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Immunoglobulin E in patients with ischemic heart disease

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Abstract

Background: *In recent years, increased serum immunoglobulin E (IgE) concentration in patients with cardiovascular diseases has been generating more and more interest. It is as yet unknown, however, if the increased IgE level is a marker of future coronary incidents and whether it may be regarded as an ischemic heart disease risk factor, or if it is indicative of the participation of antibodies in an inflammatory reaction to tissue damage. The aim of the study was to evaluate what significant changes in the total IgE concentration occur in patients with different forms of ischemic heart disease (IHD) and whether the concentration differs in comparison to healthy people. Additionally, we evaluated the dynamics of serum IgE concentration in patients with acute myocardial infarction.*

Methods: *The study included 195 patients: 80 acute myocardial infarction (AMI) patients, 58 patients with troponin-negative acute coronary syndrome (ACS) and 57 patients with stable angina pectoris, with negative personal and family history of allergy. The control group consisted of 39 healthy, age-matched individuals. Serum IgE concentration measurements were carried out with an Uni-cap Total IgE kit, using the FEIA technique.*

Results: *In patients suffering from any form of ischemic heart disease, significantly increased concentrations of serum immunoglobulin E were found, as compared to the control group of healthy individuals. Changes of IgE serum concentration on the 1st day, 7th day, 14th day and 40th day after AMI did not reveal any significant differences. Males with AMI turned out to have significantly higher immunoglobulin concentrations than females.*

Conclusion: *The observed higher serum IgE concentration in patients with IHD may serve as evidence contribution to atherogenesis and myocardial ischemia.* (Cardiol J 2008; 15: 122–128)

Key words: immunoglobulin E, ischemic heart disease, allergy, atherogenesis

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Introduction

In recent years, increased levels of serum immunoglobulin E (IgE) in patients with cardiovascular diseases have been generating more and more interest [1–8].

The mainstream discussion touches upon the basic problem of the etiopathogenesis of this phenomenon. So far, it has not been discovered whether the increased IgE concentration is a marker of the contribution of the immune mechanism to the development of the atherothrombotic process, thus being a risk factor of ischemic heart disease (IHD), or whether it is only indicative of the participation of the antibodies in the inflammatory reaction to tissue damage.

The results of the study by Criqui et al. [1], carried out on a group of 262 men and 315 women aged 38–82, suggest a causative role of IgE in cardiovascular diseases. The study revealed a statistically significant positive correlation between increased serum IgE levels in males and previous myocardial infarction, stroke and peripheral arterial disease ($p < 0.05$), irrespective of total cholesterol and LDL levels. The relation was stronger than the influence of other risk factors, taking into account the total cholesterol and LDL levels, the number of cigarettes smoked a day, diastolic blood pressure, fasting blood glucose level and age.

Other researchers paid attention to immunoglobulin E as a harbinger of acute myocardial infarction, but at the same time to the protective role of increased IgE concentrations against death from acute myocardial infarction (AMI) [4]. Szczeklik et al. [5] found a smaller number of events of sudden cardiac arrest and cardiogenic shock in patients with acute myocardial infarction and baseline IgE levels above 200 kU/L, compared to patients with low initial immunoglobulin concentrations. In the group with AMI and previous angina pectoris symptoms observed by Tokac et al. [9], high IgE concentrations related to a smaller number of complications such as heart failure and life-threatening arrhythmias. In patients with high IgE concentrations and atopy, elevated serum levels of endogenous heparin [10], delayed thrombin generation [11], shortened platelet survival [12, 13], prolonged bleeding [11, 14] and impaired platelet aggregation were found [15].

The aim of the study was to evaluate IgE serum concentrations in patients with different forms of IHD, compared to healthy humans. Additionally, we evaluated the dynamics of changes in IgE concentrations in patients after AMI.

Methods

The study included 195 patients with IHD: 80 patients with acute myocardial infarction, aged 55 ± 9 years on average, 58 patients with troponin-negative acute coronary syndrome (ACS), aged 56 ± 8 years on average and 57 patients with stable angina, aged 54 ± 8 years on average, without cardiac arrest or cardiogenic shock before admission to hospital, without concomitant chronic diseases and with a negative personal and family history of allergy. The inclusion criteria for the stable angina group were: documented previous myocardial infarction, or either coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA) procedure performed at least one year before inclusion in the study. The control group included 39 healthy individuals, aged 53.5 ± ± 8.0 years on average. All study participants gave their informed consent.

Blood was sampled from all ACS patients immediately after admission to hospital and before essential treatment. The first dose of oral aspirin (325 mg) was given within the confines of first aid. Some patients required administration of sublingual glyceryl trinitrate or intravenous morphine. Fasting blood samples were taken from the stable angina pectoris group and from the control group in the morning (between 7 and 9 a.m.), after 30-minute rest, in supine position.

Serum IgE concentration measurement was carried out with a Uni-cap Total IgE kit, using the FEIA technique, in accordance with WHO standards. The test sensitivity was 89%, and specificity 95%. No physiological cross-reactivity with immunoglobulins in A, D, M or G class was observed.

In all evaluated patients, apart from determining the total concentration of immunoglobulin E, we tested immediate skin reaction to selected most-frequent external allergens in order to exclude atopy, irrespective of negative personal and family history of allergy.

Time elapsing since the onset of pain until admission to hospital did not exceed six hours on average.

The statistical analysis was performed with the use of StatSoft® Statistica 6.0 for Windows.

The Regional Ethics Committee of the Medical University in Bydgoszcz gave its assent to the study.

Results

The initial characteristics of the study group are presented in Table 1.

Figure 1 shows the comparison of the distribution of total IgE concentration in AMI patients

Table 1. Distribution of selected ischemic heart disease risk factors in the study group.

Risk factor	Myocardial infarction (n = 80)	Unstable angina (n = 58)	Stable angina (n = 57)
Current smokers	50 (62.5%)	15 (25.9%)	12 (21.1%)
Past smokers	20 (25.0%)	25 (43.1%)	36 (63.1%)
Hypertension	28 (35.0%)	29 (50.0%)	17 (29.8%)
Total cholesterol > 200	56 (70.0%)	42 (72.4%)	37 (64.9%)
Triglycerides > 200	14 (17.5%)	15 (25.9%)	6 (10.5%)
Body mass index > 30	17 (21.3%)	16 (27.6%)	12 (21.05%)
Family history of myocardial infarction < 65 years	25 (31.3%)	17 (29.3%)	25 (43.8%)

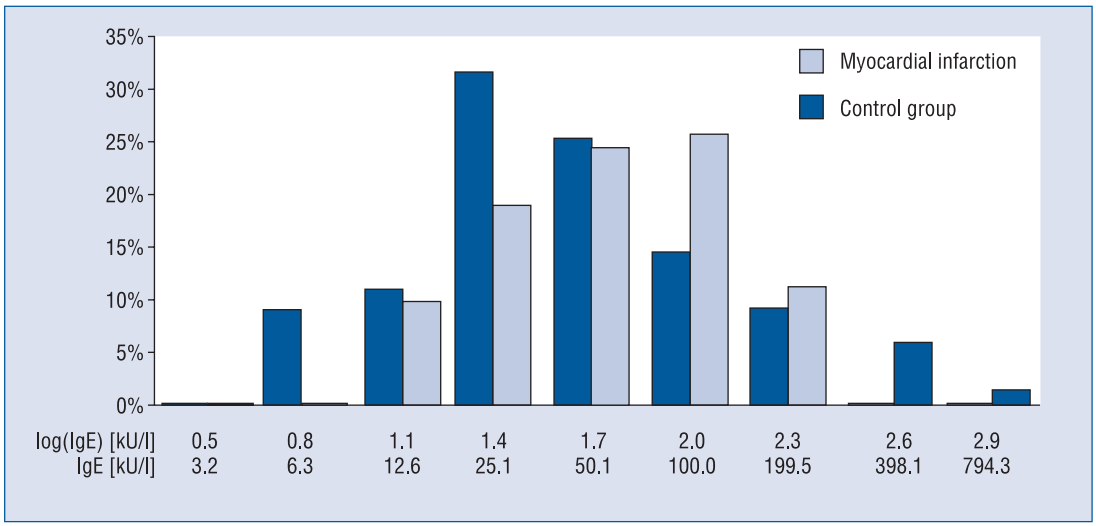

Figure 1. Distribution of total IgE levels expressed in logarithmic units in acute myocardial infarction patients compared to the control group.

with the control group. IgE distribution in AMI patients is clearly shifted towards higher values. At the same time, a sharp reduction of high IgE values in the control group was found. Mean values of serum IgE concentrations, both in AMI patients and in the evaluated patients with IHD, turned out to be significantly higher, compared to the mean concentration in the control group ($p < 0.05$).

Table 2 presents collective data of mean values and ranges of IgE concentrations in the evaluated groups. The table suggests that mean IgE values in patients with AMI, troponin-negative ACS or stable angina were significantly higher than in the control group. The upper limit of normal concentrations was defined as mean IgE concentration in the control group 36.73 + 2 standard deviations, i.e. 102.59 kU/L. Mean IgE concentration in AMI patients was higher comparing to both troponin--negative ACS and stable angina patients, but it did not reach statistical significance. It must be underlined, however, that the majority of the stable angina group were patients with previous myocardial infarction in anamnesis (79%), whereas in the ACS and stable angina group *en bloc*, previous MI patients accounted for 54%.

Figure 2 shows the dynamics of mean IgE concentrations in the course of AMI. The mean IgE concentrations measured at the 7th, 14th and 40th days after the infarction did not reveal any statistically significant difference compared to the baseline concentration.

Observations of the dynamics of mean IgE concentrations in AMI patients with initial serum IgE concentration below and above 100 kU/L did not reveal statistical significance of increments of IgE values determined at the 7th, 14th and 40th days. The number and proportion of patients with IgE level above 100, 150 and 200 kU/L on days 7, 14 and

Table 2. Mean values and ranges of IgE concentrations in studied groups.

	Acute MI (n = 80)	Troponin negative ACS (n = 58)	Stable AP (n = 57)	Control group (n = 39)
Arithmetic mean [kU/L]	77.18	56.07	53.88	36.73
Standard deviation	117.52	53.68	52.86	32.93
Geometric mean [kU/L]	40.04*	35.86*	35.86*	24.90
Confidence interval 95%	31.37–51.11	27.55–46.69	29.50–46.30	18.21–34.05
Minimal value [kU/L]	6.5	2.3	5.5	4.2
Maximal value [kU/L]	775.2	250.2	230.0	117.3
p*	0.05	NS	0.05	–

*p for log(IgE) compared to control group; MI — myocardial infarction; ACS — acute coronary syndrome; AP — angina pectoris

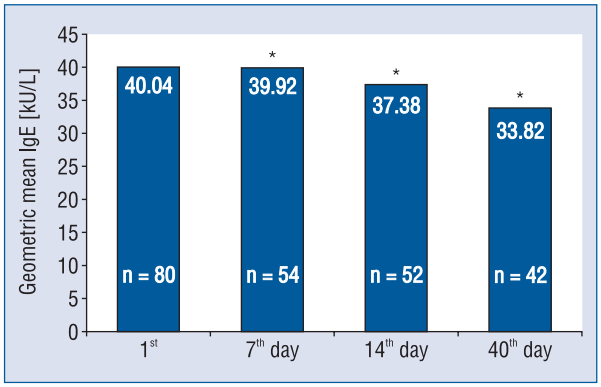

Figure 2. Dynamics of mean IgE values in acute myocardial infarction patients; *p = NS for log(IgE) in comparison to the baseline.

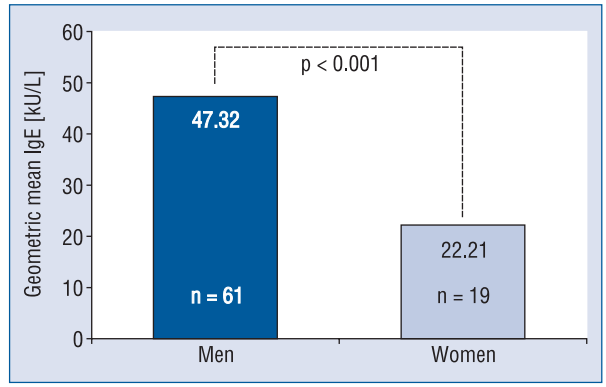

Figure 3. Mean initial serum IgE concentration in males and females with acute myocardial infarction.

40 after the infarction did not differ significantly in comparison to the proportions in the baseline determination.

The comparison of the distribution of total IgE concentrations in AMI men, when compared to AMI women, revealed differences in the highest IgE values in both studied groups. Figure 3 shows that the mean initial serum IgE concentration in men with AMI was significantly higher than in women ($p < 0.001$).

Discussion

Undoubtedly, ischemic heart disease has a complex and multifactorial etiology. Although it seems that nowadays the main risk factors have been thoroughly explored, it is estimated that in many cases of MI patients the main predisposing factor has not been successfully diagnosed.

Numerous researchers have highlighted the potential importance of immunoglobulin E which was reported to protect patients against sudden death in the course of AMI [4, 11, 16]. At the same time, increased or lowered levels of other immunoglobulins were more-often associated with an adverse course of the disease [17, 18]. Explaining the role of IgE in the pathomechanism of coronary artery disease is by no means easy because the biological importance of the immunoglobulin has not been fully explained.

Healthy and non-atopic individuals were found to have low total IgE concentrations, ranging from 0.4 to 80 kU/L, which amounts to 0.001% of all immunoglobulin concentration [19]. This is related to the short half-life of the antibodies and their affinity to Fc-binding sites on mast cells and basophils. Receptor-bound IgE can remain in tissue for about 30 days, which may explain the cause of its low serum concentration in some patients.

IgE levels in healthy people are fairly stable; in clinical observations, no individual changes in the concentration were found throughout the period from 6 months to over 5 years. The lowest levels are reported in the population below 70 years of age [20];

higher values are observed in males than in females [20, 21].

Uniform reference ranges have not been set and they may vary considerably from population to population. Burney's observations within the European Community Respiratory Health Survey, which analyses the distribution of total and allergen-specific IgE antibodies in Europe, revealed diversified patterns of IgE distribution in different countries [22].

A high occurrence of atopy results in difficulties when evaluating the postulated reactions between higher IgE concentrations in serum and the course of acute myocardial infarction. Obviously, high IgE levels in AMI patients may reflect atopy, and bear no relation to the atheromatic process in coronary arteries. It is noticeable that in the majority of published studies on IgE levels in patients with myocardial ischemia, some of the evaluated patients had allergy in anamnesis, and allergy may have been partially responsible for the increased IgE levels both in the studied and control groups [3, 5].

One of the most important issues of the present study was to answer the following question: is serum IgE concentration in patients with various forms of ischemic heart disease different from that found in healthy humans?

In the studied groups, serum IgE concentrations turned out to be highest in AMI patients, and significantly different from the control group, which was in accordance with studies by other authors. However, no significant difference was reported between AMI patients, patients with troponin-negative ACS, and the stable angina pectoris group consisting of patients with previous MI (79%) and those who underwent CABG and PTCA procedures (21%). Similarly, in the control group mean IgE concentration appeared to be significantly lower than in both ACS and stable angina pectoris patients. Similar differences in patients with ischemic heart disease as compared to the control group were observed by other authors [6, 7].

Mean IgE values turned out to be close or lower to those reported by other authors, both in studied groups and in the control group [2, 3, 5]. The rationale behind this fact, among other things, is that our study enrolled only patients with negative allergic anamnesis and did not include people with concomitant chronic diseases or those resuscitated before admission to hospital, having taken into account the fact that those factors might influence the results.

Mean baseline serum IgE concentration in AMI males was distinctly higher than in females ($p < 0.001$), which was confirmed by comparing the distribution of total IgE concentrations in males and females with AMI. The results we obtained are compliant with observations of other authors who found, based on population studies, similarly higher IgE concentrations in males than in females [20, 21].

Criqui et al. [1] claim that the increased serum IgE level in males is related to a higher incidence of cardiovascular diseases. A similar dependence was not found in females, for whom age proved to be the only independent risk factor. Women were reported to have lower IgE levels and a lower incidence of cardiovascular diseases. Mean IgE concentrations in a group of patients studied by Korkmaz et al. [3] were significantly higher in patients with IHD, both male and female.

The results of the research by Langer et al. [4] turned out to be extremely interesting; the prospective observation of 621 patients throughout an average period of about nine years revealed a significant relation between the increased serum IgE level and the incidence of AMI in males. IgE concentrations above 200 kU/L were closely related to a seven-times-higher incidence of non-fatal AMI in patients without preceding coronary incidents in anamnesis. Smoking, irrespective of its influence on IgE concentration, did not weaken the direct relation between IgE level and infarction. The authors claim that higher IgE serum concentration may be an AMI marker, and that the relation is independent of allergy. They did not report a higher occurrence of ACS in patients with positive anamnesis for allergy. The lack of such a relation for women is explained by a smaller number of females participating in the study and by the lower IgE concentrations which they displayed [4].

A vitally important aspect of the evaluation of the role that IgE plays in AMI is answering the question of whether elevated IgE levels may be indicative of the immunoglobulin participation in the atherogenesis, or if the IgE concentration increasing in the course of infarction might be an indication of the inflammatory reaction to tissue damage. Based on the observations made so far, it can be speculated that IgE may play a twofold role; however, the problem has not been fully explained and requires more insight.

Szczeklik et al. [16] observed, in AMI patients, an increase in serum IgE concentration starting from day three after the infarction, a maximal increase on day seven, and then a slow decline until the end of week three. In patients with baseline IgE levels exceeding 200 kU/L, they found a more pronounced and long-lasting increase of the antibodies, and, of great importance, a lower incidence of sudden cardiac arrest and cardiogenic shock, compared

to patients with low initial IgE levels. A similar rise of IgE concentrations was reported by Erdogan et al. [7]. The researchers claim that the observed increase of IgE in the course of infarction is indicative of an inflammatory reaction similar to changes of acute phase proteins since a similar reaction of IgE was noticed in patients after surgery or coronary stenting [23, 24].

In our study we did not observe dynamic changes in IgE concentrations in patients with initial levels below 100 kU/L or above 100 kU/L. We did not find a significant rise in the rate of IgE concentrations above 100 kU/L, 150 kU/L and 200 kU/L on the 7th, 14th and 40th days after infarction. Similarly to our previous studies, IgE levels measured in AMI patients on days 7, 14 and 40 did not reveal any statistical difference from the baseline concentration [25].

The increase in IgE concentration in the course of AMI was not confirmed by other researchers. Büyükberber et al. did not find any significant differences between mean IgE concentrations measured at 6 and 12 hours, and on the 4th and 8th days after AMI [26]. Korkmaz et al., who observed only minute changes of IgE after AMI, arrive at the conclusion that IgE is not a response to the disease. Remaining closely related to other risk factors, it might play a causative role in the pathomechanism of ischemic heart disease, both for males and females [3].

Conclusions

1. Ischemic heart disease patients without atopy revealed higher concentrations of serum immunoglobulin E in comparison to the control group of healthy individuals.
2. Serial measurements of immunoglobulin E concentrations after acute myocardial infarction did not reveal any significant changes.
3. Males with acute myocardial infarction proved to have significantly higher levels of immunoglobulin E in comparison to females.
4. The observed higher levels of immunoglobulin E in patients with ischemic heart disease may serve as evidence that the immunoglobulin takes part in the atherogenesis and in ischemic heart disease development.

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