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Review Article

Fibrinogen and Atherosclerosis

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Abstract:

Cardiovascular disease has a multifactorial origin. Among these risk markers, fibrinogen is the most prominent. Interest in the role of fibrinogen in the atherogenic process is long-standing. In the 1960s, one of the first studies correlating fibrinogen and coronary artery disease was published. Since then, much evidence has been accumulating establishing elevated plasma levels of fibrinogen as an independent risk factor for coronary artery disease. As in acute myocardial infarction, fibrinogen is also elevated in cases of cerebrovascular accident and peripheral artery disease. It is noteworthy that fibrinogen levels are elevated in patients with transient ischemic attacks, suggesting that fibrinogen levels should be elevated before necrosis occurs. It is known that plasma fibrinogen is a dimer made up of alpha, beta and gamma chains, whose union is made through disulfide bonds. Measures to reduce plasma fibrinogen include diet, alcohol, physical activity, and drugs. Since fibrinogen is a risk factor for coronary artery disease, measures to reduce its levels should be adopted. In the future, with the evolution of genetic studies, the detection of individuals predisposed to hyperfibrinogenemia may be performed. It is up to pharmaceutical research to continue the investigation of effective and easy-to-use drugs to reduce fibrinogen levels.

Key words: fibrinogen; acute myocardial infarction; risk markers; cerebrovascular accident; atherogenesis; thrombosis; platelet aggregation

Abbreviations

AMI: Acute Myocardial Infarction

CAD: Coronary Artery Disease

CVA: Cerebrovascular Accident

CVD: Cardiovascular Disease

RFLP: Restriction Fragment Lenght Polymorphism

Introduction

Cardiovascular disease (CVD) has a multifactorial origin. No risk factor related to it is strictly essential or sufficient for its triggering, if analyzed in isolation [1]. In general, the greater the number or severity of risk markers observed, the greater the likelihood of early morbidity and mortality. In addition, the relationship between the risk markers seems to be one of multiplication, and not simply of addition [2]. Therefore, the recognition of the factors involved in the development of CVD is essential, as it allows a better understanding of its pathogenesis and directs the development of preventive and therapeutic plans.

In recent years, several studies have pointed to the association between components of the hemostatic system and atherosclerosis [3-6]. Among these risk markers, fibrinogen is the most prominent.

It has been demonstrated, both in case-control and cohort studies [7], that the elevation of its levels maintains a positive correlation with the development of coronary heart disease. The mechanisms by which fibrinogen contributes to the development of atherosclerosis are not yet fully understood. It is known that it acts on the coagulation process, modifies blood flow (fibrinogen is one of the main determinants of blood viscosity) and interferes with platelet aggregation and endothelial function [8]. In addition, both fibrinogen and its breakdown products stimulate the proliferation and migration of smooth muscle cells. This fact denotes the involvement of fibrinogen in the early stages of atheromatous plaque formation [3].

Interest in the role of fibrinogen in the atherogenic process is long-standing. In 1960, Merskey et al. published one of the first studies correlating fibrinogen and coronary artery disease (CAD) [9]. Since then, much evidence has been accumulating establishing elevated plasma fibrinogen levels as an independent risk factor for CAD. All in all, high level of fibrinogen is considered a risk marker or a risk factor for

cardiovascular disease [10].

Clinical and epidemiological evidence

Clinical evidences: among the clinical evidence, we can highlight the studies carried out with patients with angina pectoris. Many have shown that fibrinogen levels are elevated in these patients [8,11]. Some even correlate the extent of CAD and elevated fibrinogen levels, suggesting an association between clinical and biochemical abnormalities [12]. In a study involving 229 patients of both genders, aged between 25 and 82 years, who underwent coronary angiography, Handa et al. demonstrated that there was a progressive increase in fibrinogen levels according to the severity of coronary atherosclerosis (the magnitude of the disease was evaluated in terms of the number of vessels involved with stenosis greater than or equal to 75%, and according to the Gensini score) [13].

The ECAT (European Concerted Action on Thrombosis and Disabilities) Angina Pectoris Study, a Multicenter European study investigating the pathogenesis and possible predictive value of the hemostatic system in the progression of atherosclerosis, is in agreement with that of Handa et al. with regard to the association between elevated fibrinogen levels and patients with coronary stenosis (less than or equal to 50%). However, the extent of arteriosclerosis and fibrinogen levels was only found when the parameter was the number of coronary arteries with total occlusion [14].

Therefore, in addition to being a risk factor for CAD, fibrinogen is considered an indicator of severity for coronary atherosclerosis.

Regarding the relationship between acute myocardial infarction (AMI) and fibrinogen plasma levels, the data in the literature are similar to those previously reported. In other words, in AMI, fibrinogen levels are elevated. Hamsten et al., in a study on hemostatic changes after AMI, demonstrated a correlation between the extent of necrosis and the increase in fibrinogen [15]. Another interesting finding is the one reported by Fulton and Ductett in a prospective study: when analyzing 120 patients who had suffered AMI, reinfarction only occurred in those who had higher initial fibrinogen levels [16].

The data presented in relation to angina pectoris and AMI make us realize that the increase in fibrinogen levels contributes to the pathogenesis of these events, being, therefore, more than an acute phase reaction.

As in AMI, fibrinogen is also elevated in cases of cerebrovascular accident (CVA) [17] and peripheral arterial disease [18]. It is noteworthy that fibrinogen levels are elevated in patients with transient ischemic attacks, suggesting that fibrinogen levels should be elevated before necrosis occurs.

In cases of peripheral arterial disease, fibrinogen has been described as an important screening test for asymptomatic stages [18]. In both CVA and peripheral arterial disease, the measurement of fibrinogen has prognostic value: the higher its plasma concentration, the worse the clinical outcome. In the case of CVA, elevated fibrinogen levels limit cerebral perfusion, reducing blood flow to areas adjacent to tissue infarction [19]. In peripheral arterial disease, hyperfibrinogenemia, through its action on plasma viscosity and red blood cell aggregation, potentiates the hemodynamic effects of ischemic vascular lesions [20].

The fact that fibrinolytic agents have been reported to be clinically effective in CAD and claudication is perhaps one of the most significant clinical evidences [21].

Epidemiological evidence: several epidemiological articles [10] conclude that fibrinogen can be considered an independent risk factor for CAD.

The Northwick Park Heart Study was one of the first prospective epidemiological studies to draw attention to the association between fibrinogen and atherosclerotic disease. It involved a sample of 1511 white men, aged between 40 and 64 years. The mean follow-up ranged from 7.3 to 13.5 years. In this study [22], the incidence of cardiac events was higher in patients who had elevated fibrinogen levels at the beginning of the study. Through multiple regression analysis, it was shown that the association between fibrinogen levels and ischemic cardiac events is independent of other risk markers. Also in the same study, fibrinogen had a higher prognostic value than cholesterol in relation to the risk of AMI [23-28].

In the Gothenburg Study [29], 792 54-year-old men were followed over a period of about 13.5 years. A total of 92 cases of AMI and 37 cases of CVA were revealed. In univariate analysis, fibrinogen was listed as a risk factor for AMI and CVA. However, in multivariate analysis, it only maintained this role in relation to CVA. An interesting finding was the additive effect found between elevated systolic pressure levels and fibrinogen in relation to the risk of CAD [30].

The Leigh Study involved a smaller number of participants (297 men), but their data were similar to those of previous studies. Like the Gothenburg study, his results emphasize the relationship between fibrinogen levels and blood pressure. The incidence of ischemic cardiac events was significantly higher among hypertensive patients, who had elevated fibrinogen levels [31].

The Framingham Study [32] stood out for the fact that it involved individuals of both genders. A total of 1315 individuals participated in it. In multivariate analysis, the predictive value of fibrinogen for cardiovascular events was independent of established risk markers. In addition, its prognostic value was found to be at least of equal magnitude to that of the other risk markers. It is worth noting that the study draws attention to the dose-dependent relationship between smoking and fibrinogen. This relationship was so significant that the authors even postulated that the increase in fibrinogen levels would be one of the mechanisms by which smoking would promote CVD [25,30,33-35].

The PROCAM (Prospective Cardiovascular Munster Study) [36] aimed to identify individuals at high risk for CVD. Through the analysis of the components of the hemostatic system of the patients (2,187), it was possible to demonstrate that the initial concentrations of fibrinogen were significantly elevated in those who later became affected by AMI or sudden cardiac death, when compared to the others [37,38].

The ARIC Study (Atherosclerosis Risk in Communities), a prospective, multicenter study focused on the etiology and natural history of atherosclerosis, concluded that both thrombosis and fibrinolysis participate in the early stages of the atherosclerotic process [39]. In addition, there has been an increase in fibrinogen levels as a function of age, smoking, obesity, diabetes, fasting serum insulin, low-density lipoprotein cholesterol (LDL-c), lipoprotein(a), leukocyte count, and menopause. Alcohol consumption, exercise, high-density lipoprotein cholesterol (HDL-c) and use of hormone replacement during menopause were associated with decreased levels of hormone replacement therapy [39].

In a meta-analysis of epidemiological studies involving the participation of fibrinogen in the atherosclerotic process, Ernst and Resch demonstrated that fibrinogen is an independent risk factor for CAD [31]. As illustrated in Kaplan-Meier analysis, the high-fibrinogen group recorded a much higher Main Adverse Cardiovascular and Cerebrovascular Events (MACCEs) rate (Log-Rank test: $P < 0.001$) (Figure 1) [40].

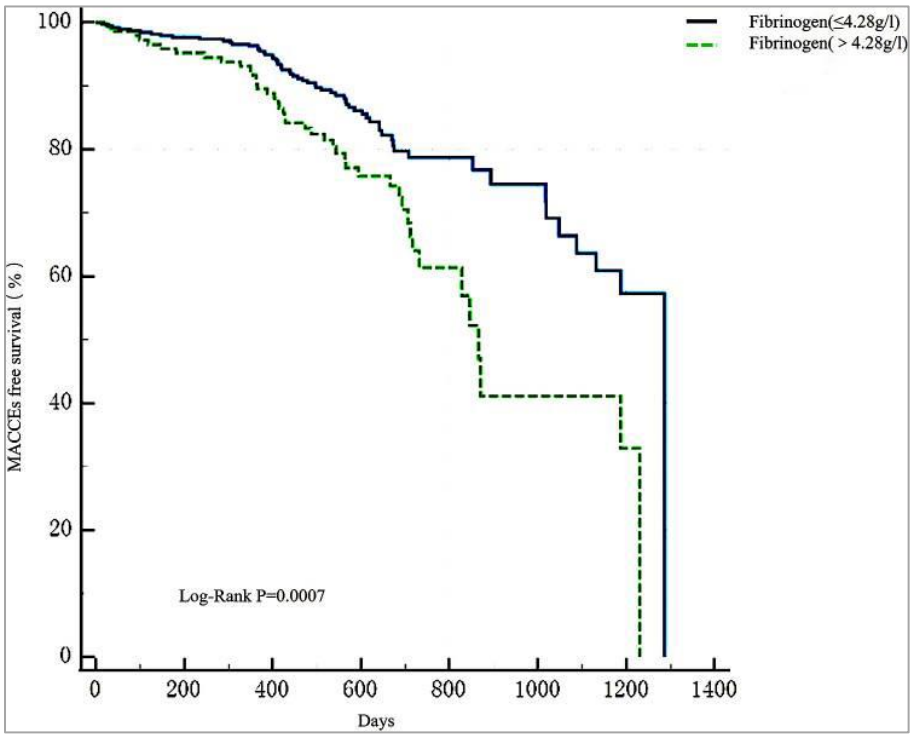

Figure 1: Kaplan-Meier survival analysis of Main Adverse Cardiovascular and Cerebrovascular Events (MACCEs) found that there was a higher occurrence of MACCEs in the high-fibrinogen group (Log-Rank test: P = 0.0002).

Determinants of fibrinogen plasma concentration

Since clinical and epidemiological evidence leaves no doubt regarding the participation of fibrinogen in the atherosclerotic process, it is necessary to know the determining factors of its plasma concentration. An increasing number of studies [10] demonstrate the influence of age, smoking, obesity, hypercholesterolemia, diabetes mellitus, alcohol consumption, oral contraceptive use, and menopause in determining plasma fibrinogen levels. However, despite many investigations and experimental studies, the true extent of the genetic contribution remains uncertain.

Fibrinogen and genetic inheritance: the heritability for plasma fibrinogen concentration was established by Hamsten et al. as being 51% [41]. The mode of inheritance still remains unknown [3].

It is known that plasma fibrinogen is a dimer consisting of alpha (α), beta (β) and gamma (y) chains, whose union is made through disulfide bonds [42].

Each fibrinogen strand is encoded by different messenger RNA, and its genes lie on the long arm of chromosome 4 [43].

Molecular biology, through the analysis of restriction fragment lenght polymorphisms (RFLPs), has enabled the identification of genetic variations responsible for the determination of plasma fibrinogen levels [43]. This type of analysis is able to identify genetic polymorphisms using a variety of chromosomal probes and restriction enzymes. Studies of RFLPs in Caucasian populations indicate that β-chain gene polymorphisms are associated with higher plasma levels of fibrinogen [43,44]. It is believed that the markers of the β chain gene have a stronger correlation with fibrinogen levels than those referring to the other chains (α and ˉy), due to the fact that hepatic synthesis of the β chain is a limiting factor in the rate of fibrinogen formation [42,45].

Much remains to be investigated regarding the real genetic impact on fibrinogen concentration. In the future, the use of RFLPs may be useful in assessing the risk of CAD, since this method will make it possible to identify individuals with a predisposition to high levels of fibrinogen [45].

Other determinants of fibrinogen levels

Association with other risk markers: in addition to genetic predisposition, other factors already mentioned influence the plasma determination of fibrinogen. They are:

Age: many studies focus on the relationship between fibrinogen levels and age. Balleisen et al. [46], in a prospective epidemiological study involving 3186 individuals of both genders, revealed that there was a direct and significant correlation between age and fibrinogen levels. There are several articles presenting similar data [47]. However, Ernst et al. discuss this correlation, suggesting that, in part, it may be influenced by the selection criteria adopted: older individuals are more susceptible to presenting diseases associated with high fibrinogen levels. Therefore, if stricter selection criteria were adopted in order to exclude "hidden" diseases, the age/fibrinogen ratio would disappear [21]. It is worth noting that fibrinogen levels are elevated in C. pneumoniae and H. pylori infections [30].

Smoking: the studies are concordant with regard to the relationship between smoking and fibrinogen. Smoking is capable of increasing fibrinogen levels in healthy individuals [46,48]. Comparing smokers, ex-smokers and non-smokers, it is found that there is a decreasing relationship in fibrinogen levels, with the lowest being observed among those who have never smoked [48]. It is known that the effect of smoking on fibrinogen concentration is dose-dependent [49] and reversible with its cessation [50]. Although fibrinogen concentration declines after about two weeks of abstinence from smoking, it takes an average of five years for the levels of ex-smokers to become similar to those of non-smokers [51].

Blood pressure: the relationship between blood pressure levels and fibrinogen concentration is well known. Hypertensive patients have higher fibrinogen levels than normotensive patients [52]. Among

hypertensive patients, the concentration of fibrinogen is higher in the forms of malignant and renopaarenchymal hypertension [53].

Diabetes mellitus: fibrinogen is elevated in both type I and type II diabetes [54]. The highest levels of fibrinogen are found among those with microvascular involvement [55].

Obesity: elevated fibrinogen levels are also seen among obese individuals. The increase in plasma fibrinogen concentration is directly related to body mass index [46,56] and skinfold thickness [21,57]. Adults with adequate weight in childhood have lower fibrinogen levels [58].

Hyperlipidemia: several studies have reported a correlation between fibrinogen levels and lipid profile [24,25,30,33-37]. The PROCAM study demonstrated a direct and significant relationship between fibrinogen levels and cholesterol and triglycerides in both men and women [37]. There is also a positive correlation with the levels of total cholesterol, LDL-c and apoprotein B [58].

In individuals with familial hypercholesterolemia, elevated fibrinogen levels are added to an increase in platelet aggregation [12].

Hyperfibrinogenemia and a significant reduction in fibrinolytic activity have been reported in patients with severe hypertriglyceridemia [59].

Oral contraceptives: there is a dose-dependent relationship between the use of oral contraceptives and fibrinogen levels [46].

Stress and social class: some studies focus on a direct, but reversible, relationship between stress and fibrinogen levels. The association described between fibrinogen and social class has been attributed, in part, to different levels of stress [58,60].

Measures to reduce plasma fibrinogen

Diet: some isolated studies report that dietary measures are related to decreased fibrinogen levels. The vegetarian diet [61], the high-carbohydrate and low-fat diet [62], and the diet containing large amounts of omega 3 and 6 acids have been described as able to reduce the plasma concentration of fibrinogen. However, most authors believe that diet is not capable of influencing the determination of fibrinogen levels.

Alcohol: moderate alcohol consumption is related to lower fibrinogen levels [63].

Physical activity: there is a difference between the fibrinogen levels of sedentary individuals and those who engage in regular physical activity. The higher the activity, the lower the fibrinogen level [64].

Drugs: to date, there is no known ideal drug for lowering plasma fibrinogen levels. Some lipid-lowering drugs have been shown to reduce fibrinogen levels [65], such as fibrate analogues. The mechanism by which they act remains unclear. It is speculated to be through reduced hepatic synthesis of fibrinogen [66]. Beta-blockers and omega-3 fatty acids are also associated with a relative, but significant, decrease in fibrinogen levels.

Uroxinase and streptokinase have fibrinolytic properties [67]. However, they are expensive therapies that require constant monitoring. Its use is reserved for restricted clinical conditions.

The above measures (physical activity, diet and use of certain medications) aim to reduce fibrinogen levels. To date, there is no consensus regarding the concept of optimal levels. Most laboratories consider values between 150 and 400 mg/dl to be normal (based on the Gaussian distribution). Some of the prospective studies divide fibrinogen values into tertiles [24,35,37]. A higher incidence of cardiovascular events was observed in patients whose fibrinogen levels were in the upper tertile. The majority of laboratories adopt as epidemiological risk level those above 300 mg/dl. Although the Framingham and Northwick Park studies refer to values of 310 and 320 mg/dl, respectively, as markers of the highest risk tertile, we believe that we will provide our patients with a greater margin of protection if we reduce fibrinogen levels to values below 270 mg/dl. It is worth remembering that the Leiden Thrombophilia Study (LETS) considers that fibrinogen levels above 500 mg/dl increase the thrombotic risk by four times. The method adopted for fibrinogen measurement is the Automated Clauss method (koagulab 32-S). This choice is due to the fact that this is a well-established method capable of measuring the active fibrinogen part, and whose calibration technique is performed with internationally calibrated plasma of the referred value [68].

Conclusion

Since fibrinogen is a risk factor for CAD, measures to reduce its levels should be adopted. In the future, with the evolution of genetic studies, the detection of individuals predisposed to hyperfibrinogenemia may be performed. It is up to pharmaceutical research to continue the investigation of effective and easy-to-use drugs to reduce fibrinogen levels.

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None.

Conflict of interest

None.

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