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REVIEW

Fibrinogen and cardiovascular disease: Genetics and biomarkers

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ABSTRACT

Several prospective epidemiological studies and clinical observations provided evidence regarding fibrinogen and coronary artery disease (CAD). Many of these studies firmly correlate fibrinogen with CAD. However, it is uncertain whether this relation is causal or reflects genetic variability and residual confounding by other risk factors. Several polymorphisms on fibrinogen chain genes affect its levels, however only few of the genetic variants are associated with increased cardiovascular risk. As regards the role of fibrinogen in myocardial infarction (MI) studies indicate that genetic variations have at best a modest impact on the process resulting in MI. Therefore, the screening of fibrinogen genes might not be useful for the assessment of the risk of MI. However, the findings that specific genotypes lead to specific differences in fibrinogen levels, but may not be linked to cardiovascular risk, complicates the hypothesis of causality of fibrinogen in the pathogenesis of cardiovascular disease.

1. Introduction

Despite of the fact that previous studies have reported a wide range of data regarding the potential role of fibrinogen as a biomarker of cardiovascular disease, the role of plasma fibrinogen levels as a cardiovascular risk factor remains controversial.[1] Prospective observational studies along with case–control studies have demonstrated that fibrinogen levels are predictive of coronary artery disease (CAD) risk (Table 1).[2] However, already existing atherosclerosis might increase fibrinogen levels, and thus, reverse causality leads fibrinogen to predict future CAD events.[3] Additionally, high fibrinogen levels are observed in several population subgroups with increased CAD risk.[4] Importantly, specific members of the fibrate class such as clofibrate and bezafibrate, which lower fibrinogen levels failed to show, in randomized controlled studies, any beneficial effect.[5,6] Thus, it is still obscure whether fibrinogen is a causal factor for CAD or merely serves as a marker of both preexisting disease status and other causal factors.

Furthermore, several studies have demonstrated that genetic polymorphisms related to plasma fibrinogen levels could be used to examine whether fibrinogen is a causal factor with respect to CAD.[7] The association between CAD risk and a polymorphism related to increased fibrinogen levels is not susceptible to reverse causation or confounding and it is unlikely that behavioral and socioeconomic confounding factors will be related to the distribution of the studied polymorphism.

In the present review article we sought to highlight the role of fibrinogen as a biomarker in CAD. Therefore, we discuss two crucial issues including the association between fibrinogen levels and CAD as well as the impact of gene polymorphisms and genetic variation of fibrinogen.

2. Structure and function

Fibrinogen is a soluble glycoprotein, with a molecular weight of 340 kDa and consists of three polypeptide chains linked to each other by disulphide bonds. It is mainly synthesized in the liver and regulates plasma viscosity while induces reversible red cell aggregation.[8] The final common step of the extrinsic and intrinsic systems of coagulation involves the activation of factor X to Xa and the subsequent activation of prothrombin to thrombin. Thrombin promotes the cleavage of fibrinogen into fibrin monomers which are linked to each other, with the support of factor XIII, to form a stable fibrin clot (Fig. 1).[8]

Additionally, fibrin deposition plays a key role in the initiation of atherogenesis as well as in the growth of atheromatous lesions. Atherosclerotic plaques are characterized by a high amount of fibrin, fibrinogen and its degradation products. In the arterial intima, fibrin stimulates smooth muscle cell proliferation and migration, attracts leukocytes and affects endothelial permeability and vascular tone. In advanced lesions, fibrin participates in the formation of the lipid core of the atherosclerotic lesion by binding low-density lipoproteins and lipids.[9]

Importantly, fibrinogen facilitates platelet aggregation by binding to the glycoprotein IIb/IIIa receptor on the platelet surface and increases the reactivity of platelets augmenting their degranulation in

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Table 1
Fibrinogen levels and cardiovascular disease.

Study	Population	Follow up	CVD	Prognostic significance
Rana et al.[41]	25,000 apparently healthy individuals (45–79 years)	6 years	CAD	Significantly higher among cases than controls ($p<0.05$)
Chuang et al.[42]	3281 adults (>20 years of age)	10.4 years	IS	Fibrinogen independently predicted future IS risk ($p<0.05$)
del Zoppo et al. [43]	Data from STAT and ESTAT trials (870 participants)	8 years	Outcome of IS	Patients with lower fibrinogen levels had better outcomes in both studies ($p<0.0006$ in ESTAT)
Rizzo et al.[44]	127 asymptomatic hypertensive women	5 years	Atherosclerosis	Fibrinogen levels were associated with the extension of carotid clinical and subclinical atherosclerosis ($p<0.0001$ and $p=0.0298$ respectively)
Green et al.[45]	5115 black and white adults (aged 18–30 years at baseline)	13 years	Atherosclerosis	Higher levels of fibrinogen positively associated with CAC and CIMT ($p<0.001$ in both cases)
Tzoulaki et al. [46]	809 men and 783 women (aged 55 to 74 years)	17 years	CVDs MI and IS	Fibrinogen levels were higher in people who developed CVD, MI, and stroke ($p<0.001$ for all cases)
Sjoland et al.[47]	729 patients undergoing CABG	10 years	Long-term mortality	Patients with high levels had increased mortality ($p=0.0005$) After adjustment for specific factors ($p=$NS)
Lawlor et al.[48]	3745 women (60–79 years)	12.641 person-years	CHD	Adjustment for confounding factors attenuated the association between fibrinogen and CHD OR: 1.29 (1.12, 1.49) to 1.09 (0.93, 1.28)
Smith et al.[49]	2398 men (49 to 65 years)	13 years	CHD IS	Significant associations of fibrinogen with risk of CHD ($p=0.005$) but not with IS ($p=$NS)
Fibrinogen studies collaboration[50]	154,211 participants (31 prospective studies)	1.38 million person-years	Major CVDs	HR per 1 g/l increase for CHD and IS 1.8 after adjustment for vascular risk factors
Pineda et al.[51]	237	–	MI	Cases had higher fibrinogen levels ($p=0.006$) In a multivariate analysis, fibrinogen levels were independently associated with cases ($p=0.038$)
Tousoulis et al. [52]	30 patients	–	MI	Lower levels in non-Q wave MI ($p<0.05$) No association with the presence or absence of Q waves ($p=$NS)
Folsom et al.[53]	14,477 healthy adults (45 to 64 years)	5.2 years	CHD	RR of developing CHD significantly higher ($p\leq0.05$)
Robinson et al. [54]	170 subjects with family history of MI vs. healthy	–	MI	Subjects with a dual parental and sibling history of MI had higher fibrinogen levels ($p<0.05$)
Espinola-Klein et al.[55]	719 patients undergoing coronary angiography	6.5 years	–	Greater mortality in those with high fibrinogen levels ($p<0.0001$) Predictive value of fibrinogen for mortality HRR: (95% CI) 2.2, $p<0.01$

ACS: acute coronary syndromes; CABG: coronary artery bypass grafting; CAC: coronary artery calcification; CAD: coronary artery disease; CHD: coronary heart disease; CI: confidence interval; CIMT: carotid intima-media thickness; CVD: cardiovascular disease; ESTAT: European Stroke Treatment with Ancrod Trial; HR: hazard ratio; HRR: hazard risk ratios; IS: ischemic stroke; LDL: low-density lipoprotein; MI: myocardial infarction; NS: non-significant; OR: odds ratio; RR: relative risk; STAT: Stroke Treatment with Ancrod Trial; vs.: versus; –: not studied or not reported or not available while searching in PUBMED.

response to adenosine disphosphate. The effects of fibrinogen on platelet function may be relevant to clinical conditions in which hyperaggregability of platelets is associated with hyperfibrinogenemia and thrombosis.[10] Moreover, fibrinogen is not only a coagulation factor, but also an acute phase reactant. Mild and chronically inflammatory stimuli, such as smoking and advanced atherosclerosis exhibit a mild increase of fibrinogen levels, with interleukin-6 (IL-6) being the main inflammatory inducer of fibrinogen.[11]

3. Fibrinogen levels as a biomarker of coronary artery disease

Over the last decades numerous prospective epidemiological studies and clinical observations provided data on plasma fibrinogen levels with regard to CAD. Many of these studies firmly correlate fibrinogen levels with CAD (Table 1). However, it is uncertain whether this relation is causal or reflects residual confounding by other risk factors.

In the Northwick Park Heart Study, men were tested for a range of clotting factors, including fibrinogen.[12] At 10 years follow-up, multiple regression analyses showed an association between fibrinogen and fatal and non-fatal myocardial infarction (MI), which was independent of other risk factors and approximately half of all the coronary events occurred in the highest tertile of fibrinogen. In another study, the PROspective CArdiovascular Munster,[13] the incidence of coronary events in the upper tertile of the plasma fibrinogen distribution was 3.0-fold higher than in the lower tertile. Other epidemiological data[14] have reported that plasma fibrinogen was a strong and independent risk factor for MI and sudden death, particularly in patients with preexisting CAD. In the Atherosclerosis Risk in Communities study of adults also without history of CAD, the relative risk of developing CAD (during an average follow-up of 5.2 years) was significantly higher for individuals with elevated plasma fibrinogen levels (1.76 for men and 1.54 for women), and the associations of fibrinogen and white blood cell count with the risk of recurrent CAD events were positive, but not statistically significant after adjusting for other CAD risk factors.[15]

There is evidence that fibrinogen concentration is positively correlated with the severity of the underlying CAD (Table 1).[16] Plasma fibrinogen levels are higher in patients with unstable angina than in patients with stable angina and higher in patients with severe vasospastic angina than in those with mild vasospastic angina and stable angina.[17] The Angina Prognosis Study in Stockholm study[18] showed that plasma levels of fibrinogen were independent predictors of CAD death or non-fatal MI, as well as the risk of revascularization, while treatment given did not influence significantly the prognostic impact of fibrinogen.

3.1. Fibrinogen levels as a biomarker of myocardial infarction

As regards myocardial infarction (MI) a case–control study[19] reported that the mean levels of fibrinogen, 3 to 6 months after hospitalization, were significantly higher compared to healthy controls. The age-adjusted odds ratio for CAD in the highest vs. the lowest quartile of plasma fibrinogen was 6.0 (95% CI, 3.5 to 10.4). A prospective study[20] evaluated fibrinogen levels in men surviving after a MI 6 months before they entered the study. Fibrinogen was