Fibrinogen and Coronary Risk

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Current Review of Cardiology 1999, **1:**112–118
Current Science Inc. ISSN 1523-3782

The notion that fibrinogen is strongly, consistently, and independently related to coronary risk has been widely accepted. The evidence is based on numerous prospective epidemiological studies and clinical observations. However, the reasons why fibrinogen is elevated in coronary disease and in atherosclerosis are only incompletely understood. All cells involved in the atherogenetic process are able to produce cytokines which induce an acute phase reaction. The potential pathophysiologic mechanisms by which elevated fibrinogen levels mediate coronary risk are manifold: It forms the substrate for thrombin and represents the final step in the coagulation cascade; it is essential for platelet aggregation; it modulates endothelial function; it promotes smooth muscle cell proliferation and migration; it interacts with the binding of plasminogen with its receptor; and finally it represents a major acute phase protein. Whether or not fibrinogen is causally involved in atherothrombogenesis still remains to be determined, and even though other unsolved issues await conclusive answers, fibrinogen has emerged as an important additional marker of coronary risk.

Introduction

Although the risk factor concept for coronary heart disease (CHD) has been well established over the past 5 decades, we are becoming increasingly aware that the prediction of future events based on the knowledge of high plasma cholesterol, smoking, and hypertension is limited. Approximately 50% of patients who present with acute coronary syndromes (ACS) do not have these risk factors [1].

Markers of coagulation and fibrinolysis, and more recently inflammatory markers, have gained widespread interest, based on the pivotal role of thrombosis and inflammation in ACS and the increasing knowledge of their involvement in atherogenesis [2]. By far the largest body of evidence exists for fibrinogen, which happens to be a marker of coagulation and inflammation, and also influences fibrinolysis. There have been a number of overviews during recent years [3••,4••], covering this topic in depth. The issue was discussed most recently at the fourth International Fibrinogen Symposium in Paris, France [5]. This review briefly updates new important findings linking fibrinogen with CHD.

Epidemiologic Evidence

Prospective studies

The evidence from prospective studies demonstrating an association between fibrinogen levels at baseline and future coronary events (acute nonfatal and fatal myocardial infarction [MI], AMI, and coronary death) is unequivocal. The published data are remarkably strong and consistent, despite the diversity of populations studied, the variable length of follow-up, different definitions of endpoints, and the various analytical methods applied in the absence of an International Standard at the time most of these studies were done. Furthermore, almost all studies relied on one single determination of fibrinogen. Thus, the risks derived from these studies are most likely to represent an underestimation of the true risk, based on the concept of the regression dilution bias. The latest meta-analysis [3••], covering 18 studies with a total of 4018 CHD cases, yielded a combined risk ratio or relative risk (RR) of 1.8 (95% confidence interval, CI, 1.6–2.0), if individuals in the top third of the baseline measurements were compared with those in the bottom third. However, most of the individuals were within the commonly accepted range of reference (2.0–4.5 g/L) and the absolute difference between cases and non-cases was small and in the order of 0.2 g/L.

Since the association between fibrinogen and CHD in women was not well established in earlier studies, the Scottish Heart Health Study [6] addressed this issue. The study found an even higher risk (combined endpoint: fatal and nonfatal CHD) in women than in men, if the top quintile of the fibrinogen distribution was compared with the bottom quintile (multivariable RR 2.54, 95% CI, 0.92–6.82 in women versus 1.73, 95% CI, 1.04–2.86 in men). The magnitude of the association was similar in women with and without evidence of CHD at baseline. Furthermore, fibrinogen was also important as a risk factor for coronary death and total mortality in both sexes. However, in most analyses, only the risk differences between the extreme fifths were significant, suggesting a threshold effect in this study. Fibrinogen was a significant predictor of CHD risk in two populations with claudication from Scotland [7,8] and in a group at particularly high risk, diabetic patients with end-stage renal failure [9]. Two long-term observational studies in populations with greatly differing risk have investigated

the association between plasma viscosity (which is determined to some extent by fibrinogen) and CHD. The studies reported a multivariable RR of 2.3 (95% CI, 1.7–3.2) [10] and of 3.3 (95% CI, 1.2–9.3) [11], respectively, if the top quintiles of the distributions at baseline were compared to the bottom quintiles.

Cross-sectional studies

Given the strong and consistent relationship between fibrinogen and CHD, there is only little room for cross-sectional analyses since, by definition, they cannot contribute to establishing a potential causal relationship. Thus, they may only be of some value in less thoroughly studied specific populations.

The association between fibrinogen and CHD has almost exclusively been studied in Western populations. One recent case-control study from India [12] has reported an odds ratio (OR) of 4.4 (95% CI, 2.4–19), if subjects with fibrinogen levels above 3.0 g/L, a fairly well accepted cut-point derived from various studies, were compared to those with values below. However, fibrinogen levels in Indians seemed to be even higher than in Western populations and did show only few associations with other risk factors in another, albeit relatively small study [13].

Data from the NHLBI Family Heart Study [14] have confirmed earlier studies showing an association between fibrinogen and subclinical carotid disease, but were not able to demonstrate a difference in fibrinogen between high CHD risk families versus random families.

Clinical Evidence

Like other acute phase proteins, fibrinogen is clearly elevated in AMI [15]. The associations with the angiographic extent and severity and with the clinical presentation (stable versus unstable angina) of coronary atherosclerosis, however are less clear. Although some studies have found increasing levels of fibrinogen to be correlated with the number of diseased vessels, and in particular with occluded vessels, others have not [16]. Two recent studies, one in women [17] and one in both genders [18], have reported moderately strong positive correlations (r=0.36 and r=0.30, respectively), whereas in a much larger study no such relation was seen [19].

Kruskal *et al.* [20•], in a relatively small study, were the first to report differences in fibrin- and fibrinogen-related antigens between patients with stable and unstable angina pectoris, healthy controls, and patients with other than coronary disease. Values were highest in unstable patients and lowest in healthy controls, with intermediate values in stable angina pectoris patients and in non-coronary patients.

Treatment strategies for patients with unstable angina pectoris and non–Q-wave MI are still controversial. Adequate risk stratification of these patients is crucial. The association of fibrinogen on admission with clinical outcome might therefore be of considerable interest. Recently, results from two large clinical trials have highlighted the prognostic value of fibrinogen in patients with unstable angina or non–Q-wave MI. In the TIMI IIIB Trial [21•], fibrinogen was measured serially in 1,473 patients and related to MI, death, and spontaneous ischemia, separately, and as a combined endpoint. No association was found between pretreatment fibrinogen and in-hospital MI and death. In contrast, patients with spontaneous ischemia and unstable patients on admission suffering from the combined endpoint during in-hospital stay (at 10 days) had higher fibrinogen concentrations (approximately 0.2 g/L, $P = 0.0001$) than those without these events. Fibrinogen was measured in 965 patients with an ACS participating in the FRISC trial [22], which assessed the effect of low-molecular weight heparin on clinical outcome. During a follow-up of five months, the probabilities of death were 1.6%, 4.6%, and 6.9% ($P = 0.005$) and the probabilities of death and/or MI were 9.3%, 14.2%, and 19.1% ($P = 0.002$), respectively, according to tertiles of fibrinogen at baseline. Similar strong associations with death were seen for C-reactive protein (CRP). In another study in 211 consecutive patients with severe unstable angina [23•], fibrinogen and other markers of inflammation were related to in-hospital outcome. Increased fibrinogen levels on admission were clearly related to the occurrence of refractory unstable angina with an almost threefold increased risk in those in the highest quartile compared to those in the bottom quartile. Slightly less strong associations were found with CRP. These data clearly strengthen the pathobiologic link between atherosclerosis, thrombosis, inflammation, and coronary events.

Determinants

Genetic factors

A genetic determination of fibrinogen levels undoubtedly exists, although current estimates of the degree to which plasma fibrinogen is genetically regulated vary. The use of path analysis in families suggests that up to 50% of variation in plasma fibrinogen levels may be hereditary. Studies in twins have suggested that environmental factors have a greater influence on plasma fibrinogen than genetic factors, with maximum inheritability estimates in the region of 30%. An increasingly high proportion of such variation can be explained by fibrinogen gene polymorphisms, *eg*, several polymorphisms have been identified in the beta-fibrinogen gene [24].

Recently, the relationship between the -455 G/A b-fibrinogen gene polymorphism and fibrinogen levels in the development of CHD has been studied in subjects with NIDDM [25]. Genotype and fibrinogen levels were significantly associated with CHD with an OR of 1.77 (95% CI, 1.08–2.90) for having CHD in individuals homozygous for the G allele compared to those with the A allele; and an OR of 1.60 (95% CI, 1.00–2.60) was found for an increase of 1g/L in fibrinogen level; but no association could be

demonstrated between levels and genotype. This is in contrast to a number of studies in which carriers of the A-455 allele, who represent approximately 20% of the population, have consistently shown on average 7%–10% higher fibrinogen levels than those with the GG genotype [26]. The association of the Bcl I b-chain fibrinogen polymorphism with the risk of familial MI and its relationship with fibrinogen levels was studied in a sample of GISSI-2 patients [27]. In multivariable analysis, the B2 allele of the Bcl I polymorphism was associated with a more than two-fold increased risk of MI (OR 2.4; 95%CI, 1.3–4.6), and furthermore showed the highest levels of fibrinogen in cases and controls.

There is now increasing evidence that gene-environment interactions are important. High fibrinogen genotypes, like the b-fibrinogen, appear to influence individual responses to environmental factors such as cigarette smoking [28]. Another recently reported interaction concerns the individual's response to strenuous exercise. The degree of fibrinogen rise seen in 156 male British Army recruits during a 10-week basic training exercise was strongly related to the presence of the A allele of the b-fibrinogen gene [29]. In a large group of apparently healthy subjects, increased fibrinogen levels were independently related to the A allele, especially in younger men and in women [30]. Thus, further studies should be undertaken to evaluate the associations and interactions between the fibrinogen gene and a variety of risk factors. This might offer the opportunity to identify those individuals who are at a particular high risk of a thrombotic event in response to a specific environmental stimulus.

Other cardiovascular risk factors

Fibrinogen is associated with most of the conventional coronary risk factors (Table 1) and an update on this issue has recently been published [31]. The large PRIME Study [32] in 10,500 healthy men aged 50 to 59 years, from three MONICA centers (MONitoring of trends and determinants in CArdiovascular disease) in France and the Belfast MONICA, confirmed the positive associations of fibrinogen with age, body mass index (BMI), waist-to-hip ratio, smoking, diabetes, and LDL cholesterol. The negative associations with alcohol consumption, educational level, leisure activity, HDL cholesterol and triglycerides could also be confirmed, but seemed to be less strong than reported from other studies [overview in 4]. The ARIC Study [33] reported a moderately strong association with prevalent hypertension (>140/90 mm Hg) in men and women, but only a weak association with incident hypertension ($P = 0.045$ for trend) in men and no association in women. Data from the PROCAM Study [34] showed no independent association between fibrinogen and prevalent hypertension in middle-aged men. Finally, hypobetalipoproteinemia (LDL cholesterol level <70mg/dL) has been found to be associated with low levels of fibrinogen and other hemostatic risk factors in 1,878 individuals from the Framingham Offspring Study [35•]. This suggests that lipid-lowering therapy may decrease cardiac events at least in part through a reduction in thrombotic tendency. However, this should be studied prospectively in appropriately designed clinical trials.

Other determinants

Data showing an association between chronic infection with *Helicobacter pylori* and fibrinogen levels are controversial. After initially positive reports, meta-analysis [36], and better-controlled clinical studies suggest no appreciable impact of serologically diagnosed chronic infection on fibrinogen levels [37,38]. Similar controversial results have been reported for *Chlamydia pneumoniae* [39,40]. Confounding by the clinical presentation of atherosclerotic disease (chronic stable vs unstable angina) may in part explain these differences.

However, in one recent smaller randomized study in patients with chronic CHD who were seropositive for *H. pylori* or *C. pneumoniae,* fibrinogen levels decreased during six months in the group treated with an antibiotic [41]. In the much larger ACADEMIC Study [42], in CHD patients seropositive to *C. pneumoniae,* despite a decrease in the levels of four markers of inflammation, no differences in antibody titers and clinical events were observed, thus leaving the issue open for further debate.

Table 1. Factors Influencing the Plasma Fibrinogen Level

Positive	Negative
Age	HDL cholesterol
Female gender	Estrogen replacement
Smoking	Alcohol
Diabetes	Endurance exercise
Body weight	Leisure activity
LDL cholesterol	Physical fitness
Triglycerides	Social class
Lipoprotein(a)	Education level
Serum insulin	Birth weight
Glycemic control	Chronic hepatitis
Microalbuminuria	
Hypertension	
Homocysteine	
Pregnancy	
Oral contraceptives	
Menopause	
Inflammation	
Infection	
Immune diseases	
Malignancy	
Stress	
Winter season	

HDL–high-density lipoprotein; LDL–low-density lipoprotein.

Mechanisms

Since an independent association between fibrinogen and future CHD has been convincingly demonstrated, thus clearly establishing its role as a risk marker, it seems appropriate to discuss the potential pathophysiologic mechanisms that may link elevated fibrinogen to atherogenesis and its thrombotic complications. Apart from its pivotal role in the coagulation cascade as the substrate for thrombin, there is evidence of multiple mechanisms suggesting that fibrinogen indeed may be involved in both the early and the later stages of the atherothrombotic process.

Atherogenesis

Fibrinogen binding to endothelial cell (EC) receptors (ICAM-1) causes the release of vasoactive mediators [43]. Fibrin(ogen) and fibrin(ogen) degradation products modulate EC permeability, thus enhancing their deposition in the subendothelial space, and further promoting EC migration. Fibrin(ogen) and its degradation products have been shown to promote smooth musclecell (SMC) chemotaxis and proliferation, and induce monocyte chemotaxis. Fibrin(ogen) provides an adsorptive surface for the extracellular accumulation of low density lipoproteins (LDL) [44]; it further facilitates cholesterol transfer from platelet to monocytes/macrophages and may therefore play a role in foam cell formation [45]. Through all these effects fibrin(ogen) may be involved in the early stages of plaque formation.

Platelet aggregation and thrombus formation

Fibrinogen binds to glycoprotein (GP) IIb/IIIa receptors on the platelet membrane and promotes aggregation and formation of platelet-rich thrombi. Elevated plasma fibrinogen levels increase the velocity of platelet aggregation and also increase platelet reactivity [46].

Fibrin thrombus formation

Fibrinogen is the precursor of mural fibrin thrombi and affects thrombus size, structure, and deformability. Elevated fibrinogen levels lead to larger thrombi and formation of tight and rigid network structures [47], decrease the deformability of the clot, and render it less amenable to endogenous fibrinolysis [48]. Recent data also show that high fibrinogen levels interfere with the binding of plasminogen to its receptor [49•], thus leading to impaired fibrinolysis.

Plasma and blood viscosity

Fibrinogen is a major determinant of plasma viscosity (explaining about 50% of its variability), of whole blood viscosity, and of red blood cell aggregation. Elevated blood and plasma viscosity may lead to impaired microcirculatory flow and endothelial shear-stress damage, and predispose to thrombosis [50].

Other mechanisms

The fact that fibrinogen is an acute phase reactant also deserves consideration, and atherosclerosis bears similarities to an inflammatory process. Elevated levels of fibrinogen might be an indicator of an underlying low-grade inflammation, the cause of which remains unclear, but may be initiated by various stimuli like oxidized LDL [2], several cytokines [51], oxygen free radicals, other factors, and possibly, but not very likely, by chronic infections [52]. The "inflammation hypothesis" is further supported by the fact that a variety of other systemic markers of inflammation are also related to CHD [3]. Interestingly, in the Artherosclerosis Risk in Communities (ARIC) Study [53], in which a large array of hemostatic parameters was investigated prospectively, only those that were also acute phase proteins (fibrinogen, factor VIII, and von Willebrand factor), turned out to be independent predictors of CHD.

Lowering Fibrinogen

If high fibrinogen were the cause of CHD or would at least mediate part of the coronary risk associated with other factors, interventions to reduce its plasma levels, or interfering with some of its biologic functions might seem desirable. Changes in lifestyle, like smoking cessation, reducing body weight, or regular endurance exercise [54] have all been shown to reduce fibrinogen levels considerably. In addition to their main mode of action, various drugs decrease plasma fibrinogen levels, although the evidence is not conclusive in a several of them (Table 2) [55]. Fibric-acid derivatives are by far the most important compounds thatconsistently have been shown to reduce fibrinogen with only one exception, gemfibrocil. Because the molecular mechanisms that may explain fibrate-induced reductions of fibrinogen are not known, this issue has recently been addressed. Studies in rodents have shown that the basal levels of plasma fibrinogen are regulated by peroxisome proliferator-activated receptor (PPAR) a and that fibrate -suppressed expression of fibrinogen is mediated through PPARa [56••]. Fenofibrate was found to inhibit interleukin (IL)-1 induced production of IL-6, prostaglandin and expression of cyclooxygenase (COX)-2 in aortic SMC through activation of PPARa. In hyperlipidemic patients, fenofibrate treatment decreased concentrations of IL-6, CRP, and fibrinogen [57•]. Interference with cytokine-induced signaling pathways may thus constitute one mechanism by which activated PPARa negatively regulate fibrinogen gene expression. Treatment with gemfibrocil, a fibrate that does not lower plasma fibrinogen levels, was shown to reduce local fibrin(ogen) deposition in animals in vivo [58] . Yet, results of clinical trial in fibrates are still inconclusive. In the Bezafibrate Intervention Prevention Study (BIP) [59], a 9% reduction of fibrinogen was not associated with a decrease in cardiac events in patients with CHD. Only in post-hoc analyses in patients with high baseline fibrinogen values did lowering of fibrinogen show a significant reduction in primary endpoints. The effect of statins on fibrinogen has not been well studied and the available data are highly controversial. The effect of low-

dose heparin on plasma fibrinogen was studied in 20 asymptomatic patients with previous MI and in 20 patients with stable angina in a randomized crossover trial over 6 months. At the end of the treatment period significant decreases in fibrinogen (3.3±0.5 g/L vs 2.5±0.6 g/L, $P<0.001$), in prothrombin fragment 1+2, thrombin-antithrombin, and fibrinopeptide A were observed, compared with the pretreatment period [60]. Hormone-replacement therapies (HRT), applied either transdermally or orally, as estrogen-monotherapy or in combination with progesterone, have been found to be associated with lower fibrinogen values in a number of studies [61,62], but not in all [63]. Raloxifene, a selective estrogen receptor modulator, significantly lowered fibrinogen by 12% to 14% over six months [64], and HRT in 22 elderly men reduced fibrinogen short-term [65]. Interestingly, HRT was associated with an improved long-term outcome after coronary angioplasty in postmenopausal women [66]. However, in a recent study in postmenopausal women with established CHD no reduction in the overall rate of coronary events could be demonstrated and even an increase was seen in the rate of thromboembolic events [67]. Therefore, further research is required to define more precisely the patient groups that might benefit from this treatment.

Table 2. Drugs to Lower Fibrinogen Levels

Fibrates
Other lipid-lowering drugs
Nicotinic acid
Beta-adrenergic receptor blockers
Propranolol
Celiprolol
Atenolol
Ticlopidine
Pentoxifylline
Vasodilators
ACE-inhibitors (lisinopril)
Calcium channel blockers (nisoldipine)
Hormones
Estrogen
Stanozolol
Fibrinolytics
LDL-apheresis

ACE-angiotensin-converting enzyme; LDL-low-density lipoprotein.

Should fibrinogen be measured routinely?

To answer this question, several issues have to be addressed. Measurements should be accurate and standardized. The accuracy of various methods seems to be acceptable but, despite the fact that an International Standard is available, it is not widely used. Different types of instruments, reagents, and methods of clottable fibrinogen assay create further problems for accurate comparisons between various laboratories, which is a prerequisite before screening might be recommended.

Fibrinogen is an acute phase protein and as such shows high variability. The intra-correlation of repeatedly measured fibrinogen values is approximately 0.6 [3]. Despite its variability and the wide variation of different assays used, the association between fibrinogen and CHD, based on a single measurement, is strong and consistent. However, accurate classification of an individual's fibrinogen may require several measurements over several weeks [68], which is commonly done in the evaluation of other risk factors. Because changes in fibrinogen are unspecific, other causes for its elevation, like intercurrent infections or noncardiac diseases, have to be excluded before it can be interpreted in terms of cardiovascular risk assessment. Finally, despite the fact that strong and consistent associations with CHD have been shown, the proof of a causal involvement of fibrinogen is still pending. In view of these limitations, screening of the general population cannot be recommended. Measurements of fibrinogen however, should be encouraged in individuals at high risk for coronary complications, because they add to the prediction of conventional risk factors [6], If values are found to be ≥ 3.0g/L, this should lead to more aggressive treatment with lipid-lowering drugs, or other medication proven to be effective in reducing coronary events.

Conclusions

Fibrinogen undoubtedly represents a strong and independent risk factor for CHD, based on numerous large prospective epidemiological studies. Fibrinogen is clearly associated with a variety of conventional risk factors, and several polymorphisms of the fibrinogen gene might predispose to elevated fibrinogen in response to various environmental stimuli. Clinical data indicate that the addition of fibrinogen may represent a useful marker for better risk stratification of patients with unstable angina pectoris, and an abundance of mechanisms exist that make a direct link between fibrinogen and clinical events likely and plausible. Various non-pharmacological measures and drugs are available that can lower fibrinogen values appreciably. However, much more research is needed until we fully understand the complex interplay between fibrinogen and atherothrombosis.

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