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Immunoglobulin E as a marker of the atherothrombotic process in patients with acute myocardial infarction

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Abstract

Background: *Clot formation is a crucial moment in the patophysiology of acute coronary syndromes. The aim of this research was to assess the relationship between immunoglobulin E (IgE), lipid parameters and chosen hemostatic markers. The role of IgE as a possible participant in the atherothrombotic process was also investigated.*

Methods: *A total of 80 patients with acute myocardial infarction (MI) was enrolled in the study. Concentrations of IgE, plasma lipid parameters, lipoprotein(a), markers of thrombin generation (TAT, AT III), markers of fibrinolysis (tPA:Ag, PAI-1:Ag, PAP, D-dimers) and markers of endothelial damage (von Willebrand factor) were measured in blood samples collected immediately after admission, before any treatment administration.*

Results: *In patients with acute MI and with IgE concentration above 100 kU/l, IgE values were strongly, positively correlated with LDL concentration ($p < 0.05$), lipoprotein(a) concentration ($p < 0.02$) and negatively correlated with HDL plasma levels ($p < 0.02$). Exclusion of patients with IgE concentration lower than 150 kU/l strengthened the correlation between IgE concentration and LDL ($p < 0.002$) and lipoprotein(a) ($p < 0.01$) levels. It also revealed a significant correlation between IgE and TAT ($p < 0.001$), IgE and AT III ($p < 0.002$), and IgE and D-dimers ($p < 0.05$). IgE and TAT values measured 7, 14 and 40 days after infarction also showed significant positive correlation between increments of these parameters.*

Conclusions: *In patients with acute MI, a significant increase of thrombinogenesis and fibrinolysis markers is observed. Positive correlation between IgE concentration above 100 kU/l and markers of thrombinogenesis activation, lipid parameters and lipoprotein(a) levels, with significance increasing with IgE concentration and constant positive correlation between*

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increments of IgE and TAT, can serve as evidence of IgE participation in the atherothrombotic process. (Cardiol J 2007; 14: 266–273)

Key words: myocardial infarction, markers of thrombinogenesis and fibrinolysis, immunoglobulin E

Introduction

In clinical practice, we very often observe people with ischemic heart disease (IHD) with no generally known predisposing risk factors diagnosed, which confirms that the variety of causes of acute coronary syndromes is still not fully explained. The role of immunity mechanisms in the development of atherosclerosis and its thrombotic complications has been recognised and appreciated [1–3] in the last 20 years. In the blood circulation of patients with atherosclerosis, antibodies against oxidised LDL have been detected, as well as circulating immunity complexes consisting of LDL and antibodies against them [4]. In some myocardial infarction (MI) patients, high concentrations of antibodies against chlamydia pneumoniae have been found, which suggests that atherosclerosis and its thrombotic complications may have an infectious etiology [5, 6].

Recently, attention has been drawn to increased serum immunoglobulin E (IgE) concentrations in patients with cardiovascular diseases, and myocardial infarction in particular [7–10]. It is assumed that there exist many relations between IgE concentrations and antigen-activated mast cells, and the progression of atheromatic changes and thrombotic complications. It has therefore been stated that local antigen stimulation of mast cells, on the surface of which IgE is found, may lead to foam cell formation within arterial walls [11, 12]. The activation of mast cells with the use of "physiological stimulants", such as IgE, C3 and C5, causes the discharge of mediators such as histamines, heparin and neutral proteases [12]. However, it was concluded that mast cells might also be activated to degranulation without IgE, for instance by means of complement, lymphocytes T and macrophages [13]. The fact that mast cells are present in atheromatic lesions beside activated lymphocytes T, complement components, macrophages and cytokines, proves that mastocytes are among the main cells in atherogenesis [2, 14]. It was observed that the progress of atheromatic changes in coronary arteries is connected with a greater number of mast cells in adventitia of coronary vessels that are also present between myocytes and in the arterial intima. Disruption of atheromatic plaque leads to adhesion and aggregation of platelets, as well as to thrombin activation and fibrin formation. A disturbed hemostatic balance is evident mainly in the activation of coagulation cascade, a clinical consequence of which may be the partial or full closure of a vessel with symptoms of unstable angina pectoris, myocardial infarction or sudden cardiac death [15].

In the last decade, the list of markers enabling the detection of thrombotic risk [16] has widened. The most important are thrombin-antithrombin III complexes (TAT); they reflect the intensity of thrombinogenesis in vivo and belong to the most sensitive and most specific markers of thrombosis [17]. Among factors crucial for the development of IHD are: fibrinogen, factor VII, von Willebrand factor (vWF), tissue plasminogen activator (t-PA), plasminogen activator inhibitor type 1 (PAI-1) and lipoprotein(a) [Lp(a)]. Some of them (vWF, t-PA, Lp(a) and fibrinogen) were described as independent biological risk factors, on the basis of which the occurrence of coronary episodes may be predicted [18].

The key enzyme, which is formed during the activation of fibrinolysis, is plasmin. The test evaluating the amount of the forming plasmin is the determination of plasmin-α_2-antiplasmin (PAP) concentration. PAP complex determination is a relatively new method of examining the fibrinolytic system, and their increased concentration serves as evidence of intensified plasminogenesis in vivo. Plasmin acting on the fibrin net results in the formation of various size fragments, the smallest of which are D-dimers (DD). Increased concentrations of DD are evidence not only of the activated coagulation system, but also of active fibrinolysis [19].

Bearing in mind the significance of the problem of coronary heart disease in developed countries, as well as its scientific and practical aspects, the study has been undertaken to explain whether and what relation there is between IgE and coagulation and fibrinolysis markers, endothelium damage and lipid parameters, in patients with acute myocardial infarction. Furthermore, it has been checked if the relation is dependent on concentrations of the evaluated parameters.

Methods

The study included 80 STEMI patients, without cardiac arrest or cardiogenic shock before admission to hospital, without any concomitant chronic inflammatory diseases and without personal or family history of allergy, aged 37–70 (average age 55; 52 males), and 39 healthy persons (average age 52.5; 28 males). Myocardial infarction was diagnosed on the basis of typical anamnesis, typical changes in serial ECGs and laboratory tests confirming cardiomyocytes necrosis, i.e. troponin I and the fraction of creatine phosphokinase (CK-MB).

Blood for examination was sampled immediately after admission to hospital and obtaining the patients' written consent and before standard treatment administration. Fasting blood samples were taken from the control group in the morning (between 7 and 9 a.m.), after 30 minutes' rest, in supine position; the venopuncture was done in the antecubital region with no venostasis.

TAT complex concentrations were measured with a Enzygnost TAT kit manufactured by Behring-Marburg (ELISA) (normal range 1.0–4.1 μg/l). Biological activity of antithrombin III in serum was determined with the use of chromogenic substrate and spectrophotometry with the Berichrom Antithrombin III test by Boehringer Mannheim (normal values: 80–120%). Tissue plasminogen activator antigen (t-PA:Ag) was examined by means of the Imulyse® t-PA test by Biopool (normal range: 3––10 ng/ml). The concentration of tissue type plasminogen activator inhibitor type 1 (PAI-1:Ag) was determined by the Imulyse® PAI-1 test by Biopool (normal range 4–43 ng/ml). The concentration of plasmin-α_2-antyplasmin (PAP) complexes was measured using Enzygnost PAP test by Behring Marburg (normal range: 120–700 ng/ml). The concentration of D-dimers was determined by means of VIDA kit by BioMeriéux, using the immunoenzymatic method with fluorescent readout (normal range: 70–500 ng/ml). The concentration of von Willebrandt factor was determined using the Asserachrom® vWF test by Diagnostica Stago--Boehringer Mannheim (normal values 50–160%). The fibrinogen concentration was measured by means of the colorimetric method using Hemola fibrinomat test by Biomerieux (normal range 2.0––4.0 g/l). Lp(a) was determined by an immunoenzymatic ELISA method using a CORMAY kit (normal values up to 30 mg%). Serum IgE was measured using the Pharmacia Uni-cap Total IgE kit by FEIA technique, on an automatic analyser Unicap 100, in accordance with the WHO 75/502 standard.

In all patients we evaluated concentrations of total cholesterol, LDL and HDL cholesterol fractions and triglycerids, using the enzymatic test manufactured by Biomerieux.

The time elapsing from the onset of pain until admission to hospital did not exceed six hours, on average. Statistical analysis was performed with the use of Statistica 5.0 for Windows 95 by StatSoft®. Local research Ethical Committee at the Medical University in Bydgoszcz gave its consent to the study.

Results

The comparison of baseline lipid parameters and markers of coagulation, fibrinolysis and endothelium damage in MI patients and in the control group revealed highly significant differences; mean concentrations of TAT, PAI-1:Ag, PAP and t-PA:Ag considerably exceeded norms in the MI group (Table 1, 2).

The correlation of IgE concentrations with the concentrations of selected markers of coagulation, fibrinolysis and endothelium damage in MI patients, regardless of the level of IgE concentration, did not reveal any statistical significance apart from a negative correlation with PAP.

The correlation of log (IgE) with the evaluated parameters in MI patients with IgE concentration above 100 kU/L revealed a statistically significant correlation with LDL ($p < 0.05$) and Lp(a) ($p < 0.02$) and a negative correlation with HDL ($p < 0.02$). Also, a positive correlation was observed with total cholesterol, TAT and AT III but with no statistical significance (Table 3).

The exclusion of patients with IgE concentrations below 150 kU/L strengthened the correlation

Table 1. Comparison of lipid parameters in myocardial infarction patients (MI group, n = 80) and in control group (n = 39).

	CH [mg/dl]	HDL [mg/dl]	LDL [mg/dl]	TG [mg/dl]	Lp(a) [mg/dl]
MI group	233.70 ± 47.67	47.81 ± 13.94	155.67 ± 41.09	147.95 ± 64.45	49.81 ± 32.35
Control group	201.64 ± 28.67	50.05 ± 11.15	129.32 ± 27.63	115.61 ± 47.40	30.63 ± 22.93
p	0.001	NS	0.001	0.001	0.01

Table 2. Comparison of baseline hemostatic parameters in myocardial infarction patients (n = 80) and in control group (n = 39).

Parameter (units)	Myocardial infarction (x ± SD)	Control group (x ± SD)	p
Thrombin generation markers			
TAT [mg/l]	23.06 ± 33.09	3.41 ± 1.76	0.001
Log(TAT)	0.99 ± 0.55	0.48 ± 0.21	0.001
ATIII [%]	115.16 ± 17.34	99.44 ± 10.49	0.001
Fibrinolysis system markers			
t-PA:Ag [ng/ml]	13.50 ± 8.02	7.74 ± 2.84	0.001
PAI-1:Ag [ng/ml]	29.14 ± 26.26	20.84 ± 9.08	0.02
PAP [ng/ml]	947.55 ± 805.30	236.04 ± 66.41	0.001
D-dimers [ng/ml]	614.09 ± 946.01	221.38 ± 101.06	0.001
Endothelium damage markers			
vWF [%]	144.46 ± 32.22	100.58 ± 12.91	0.001
t-PA:Ag [ng/ml]	13.50 ± 8.02	7.74 ± 2.84	0.001
Other selected hemostasis parameters			
Platelets [G/L]	233.04 ± 57.37	224.05 ± 48.82	NS
Fibrinogen [g/l]	3.81 ± 1.03	3.04 ± 0.54	0.001
APTT [s]	29.75 ± 5.01	31.44 ± 5.51	NS
INR	0.92 ± 0.07	0.91 ± 0.06	NS

Table 3. Correlation of log(IgE) with lipid and hemostatic parameters in myocardial infarction patients with baseline IgE level above 100 kU/l.

Covariables	Correlation coefficient (r)	Significance level (p)
Lipid parameters		
CH [mg/dl]	0.22	NS
HDL [mg/ml]	–0.40	0.05
LDL [mg/dl]	0.40	0.05
TG [mg/dl]	–0.11	NS
Lp(a) [mg/dl]	0.51	0.02
Thrombin generation markers		
TAT [mg/l]	0.29	NS
Log(TAT) [mg/l]	0.20	NS
ATIII [%]	0.21	NS
Fibrinolytic system markers		
t-PA:Ag [ng/ml]	–0.10	NS
PAI-1:Ag [ng/ml]	–0.13	NS
PAP [ng/ml]	–0.16	NS
D-dimers [ng/ml]	0.02	NS
Endothelium damage markers		
v. Willebrand [%]	–0.17	NS
t-PA:Ag [ng/ml]	–0.10	NS

Table 4. Correlation of log(IgE) with lipid and hemostatic parameters in myocardial infarction patients with baseline IgE level above 150 kU/l.

Covariables	Correlation coefficient (r)	Significance level (p)
Lipid parameters		
CH [mg/dl]	0.35	NS
HDL [mg/ml]	–0.40	NS
LDL [mg/dl]	0.74	0.002
TG [mg/dl]	–0.39	NS
Lp(a) [mg/dl]	0.63	0.01
Thrombin generation markers		
TAT [mg/l]	0.76	0.001
Log(TAT) [mg/l]	0.68	0.002
ATIII [%]	0.54	0.02
Fibrinolytic system markers		
t-PA:Ag [ng/ml]	–0.02	NS
PAI-1:Ag [ng/ml]	–0.44	NS
PAP [ng/ml]	0.11	NS
D-dimers [ng/ml]	0.44	0.05
Endothelium damage markers		
v. Willebrand [%]	0.21	NS
t-PA:Ag [ng/ml]	–0.02	NS

of log(IgE) with LDL ($p < 0.002$) and Lp(a) ($p<0.01$) and revealed a strong correlation with TAT ($p < 0.001$), ATIII ($p < 002$) and a weaker but significant correlation with DD ($p < 0.05$). Still, there existed a positive and almost statistically significant correlation with the total cholesterol level and a negative one with HDL (Table 4).

Further exclusion of patients with IgE concentrations below 200 kU/L revealed a maintained positive correlation of increased concentrations of

Table 5. Correlation of log(IgE) with lipid and hemostatic parameters in myocardial infarction patients with baseline IgE levels above 200 kU/l.

Covariables	Correlation coefficient (r)	Significance level (p)
Lipid parameters		
CH [mg/dl]	0.62	0.05
HDL [mg/ml]	–0.07	NS
LDL [mg/dl]	0.67	0.02
TG [mg/dl]	–0.10	NS
Lp(a) [mg/dl]	0.47	NS
Thrombin generation markers		
TAT [mg/l]	0.81	0.001
Log(TAT) [mg/l]	0.80	0.002
ATIII [%]	0.59	0.05
Fibrinolytic system markers		
t-PA:Ag [ng/ml]	0.07	NS
PAI-1:Ag [ng/ml]	–0.50	NS
PAP [ng/ml]	–0.05	NS
D-dimers [ng/ml]	0.42	NS
Endothelium damage markers		
v. Willebrand [%]	0.30	NS
t-PA:Ag [ng/ml]	0.07	NS

log(IgE) with total cholesterol ($p < 0.05$) and LDL ($p < 0.02$), together with a positive and almost statistically significant correlation with Lp(a). A strong correlation with log(TAT) ($p < 0.002$) and a positive significant correlation with AT III ($p < 0.05$) was still maintained (Table 5).

The correlation between the positive or negative increments of values of IgE and simultaneous increase in concentrations of the thrombinogenesis markers, for which the strongest correlation with IgE was proven, showed that on the 7th, 14th, and 40th days after the infarction, a positive significant correlation of IgE concentration increments with TAT concentration increase was maintained. This served as evidence for the previously found relation between IgE concentration and TAT levels in MI patients (Table 6).

Table 6. Correlation between increments of IgE values and increments of coagulation activation markers in patients in the course of myocardial infarction.

Parameters	Day 1–7 (n = 54)		Day 1–14 (n = 52)		Day 1–40 (n = 42)	
	r	p	r	p	r	p
TAT [mg/l]	0.38	0.02	0.32	0.05	0.44	0.02
ATIII [%]	0.18	NS	0.19	NS	–0.14	NS

Discussion

While discussing the role which immunoglobulin E may play in the atherothrombotic process the result of which is myocardial infarction, one should ask what relation exists between IgE and other main factors of the atherothrombotic process, namely lipid disorders and intravascular coagulation activation markers.

A significant increase of coagulation activation markers in myocardial infarction has been noted by many authors. TAT complex concentrations were highest during the first 24 hours after infarction [20, 21]. Szczeklik et al. [20] found significantly increased levels of TAT complexes in the majority (90%) of the group of 100 AMI patients. Maintained high concentrations of TAT complexes predicted a worse prognosis. They were observed in patients with reinfarction and heart failure. The authors' own study revealed significantly increased levels of TAT complexes in 70% of the patients with myocardial infarction. The highest values were observed at baseline; lower but not significantly: on the 7th, 14th and 40th days. The analysis of the results of the prospective Nortwick Park Heart Study (NPHS) in patients without initially diagnosed IHD allowed the authors to conclude that the majority of cardiac deaths concerned people with extreme AT III activity (high or low) diagnosed previously [22]. The conclusions emerging from the results of both PLAT and the Rotterdam studies imply that patients with active atheromatic process have increased levels of ATIII activity, which is a result of the activation of defence mechanisms against prothrombotic influences and clearly indicates that the increased risk of cardiovascular diseases is associated with increased ATIII activity [23, 24]. In the literature, the majority of authors stress the increased concentration of t-PA:Ag as a myocardial infarction factor. The high concentration of t-PA, as a risk of myocardial infarction, is often accompanied with high PAI-1 activity. It has been suggested that the high PAI-1 activity is responsible for the impaired fibrinolytic plasma activity and may play an important role in the clot formation in coronary arteries [25, 26]. Increased PAP and DD concentrations turned out to be independent MI risk factors. Activation of fibrinolysis, as secondary to coagulation activation, brings about increased concentrations of the markers, which, even in the early stage of observations, prognosticate coronary incidents, particularly myocardial infarction and sudden

cardiac death [27]. In patients with atherosclerosis and IHD, the von Willebrand factor was also increased. The von Willebrand factor indicates the increased risk of MI, reinfarction and death [25].

In the evaluated group of patients with acute myocardial infarction, as compared to the control group, we found significant differences in concentrations of thrombin generation markers, fibrinolytic system and endothelium damage markers.

Bearing in mind literature reports and the author's own research on increased IgE concentrations in patients with IHD, especially in myocardial infarction, as well as increased lipid parameters and markers enabling detection of thrombotic risk in those patients, it seemed necessary to evaluate correlations of IgE with both lipid parameters and with representative hemostatic markers. The evaluation of relations between immunoglobulin E with coagulation and fibrinolysis markers may have cast light on the IgE role as a possible co-participant of IHD pathogenesis.

In the available literature we have not come across any reports on IgE relation with markers of hemostatic disorders in humans, apart from the observations by Szczeklik et al. [8], who were the first to draw attention to the delay in thrombin generation in MI patients and the high serum IgE concentration (geometrical mean > 70 kU/L). It seemed indispensable to broaden the evaluation of the possible relation of IgE to not only include thrombin generation markers, but also other markers of activation of coagulation cascade, markers of plasma fibrinolysis and markers of endothelial damage.

The correlation of IgE with the above mentioned factors in all patients with coronary artery disease included in the study, regardless of the level of IgE concentration, did not reveal a statistical significance, apart from the negative and statistically significant correlation with PAP in MI patients ($p < 0.05$). The correlation of IgE concentration with log(TAT) was close to statistical significance. Nevertheless, in patients with myocardial infarction but with IgE concentration above 100 kU/L and above 150 kU/L and 200 kU/L, we found statistically significant positive correlations of log(IgE) with lipid parameters and parameters of thrombinogenesis.

The possible relation of dyslipidemia and immune deficiencies with acute coronary syndromes was presented in the five-year prospective observation of men with lipid disorders within the Helsinki Heart Study, which attempted to evaluate the relation between the serum levels of immunoglobulins E, A and G, and the size of coronary incident risk (fatal or non-fatal myocardial infarction, or sudden cardiac death). The results of the study showed that the risk of coronary heart disease remained significantly correlated with IgE concentration, regardless of other risk factors, such as: age, smoking and high blood pressure. The risk in patients with IgE concentration in the highest quartile was as much as 2.8 times higher compared to patients whose serum concentration of immunoglobulin were in the lowest quartile.

Having found a close relation between increased concentrations of immunoglobulins and increased concentration of lipids in plasma, particularly cholesterol in patients with myocardial infarction, the authors came to the conclusion that immune mechanisms participate in the development of atherothrombotic process, the result of which is myocardial infarction [28]. In our study, similarly to the above mentioned studies, neither triglycerides nor HDL cholesterol displayed so close a relation with increased IgE concentrations as the level of total cholesterol and LDL cholesterol. What catches the attention, however, is the relation between IgE and lp(a), that combines the influence of lipid and thrombotic factors on atherosclerosis [29, 30].

A positive correlation between higher IgE values and TAT complexes and ATIII, as well as with total cholesterol, LDL and Lp(a) found in our study, may show the relation of the immunoglobulin with factors playing an important role in the atherothrombotic process. The relation between IgE concentrations and fibrinolysis markers in our study was not very convincing. Even though we observed a negative correlation of IgE with PAP complexes in all the MI patients, it was not significant at higher IgE concentrations.

It is quite difficult to evaluate the direct correlation between IgE concentration and the studied markers of intravascular coagulation and fibrinolysis activation in patients in the first hours after infarction. This results from considerable and multidirectional changes in hemostasis entailed by the infarction itself as well as by the administered treatment. Our study revealed that on the 7^{th}, 14^{th} and 40^{th} days after the infarction a positive significant correlation was maintained between IgE concentrations and the increase in TAT concentrations, which confirmed the relation between the two parameters on the first day of the infarction, as proved before ($p < 0.02$, 0.05 and 0.02 respectively).

In the existing publications, we have not come across any other similar observations concerning the relation between IgE dynamics and those sensitive thrombinogenesis markers in acute myocardial infarction.

Conclusions

1. In patients with acute myocardial infarction, a significant increase in plasma levels of markers of thrombinogenesis and fibrinolysis activation is observed.
2. The positive correlation between IgE concentrations above 100 kU/L with lipid parameters and intravascular coagulation activation markers, with significance increasing with higher IgE levels as well as positive correlation between increments of serum IgE levels and TAT complexes, may serve as evidence of the significant relation between this immunoglobulin and factors playing a vital role in the atherothrombotic process in myocardial infarction patients.
3. The increased concentration of IgE may be regarded as a marker of atherosclerosis and a witness of hemostatic risk factors of ischemic heart disease.

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