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THE FEATURES OF AUTOIMMUNITY IN COMPLICATED ATHEROSCLEROSIS: A PILOT STUDY

Poletaeva A.A.[1], Pukhalenko A.I.[1], Ryabkova V.A.[2,3], Sobolevskaia P.A.[2], Vasil'eva M.A.[4], Koshkina I.A.[5], Zakharova L.B.[2], Korovin A.E.[2,6], Gurevich V.S.[2,4], Churilov L.P.[2,7]*

[1]Clinical and Diagnostic Laboratory "Biomarker", Moscow, Russia
[2]St. Petersburg State University, St. Petersburg, Russia.
[3]Pavlov First St. Petersburg State Medical University, St. Petersburg, Russia
[4]L.G. Sokolov North-West Regional Scientific Clinical Center, St. Petersburg, Russia
[5]Medical Center LLC "Doctor Koshkina", Moscow, Russia
[6]S.M. Kirov Military Medical Academy, St. Petersburg, Russia
[7]St. Petersburg Research Institute of Phthisiopulmonology, St. Petersburg, Russia

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Abstract

Background: *There is increasing evidence that autoimmunity plays an essential role in atherogenesis. At the same time, changes in the profile of natural autoantibodies (AAb) are characteristic not only of autoimmune, but also of all somatic diseases in general, since AAb can, without being the cause of the disease, respond to illness-related changes being a kind of bioregulators of homeostasis and/or immunological clearance factors.*

Methods: *The enzyme immunoassays ELI-Cardio-Test was used to determine changes in serum content of a 12 natural AAb towards the autoantigens, which are the markers of pathological changes in myocardium and blood vessel walls, in 5 patients with diagnosis of severe complicated atherosclerosis and 5 healthy individuals.*

Results: *patients with atherosclerosis were characterized by significantly more frequent and pronounced deviations in the autoimmunoreactivity against platelet membrane antigen (TrM) than healthy controls. The level of other natural AAb did not differ between study groups.*

Conclusions: *It is not possible to distinguish between individuals without atherosclerosis and those with severe atherosclerosis, based on the overall picture of the autoimmune profile for manufacturer-selected antigens. However, the obvious discordance of groups in terms of autoimmunoreactivity to TrM merits further study. Perhaps, it is worth for a manufacturer to modify the set of autoantigens in this panel and focus more on the autoimmunity against platelet antigens as well as add the appropriate information about anti-TrM autoimmunity to the kit leaflet.*

Keywords: *atherosclerosis, autoimmunity, natural autoantibodies, platelets.*

Introduction

Atherogenesis has been considered for many years as an example of chronic productive inflammation of the arteries caused by atherogenic lipoproteins, and, despite the systemic nature of lipid metabolism disorders and the general effect of a number of its other risk factors, the atheromas *per*

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Address for Correspondence:
Leonid P. Churilov, MD, PhD
St. Petersburg State University,
7-9 Universitetskaya Emb, 199034, St. Petersburg, Russia
Tel.: (+7) 9043363017
E-mail: elpach@mail.ru

se are just local foci of a peculiar arteritis. Since the immune system is an indispensable participant in any chronic inflammation, the formation and strengthening of the immunopathological and, in particular, autoimmune concept of atherogenesis is quite understandable [*Pirillo A., et al, 2018*]. More than half a century ago, a French group showed for the first time that in lupus nephritis autoantibodies (AAb) from the blood sera of patients were able to block lipoprotein lipase and cause hyperlipoproteinemia thus accelerating atherogenesis [*Beaumont J.L. et al., 1967*]. In the USSR, from the very beginning of the 1970s, several teams repeatedly demonstrated autoimmune phenomena during experimental and clinical atherosclerosis [*Khodzhaev A.Kh., Mirochnik L.M., 1971; Golod I.S., Ponizovskaia E.V., 1972; Klimov A.N. et al., 1988*]. The existence of antibodies to cholesterol and lipoproteins in blood sera, including those obtained from clinically healthy individuals, was discovered as early as the 1980s [*Alving CR, Swartz GM Jr., 1991*]. But the significance of such AAb could be regarded in the context of atherogenesis equivocally: both as sanogenic (prevention of antigen penetration into the vascular wall) and as pathogenic one (eliciting immune complex vasculitis). The outstanding Hungarian pathophysiologist Šandor Gerő (1904-1992) was the first experimenter who tried to vaccinate rabbits against atherosclerosis with the β-lipoproteins and showed the sings of experimental cholesterol-induced atherogenesis inhibition after that [*Gerő S. et al., 1959*]. But later some contradictory data accumulated, and it turned out that immunization with lipoproteins can also produce pro-atherogenic effects [*Horvath I. et al., 1998*]. The Hungarian researchers used to reveal immune complexes containing low-density lipoproteins (LDL) and, less often, also high-density lipoproteins (HDL) in the blood sera and ateromas of patients with coronary heart disease (CHD), as well as the signs of increased cell-mediated autoimmunity against LDL in patients with CHD, but not in healthy donors [*Szondy E. et al., 1983*]. The acceleration of atherogenesis by immunization with the lipoproteins was achieved. The induction of the foam cell formation common in atheromas by immune complexes with the participation of LDL during their unregulated uptake by macrophages was demonstrated. Thus the existence of antilipoprotein autoimmunity impact on atherogenesis became clear [*Klimov A.N. et al., 1985*].

Seemingly contradictory data on the sanogenicity or, on the contrary, pathogenicity of anti-lipoprotein autoimmunity began to acquire harmony when it was found that antibodies directed against some neoantigens — modified, primarily oxidized and glycated LDL and very low density lipoproteins (VLDL) — dysplay obvious pro-atherogenic potential [*Virella G., Lopes-Virella M.F., 2003*]. An autoimmune concept of atherogenesis has been formed, closely linked to the etiological role of its infectious triggers. The very hypothesis of the autoimmune nature of atherosclerosis was first formulated in detail in 1991 [*Clerc G., 1991*]. In the second half of the 1990s, Georg Wick and Qingbo Xu developed a general concept of atherosclerosis as an autoimmune disease, not excluding its early stages [Wick G., Xu Q., 1999]. They pointed out that one of the prerequisites for that is the widespread antigenic mimicry between the proteins of common pathogenic microorganisms or opportunistic pathogens present in the human microbiota (for example, *Helicobacter pylori*) and autoantigens of arterial wall, in particular, those evolutionarily conserved, like heat shock proteins expressed by damaged cells. Soon, decisive evidence of the immune system involvement in atherogenesis was obtained: athymic mice with total T-cell immunodeficiency, despite experimentally induced severe hyperlipidemia, did not develop atherosclerosis [*Emeson E.E. et al., 1996*]. This approach brought together the immunopathological and infectious concepts of atherogenesis. Indeed, according to the well-known principle of presumption, proclaimed by Y. Shoenfeld and N.R. Rose "Everything is autoimmune and infectious until proven otherwise" [*Shoenfeld Y. et al., 2015*].

Adaptive immunity, both humoral and cellular, is an important participant in atherogenesis from its first to the last stages. Due to the production of inflammatory mediators, even at an early stage, the focus of atherogenesis becomes a zone where antigen-presenting cells and lymphocytes, attracted there by chemokines, express increased amounts of co-stimulatory molecules during their interactions. This phenomenon, in accordance with the danger hypothesis by P. Matzinger, prolongs the

existence of immunosynapses and thereby enhances the response to self antigens and neoantigens located in the ateroma, to a pathological degree of intensity [*Gallucci S, Matzinger P., 2001*]. Unlike many classical monotargeted autoimmune diseases, atherosclerosis, according to current data, involves AAb and autoreactive lymphocytes hitting several autoantigens. These are antigens that mimic microbial ones and/or belong to proteins involved in lipid metabolism and hemostasis. The role of AAb to heat shock proteins HSP65 and HSP60 in atherogenesis has been postulated, as well as antibodies to oxidized LDL (oxLDL), to minor lipoprotein Lp(a), and to prothrombin (PT). There are also strong witnesses for the participation of AAb to β2-glycoprotein I (β2GPI) in atherogenesis [Shoenfeld Y., 2000; Shoenfeld Y. et al., 2000, 2001a, 2001b]. Finally, an atherogenesis acceleration in LDL-receptor deficient mice based on their passive immunization by adoptive transfer of β2GPI-specific T-lymphocytes was created [*George J. et al., 2000*]. It is known that the β2GPI autoantigen serves as a central target in the pathogenesis of the antiphospholipid syndrome, with its impaired hemostasis [*Sheng Y. et al., 1998*]. Therefore, it can be assumed that atherosclerotic autoimmunity can be especially important for the formation of thrombotic complications of atheromas. There are also epidemiological data on an increased risk of cardiovascular diseases in the presence of high titers of AAb to tissue debris antigens such as cardiolipin and citrulline-containing vimentin [*Iseme R.A. et al., 2017*].

At the same time, the above list of potential targets of the autoimmune response in atherosclerosis and in its complications cannot be considered complete: it may include other autoantigens expressed by the heart, blood vessels or those marking atherosclerosis complications, for example, aneurysms (glycoprotein AAAP-40), myocardial diseases (cardiac troponin, etc.) or sudden cardiac death (adrenergic receptors, ion channels etc.) [*Xia S. et al., 1996; Ryabkova V.A. et al., 2019*]. Due to existence of physiological regulatory autoimmunity and natural functional AAb, *per se* the detection of AAb to a given self antigen cannot be perceived as a synonym for the presence of an autoimmune disease [*Pashnina I.A. et al., 2020*]. What matters is the degree of autoimmunity, as well as the ratio of its various «spectral lines» in overall profile of autoimmune reactivity. On the other hand, changes in this profile are characteristic not only of autoimmune, but also of all somatic diseases in general, since AAb can, without being the cause of the disease, respond to illness-related changes being a kind of bioregulators of homeostasis and/or immunological clearance factors [*Poletaev A.B., Churilov L.P., 2022*].

One of the ways to assess changes in the autoimmune profile is a set of methods of the ELI-Test group (an abbreviation for Enzyme-Linked-Immuno-Test); a type of non-competitive enzyme immunoassay). The method is based on assessing the degree of binding of the patient's serum to a panel of antigens immobilized on a solid carrier, against a pool of sera from 5000 healthy donors serving as a reference for comparison.

All methods of the ELI-Test group are based on the analysis of the profiles of the serum immunoreactivity of the individual and the detection of immunoreactivity positive either negative peaks, abnormal in comparison with the average individual content of AAb [*Poletaev A.B., Rizzo C., 2019]*. One of diagnostic kits of this group is ELI-Cardiotest assessing the spectrum and intensity of autoimmune reactivity against 12 antigens expressed in cardiovascular system *[ELI-Cardiotest instruction, 2022*].

In this pilot study we evaluated the diagnostic possibilities of ELI-Cardiotest double-blindly, using impersonal sera samples from patients with diagnosis of severe complicated atherosclerosis confirmed in the hospital and from healthy individuals, who successfully underwent the profound clinical health check.

Material and Methods

We defined individual normalized levels of AAb against 12 autoantigens, which are the markers of pathological changes in myocardium and blood vessel walls, using standardized ELISA test systems for semi-quantitative serum AAb evaluation (ELI-Cardio-test-24 by Medical Research Center "Immunculus", Moscow, Russia). The antigens used in the test systems are listed in Table 1.

The pooled control serum was a preparation of polyclonal immunoglobulins of the IgG class, synthesized by B-lymphocytes in response to antigenic stimuli that occurred throughout the life of donors.

Table 1.

List of antigens, included in the test systems ELI-Cardio-test.

No	Antigen	Abbreviation
1.	Double stranded deoxyribonucleic acid	DNA
2.	β2-glycoprotein-I	β2-GP
3.	Membrane antigen of cardiomyocytes	Com
4.	Cytoplasmic antigen of cardiomyocytes	Cos
5.	β1-adrenergic receptors of cardiomyocytes	β-Adr-R
6.	Cardiomyosin L	CardioM
7.	Platelet membrane antigen	TrM
8.	Cytoplasmic antigen of neutrophils	ANCA
9.	Nitric oxide synthase	NOS
10.	Plasminogen/angiostatin	Plasm
11.	Pregnancy-associated plasma protein A	PAPP-A
12.	Collagen	Coll

Immunoglobulins in the control serum were obtained from the blood serum of more than 5000 healthy donors, and brought to a concentration close to physiological (16 *mg/mL*). Thus, pooled control serum contained population-normalized IgG class polyclonal antibodies to each of the studied antigens, and was used as a universal standard for all tested antigens. Depending on the studied antigen, the pooled control serum was diluted to a final concentration, which was derived on the basis of studies of the level of AAb of a large cohort of individual serum samples from healthy donors. The content of AAb to the studied antigens was evaluated in the conventional units of optical density, and compared to their content in a control pool of sera from healthy donors (taken for 100%). Then, the average individual immunoreactivity (AIR) of the studied samples for each of the antigens in comparison with the pooled control serum was calculated according to the formula:

$$AIR=\frac{\frac{R(ag1)\times 100}{R(k1)}-100+\frac{R(ag2)\times 100}{R(k2)}-100+\cdots+\frac{R(agN)\times 100}{R(kN)}-100}{12}$$

AIR—the average reactivity of an individual patient's serum to all studied antigens, expressed as a percentage of the average reactivity of the pooled control serum with the same antigens.

R (ag1, 2, N)—reactivity (in units of optical density) of the patient's serum with studied antigens.

R(k1, k2, N)—reactivity (in units of optical density) of the pooled control serum with studied antigens.

The normal (physiological) levels of individual AIR are restricted by the range from −30% to 0% (or conditional units) of the control sample AIR. To construct immunoreactivity profiles, the deviation (as a percentage of the individual AIR) of the patient's serum reactivity with each of the antigens was calculated using specialized software according to the formula:

$$R(dev)agN=\frac{R(agN\times 100}{R(kN)}-100-AIR$$

R(dev)agN—deviation (as a percentage of the AIR) of the patient's serum reactivity with antigen N.

R (agN)—reactivity (in units of optical density) of the patient's serum with studied antigens.

R(kN)—reactivity (in units of optical density) of pooled control serum with studied antigens.

The normal (physiological) R(dev)agN for each AAb is restricted by the range from −15% to +10% (or conditional units) from the individual AIR.

The Mann–Whitney U test was applied to compare mean R(dev)agN values between patients and healthy individuals.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of The Federal State Budgetary Institution 'North-Western District Scientific and Clinical Center Named after L.G. Sokolov Federal Medical and Biological Agency' (protocol code 7 of 08-12-2022). Informed consent was obtained from all subjects involved in the study. All participants were male.

Results and discussion

This pilot study involved 5 patients diagnosed with severe complicated atherosclerosis (accompanied by obesity and diabetes mellitus type II) in the hospital (ASK), and 5 healthy individuals, who successfully underwent the profound clinical health check (HC). The age characteristic of the group was similar. The results of ELI-Cardio-test are shown in Table 2.

In the group of ASC patients, the total number of abnormal AAb levels was 16, and in the group of HC donors it was 15. Individual autoreactivity profile of the patient №1, who had the largest number of the abnormal deviations of the serum reactivity with the studied antigens, is presented in the Figure 1.

Table 2.

Patients' characteristics and the results of ELI-Cardio test. The table shows deviations (as a percentage of the AIR) of the patient's serum reactivity with the studied antigens.

No.	Group	DNA	β2-GP	Com	Cos	β-Adr-R	CardioM	TrM	ANCA	NOS	Plasm	PAPP-A	Coll
1	HC	-24	-21	21	-2	17	4	-7	9	3	-8	-1	15
2	HC	2	13	6	-25	6	-4	-1	-17	48	-10	15	7
3	HC	16	13	-8	-8	0	3	-9	-13	1	0	18	-2
4	HC	-13	-4	4	-26	3	3	-7	-10	4	11	-3	5
5	HC	-1	-11	0	-6	0	-7	1	-9	4	0	3	22
6	ASC	-13	-4	-3	-18	13	3	11	-11	14	4	1	14
7	ASC	-35	-14	2	-1	-14	5	31	-3	4	14	-3	21
8	ASC	-4	-9	7	2	-5	-2	17	-3	55	-5	12	7
9	ASC	1	-5	16	-12	7	-10	12	-9	3	0	0	9
10	ASC	-8	2	4	-15	14	-3	1	-1	-3	4	-2	35

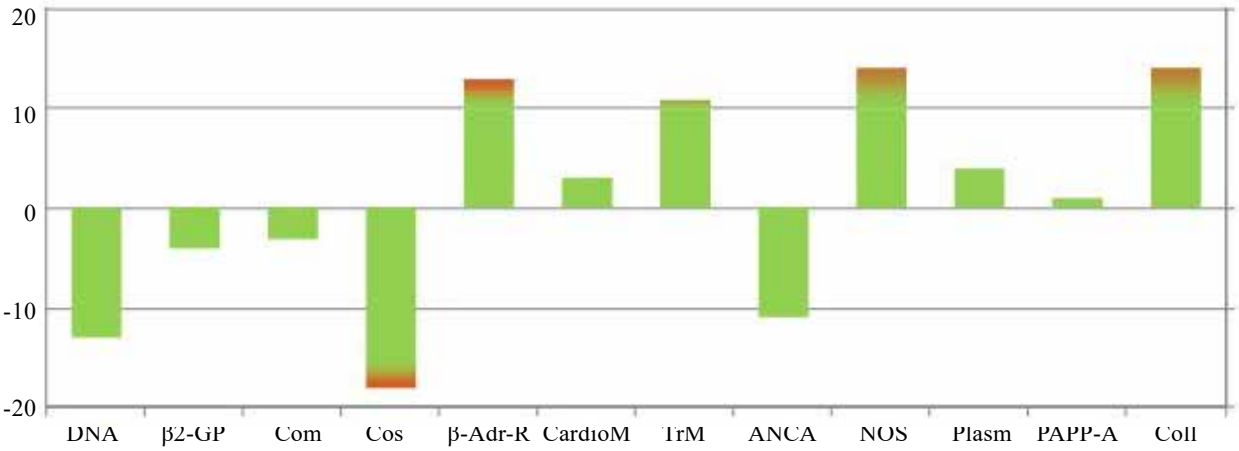

Figure 1. *Individual autoreactivity profile of the patient №1. The bars represent the relative content of the autoantibodies to the studied autoantigens (as a percentage of the average individual immunoreactivity) in the patient's serum*

The greatest discrepancy between the group of healthy people and the group of patients with atherosclerosis was found for the autoimmunoreactivity against platelet membrane antigen (TrM). In 4 out of 5 patients with atherosclerosis, this indicator exceeded the norm (mean level +14.2), but it was not changed in any of the healthy individuals (mean level -5.2). The difference of autoimmunoreactivity against TrM between groups was statistically significant (p value = 0.008).

Contrary to literature-based expectations, autoimmunity profile against autoantigens β2GP-1, PAPP-A and ANCA, which are involved in pathogenesis of atherosclerosis and vasculitis, did not differ between groups. For the AAb to such autoantigens as CardioM, β2-GP, and for ANCA, no abnormalities were observed in the ASC group.

Conclusion

Thus, it is not possible to distinguish between individuals without atherosclerosis and those with severe atherosclerosis, based on the overall picture of the autoimmune profile for manufacturer-selected antigens.

However, the studied method, judging by the obtained results, has a certain diagnostic power in relation to thrombophilic changes, associated with atherosclerosis (the obvious discordance of groups in terms of autoimmunoreactivity to TrM). Perhaps, it is worth for a manufacturer to modify the set of autoantigens in this panel and focus more on the autoimmunity against platelet antigens as well as to add the appropriate information about the significance of anti-TrM autoimmunity to the kit leaflet [4].

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Address for correspondence:

Yerevan State Medical University
2 Koryun Street, Yerevan 0025,
Republic of Armenia

Phones:

(+37410) 582532 YSMU
(+37493 588697 Editor-in-Chief
Fax: (+37410) 582532
E-mail:namj.ysmu@gmail.com, ysmiu@mail.ru
URL:http//www.ysmu.am

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