atheromatous plaque, while it contributes to the development of acute coronary syndromes via its interaction with other inflammatory substances, endothelium and thrombotic molecules. The vast majority of studies focusing on the association between fibrinogen levels and CAD, even gene-related, demonstrated a



positive correlation, while others failed to show any correlation. In addition, several gene polymorphisms of fibrinogen chains are associated with cardiovascular events and fibrinogen levels. Although fibrinogen is used widely in clinical practice and epidemiological studies have evaluated its role in CAD, there are still aspects that need further investigation. Thus, many more large scale studies are required to evaluate the association of fibrinogen with advanced atherosclerosis.

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