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Fibrinogen as a Cardiovascular Risk Marker

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ABSTRACT

International comparations show that the level of fibrinogen increases with the national risk of is chemic heart disease except in rural Africa and Eskimos who have high levels of fibrinogen despite the low risk of ischemic heart disease. Fibrinogen is a probable cofactor of multi factorial disease, atherosclerosis in cardiovascular disease. Epidemiological studies have shown that fibrinogen levels are a strong and consistent primary and secondary risk factor for coronary artery disease, cerebral and peripheral arterial disease, as well as is associated with prevalence of arterial disease in these three sites. Epidemiological studies also suggest that fibrinogen may be an important link between genetics (difference in nationality, family history, fibrinogen genotype) and environmental influences (fetal development, smoking, alcoholism, obesity, diabetes, infections, menopause, estrogen use) and the development of arterial disease. Fibrinogen level is the major determinant of cardiovascular risk in people with hypercholesterolemia, hypertension or diabetes; should then be included in the cardiovascular risk profile and clinical management. Persistent fibrinogen greater than 3.0 g/L is associated with significant increase in cardiovascular risk and indicates the target population for intervention. Epidemiological and path physiological studies show that there are at least four possible mechanisms by which fibrinogen can promote arterial disease: atherogenesis, platelet aggregation and thrombus formation, fibrin thrombus formation, increased plasma and blood viscosity. Clinical studies have shown that reducing plasma fibrinogen increases blood flow, reduces platelet aggregability, reduces plasma and blood viscosity, and the risk of ischemic symptoms and events. The reduction of fibrinogen needs to be considered in people with ischemic symptoms and those at high risk of arterial disease, also by lifestyle (smoking) or drug therapy (fibrates). Further studies of fibrinogen reduction are desirable for prevention and symptomatic treatment of arterial disease.

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Introduction

In the last 20 years the number of epidemiological, physiological and clinical studies that show the impact of plasma fibrinogen levels on arterial disease of the heart, brain and limbs has increased.

Basic aspects of fibrinogen

Fibrinogen is a high molecular weight glycoprotein (340,000 Da), which circulates in plasma at concentrations ranging from 1.5 to 4.5 g/L (150 - 450 mg/dl). It is a long molecule composed of three polypeptide chain pairs (alpha, beta, gamma) synthesized in the liver. It exists in platelets, stored in alpha granules from which it is released in the aggregation and activation of platelets.

It's half a life of 100 hours. Its catabolism is little known and fibrinolysis contributes little to its removal from circulation. It crosses the vascular endothelium through the arterial wall and

by the microcirculation reaching the tissues in the inflammatory states traditionally, the interest in fibrinogen comes from coagulopathies. Soluble fibrinogen is the precursor of insoluble fibrin that is an important component of hemostatic buffer that develops after vascular injury. Thrombin converts fibrinogen into fibrin monomers, which polymerizes and is bound by factor XIII forming the stable clot. The minimum fibrinogen level required for hemostasis is 0.5 to 1.0 g/L. Levels below 0.5 g/L are associated with excessive bleeding after injuries or surgeries, most rarely with congenital diseases (afibrinogenomy and dysfibrinogenomia) and often with severe acute liver disease due to reduced liver synthesis, pathological fibrinolysis, and thrombosis.

Fibrinogen plays an important role in platelet aggregation, its molecule interacts with membrane receptors, glycoproteins IIb and IIIa binding platelet aggregates. Low fibrinogen levels prevent primary and secondary hemostasis causing bleeding.

Fibrinogen is involved in acute phase protein reactions by injury, surgery, acute infection, or infarction. A few hours after these events, hepatic synthesis of fibrinogen and acute phase proteins increase, probably due to hepatocyte stimulation by fibrin degradation product (FDP) or activating monocytes (produce cytokines such as interleukin-6). Such protein reactions presumably play a role in hemostasis and inflammation after tissue injury. Fibrinogen levels peak at 3 to 5 days after the onset of inflammation, which is two to four times the baseline value and returns to normal with the resolution of the inflammatory process.

Fibrinogen is chronically elevated in chronic infections, chronic inflammatory diseases such as rheumatoid arthritis and malignant diseases, which increases plasma viscosity and erythrocyte sedimentation rate (ESR), both of which are used to monitor plasma protein reactions as a measure of disease activity.

Measurement of plasma fibrinogen

With the advent of evidence that the increase in fibrinogen, within normal blood, is a significant predictor of cardiovascular risk, it has become important to define its value in the population and standardize the measurement method. Several methods have been used:

- Coagulation methods, using thrombin that transforms fibrinogen into fibrin, where one can measure the time of clot formation (Clauss Method), measure a function of fibrinogen (fibrin formation that requires citrate as a rapidly processing anticoagulant).

- Precipitation methods can be quantified by nephelometry, turbidimetry or centrifuge.

- Immunological methods employing specific antibodies are quantified by radial immunodiffusion or enzyme immunoassay.

Precipitation and immunological methods require anticoagulation with ethylenediamine tetraacetic acid (EDTA) and can be compared with clot methods. They do not measure fibrinogen coagulability and may be normal in the presence of bleeding due to low levels of functional fibrinogen.

Nephelometry seems to be less interesting as a predictor of cardiovascular events than the clot method.

Immunological and precipitation methods tend to give higher results than the clot method because not all circulating fibrinogen is coagulable.

Whatever method is used, a fibrinogen pattern is needed. The average fibrinogen values reported in epidemiological studies have varied greatly (2.0 to 4.0 g/L) partly due to the use of different commercial patterns, methods, factors, population selection and perhaps true differences. However, the increased risk of cardiovascular events in the third percentile of fibrinogen values is similar to all prospective primary studies.

With the use of international reference standards in the measurement of fibrinogen, levels > 3.0 g/L (which corresponds to the cutoff point defining the third percentile in the mean age of the population) will be used to define increased risk of cardiovascular events. As for other risk factors, three measures are desirable to establish the baseline level and exclude transient elevations due to acute diseases.

Determination of fibrinogen in the general population

It is important to know the main determinant factors of fibrinogen levels in the general population. To know the relationship between fibrinogen levels and arterial disease as well as to interpret it is to predict the individual risk of cardiovascular disease.

- Geographical variations

International comparations show that the level of fibrinogen increases with the national risk of ischemic heart disease except in rural Africa and Eskimos who have high levels of fibrinogen despite the low risk of ischemic heart disease. Therefore, fibrinogen is a probable cofactor of this multifactorial disease.

Japanese men have significantly lower fibrinogen levels than Caucasian men in the United States, which is consistent with their low risk of ischemic heart disease and thrombosis and their higher risk of bleeding.

- Age and smoking

They are the two major determinants of fibrinogen levels in the West. Even with normal blood pressure and cholesterol, fibrinogen levels increase with age, from 2.0 to 3.0 g/L, from puberty to old age, using the Clauss method (clot).

At all ages, the fibrinogen levels of the usual smokers are 0.3 g/L higher than those of non-smokers, i.e., regular smokers have the same level of fibrinogen as non-smokers 20 years older than them. Increased fibrinogen in smokers is dose dependent and may result in part in acute phase response due to tobacco-induced injury of the pulmonary epithelium and/or arterial endothelium leading to local stimulation of macrophage monocytes with cytokine release and FDP formation.

By stopping smoking, fibrinogen levels fall, but take 20 years to return to the same level as individuals who have never smoked, it also takes 20 years for the risk of ischemic heart disease in former smokers to return to that of people who have never smoked.

- Sex, oral contraceptives, pregnancy, menopause and hormone replacement therapy

Women have slightly higher fibrinogen levels than men at all ages. The use of estrogens (oral contraceptives) increases fibrinogen levels. It also increases during pregnancy and after menopause, such as the risk of ischemic heart disease. While some prospective studies have shown that hormone replacement therapy increases fibrinogen levels, recent studies have shown that it does not.

- Obesity, glucose intolerance, diabetes and exercise

Fibrinogen levels rise with body mass index and glycemia. It's high in diabetics. Exercise can decrease fibrinogen levels contributing to the protective effect against ischemic heart disease.

- Blood pressure and serum lipids

Fibrinogen levels show a weak correlation with blood pressure, cholesterol and triglycerides in the general population. The correlation is stronger in women than in men.

- Alcohol and liver disease

Drinkers have lower levels of fibrinogen than non-drinkers. Lower fibrinogen levels are also found in hepatitis B carriers. These two effects may reflect decreased synthesis of hepatic fibrinogen and may contribute to decreased risk of ischemic heart disease in moderate drinkers and hepatitis B carriers.

- Social and occupational factors

While some studies show that low social level and occupational stress are associated with increased fibrinogen, this association may be due to other factors such as smoking, obesity and exercise.

- Genetic and environmental factors

Environmental factors account for less than 20% of interindividual variability and fibrinogen levels in the population. Genetic factors contribute from 30 to 50%.

Low birth weight has been associated with increased fibrinogen levels and also increased risk of ischemic heart disease.

Fibrinogen and primary prediction of arterial disease

Prospective studies have confirmed the initial report from the Northwick Park Heart Study[1], which says that fibrinogen level is a strong primary risk factor for cardiovascular events. The analysis of the studies showed that the third percentile of the population with high fibrinogen levels has a relative risk for such events of 2.3 when compared to the percentile of low fibrinogen levels. The finding is highly consistent. In this study, fibrinogen seems to be an independent predictor of cardiovascular events.

The results of Caerphilly and Speedwell Collaborative Heart Disease Studies[2] indicate that plasma viscosity: is also a risk marker for ischemic heart disease, partly due to the strong association with fibrinogen levels, as well as fibrinogen and viscosity present as strong markers of ischemic heart disease.

The relationship between high fibrinogen level and increased risk of cardiovascular events seems to be synergistic with the risk of increased cholesterol and blood pressure.

The PROCAM study[3] shows a similar finding for LDL-C and fibrinogen in predicting ischemic heart disease, while the Gothenburg Study shows similar findings for hypertension and fibrinogen.

Fibrinogen and prevalence of arterial disease

Several studies currently show that fibrinogen level is associated with prevalence of arterial disease in the population. The Scot-Heart Health Study[4] points to the association between prevalence of ischemic heart disease (previous myocardial infarction or angina). This study showed a high incidence of ischemic heart disease associated with a high level of fibrinogen. This association was stronger in men than in women, stronger for myocardial infarction than for angina. This study also showed a significant increase in fibrinogen in people with claudication, diabetes, hypertension, and a history of premature ischemic heart disease.

In the Scot-Heart Study[4], symptomatic and asymptomatic peripheral arterial disease was associated with fibrinogen in populations aged 55 to 75 years. Fibrinogen levels have also been associated with the extent of peripheral arterial disease.

It is noteworthy that smoking and fibrinogen have an interactive effect on the extent of arterial disease, which may reflect endothelial damage by tobacco, in addition to fibrinogen can infiltrate the arterial wall and increase the extent of atherosclerosis.

Together, the studies show that fibrinogen level consistently increases the risk of arterial disease and events in the presence of the greatest conventional risk factors for ischemic heart disease (LDL-C), hypertension and peripheral arterial disease (smoking). Fibrinogen is associated with the severity of angiographic data.

Fibrinogen levels are associated with the prevalence of carotid atherosclerosis in the mentioned studies and carotid stenosis seen on angiography.

Fibrinogen as a secondary predictor of arterial disease

Fibrinogen level and plasma viscosity are predictors of recurrent cardiovascular events and death due to infarction and stroke. This also applies in patients with claudication, progress of carotid stenus, and femoropopliteal occlusions.

Fibrinogen and arterial disease: cause or consequence?

Fibrinogen levels are consistently associated with risk of arterial events (coronary, cerebral, or peripheral) in the general population. It is suggested that this association is partly due to arterial disease that causes an increase in fibrinogen levels (and other hematological variables) causing the "Hematological Stress Syndrome". It is likely that the increase in fibrinogen levels that precedes arterial events are not only indications of occult arterial disease, but rather that they reflect the preexistence of the "prothrombotic state". For example, high fibrinogen genotype is associated with peripheral arterial disease in the general population, suggesting that high fibrinogen levels precede the disease. The strong association of fibrinogen with the prevalence of myocardial infarction compared to the prevalence of angina.

The fibrinogen level is associated with thrombotic status as well as with atherosclerosis. This hypothesis is consistent with the reduction in the risk of myocardial infarction with clofibrate treatment, which decreases fibrinogen and cholesterol. Finally, indifferent to fibrinogen increases in genetic influences and environmental factors such as smoking, there are several biological mechanisms plausible by hyperfibrinogenomia that can promote arterial disease and cardiovascular events.

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Mechanisms by which fibrinogen can promote arterial disease

There are at least four mechanisms by which increased fibrinogen can cause arterial disease:

- Atherogenesis

Fibrinogen infiltrates the arterial wall; it is also the precursor of fibrin mural thrombus that is embedded in the arterial wall promoting atherosclerosis (Rokitansky - Duguid hypothesis). Within the arterial wall, fibrin binds to coagulation factors, promoting its own formation, binds to LDL, and is converted into degradation products, which stimulate the proliferation of smooth muscle cells, as well as lipids do by macrophages; all these processes favor atherogenesis. The importance of fibrinogen and fibrin in atherogenesis is suggested by the effective protection of defibrination in animal models. As previously seen, fibrinogen levels correlate with the presence and extent of coronary artery disease, cerebral and peripheral in men. The importance of fibrinogen and FDP in human atherogenesis is assumed by the predictive value of plasma fibrinogen and plasma FDP both for progression of peripheral arterial disease, prediction of cardiovascular events in patients with claudication.

- Platelet aggregation and thrombus formation

Fibrinogen level is an important determinant of platelet aggregation. Each end of the fibrinogen molecule binds to the IIb and IIIa receptors of the platelet membrane, aggregating adjacent platelets. High fibrinogen levels increase platelet aggregation (causal role) and its decrease by dysfibrinizing enzymes reduces platelet aggregation. In addition, platelet aggregability increases after adding fibrinogen to low levels of it. By increasing platelet aggregation, high levels of fibrinogen may promote platelet-rich thrombus formation that contributes to atherosclerosis, occlusive thrombosis and arterial stenosis (where high stress activates platelets), and microvascular ischemia (Figure 1).

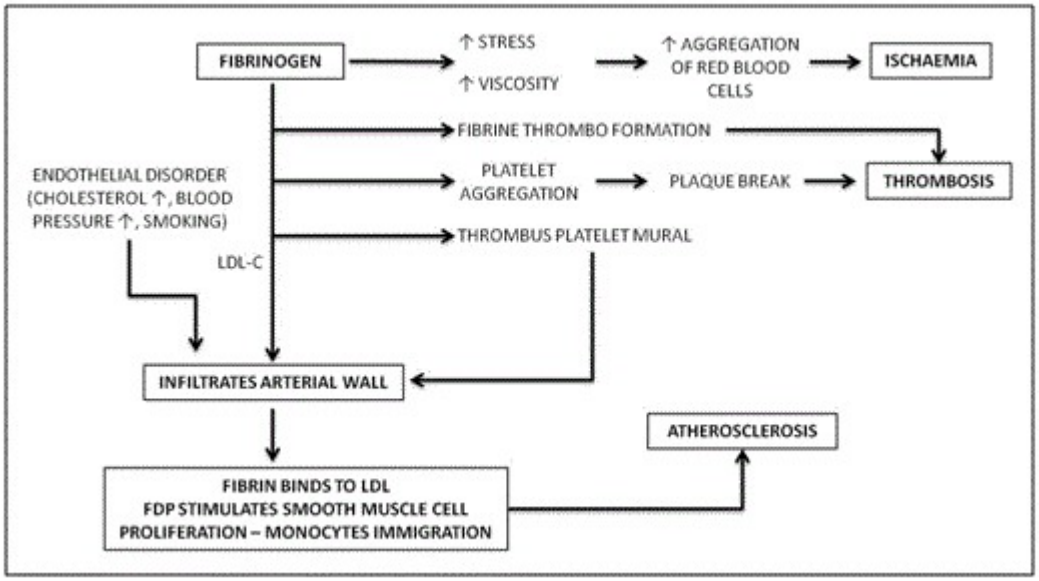

Figure 1.

Fibrinogen relations in atherosclerosis

- Fibrin thrombus formation

Fibrinogen level affects the formation, structure and lipidability of fibrin thrombus. There is increased evidence in experimental (animal) and population studies that high fibrinogen levels were associated with increased tendency to fibrin formation and increased fibrin thrombus size. The increase in fibrinogen also alters the structure of fibrin thrombus, reducing its lipidability in vivo and in vitro. Each fibrin-rich thrombus tends to cause distal arterial stenosis, where blood flow is low, which allows interaction of activated platelets, leukocytes, coagulation factors, as well as thrombin and fibrin generation.

- Plasma and blood viscosity

Fibrinogen level is an important determinant of plasma viscosity and whole blood (flow resistance). Due to its high molecular weight and asymmetry it determines the viscosity of plasma and is a strong predictor of cardiovascular events. In the presence of peripheral arterial stenosis in the elderly (Scot-Heart Study)[4] increased plasma viscosity was associated with increased risk of intermittent claudication. This fact suggests that in the presence of arterial stenosis that reduces perfusion pressure, increased viscosity of plasma reduces blood flow in the microcirculation which leads to ischemia. On the other hand, the reduction of plasma viscosity by exercise, smoking cessation or reduction of fibrinogen by clofibrate increases the walking distance of patients with claudication.

As fibrinogen increases, the viscosity of whole blood increases due to increased viscosity of plasma. Increased blood viscosity can increase stress on blood flow by arterial stenosis favoring platelet-rich thrombus. Thus, fibrinogen attached to the membrane receptor of adjacent cells is an important determinant of red blood cell aggregation under low flow conditions. Increased fibrinogen levels result in increased blood viscosity under low flow conditions; this occurs in bifurcities and arterial curves (favoring atherogenesis), arterial stenosis (favoring fibrin-rich thrombosis) and ischemic microcirculation, especially in the evans where red blood cells aggregate promoting leukocyte stout (favoring ischemia).Increased fibrinogen can therefore promote atherogenesis, thrombogenesis and ischemia.

Therapeutic reduction of fibrinogen levels

- Acute reduction: acute reduction of fibrinogen levels in plasma may also be performed by the injection of thrombolytics or defibrinating enzymes or plasmapheresis. Acute reduction of fibrinogen (and hence in plasma and blood viscosity) may be one of the mechanisms responsible for the clinical benefit of thrombolytic agent in acute myocardial infarction, peripheral arterial occlusion, and venous thromboembolism. Defibrinating agents (which has no direct thrombolytic effect) have been used to increase blood flow in the leg in patients with peripheral arterial disease and be effective in the prevention and treatment of venous thromboembolism; these agents not only facilitate bleeding risks and onset of thrombosis.

- **Chronic reduction**: chronic reduction in fibrinogen level can be performed by reducing smoking (although mild years), by physical exercise and in diabetic patients by improving diabetes control.

Decreased fibrinogen can be performed by chronic urokinase therapy (which seems to increase myocardial perfusion and reduce the frequency of attacks in angina patients), by extracorporeal precipitation induced by LDL-C heparin and fibrinogen in hyperlipidemias, and by drugs that reduce

hepatic fibrinogen synthesis. The latter group includes anabolic steroids ticlopidine, pentoxifyphiline, and fibrates from the lipid-lowering group. Anabolic steroids are limited by many adverse effects, including hormonal effects such as hirsutism, hyperlipidemia, increased hematocrit, while ticlopidine is limited by risks of neutropenia and gastrointestinal disorders.

Fibrates (bezafibrate, ciprofibrate, clofibrate and fenofibrate) consistently decrease fibrinogen levels by 10-20%, representing a substantial potential for reduction in primary and secondary cardiovascular risk according to epidemiological studies. In contrast, resins seem to have little effect on plasma fibrinogen levels. Clofibrate significantly reduced the risk of myocardial infarction, especially in people at increased risk of ischemic heart disease, who also had a high fibrinogen, smoking and hypertensive level. Many cholesterol-lowering studies have emerged in the secondary prevention of ischemic heart disease using drugs that also reduce plasma fibrinogen levels, generally fibrates[5-24].

Fibrate therapy also reduces blood and plasma viscosity and increases blood flow in the legs and improves walking in patients with claudication.

It is clear the need for further studies of fibrinogen reduction by fibrates in the primary and secondary prevention of cardiovascular disease, particularly because other lipid-lowering drugs do not change this important cardiovascular risk factor. A great study with bezafibrate is being done.

Many studies of the effects of fibrinogen reduction on ischemia, usually on intermittent claudication, arterial occlusion followed by thrombolysis, angioplasty, by-pass, and endarterectomy are indicated.

Conclusions

Epidemiological studies have shown that fibrinogen levels are a strong and consistent primary and secondary risk factor for coronary artery disease, cerebral and peripheral arterial disease, as well as is associated with prevalence of arterial disease in these three sites.

Epidemiological studies also suggest that fibrinogen may be an important link between genetics (difference in nationality, family history, fibrinogen genotype) and environmental influences (fetal development, smoking, alcoholism, obesity, diabetes, infections, menopause, estrogen use) and the development of arterial disease.

Fibrinogen level is the major determinant of cardiovascular risk in people with hypercholesterolemia, hypertension or diabetes; should then be included in the cardiovascular risk profile and clinical management. Persistent fibrinogen greater than 4.0 g/L is associated with significant increase in cardiovascular risk and indicates the target population for intervention.

Epidemiological and pathophysiological studies show that there are at least four possible mechanisms by which fibrinogen can promote arterial disease: atherogenesis, platelet aggregation and thrombus formation, fibrin thrombus formation, increased plasma and blood viscosity.

Clinical studies have shown that reducing plasma fibrinogen increases blood flow, reduces platelet aggregability, reduces plasma and blood viscosity, and the risk of ischemic symptoms and events. The reduction of fibrinogen needs to be considered in people with ischemic symptoms and those at high risk of arterial disease, also by lifestyle (smoking) or drug therapy (fibrates).

Further studies of fibrinogen reduction are desirable for prevention and symptomatic treatment of arterial disease.

Acknowledgments

In memoriam Francisco Luís Stocco Cotrim

Conflicts of interest

No conflict of interest.

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