Original paper

Preprocedural fibrinogen levels and MACE after percutaneous coronary intervention

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Abstract

Introduction: Fibrinogen is a risk factor for cardiovascular disease and is related to the severity of coronary atherosclerosis. According to many studies elevated fibrinogen levels in patients with coronary angioplasty can be useful in predicting target vessel revascularization (TLR) and major adverse cardiac events (MACE).
Material and methods: The studied group included 33 patients (10 – female and 23 males; mean age 62.9±8.9 years). The control group consisted of 30 persons (9 – females and 21 maels; mean age 61.8±9.8) who did not develop MACE during 12 months of follow-up. All patients were hospitalized from the beginning of 2003 to March of 2004 for acute coronary syndrome (ACS) and underwent percutaneous coronary intervention (PCI). Preprocedural concentrations of fibrinogen were measured in all patients. The aim of our study was to assess the preprocedural level of fibrinogen in patients developing MACE in comparison to patients from the study group.
Results: We have not found statistically significant differences in the level of fibrinogen between the studied groups and the levels of fibrinogen persisted within the normal range of values.
Conclusions: The level of fibrinogen within the normal limits can not define the group of patients after ACS who are at a high risk for developing MACE.

Key words: MACE, restenosis, inflammation, fibrinogen.

Introduction

An angioplasty is a modern, safe and effective way to unblock coronary arteries. The implanted stent or ballon angioplasty serves as a scaffold that keeps the artery open [1, 2]. Currently in about 80-90% procedures metal or sometimes drug eluting stents are being used [3]. Stents implantation increases safety of the treatment in coronary artery disease, which was confirmed in randomized studies SYNTAX (SYNergy Between PCI with TAXUS and Cardiac Burgery) BENESTENT and STRESS [4, 5]. However, there are some limitations associated with angioplasty and stenting. Percutaneous interventions trigger inflammatory reactions leading to the development of intimal hyperplasia and activation of the inflammatory process which results in restenosis of the stented vessel [6]. Restenosis, the re-narrowing of a coronary artery – occurs within 3-6 months in 20-30% of patients who have had PCI (percutaneus coronary intervention) [7], can lead to many

critical endpoints – MACE (major adverse cardiac events). Its risk depends on the length and type of stents and many other factors i.e. level of cholesterol, triglicerydes, alcohol abstinence, diabetes mellitus [8]. Determination of the risk group for restenosis is crucial for a further follow up of patients after PCI. It has been stated in many studies that there is dependence between inflammatory markers like CRP, IL6, fibrinogen and restenosis, MI recurrency, cardiac death. Elevated levels of these markers are seen also in atherosclerosis of the carotid arteries and in patients with stroke [9]. There are some studies confirming the predictive power of these factors in anticipation of MACE in patients treated with PCI [10, 11]. Fibrinogen as acute phase protein can be a predictive factor as well. The aim of our study was to assess if the preprocedural levels of fibrinogen are higher in patients who developed MACE than in patients who did not reveal any adverse events.

Material and methods

The studied group included 33 patients (10 females and 23 males; mean age 62.9±8.9 years), treated with PCI for the acute coronary syndrome (ACS), who developed MACE during 12 months follow up period, the control group consisted of 30 persons (9 – females and 21 males; mean age 61.8±9.8) who did not develop MACE during 12 months of follow-up. The both groups were comparable in gender and age (complete characteristics of the group in Table I). The active inflammatory process was excluded based on physical examination. All patients were hospitalized from the beginning of 2003 to March of 2004 for acute coronary syndrome and were treated with percutaneous coronary intervention (PCI). Afterwards the patients were followed for 12 months and MACE was analyzed based on the history from 12 follow-up months. The endpoint MACE (Major Adverse Cardiac Events) was defined based on the combined incidence of objective clinical endpoints (death attributed to the heart, myocardial infarction) and more subjective clinical endpoints (emergent coronary artery bypass graft surgery, or CABG, and target lesion revascularization-TLR). TLR (target lesion revascularization) was defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel. On admission to the hospital peripheral blood was taken from all patients and fibrinogen and other inflammatory markers were assessed. The reference range of values for fibrinogen from our laboratory is 140-450 mg/dl. The elevated level was determined as higher than 450 mg/l. Other parameters were also estimated, such as WBC, ESR, glycated hemoglobin (HbA_{1C}), lipid disorders (expressed as: total cholesterol-TCH, high density lipoprotein cholesterol-HDL, low density lipoprotein cholesterol-LDL, triglycerides-TG) and body mass index (BMI).

Coronarography

Coronarography and PCI were performed in all subjects in acute coronary syndrome using Seldinger's or Sones' methods. A coronarography was made on a Shimadzu angiograph with the Digitex 2400 system in the Departament of Interventional Cardiology, Cardiodiabetology and Cardiac Rehabilitation.

Biochemical determination

On the first day of hospitalization blood samples were collected from peripheral veins of all patients. Laboratory testing was performed in the Department of Laboratory Diagnostics of Medical University of Lodz. Fibrinogen was detected by Clauss' methods (Multifibren U; Dade Behring Diagnostics; Behring Fibrintimer). White blood cell counts were performed on a Pentra 80 Automated Blood Cell Analyzer.

Table I. The characteristic of studied groups

	MACE	Control group	Statistical significance
Number of patients	33	30	NS
Sex (M/F)	23/10	21/9	NS
Age	62.9±8.9	61.8±9.8	NS
BMI	28.6±3.9	28.3±4.1	NS
HbA_1c	6.5 (6.0-8.3)	6.3 (5.8-7.1)	NS
TCH	5.9±1.4	6.1±1.7	NS
HDL	1.4±0.5	1.4±0.3	NS
LDL	3.6±1.4	3.6±1.4	NS
TG	2.0 (1.1-2.4)	1.3 (0.7-2.2)	NS

M – male, F – female, BMI – body mass index, HbA1c – glycated hemoglobin, TCH – total cholesterol, HDL – high density lipoprotein cholesterol, LDL – low density lipoprotein cholesterol

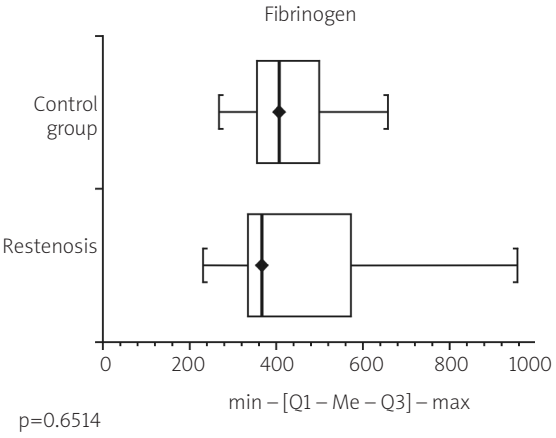

Figure 1. Concentrations of fibrinogen in both groups

Statistical analysis

For all parameters the arithmetic mean with standard deviation ($\bar{\chi}$SD) and median (Me), first and second quartile (1Q – 3Q) with minimal and maximum value (min – max) were acounted. The normality distribution of data in the sample was searched by the Shapiro-Wilk test. The statistical significance was estimated by the t-Student test for parametric distribution and Mann-Whitney U test for nonparametric distribution. Statistic calculations and graphical analysis was made by the Stats Direct program (StatsDirect Ltd., Cheshire, UK). The studies were made basing on rules of the local Ethics Commission. All patients agreed to take part in the study.

Results

We have not found statistically significant differences in the level of fibrinogen between the studied groups. The levels of fibrinogen persisted within the normal range of values (Figure 1). However, other inflammation parameters (ESR, WBC) were higher in the MACE group in comparison to the control group (Table II). In the MACE group re-PCI was observed more often than CABG and cardiac death (Table III). In the MACE group and the control group the mean level of fibrinogen was 367.1 (331.8 – 576.2) vs 406.6 (358.5 – 487.8) p=0.6514, WBC: 10.3±3.4 vs 9.6±2.9 p<0.05, ESR: 14.0 (10.0 – 23.5) vs 12.0 (8.0 – 19.0) p<0.05. There were no statistically significant differences in the WBC number, ESR, level of glycated hemoglobin and lipid parameters.

Table II. The characteristic of MACE group

MACE	Number of patients	Sex (M/F)
Re-PCI	25	17/8
CABG	5	3/2
Cardiac death	3	3/0

M – male, F – female, BMI – body mass index, MACE – major adverse cardiac evens, re-PCI – repeat percutaneus coronary intervention, CABG – coronary artery bypass graft

Table III. Results of fibrinogen, WBC and ESR

	Fibrinogen	WBC	ESR
MACE	367.1 (331.8-576.2)	10.3±3.4	14.0* (10.0-23.5)
Control group	406.6 (358.5-487.8)	9.6±2.9	12.0* (8.0-19.0)

**p<0.005*
WBC – white blood cells, ESR – erytrocite sedimetation rate

Discussion

Despite the huge progress made in the treatment of ACS, restenosis is still an important adverse event in patients who underwent PCI. Restenosis is provoked by an inflammatory process [6], therefore measurement of inflammatory markers such as CRP, ESR, WBC and fibrinogen could be helpful in predicting patients with a high risk for restenosis and MACE.

Numerous studies confirmed the predictive role of elevated inflammatory markers such as CRP, ESR, Lp(a) in restenosis and MACE [11, 12].

Prospective epidemiological studies clearly demonstrated that fibrinogen is an independent risk factor for coronary events [13]. Moreover, angiographic studies reported the association between fibrinogen and the presence and severity of coronary stenoses, suggesting that fibrinogen is involved in the progression of spontaneous coronary atherosclerosis [14]. Although platelets and thrombosis contribute to the pathogenesis of restenosis, few clinical data are available concerning the relations between restenosis and proteins of the coagulation and fibrinolytic systems [10]. In our study we have not found any significant difference in the fibrinogen level between the groups with and without MACE. While in some studies preprocedural levels of fibrinogen were related to MACE and restenosis [11, 15], other studies are coherent with our results [10, 16]. The first work published in 1995 was trying to describe fibrinogen as a predictive factor for restenosis [10]. In this work fibrinogen levels were similar in patients with or without restenosis when measured before or immediately after angioplasty, but when patients came 6 months after angioplasty fibrinogen levels were significantly higher in the group with restenosis. So fibrinogen measured before angioplasty did not identify patients at risk for restenosis [10]. Also Monraats et al. concluded that baseline preprocedural fibrinogen levels are not associated with an increased risk of TVR or combined endpoint in the population with coronary stent placement. In this study the authors

have not found any correlation of -455G/A polymorphism of the fibrinogen beta-gene and a higher risk of restenosis. However, other studies showed that preprocedural levels of fibrinogen can be an independent risk factor for restenosis [15]. However, the Rahel's study clearly supports the role of inflammation in restenosis after PCI as measured in statistically higher levels of Lp(a) and fibrinogen in patients with MACE and CRP in patients with repeat angina [11]. According to Bannermo CRP and fibrinogen concentrations measured in patients during the acute phase of myocardial infarction treated with thrombolysis were associated with cardiovascular death or a new myocardial infarction during the follow-up in the univariate analysis [17].

So at the present moment it is hard to say if we can use the fibrinogen level as a predicting factor for MACE and restenosis. As in most of the studies preprocedural levels have not differed for restenosis patients, the differences observed in the MACE group could result from the elevated levels of fibrinogen in patients with fatal outcome (cardiac death). In our study in the MACE group there were only 3 persons who died during 12 months follow-up period.

According to Coppola plasma fibrinogen levels were the only independent predictor of mortality in a 42-month follow-up post- acute myocardial infarction [18] But fibrinogen level is perceived as an independent risk factor for mortality from a broad spectrum of diseases in elderly men, not only cardiovascular diseases but also cancers [19]. Therefore in some works elevated preprocedural levels of fibrinogen could have been a risk factor for cardiac death and no just restenosis. Interestingly, in many published studies fibrinogen levels were higher than the reference limit of values while in our study fibrinogen levels remain within the normal ranges.

Moreover, in most of the studies, the mean age of the patients was higher than in our study [12, 17]. It is known that fibrinogen levels rise with age of the patients [9, 17].

Elevated serum levels of different inflammatory markers are seen in many other cardiovascular diseases such as stroke, atherosclerosis of carotid and limb arteries [20, 21]. The most predictable, among many inflammatory markers for myocardial infarction, coronary unstability and stroke is C-Reactive Protein (CRP) [22]. Elevated baseline C-reactive protein portends a heightened risk of 30-day death or myocardial infarction after a coronary intervention. Coupled anatomic, clinical, and inflammatory risk stratification demonstrates a strong predictive utility among patients undergoing a percutaneous coronary intervention and may be useful for guiding future strategies [23]. CRP levels measured 3 months after acute events are not associated with subsequent events whereas fibrinogen concentrations show a borderline prognostic significance [17]. Also C-reactive protein and fibrinogen do not carry the same independent prognostic information after acute myocardial infarction treated with thrombolysis as in studies previously reported for patients with unstable angina or non-Q-wave myocardial infarction [17].

Conclusions

The level of fibrinogen within the normal limits can not define the group of patients after ACS who are at a high risk for developing MACE.

References

1. Serruys PW, Luijten HE, Beatt KJ, Geuskens R, de Feyter PJ, et al. Incidence of restenosis after successful coronary angioplasty: a time-related phenomenon. A quantitative angiographic study in 342 consecutive patients at 1, 2, 3, and 4 months. Circulation 1988; 77: 361-71.
2. Dangas G, Kuepper F. Cardiology patient page. Restenosis: repeat narrowing of a coronary artery: prevention and treatment. Circulation 2002; 105: 2586-7.
3. Holmes D, Berger P. Complex intervention. Textbook of interventional cardiology. 2003: 201.
4. Kiemeneij F, Serruys PW, Macaya C, Rutsch W, Heyndrickx G, et al. Continued benefit of coronary stenting versus balloon angioplasty: five-year clinical follow-up of Benestent-I trial. J Am Coll Cardiol 2001; 37: 1598-603.
5. Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med 1994; 331: 496-501.
6. Toutouzas K, Colombo A, Stefanadis C. Inflammation and restenosis after percutaneous coronary interventions. Eur Heart J 2004; 25: 1679-87.
7. Zalewski A. About the vessel wall biology [Polish]. Kardiol Pol 2000; 53: 40-2.
8. Dudek A, Wojciechowski P, Buszman P. The influence of coronary heart disease risk factors and alcohol abstinence on stenocardial sypmtoms and cardiac event recurrence aftef coronary stent implantation [Polish]. Post Kardiol Interw 2005; 1: 51-6.
9. Mackie IJ, Kitchen S, Machin SJ, Lowe GD. Guidelines on fibrinogen assays. Br J Haematol 2003; 121: 396-404.
10. Montalescot G, Ankri A, Vicaut E, Drobinski G, Grosgogeat Y, et al. Fibrinogen after coronary angioplasty as a risk factor for restenosis. Circulation 1995; 92: 31-8.
11. Rahel BM, Visseren FL, Suttorp MJ, Plokker TH, Kelder JC, et al. Preprocedural serum levels of acute-phase reactants and prognosis after percutaneous coronary intervention. Cardiovasc Res 2003; 60: 136-40.
12. Koukkunen H, Penttila K, Kemppainen A, Halinen M, Penttila I, et al. C-reactive protein, fibrinogen, interleukin--6 and tumour necrosis factor-alpha in the prognostic classification of unstable angina pectoris. Ann Med 2001; 33: 37-47.
13. Montalescot G, Collet JP, Choussat R, Thomas D. Fibrinogen as a risk factor for coronary heart disease. Eur Heart J 1998; 19 (Suppl H): H11-7.
14. Ernst E. Fibrinogen: its emerging role as a cardiovascular risk factor. Angiology 1994; 45: 87-93.
15. Otsuka M, Hayashi Y, Ueda H, Imazu M, Kohno N. Predictive value of preprocedural fibrinogen concerning coronary stenting. Atherosclerosis 2002; 164: 371-8.

16. Monraats PS, Rana JS, Zwinderman AH, de Maat MP, Kastelein JP, et al. -455G/A polymorphism and preprocedural plasma levels of fibrinogen show no association with the risk of clinical restenosis in patients with coronary stent placement. Thromb Haemost 2005; 93: 564-9.
17. Bennermo M, Held C, Hamsten A, Strandberg LE, Ericsson CG, et al. Prognostic value of plasma C-reactive protein and fibrinogen determinations in patients with acute myocardial infarction treated with thrombolysis. J Intern Med 2003; 254: 244-50.
18. Coppola G, Rizzo M, Abrignani MG, Corrado E, Di Girolamo A, et al. Fibrinogen as a predictor of mortality after acute myocardial infarction: a forty-two-month follow-up study. Ital Heart J 2005; 6: 315-22.
19. Yano K, Grove JS, Chen R, Rodriguez BL, Curb JD, et al. Plasma fibrinogen as a predictor of total and cause-specific mortality in elderly Japanese-American men. Arterioscler Thromb Vasc Biol 2001; 21: 1065-70.
20. Speidl WS, Exner M, Amighi J, Kastl SP, Zorn G, et al. Complement component C5a predicts future cardiovascular events in patients with advanced atherosclerosis. Eur Heart J 2005; 26: 2294-9.
21. Sabeti S, Exner M, Mlekusch W, Amighi J, Quehenberger P, et al. Prognostic impact of fibrinogen in carotid atherosclerosis: nonspecific indicator of inflammation or independent predictor of disease progression? Stroke 2005; 36: 1400-4.
22. Arroyo-Espliguero R, Avanzas P, Cosin-Sales J, Aldama G, Pizzi C, et al C-reactive protein elevation and disease activity in patients with coronary artery disease. Eur Heart J 2004; 25: 401-8.
23. Chew DP, Bhatt DL, Robbins MA, Penn MS, Schneider JP, et al. Incremental prognostic value of elevated baseline C--reactive protein among established markers of risk in percutaneous coronary intervention. Circulation 2001; 104: 992-7.