

Artículo de investigación

Circulating markers of vascular damage as predictors of cardiovascular events in atherosclerosis and metabolic disorders

Циркулирующие маркеры повреждения сосудов как предикторы сердечно-сосудистых событий при атеросклерозе и метаболических нарушениях

Recibido: 6 de agosto del 2019

Aceptado: 10 de septiembre del 2019

Written by:

Tarasov A. A.²⁹**Babaeva A. R.**³⁰**Osadchuk M.A.**³¹**Reshetnikov V. A.**³²**Korzhenkov N. P.**³³**Solodenkova K. S.**³⁴**Trushin M.V.**³⁵**Abstract**

The article presents the results of cluster analysis of the contribution of immune inflammation and endothelial dysfunction (ED) markers to the frequency and severity of cardiovascular events (CVE) in cohorts of patients with asymptomatic atherosclerosis (AAS), coronary artery disease (CAD), type 2 diabetes mellitus (T2DM) and metabolic syndrome (MS) during a 3-year prospective observation.

Results Circulating markers of ED and immune inflammation, such as ET-1, IL-1 β , TNF- α , antibodies to collagen type I and III, and antibodies to chondroitine sulfate (CS) contribute to cardiovascular (CV) manifestation in AAS. In CAD patients ET-1, eNOs, antibodies to collagen, as well as IL-6 and vWf are the main contributors. In T2DM without clinical manifestation of CAD, the set of markers associated with the adverse events includes ET-1, eNOs, IL-6, anti-C, and anti-HA. In CAD combined with T2DM, the cluster of markers associated with the adverse events includes vWf, TNF- α , eNOs, IL-6, anti-C, anti-HA and CRP. In AAS without MS, the key contributors are ET-1

Анотація

В статті представлені результати кластерного аналізу вклада маркерів імунного запалення та ендотеліальної дисфункції (ЕД) в частоту і тяжкість серцево-сосудистих подій в когортах пацієнтів з бессимптомним атеросклерозом (ААС), ішемічної хворобою серця, сахарним діабетом 2 типу (СД 2-го типу) і метаболічним синдромом (МС) в течение 3-літнього проспективного спостереження. Циркулюючі маркери ЕД і імунного запалення, такі як ET-1, IL-1 β , TNF- α , антитіла до колагену I і III типів і антитіла до хондроїтинсульфату (CS) сприяють проявленню серцево-сосудистих захворювань (ССЗ) при ААС. У великих ІБС основними факторами являються ET-1, eNOs, антитіла до колагену, а також IL-6 і vWf. При СД 2-го типу без клінічної манифестації ІБС набір маркерів, асоційованих з побічними явленнями, включає ET-1, eNOs, IL-6, anti-C, і anti-HA. При ІБС в поєднанні з СД2, кластер маркерів, асоційованих з негативними подіями стосуються vWf, TNF- α ,

²⁹ Volgograd State Medical University, 1, Pavshikh Bortsov Sq., Volgograd, 400131, Russia³⁰ Volgograd State Medical University, 1, Pavshikh Bortsov Sq., Volgograd, 400131, Russia³¹ I.M. Sechenov First Moscow State Medical University (Sechenov University), 119991, Moscow, Trubetskaya str., 8, p. 2, Moscow, Russia.³² I.M. Sechenov First Moscow State Medical University (Sechenov University), 119991, Moscow, Trubetskaya str., 8, p. 2, Moscow, Russia.³³ I.M. Sechenov First Moscow State Medical University (Sechenov University), 119991, Moscow, Trubetskaya str., 8, p. 2, Moscow, Russia.³⁴ I.M. Sechenov First Moscow State Medical University (Sechenov University), 119991, Moscow, Trubetskaya str., 8, p. 2, Moscow, Russia.³⁵ Kazan Federal University, Kremlyovskaya str. 18, 420008 Kazan, Russia

and vWf, and the presence of anti-C and anti-ChS; in AAS/MS patients, the key markers are IL-1 β , TNF- α , anti-C, anti-ChS, anti-HA, and CRP. In CAD without MS, the cluster of markers associated with adverse events includes ET-1, eNOs and anti-HA; in CAD/MS it includes anti-C, ET-1, and IL-6.

Conclusion. The obtained results confirm the role of systemic inflammation in the development of atherosclerosis-associated angiopathy in coronary pathology and disorders of carbohydrate metabolism, and also suggest a set of circulating markers as predictors of adverse CVE.

Keywords: Endothelial dysfunction, immune inflammation, cytokines, autoantibodies, atherosclerosis, ischemic heart disease, coronary artery disease, diabetes mellitus, metabolic syndrome.

Introduction

Atherosclerosis and CAD are some of the major global health problems today with highly unfavorable contribution to demographic indicators [Russian Statistical Yearbook, 2017]. The prevalence of atherosclerosis-associated diseases is increasing, although the death rate from CAD has significantly decreased in recent decades due to introduction of modern algorithms for early diagnosis and effective treatment [Russian Statistical Yearbook, 2017]. Another serious medical and social problem is diabetes mellitus (DM), which leads to vascular complications resulting in reduced quality of life and increased mortality. In particular, atherosclerotic angiopathies (first of all, CAD, myocardial infarction, chronic heart failure, and cerebral stroke) account for up to 80% of adverse outcomes in patients with T2DM [Algorithms..., 2017; de Rooij et al., 2009]. However, the early detection of AAS for assessment of cardiovascular risks (CVR) and effective prevention of cardiovascular events (CVE) presents serious difficulties [Boytsov et al., 2012; Kaptoge et al., 2014; Tarasov et al., 2017]. For example, the results of numerous studies indicate that the SCORE system, used to assess cardiovascular risks in a population, is not sufficiently informative; in particular, it does not reflect the presence of AAS which is typically

eNOs, IL-6, anti-C, anti-HA и CRP. При AAC без MC ключевыми факторами являются ET-1 и vWf, а также наличие anti-C и anti-ChS; у пациентов с AAC/MC ключевыми маркерами являются IL-1 β , TNF- α , anti-C, anti-ChS, anti-HA и CRP. При ИБС без MC кластер маркеров, ассоциированных с неблагоприятными явлениями, включает ET-1, eNOs и anti-HA; при ИБС/MC он включает anti-C, ET-1 и IL-6.

Полученные результаты подтверждают роль системного воспаления в развитии атеросклероз-ассоциированной ангиопатии при коронарной патологии и нарушениях углеводного обмена, а также предполагают набор циркулирующих маркеров в качестве предикторов неблагоприятных сердечно-сосудистых событий.

Ключевые слова: эндотелиальная дисфункция, иммунное воспаление, цитокины, аутоантитела, атеросклероз, ишемическая болезнь сердца, болезнь коронарной артерии, сахарный диабет, метаболический синдром.

associated with high or very high CVR [Kaptoge et al., 2014; Svistunov et al., 2018].

At present, the link between atherogenesis and endothelial dysfunction (ED) has been well established. In development of atherosclerosis, a low-intensity systemic inflammation plays an important role [Libby and Crea, 2010; Tarasov et al., 2016, 2017]. In this regard, such diagnostic and prognostic aspects of key mechanisms as endogenous risk factors for CAD and metabolic disorders are being actively studied. In our previous studies, it has been found that atherosclerosis-associated vascular lesions are characterized by overexpression of circulating markers of ED, pro-inflammatory cytokines and antibodies to the connective tissue components of the vascular wall [de Rooij et al., 2009; Svistunov et al., 2018]. The degree of increase in the level of the studied parameters depends on the severity of the clinical form of CAD, the presence of macrovascular complications in T2DM, as well as on the combination of these diseases. At the same time, AAS is also characterized by the presence of the above mentioned specific biomarkers, which suggests the possibility of using them for improved diagnostics of diseases associated with atherosclerosis and CV complications.

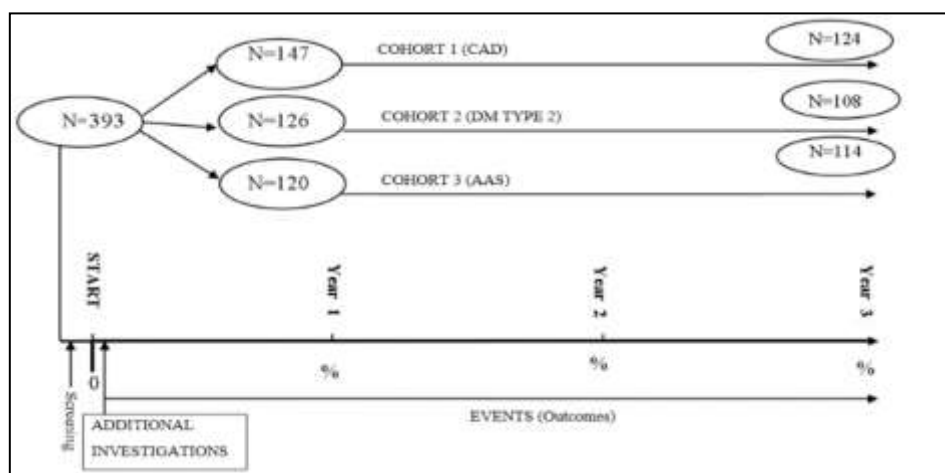
In light of these previous findings, the objective of this study is to comprehensively assess the role of cytokine imbalance and antibody production to the components of the connective tissue in the development of CVE in AAS, CAD and T2DM patients in the absence and in the presence of metabolic disorders.

Materials and methods

A total of 393 patients divided into three groups participated in the study (Fig. 1). The first group

consisted of 147 persons with clinical and/or instrumental signs of CAD. The second group included 126 persons suffering from T2DM. The third group included 120 AAS patients without clinical and instrumental signs of CAD and T2DM; they were diagnosed with AAS based on the results of instrumental studies that were additionally carried out during the screening process. People with symptomatic atherosclerotic lesions of other vascular pools, except the coronary one, were not included in the group of patients with CAD and T2DM.

Figure 1. The study design.



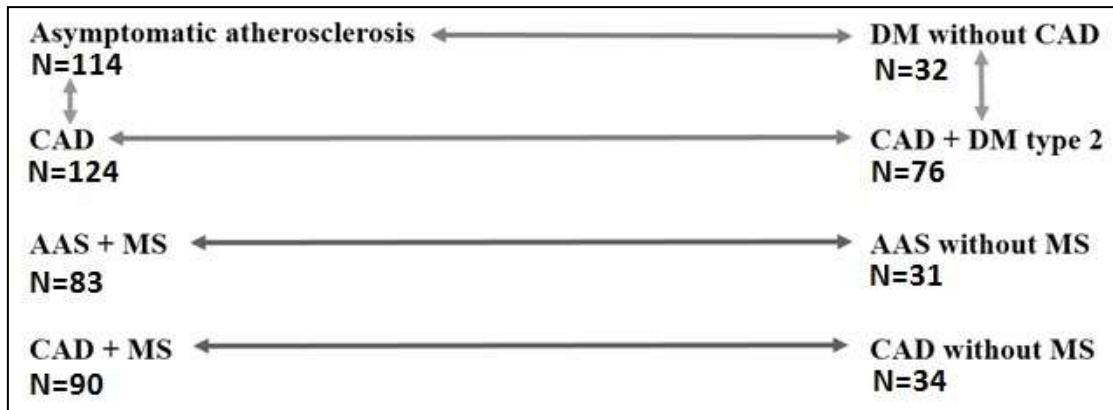
Throughout the entire observation period, patients with CAD and T2DM received a standard therapy according to the current national and international guidelines. Non-pharmacological and medical (statins) prophylaxis of CAD was performed for individuals with AAS. We initially determined the basal levels of soluble ED markers (von Willebrand factor (vWf), endothelin 1 (ET-1), endogenous NO synthase (eNOs)), auto-antibodies (antibodies to hyaluronic acid (a-HA), chondroitin sulfate (a-ChS), collagen (a-Coll)), and indicators of pro-inflammatory cytokine panel (tumor necrosis factor- α (TNF- α), interleukin 1 and 6 (IL -1, IL-6)), using an enzyme immunoassay. After 3 years, 124 people from the CAD group, 108 patients with T2DM and 114 people with AAS completed the study. To assess the pathogenetic differences regarding the effect of ED markers and immune inflammation molecules on the progression of CVD, we identified 8 cohorts for comparative analysis (Fig. 2).

To assess the role of the studied markers in the development and progression of atherosclerotic angiopathy, 2 cohorts were formed: cohort 1 included individuals with established AAS, and cohort 2 included patients with CAD. To assess the relationships between the studied markers and the atherosclerosis stage (preclinical or clinical), regardless of the presence of carbohydrate metabolism disorders, we examined cohort 3, which included patients with T2DM and AAS, and cohort 4 which consisted of patients with CAD and T2DM. To clarify the relationship of metabolic disorders and insulin resistance with the development of CVD and to analyze the role of the studied markers in this process, cohorts 5-8 were formed: cohort 5 included the patients from AAS group in combination with MS; cohort 6 – the group of patients with AAS but without MS; cohort 7 included patients with CAD in combination with MS; cohort 8 consisted of persons with CAD without MS. For a more objective assessment of pathogenic features of ED and immune inflammation in the presence of chronic hyperglycemia, it was important to conduct two

additional pairwise comparative analyses. Specifically, we compared cohort 3 (patients with T2DM without CAD) and cohort 1 (persons with AAS without T2DM); and, finally, we compared

cohort 4 (patients with CAD in combination with T2DM) and cohort 2 (patients with CAD without T2DM).

Figure 2. Cohorts of patients formed to assess the role of the studied markers in the development and progression of CAD, T2DM and AAS with and without MS.



For cluster analysis, we used the following laboratory parameters as independent variables (predictors): pro-inflammatory cytokines, markers of ED, autoantibodies, high-sensitivity C-reactive protein (hs-CRP), and an indicator of endothelial function, determined by photoplethysmometric method (EFI-EF Index). We analyzed the clinical outcomes for patients over a three-year period of prospective observation as dependent variables, which were set as semi-continuous score values from 0 to 4 depending on the nature of the complications from negligible to fatal: 0 - no adverse events for 3 years; 1 - manifestation of a chronic form of CAD; 2 - manifestation of acute coronary syndrome (ACS); 3 - death. With multiple endpoints in cluster analysis, we took into account the most adverse event. We used a K-means clustering algorithm with the number of iterations 50; the number of clusters (k) was determined empirically, based on the task to allocate a cluster of people with the highest frequency and severity of unfavorable cardiovascular events during the prospective observation period for the purpose of comparative assessment of the studied markers.

Results and discussion

As a result of the pairwise comparisons in the studied cohorts, we obtained from 2 to 4 clusters, each of which was characterized by a certain profile of the studied biomarkers. The centroids of the mean values of the studied parameters in

clusters of patients from the comparison cohorts are presented in Table 1.

Among the patients with AAS we have distinguished 3 clusters. In terms of the frequency and severity of CVE, cluster 1 and cluster 2 did not have significant differences, while cluster 3 differed significantly from clusters 1 and 2 (more advanced disease). Cluster 3 (Table 1) was characterized by ED (high levels of ET-1, vWf and low levels of eNOS), significant deviations of the cytokine panel (elevated levels of IL-1β and TNF-α) and high levels of antibodies to C I and III types, a-ChS and a-HA. Cluster 3 was also characterized by higher values of hs-CRP and lower values of EFI, although the differences in these indicators between the clusters were insignificant. Among the patients with CAD in the absence of DM, we identified 4 clusters. The greatest frequency and severity of CVE was observed in cluster 1 (Table 1). It was characterized by pronounced ED (high ET-1 and vWf, and minimal concentration of NOs) in combination with moderate hypercytokinemia and increased levels of antibodies to connective tissue antigens.

Among the patients with T2DM without CAD 2 clusters were distinguished, whereas among T2DM/CAD persons, 3 clusters were identified. In T2DM without CAD, a high frequency of CV events was observed in cluster 1. In this cluster (Table 1) we did not find any signs of a true ED (high levels of ET-1 and vWf, and low levels of

eNOS and EFl), systemic inflammatory response with a significant increase in TNF- α and IL-6, as well as more active production of autoantibodies to C I, III types and a-HA. In the cohort of patients with CAD combined with T2DM, 3 clusters were identified. The highest frequency of adverse CVE was observed in cluster 3 (Table 1), which was characterized by higher levels of ET-1, vWf, TNF- α , as well as overexpression of autoantibodies to HA. In patients with AAS in the presence and absence of MS 3 clusters of patients were identified. Among the patients with AAS with MS, the adverse CVE more often developed in cluster 2, which was characterized by pronounced immune-mediated inflammatory changes with the maximal values of all pro-inflammatory cytokines (IL-1 β , TNF- α and IL-6) and autoantibodies (anti-C, anti-CS and anti-HA), with moderate ED by type of activation.

Among the patients with AAS without MS, the adverse CVE more often developed in cluster 3, which was characterized by a higher level of antibodies to all components of the connective tissue, a significant increase in IL-6 and a moderately pronounced ED. Among the CAD/MS patients, 2 clusters were distinguished, while among the patients with CAD in the absence of MS, 3 clusters were identified. In the first case, the highest incidence and severity of adverse CVE occurred in patients in cluster 2 (Table 1), which was characterized by pronounced activation of endothelium with overexpression of ET-1 and vWf. In the same cluster, the marked immune-mediated inflammatory shifts were observed with the increase in all pro-inflammatory cytokines and production of autoantibodies to the components of the connective tissue, primarily to C types I and III.

Table 1. Centroids of average values of the studied parameters in cohorts of patients with AAS and CAD (1 pair), type 2 diabetes with CAD and without CAD (2 pairs), AAS with MS and without MS, and CAD with and without MS.

Centroids for k-means clustering (AAS (no DM))															
Number of clusters: 3															
Total number of training cases: 114															
Cluster	ET-1	vWf	eNOs	IL-1	TNF	IL-6	a-Coll	a-ChS	a-HA	EFl	C RP	Events	Number of cases	Percentage (%)	
1	1.638095	1.725714	280.3095	52.45238	14.64286	9.04762	0.19476	1.37381	1.71738	18.2619	3.3333	0.21428	42	36.84211	
2	0.733902	0.871707	355.0000	76.07303	21.61020	14.70732	0.21829	1.56829	1.73317	18.0243	3.2488	0.34146	41	35.96491	
3	1.258065	1.649032	385.5806	92.77442	23.67742	11.83871	0.2877	2.21935	2.64935	17.7096	3.43548	1.83871	31	27.19298	
Centroids for k-means clustering (CAD (no DM))															
Number of clusters: 4															
Total number of training cases: 124															
Cluster	ET-1	vWf	eNOs	IL-1	TNF	IL-6	a-Coll	a-ChS	a-HA	EFl	C RP	Events	Number of cases	Percentage (%)	
1	4.750000	1.800000	151.4500	10.50000	22.95000	21.85000	0.24150	2.27000	3.03500	0.50000	4.15500	1.50000	20	16.12903	
2	5.956250	1.681000	230.3750	10.25000	19.75000	36.68000	0.40625	2.56250	3.50000	-11.00000	5.16800	0.81250	16	12.90323	

	25	62	00	75		81	75								
	0	5	0	0		25	0								
3	5.62	2.4	259.	94.	23.	27.	0.31	3.00	2.88	-	4.2	0.00			
	352	76	529	64	41	00	411	588	823	0.4	47	000	17	13.70968	
	9	47	4	71	17	00	8	2	5	70	05	0			
		1			6	0				6	9				
4	3.52	1.5	310.	85.	18.	23.	0.20	1.99	2.23	9.5	4.0	0.23			
	112	98	267	49	38	49	380	859	943	77	18	943	71	57.25806	
	7	59	6	30	02	29	3	2	7	5	31	7			
		2			8	6					0				

Centroids for k-means clustering (DM+AAS)

Number of clusters: 2

Total number of training cases: 32

Cluster	ET-1	v Wf	eNOs	IL-1	T NF	IL-6	a-Coll	a-ChS	a-HA	EF I	C RP	Events	Number of cases	Percentage(%)
1	1.62	4.8	175.	18	38.	35.	0.33	1.76	3.35	-	4.5	1.93	16	50.00000
	250	87	312	1.1	31	31	312	875	062	6.2	56	750		
	0	0	5	5	0	0	5	0	5	00	0	0		
2	1.05	4.7	260.	17	35.	25.	0.23	1.85	2.50	2.6	5.2	0.25	16	50.00000
	562	25	875	4.4	81	18	000	625	437	87	68	000		
	5	0	0	5	0	0	0	0	5	50	75	0		

Centroids for k-means clustering (DM+CAD)

Number of clusters: 3

Total number of training cases: 76

Cluster	ET-1	v Wf	eNOs	IL-1	T NF	IL-6	a-Coll	a-Chs	a-HA	EF I	C RP	Events	Number of cases	Percentage(%)
1	2.10	5.3	280.	17	37.	28.	0.27	2.18	2.90	-	4.6	0.00	51	67.10526
	000	33	960	9.8	31	05	098	627	902	2.6	03	000		
	0	3	8	9	3	2	0	5	0	86	92	0		
2	2.06	6.0	72.5	20	30.	39.	0.75	2.75	3.75	-	7.1	0.50	2	2.63158
	000	50	000	9.5	00	50	000	000	000	15.	00	000		
	0	0	0	0	0	0	0	0	0	00	00	0		
3	2.11	6.1	211.	18	35.	34.	0.34	2.28	3.53	-	5.3	1.34	23	30.26316
	695	13	434	0.6	65	13	391	695	347	8.4	30	782		
	7	3	8	7	7	3	3	7	8	3	5	6		

Centroids for k-means clustering (AAS+MS)

Number of clusters: 3

Total number of training cases: 83

Cluster	ET-1	v Wf	eNOs	IL-1	T NF	IL-6	a-Coll	a-ChS	a-HA	EF I	C RP	Events	Number of cases	Percentage(%)
1	0.85	1.1	331.	59.	18.	12.	0.23	1.63	1.88	19.	3.1	0.16	36	43.37349
	222	02	500	44	30	16	972	611	666	50	94	666		
	2	2	0	4	6	7	2	1	7	00	44	7		
2	0.98	1.4	326.	96.	32.	13.	0.34	2.56	2.73	17.	3.4	2.00	16	19.27711
	000	73	250	50	81	56	875	250	125	06	68	000		
	0	5	0	0	0	0	0	0	0	25	75	0		
3	1.91	1.9	365.	79.	14.	11.	0.19	1.47	1.94	16.	3.4	0.74	31	37.34940
	129	21	096	67	29	51	354	096	677	16.	67	193		
	0		8				8	8	4	74	67	5		

Cluster	ET-1	v Wf	eNOs	IL-1	T NF	IL-6	a-Coll	a-ChS	a-HA	EF I	C RP	Events	Number of cases	Percentage(%)
	93			74	03	51						19	74	
	5			2	2	3						4	2	
Centroids for k-means clustering (AAS+MS)														
Number of clusters: 3														
Total number of training cases: 83														
1	0.85	1.102	331.500	59.44	18.30	12.16	0.23	1.63	1.88	19.50	3.194	0.16666	36	43.37349
2	0.98	1.473	326.250	96.50	32.81	13.56	0.34	2.56	2.73	17.06	3.468	2.00000	16	19.27711
3	1.91	1.921	365.096	79.67	14.29	11.51	0.19	1.47	1.94	16.74	3.467	0.74193	31	37.34940
	0	5	8	2	2	3	8	8	4	4	2	5		
Centroids for k-means clustering (CAD+MS)														
Number of clusters: 2														
Total number of training cases: 90														
1	3.63	1.763	299.197	89.60	21.16	22.62	0.22	2.20	2.69	9.043	4.043	0.39393	66	73.33333
2	6.27	1.829	214.500	10.29	21.70	33.95	0.38	2.66	3.22	-8.7	4.775	0.75000	24	26.66667
	3	7	0	3	3	3	3	0	0	67	0	0		
Centroids for k-means clustering (CAD (no MS))														
Number of clusters: 3														
Total number of training cases: 34														
1	3.74	1.741	289.625	82.20	15.75	25.58	0.21	2.00	1.70	5.458	4.083	0.12500	24	70.58824
2	5.44	1.560	147.600	10.82	11.20	24.60	0.17	2.34	3.62	-9.8	4.080	1.40000	5	14.70588
3	5.72	1.720	114.400	10.44	25.20	21.20	0.21	2.08	2.16	5.000	4.680	1.20000	5	14.70588
	0	0	0	0	0	0	0	0	0	00	0	0		

Among the patients with CAD in the absence of MS, a high incidence of CVE was observed in clusters 2 and 3. In these clusters (Table 1), the signs of pronounced ED and hyperproduction of pro-inflammatory cytokines and the studied

autoantibodies were found. Cluster 2 with the most unfavorable disease progression was characterized by the highest rates of a-Chs and a-HA and the maximal level of IL-1 β .

Figure 3. Centroids of average values of the investigated parameters in cohorts of patients with AAS and CAD (1 pair), type 2 diabetes with CAD and without CAD (2 pairs), AAS with MS and without MS, and CAD with and without MS.

	ET-1	vWf	eNOs	IL-1 β	TNF- α	IL-6	a-Coll	a-Chs	a-HA	CRP
AAS										
CAD										
T2DM without CAD										
T2DM with CAD										
AAS										
T2DM without CAD										
CAD without T2DM										
CAD with T2DM										
AAS without MS										
AAS with MS										
CAD without MS										
CAD with MS										

As a result of the cluster analysis, we were able to assess the contribution of each of the studied parameters to the development of adverse CVE and to identify the profile of ED and immune inflammation circulating markers reflecting the frequency and severity of CV complications depending on the stage of atherosclerosis (AAS or clinically manifested coronary atherosclerosis), and also the presence of disorders of carbohydrate metabolism (metabolic syndrome or T2DM). Schematically, the data are summarized in Fig. 3.

As follows from these data, the greatest contribution to the development of CVE in patients with AAS without T2DM is made by circulating markers of ED and immune inflammation, such as ET-1, IL-1 β , TNF- α , autoantibodies to C I and III, and CS. In patients with CAD without T2DM, ET-1, eNOs, antibodies to collagen, as well as IL-6 and vWf are the key contributors. In patients with T2DM without CAD, the set of markers associated with the development of adverse events includes ET-1, eNOs, IL-6, anti-C, and anti-HA, whereas in T2DM/CAD patients, this profile includes the reduced level of eNOs, the increased levels of vWf, TNF- α , IL-6, hs-CRP, and overexpression of antibodies to C and HA. In AAS/MS patients,

along with hs-CRP, the key contributors are the increased levels of IL-1 β , TNF- α , and antibodies to C, CS, HA. The development of CVE in the group with AAS but without MS is associated with the increased level of circulating markers of ED (ET-1, vWf), as well as antibodies to C and CS.

Obtained data are in consent with the results of numerous investigations which had demonstrated predictive value of the pro-inflammatory markers basal levels in CVE [Mueller, 2014; Ridker, 2014]. It was shown that increased levels of 'upstream' markers such as IL-6, IL-18 and TNF- α were all associated with future vascular events in an approximately log-linear manner, as were level of matrix metalloproteinase-9. However the magnitudes of these effects were smaller than that associated with the 'downstream' inflammatory biomarker, CRP. Since inflammation plays a key role in atherosclerotic plaque formation and further plaque destabilization biomarkers of plaque instability are logical candidates for early diagnosis of atherosclerotic CVD. Recent studies have shown that available assays for detection of these markers including myeloperoxidase, myeloid-related protein 8/14, pregnancy-associated plasma protein-A, and CRP have very

low diagnostic accuracy and therefore are not helpful in the early diagnosis of CVE. In this context searching for additional markers reflecting plaque instability such as anti-connective tissue antibodies and/or ED agents seems to be appropriate for diagnostic and prognostic purposes.

Conclusion

The obtained results confirm the modern inflammatory concept of atherosclerosis and suggest that the mechanisms of immune inflammation play an important pathogenic role in the development of atherosclerosis and CAD, as well as in the development of vascular complications in clinically significant metabolic disorders such as MS and T2DM. It has been established that the contribution of immune inflammation and ED to the development of CV complications depends on the stage of the atherosclerotic process and the severity of carbohydrate metabolism disorders. The most typical profiles of the studied biomarkers, reflecting a high risk of adverse CVE in AAS, CAD, T2DM, and MS, as well as in a combination of atherosclerosis and carbohydrate metabolism disorders, were identified. The obtained data are of practical interest in connection with the possibility of their use for predicting CV complications in high-risk patients.

References

- Algorithms of specialized medical care for patients with diabetes mellitus, clinical guidelines, 8th edition. // *Diabetes*. 2017; 20 (1S): 1-112. DOI: 10.14341 /DM20171S8.
- Boytsov SA, Kukharchuk VV, Karpov YA. Subclinical atherosclerosis as a risk factor for cardiovascular events. *Cardiovascular therapy and prevention*, 2012, 11 (3): 82-86.
- Kaptoge S, Seshasai SR, Gao P, Freitag DF, Butterworth AS, Borglykke A. Inflammatory cytokines and risk of coronary heart disease: new prospective study and updated meta-analysis. *European Heart Journal*, 2014, 35(9): 578–589.
- Libby P., Crea F. Clinical implications of inflammation for cardiovascular primary prevention. *European Heart Journal*, 2010, 31(7): 777–783.
- Mueller Ch. Biomarkers and acute coronary syndromes: an update. *European Heart Journal*, 2014, 35(9): 552-556.
- Ridker PM. Targeting inflammatory pathways for the treatment of cardiovascular disease. *European Heart Journal*, 2014, 35(9): 540-543.
- de Rooij S. R., Nijpels G., Nilsson P. M.. Low-grade chronic inflammation in the relationship between insulin sensitivity and cardiovascular disease (RISC) population: associations with insulin resistance and cardiometabolic risk profile. *Diabetes Care*, 2009, 32(7): 1295–1301.
- Russian Statistical Yearbook 2017. Moscow, 2017. P.85-110.ISBN 978-5-89476-440-5. Publisher of the Federal State Statistics Service, 2017.
- Svistunov AA, Babaeva AR, Osadchuk MA, Gordeeva MA, Tarasov AA, Davidov SI, Shulkina SG, Trushin MV Markers of Immune Inflammation in the Diagnosis of Coronary Complications // *J. Pharm. Sci. & Res.*, 2018, 10(9): 2269-2272.
- Tarasov AA, Babaeva AR, Gordeeva MA, Reznikova EA. Clinical and prognostic value of vascular wall lesion pathogenic markers in asymptomatic atherosclerosis. *Medical alphabet*, 2017, 3(13): 28-34.
- Tarasov AA, Reznikova EA, Davydov SI, Bochkaryova OI, Babaeva AR. Clinical and prognostic value of endothelial dysfunction markers in atherosclerosis-associated vascular lesions. *Medical alphabet*, 2016, 3(30): 5-11.