Coll. Antropol. **29** (2005) 1: 341–349

The Past Decade: Fibrinogen

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A B S T R A C T

This paper reviews the advances in understanding of fibrinogen structure and function, its genetic and environmental determinants, role in the process of hemostasis, platelet aggregation, plasma viscosity and erythrocyte aggregation, cellular and matrix interactions, inflammation, wound healing, tumor development, atherogenesis and involvement in pathogenesis of diseases, that have been made over the past decade. Future studies will seek to define precise mechanisms of complex gene-environment interactions that influence fibrinogen levels and its complex role in the pathogenesis of fibrinogen-associated diseases.

Key words: *fibrinogen, review*

Introduction

Fibrinogen is a soluble glycoprotein present in plasma that has a variety of physiological functions. Fibrinogen has an important role in the process of thrombus formation and evolution. It is a major determinant of blood viscosity and erythrocyte aggregation. Fibrinogen is both constitutively expressed and inducible during a reaction of acute phase. It is also important in cellular and matrix interactions, wound healing, inflammation, tumor development and atherogenesis.

The recent years have considerably advanced our understanding of fibrinogen structure, functions, genetic and extrinsic determinants and involvement in pathogenesis of many disease conditions. This paper reviews the progress made over the past decade.

Search Strategy

A search of papers published during the last decade (1995–2004) in journals indexed by Current Contents was performed using the search terms »fibrinogen« in combination with either »structure«, »hemostasis«, »inflammation«, »atherosclerosis«, »genetics«, »environment«, »smoking«, »obesity«, »disease«, etc., to cover the range of subtopics in this review.

Fibrinogen Structure

Fibrinogen is a complex multifunctional glycoprotein composed of two identical molecular halves, each consisting of three non-identical subunit polypeptides designated as alpha (α), beta (β), and gamma (γ) chains held together by multiple disulfide bridges[1]. Fibrinogen has a trinodular structure; one central dimeric E domain in which each dimer contains the three amino-terminal regions of polypeptides, and two distal D domains. These three nodules are linked by two coiled-coil regions[2] and contain multiple binding sites[3]. The amino terminal ends of α and β chains represent fibrinopeptides A and B (FPA and FPB).

Most of the fibrinogen is found in plasma, where it exists as a population of slightly different molecules[3]. Under normal conditions, about 70% of the fibrinogen molecules are high molecular weight fibrinogen (HMW-fibrinogen), with molecular weight (mw) of 340,000 Dalton (Da). The remaining molecules are the consequence of the proteolysis of the α chains of fibrinogen molecule[4]: loss of the C-terminal end of one α chain creates low weight fibrinogen (LMW-fibrinogen, mw 305,000 Da, about 26% of total fibrinogen), and loss of both α chains creates LMW'-fibrinogen (mw 270,000 Da, about 4% of total fibrinogen)[5,6], resulting in impaired fibrin polymerization[7].

Received for publication February 7, 2005

Physiology and Pathophysiology

Fibrinogen has a biological half-life of about 100 hours, and is synthesized predominantly in the liver[8], but also in megakariocytes[3]. The production of fibrinogen by lung and intestinal epithelium requires an inflammatory stimulus[9]. Fibrinogen polypeptide chains α, β, and γ are encoded by three different genes named α, β, and γ, clustered on the chromosome 4 in region q23–32 of approximately 50 kb, with the direction of transcription of the β gene opposite to that of the other two[10,11]. Many cytokines and other molecules influence biosynthesis of fibrinogen. For example, interleukin 1 and 6 (Il-1 and Il-6), tissue necrosis factor α (TNF-α), free fatty acids and oncostatin M stimulate fibrinogen synthesis, while interleukin 4, 10, and 13 (Il-4, Il-10, and Il-13), vitamin E, and high plasma albumin decrease synthesis of fibrinogen[12–14]. Fibrinogen and cholesterol may share a novel common regulatory pathway, because oxysterols, which suppress cholesterol biosynthesis and the uptake of LDL-cholesterol, also down-regulates constitutive fibrinogen expression[15]. It is accepted that the normal range of plasma levels of fibrinogen is from 1.5 to 3.5 g/l[16].

Thrombogenesis

Fibrinogen has an important role in the process of thrombogenesis, being the precursor of fibrin. Indeed, most of fibrinogen functions are assigned to certain structures of fibrin including double-stranded fibrin protofibrils and highly cross-linked fibrin networks. Fibrin formation is a series of highly ordered molecular interactions – a complex cascade of enzymatic reactions of blood coagulation. That cascade is comprised of two arms, the intrinsic and extrinsic pathways, that converge at factor Xa to form the common pathway. Factor Xa activates prothrombin to thrombin. Thrombin, which is a protease enzyme, induces cleavage of FPA from α chain, what is considered to be the initial step in the conversion of fibrinogen to fibrin. Removal of the FPA and also FPB from the fibrinogen α and β chains leads to spontaneous polymerization of the monomers. Lateral growth produces protofibrils, and cross-linking further creates fibrin strands. Thrombin-activated factor XIIIa introduces covalent cross links into polymers to complete and stabilize the formed thrombi[2,17]. Fibrinogen and fibrin are degraded by plasmin, an enzyme that is activated from plasminogen[18]. High fibrinogen levels lead to formation of larger and less lysable clot with tight and rigid network structure[19,20]. Moreover, elevated fibrinogen levels interact with the binding of plasminogen to its receptor, causing impaired fibrinolysis[21].

Platelet aggregation

The interaction of platelets with fibrinogen is an important event in the maintenance of haemostatic response. Fibrinogen binding to the GP IIb–IIIa receptor in activated platelets leads to platelet aggregation and formation of platelet-rich thrombi[22–25].

Plasma viscosity and erythrocyte aggregation

Fibrinogen is the major determinant of plasma viscosity and erythrocyte aggregation. Therefore, the rheological properties of the blood are adversely influenced by high plasma fibrinogen[26]. Increased viscosity may, for example, lead to impaired microcirculatory flow, endothelial damage and thrombosis predisposition[27].

Atherogenesis

Fibrinogen binding to intercellular adhesion molecule-1 (ICAM-1 – cell surface glycoprotein important in cell to cell adhesion interactions) up-regulates ICAM-1 gene expression, mediates the attachment of leukocytes, macrophages, and platelets to endothelial cells, and causes the release of vasoactive mediators[28,29]. Moreover, fibrinogen and its degradation products modulate endothelial permeability, leading to fibrinogen and fibrin deposition in subendothelial space, promoting smooth muscle cell proliferation and migration and chemotaxis of monocytes. Fibrinogen and fibrin subendothelial depositions provide an adsorptive surface for extracellular accumulation of LDL and apo(a)[30,31]. Fibrinogen accumulates in atherosclerotic plaques[32]. Through all these effects, fibrinogen may be involved in development of atherogenesis[33]. However, in studies with experimental animals, fibrinogen-deficient mice remained capable of forming atheromatous plaques[34], and a mouse strain over-expressing fibrinogen did not show increase in degree of atherosclerosis[32]. Although the conclusions from such animal models cannot be readily extrapolated to human arterial disease, such data still represent the evidence that a hypothesis about the causal function of fibrinogen in the etiology of atherosclerosis needs to be taken with caution.

Inflammation

Inflammatory process plays an important role in arterial disease, including atherosclerosis. It was found that fibrinogen regulates NF-kappaB activation and expression of inflammatory chemokines in endothelial cells, and therefore may be involved in mediation of inflammatory process[35]. Fibrinogen has another function in the process of inflammation through binding to its integrin receptor on the surface of leukocytes, facilitating chemotactic response, increasing phagocytosis, antibody-mediated leukocyte toxicity and delay in apoptosis[36,37]. Fibrinogen is also an acute phase reactant up-regulated by cytokines like interleukin 6 (Il-6) and by glucocorticoids[38,39]. In addition to the increased fibrinogen hepatic synthesis in acute response[40], intestine and lung epithelium synthesize fibrinogen after exposure to inflammatory mediators[9]. Fibrinogen also appears to have antioxidant properties[41], like some other acute phase proteins, and may act as a supplementary antioxidant defense mechanism against oxidative stress arising from inflammatory conditions[42]. Such findings do not seem to support the postulation that fibrinogen is pro-atherosclerotic agent[41]. Therefore, the question whether fibrinogen is only a marker of the inflammatory process in-

volved in atherosclerosis or a mediator (i.e., a pathogenic factor), is yet to be answered[32].

Tumors

Fibrinogen is found deposited in the majority of human and experimental animal tumors[43], suggesting that fibrinogen and its related products are important in formation of the stroma. Vascular permeability factor (VPF), also known as vascular endothelial growth factor (VEGF), is a multifunctional cytokine expressed and secreted at high levels by many tumor cells. Its presumed role is promotion of extravasation of plasma fibrinogen, leading to fibrin deposition that alters extracellular matrix of the tumor[44]. Fibrinogen has been demonstrated to determine metastatic potential of solid tumors, facilitating the stable adhesion and survival of metastatic emboli after tumor cell intravasation[45,46]. For example, in the study of the high grade bladder tumor, malignant cell lines express ICAM-1, and this expression induces a fibrinogen-mediated migration[47].

Wound healing

It has been proposed that fibrinogen plays an important role in wound healing. Fibrinogen seems to contribute significantly to cell-cell and cell-extracellular matrix interactions[1,48]. Although tissue repair and the formation of fibrotic scar can proceed in the absence of fibrinogen, it is important for appropriate cellular migration and organization within wound fields, as well as initial establishment of wound strength and stability[49]. Fibrinogen also promotes vasoconstriction at sites of vessel wall injury[1].

Genetic Determinants of Plasma Fibrinogen Levels

The genetic determinants of fibrinogen levels undoubtedly exist, although different studies reported different degrees of heritability of fibrinogen levels. This may be explained by polygenic determination of fibrinogen levels, reflecting its many roles in biochemical pathways. Genetic factors have been reported to explain 20–51% of variation in plasma fibrinogen levels[50,51].

Various polymorphisms have been identified in all three α, β, and γ fibrinogen genes[11]. However, the β-chain gene has been more extensively studied because *in vitro* studies have suggested that its synthesis is the limiting step in the production of mature fibrinogen[52]. Several β-chain gene polymorphisms have been identified (–455 G/A, –148 C/T, –854 G/A, Arg 448 Lys…), which are associated with increased fibrinogen plasma levels[25]. The promoter polymorphisms are in strong linkage disequilibrium with each other[53]. The –455 G/A mutation in the promoter region of the β fibrinogen gene is one of the most common genetic variations, present in up to 20% of general population and associated with 7–10% higher levels of fibrinogen than in persons with the GG genotype[54]. However, certain effects of β-chain gene polymorphism alone are modest and difficult to detect in population-based studies. They may be much greater in interaction with other extrinsic factors[55]. Moreover, several studies reported conflicting results, failing to demonstrate association of fibrinogen levels with some polymorphisms of α, β, and γ fibrinogen genes[56]. Therefore, the precise role of genetic polymorphisms and their clinical significance still remains unclear, and there is increasing evidence of the importance of gene-environment interactions in determination of plasma fibrinogen levels[25].

Extrinsic Determinants of Plasma Fibrinogen Levels

Smoking

Smoking has been identified as one of the most important determinants of fibrinogen levels in general population[57]. Cigarette smoking markedly increases plasma fibrinogen levels[57,58], as well as the shift from cigarette to cigar smoking[59]. Furthermore, passive smoking is also associated with increased plasma fibrinogen levels (to the levels of about 40–60% of those in active smokers)[60]. It has been estimated that up to 50% of the increase in cardiovascular disease risk in smokers might be attributable to the effects of smoking on fibrinogen[59,61]. Although cessation from smoking results in a rapid reduction in plasma fibrinogen levels[62], the overall level still remains increased[59]. It is estimated that it takes at least ten years after the cessation of smoking for fibrinogen levels to equal those of never-smokers. Former smokers usually have levels of fibrinogen between those of active and never-smokers[63].

Some studies proposed that increased fibrinogen synthesis plays a primary role in the hyperfibrinogenaemia in smokers[64]. Such effect of smoking to fibrinogen synthesis could be partly explained as a generalized inflammatory response to smoking (chronic inflammatory state of blood vessels, respiratory tract or other organs)[64].

Alcohol

Moderate alcohol consumption significantly decreases plasma fibrinogen levels[65]. Alcohol intake is thought to lower risk of coronary heart disease[66], what could be explained partly by an anti-inflammatory action of alcohol[65]. It was observed that alcohol inhibits platelet adhesion to fibrinogen-coated surface under flow[67]. In animal experimental studies, moderate levels of alcohol influenced genetic expression of fibrinogen in the hepatic cells[68]. However, the precise mechanism by which alcohol consumption lowers plasma fibrinogen levels remains unclear.

Fish oil

The beneficial effect of dietary fish oil, rich in omega-3 polyunsaturated fatty acids, on cardiovascular disease is multifactorial, and partly due to their anticoagulant action. Dietary omega-3 polyunsaturated fatty acids provoke a hypocoagulant effects in humans, associated

with influence on fibrinogen levels[69]. Similarly, omega-3-rich fish oils are thought to partly compensate the adverse effects of smoking, including its impact on fibrinogen[70].

Obesity

Obesity is associated with increased plasma fibrinogen concentration[71–73]. It has been suggested that there is a direct mechanism by which adipose tissue might regulate the levels of fibrinogen[74], proposing the secretion of Il-6 by adipose tissue as one of the possible mechanisms[73]. In addition, weight reduction can decrease plasma fibrinogen[72].

Exercise

Available evidence suggests that exercise and physical training evoke multiple effects on blood hemostasis in healthy subjects and in patients. A single exercise is usually associated with a transient increase in blood coagulation. However, the effects of acute exercise on plasma fibrinogen are not clear, as the studies reported conflicting results[75–77]. Moderate but regular exercise, however, reduces plasma fibrinogen levels[32,76]. It was observed that moderate exercise appears to enhance blood fibrinolytic activity without a concomitant activation of blood coagulation mechanisms, whereas a very heavy exercise induces simultaneous activation of blood fibrinolysis and coagulation[75]. Moreover, plasma fibrinogen concentration returns to baseline values after sedentary activity is resumed[77].

Age

Older age is associated with increased plasma fibrinogen levels[71,78]. The proposed mechanism for this association is a slower rate of disposal of fibrinogen with aging[79]. However, some studies found that advanced age is associated with elevated Il-6, possibly suggesting another mechanism for fibrinogen elevation in the process of ageing[78].

Gender

Although occasional reports did not confirmed a significant gender differences in plasma fibrinogen levels[80], in majority of papers fibrinogen levels in women were generally higher that those in men [25,32,81].

Oral contraceptives and hormone replacement therapy

A number of studies demonstrated that oral contraceptives (OC) are associated with increased fibrinogen levels[82]. Younger users have greater level of increase than older ones, while dosage and estrogen content, as well as duration of use, are both positively associated with the increase in fibrinogen concentration[81]. Plasma fibrinogen returns to normal value after cessation of taking OC[82]. Plasma fibrinogen levels tend to increase after menopause. Some studies showed that hormone replacement therapy lowers plasma fibrinogen[83], but this was not consistently confirmed in other reports[84,85].

Pregnancy

The levels of coagulation factors are increased in pregnancy, especially during the third trimester. The highest level of fibrinogen was observed before the delivery and during a first few days afterwards[39]. That may be explained partly by hormonal changes, but its cause is obviously multifactorial, including maternal inflammatory response to the conceptus and generalized acute phase response after delivery[39,86].

Low birth weight

Low birth weight is associated with an increased risk of atherothrombosis, which may be partly related to increased plasma levels of fibrinogen[87]. It was reported that reduced growth during fetal life and infancy is related to high plasma fibrinogen in adult life[88]. Other reports showed that the association between birth weight and plasma fibrinogen is abolished after the elimination of genetic influences, and therefore this association has underlying genetic causes. According to these studies, improvement of intrauterine nutrition may not lower fibrinogen levels in later life[87].

Stress and socioeconomic factors

Stress may trigger the hypercoagulable state evidenced by an increased plasmatic fibrinogen level[89]. It was noted that in healthy subjects acute mental stress simultaneously activates coagulation (including fibrinogen) and fibrinolysis. However, in patients with atherosclerosis and impaired endothelial function, procoagulant responses to acute stress are stronger than anticoagulant mechanisms and thereby promote a hypercoagulable state[90]. Chronic psychosocial stressors (as it was proposed to be, for example, low socioeconomic status) are related to a hypercoagulable state[90]. Indeed, concentrations of fibrinogen decreased substantially with increasing socioeconomic status. Circumstances earlier in life concerning childhood environment (father's social class, participant's education) were inversely associated with adult fibrinogen levels[91]. Therefore, elevation in plasma fibrinogen may be one of the pathways through which low socioeconomic status increases cardiovascular disease risk[92]. Adverse job characteristics might also be related to increased plasma fibrinogen[91]. Other studies could not demonstrate strong correlation between job strain and plasma fibrinogen[93,94].

Air pollution

It has been suggested that association between air pollution, possibly from traffic, and risk of cardiovascular events may be at least partly mediated through increased concentrations of plasma fibrinogen, possibly due to an inflammatory reaction caused by air pollution[95]. Furthermore, another study observed an increase in both Il-6 and fibrinogen concentrations during a working shift for both smoking and non-smoking tunnel construction workers[96].

Seasonality

A seasonal variation of plasma fibrinogen with higher values in winter has been observed in some studies[97]. Such finding has been attributed to an increase in respiratory tract infections during winter, but other papers provided no evidence that winter infections could be held responsible for seasonal variation in fibrinogen levels[97,98]. Although some authors found that fibrinogen displayed a circadian rhythm, with the highest values in the morning[99], others found no diurnal variation in plasma fibrinogen[100].

Infection

Studies investigating an association between fibrinogen levels and chronic infection with Helicobacter pylori and/or with Chlamydia pneumoniae have yielded inconsistent results[101–104]. After the first positive reports, further analyses suggested no clear correlation between fibrinogen concentration and these infectious agents[25].

Chronic inflammation

Chronic inflammations, such as periodontal disease or smoking-induced lung injuries, have been reported to have a potential to induce chronic increase of Il-6 and consequently elevation of fibrinogen levels[98,105].

Drugs

There are many drugs that decrease fibrinogen levels, such as beta-adrenergic receptor blockers, ACE-inhibitors, calcium channel blockers, fibrinolytics, ticlopidine and pentoxifyline[25,32,106,107] (Table 1). Fibrates are lipid--modifying agents that act through the nuclear receptor peroxisome proliferator-activated receptor alpha (PPA--Rα)[108]. In addition, most fibrates also consistently lower plasma fibrinogen levels[109]. Fibrates were reported to diminish basal and Il-6-induced fibrinogen-beta promoter activity[108]. Interestingly, statins (which form other major group of hypolipemic drugs – HMG CoA reductase inhibitors), that currently largely replace fibrates because of better clinical results in treatment of cardiovascular disease[32], generally do not decrease fibrinogen levels[32,110–114]. Although a large number of drugs is known to interfere with fibrinogen metabolism, decreasing its plasma concentration, there is still no single known drug that would selectively lower fibrinogen level[25,32].

TABLE 1
FACTORS CONSIDERED TO INFLUENCE THE LEVELS OF PLASMA FIBRINOGEN.

Associated with higher fibrinogen	Associated with lower fibrinogen
Advanced age	Younger age
Female gender	Male gender
Menopause	Cessation of smoking
Pregnancy	Regular exercise
Smoking	Physical fitness
Acute strenous exercise	Leisure activity
Sedentary lifestyle	Higher socio-economic class
Stress	Higher education level
Lower socio-economic class	Weight reduction
Lower education level	Moderate alcohol consumption
Obesity	Fish intake
Low birth weight	HDL
Diabetes mellitus	Chronic hepatitis
Serum insulin	Polyunsaturated fatty acids
Hyperglicaemia	Fibrate
LDL	Betablockers
Triglycerides	ACE-inhibitors
Lipoprotein A	Calcium channel blockers
Homocysteine	Ticlopidine
Microalbuminuria	Dipyridamole
Hypertension	Aspirin
Nephrotic syndrome	Pentoxifyline
Dental disease	Rosiglitazone
Atrial fibrillation	Biguanides
Inflammation	Vitamin A
Infection	Vitamin C
Immune disease	Vitamin E
Malignancy	Niacin
Oral contraceptives	LDL apheresis
Amphetamines	Prednisolone
Winter season	Hormone replacement therapy
Air pollution	L-Asparaginase
	Ancrod and related snake venom proteases

Fibrinogen and Human Disease

Fibrinogen is thought to be involved in many disease conditions, either as a direct pathogen factor, prognostic risk marker, or as a mediator of inflammation associated with disease pathogenesis.

Congenital afibrinogenemia and dysfibrinogenaemias

Congenital afibrinogenemia is a rare coagulation disorder with autosomal recessive mode of inheritance, characterized by a complete absence or extremely reduced levels of fibrinogen in patients' plasma and platelets. Clinical manifestations range from minimal bleeding to catastrophic hemorrhage, and patients seem to be especially susceptible to spontaneous rupture of the spleen[115,116].

The dysfibrinogenaemias are disorders characterized by structural abnormalities in the fibrinogen molecule. They are mostly inherited (traditionally named af-

ter the location of their discovery or after the place of residency of the patient), but could be also acquired as a result of underlying hepatic disease. The structural modifications result in alterations in fibrinopeptide release, fibrin polymerization, cross-linking or fibrinolysis. However, approximately 55% of patients are asymptomatic, 25% have bleeding tendency and around 20% have thrombotic complications[117].

Cardiovascular disease

The notion that fibrinogen is strongly, consistently, and independently related to cardiovascular disease risk has been extensively studied and widely accepted. The evidence is based on numerous prospective epidemiological and clinical studies, clinical observations, and meta-analyses[52,118–120]. In the PRIME study, classic risk factors explained 25% of the excess risk of coronary heart disease in Belfast compared with France, while fibrinogen alone accounted for 30% [121]. Another example is the Strong Heart Study where in adults without clinical evidence of coronary artery disease fibrinogen levels predicted later cardiovascular events and target organ damage independently of conventional risk factors [122, 123]. Increased levels of troponin and fibrinogen were found to be independently associated with unfavorable course of patients with acute coronary syndrome[124]. It was also found that fibrinogen concentrations measured during the acute phase of myocardial infarction were associated with cardiovascular death or a new myocardial infarction [125], being an independent short-term predictor of mortality[126,127]. Fibrinogen levels on admission to hospital might have an important value for risk stratification and more aggressive reduction of infarct size in patients who are treated with primary angioplasty[128]. It was also observed that increased pre-procedural fibrinogen level should be considered as a strong predictor for re-stenosis after coronary stenting, as well as high fibrinogen levels after coronary balloon angioplasty[129].

Recently published study showed that plasma fibrinogen levels are associated with a strong family history of myocardial infarction[130]. In that work subjects with a parental and sibling history of myocardial infarction had higher plasma fibrinogen levels, and also higher prevalence of angina pectoris, than the matched controls[130]. Another study demonstrated a significant increase in fibrinogen levels in the healthy, male, first-degree relatives of patients with severe coronary artery disease[131]. Therefore, plasma fibrinogen levels may indicate an inheritable risk for cardiovascular disease in subjects with a strong family history of myocardial infarction[130], but it may also be of particular importance in subjects who, other than their family history, appear to be at low risk concerning traditional coronary artery disease risk factors[131]. Another possible role of fibrinogen was observed in high risk patients with peripheral artery disease, where elevated fibrinogen levels indicate an increased risk for poor outcome, particularly for fatal cardiovascular complications[132]. Furthermore, elevated pre-procedural fibrinogen level indicates a higher risk for restenosis after balloon angioplasty and stenting of the iliac arteries[133].

Despite fibrinogen variability and many factors that influence its plasma level, the association between fibrinogen and cardiovascular disease based on a single measurement is strong and consistent[25]. The deleterious effects of this protein seem to be mediated through its role in thrombogenesis, hemorrheology, inflammation, and the atherogenic process itself[134]. However, polymorphisms in the human fibrinogen gene with higher fibrinogen levels do not increase the risk for cardiovascular disease[32,53,135]. In addition to that, elevated preoperative plasma fibrinogen levels, but not the beta-fibrinogen –455 G/A genotype predict the total mortality after coronary artery bypass grafting (CABG)[136]. Together with animal studies earlier described in this review[32,34], such findings indicated that the causal relationship between fibrinogen levels and atherogenesis remains uncertain. Some claim that fibrinogen seems to be a marker rather than a mediator of vascular disease[32], while others suggest that fibrinogen levels are partly »risk« and partly »marker of risk«, playing a role in the progression of the disease that produces it[55].

Other diseases

The association between ischemic stroke and fibrinogen is controversial, with different opinions expressed by different authors[32,137–142]. However, in adults without clinical manifestations of atherosclerotic disease, increased fibrinogen was associated with carotid intima-media thickness independently of a wide range of other important risk factors, suggesting that plasma fibrinogen may represent a systemic marker of carotid atherosclerosis[143,144]. Increased plasma level of fibrinogen is associated with the presence and severity of target organ damage in patients with essential hypertension. It was proposed that it might contribute to the development of atherosclerotic disease in these patients[145].

Although increased levels of fibrinogen were positively correlated to the risk of deep venous thrombosis, mainly in the elderly[146], other reports could not confirm the correlation between fibrinogen and risk of venous thrombosis[147]. There is also mounting evidence that chronic atrial fibrillation is associated with a prothrombotic or hypercoagulable state[148], and it was suggested an independent predictor of abnormal fibrinogen levels[149]. Some studies suggest that increase in plasma fibrinogen levels may contribute to the increased risk of stroke and thromboembolism in atrial fibrillation[150].

Increased plasma fibrinogen is also related to reduced pulmonary function and increased risk of chronic obstructive pulmonary disease[151]. Lung cells express increased levels of Il-6 during acute or chronic inflammation, and are able to synthesize fibrinogen after an inflammatory stimulus. In addition, persistent alveolar fibrinogen deposition is a morphological hallmark of severe or chronic lung injury[9].

Significantly elevated fibrinogen levels are observed in patients with diabetes type I and type II. Insulin deficiency increases fibrinogen biosynthesis, while hyperglycemia increases plasma fibrinogen levels[107]. Fibrinogen levels were found to be significantly higher in diabetic patients with retinopathy or nephropathy than in patients without these complications[152]. Metabolic syndrome X, a common condition in the general population, is characterized by dyslipidemia, hypertension, abdominal obesity, glucose intolerance or non insulin-dependent diabetes mellitus. Abnormalities of blood coagulation, including higher fibrinogen levels, have also been found in metabolic syndrome X [153–156].

Increased plasma fibrinogen levels and haemostatic abnormalities suggesting a prothrombotic state are present in patients with end-stage renal disease and could contribute to increased cardiovascular morbidity in such patients[157–159]. Moreover, it was found that elevated fibrinogen was independently associated with concentric hypertrophy of left ventricle and systolic dysfunction in patients with end-stage renal disease[160]. Another possible clinical implication of fibrinogen was described in patients with rheumatoid arthritis (RA). It was suggested that in RA fibrinogen correlates better with disease progression than widely and traditionally used erythrocyte sedimentation rate, and that it should be used as a long-term inflammatory marker[161].

An association between men with erectile dysfunction and fibrinogen was observed; such patients who smoked had significantly increased plasma fibrinogen concentration in comparison to control smokers. Similarly, men with erectile dysfunction who did not smoke had higher levels of plasma fibrinogen compared to both smokers and non-smokers without erectile dysfunction. These results support the concept that cardiovascular risk factors are predictors of erectile dysfunction and that it may be another manifestation of vascular disease[162]. Another disease condition related to elevated fibrinogen is pre-eclampsia. Pre-eclampsia is associated with a state of hypercoagulability together with an increase of fibrinogen concentration. Such findings may be a reflection of the exaggerated inflammatory response and subsequent endothelial activation, which are believed to be the key pathophysiological mechanisms in pre-eclampsia[163]. Neoplastic diseases are one of the leading causes of morbidity and mortality in the world. Extravascular, intratumoral fibrinogen and fibrin depositions are frequently observed within and around neoplastic tissue and have been implicated in various aspects of tumor growth and metastasis. A recent data suggested that the plasma fibrinogen level is a clinically important and useful marker of the extent of tumor progression in gastric cancer[164].

Conclusion

Measurement of the plasma fibrinogen has an important role in the clinical setting – at least as a marker for risk stratifications for disease development or as a marker of disease status. We may suggest to our patients comprehensive lifestyle changes – for example, cessation of smoking, regularly physical activity and maintaining a healthy body weight – that will decrease their plasma fibrinogen levels, together with other beneficial effects.

Fibrinogen is a complex and multifunctional glycoprotein that remains an interesting research subject to scientists from different fields of biomedicine – from laboratory investigators, through clinicians to epidemiologists. The knowledge about fibrinogen increased during the past decade. However, questions that need to be answered still remain. The association between beneficial effect of lowering plasma fibrinogen concentrations and development of cardiovascular disease and other pathologic conditions related to increased fibrinogen needs to be established and clarified. Further efforts should be invested in defining the precise mechanisms of complex gene-environment interactions that influence fibrinogen levels and their role in the pathogenesis of the fibrinogen-related diseases. It could be speculated that possible discovery of a drug that would specifically lower plasma fibrinogen would also explain some of these questions in the future.

Acknowledgements

This work was supported by the grant 0108330 of the Ministry of Science, Education and Sport of the Republic of Croatia.

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PRETHODNO DESETLJEĆE: FIBRINOGEN

S A Ž E T A K

Ovaj članak iznosi pregled napretka učinjenog tijekom proteklog desetljeća, u razumijevanju strukture i uloge fibrinogena, njegovih nasljednih i okolišnih odrednica, značenja u procesu hemostaze, agregacije trombocita, viskoznosti plazme, agregacije eritrocita, staničnih interakcija, upale, cijeljenja rane, razvoja tumora, aterogeneze, te uloge u patogenezi bolesti. Buduća će istraživanja nastojati definirati precizne mehanizme kompleksnih međudjelovanja između nasljednih i okolišnih čimbenika koji utječu na razinu fibrinogena i njegovu složenu ulogu u patogenezi bolesti povezanih s utjecajem fibrinogena.