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ASSESSMENT OF CHANGES IN INDICATORS OF OXIDATIVE STRESS, INFLAMMATION AND ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH CORONARY ARTERY DISEASE WITH DIFFERENT SMOKING STATUS

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Abstract:

The aim of the study was to study changes in markers of oxidative stress, inflammation and endothelial dysfunction in patients with coronary artery disease, depending on the status of smoking. Materials and methods: we examined 354 patients with a diagnosis of coronary artery disease, verified by standardized validated criteria and clinical and functional methods, aged from 47 to 75 years. The presence of coronary atherosclerosis was confirmed by coronary angiography followed by the calculation of the Gensini index. According to smoking status, patients were divided into 2 groups: 1 group - non-smokers - 188 people, 2 group - smokers - 166 people. Statistical processing of the research results was carried out using SPSS Statistics 20 software packages. Results: The study shows the characteristics of the severity of coronary atherosclerosis, calculated using the Gensini index, depending on the smoking status. Significant differences in indicators of oxidative stress and homocysteine in patients with different smoking status were revealed. In addition, the relationship between smoking status and biomarkers under study, as well as clinical and anthropometric indicators, was established.

Keywords: *smoking, oxidative modification of proteins, superoxide dismutase, coronary artery disease, Gensini index, endothelial dysfunction, inflammation.*

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INTRODUCTION:

The key element in the development of coronary artery disease is coronary atherosclerosis. [1]. In recent years, many foreign and Russian publications have emphasized the complex nature of the development of atherosclerosis [2, 3, 4].

Nowadays one of the significant risk factors for the development of CHD is smoking.

The risk of developing coronary artery disease in smoking patients increased by 2-4 times [5]. Smoking increases the risk of coronary artery disease in people of both sexes and in any age group [6-8]. For example, Tolstrup J.S. et al. [7] presented the results of an analysis of data from the Pooling Projecton Dietand Coronary Heart Disease (8 prospective studies, 1974-1996, 192067 men and 74720 women aged 38 to 77 years old, average age 51.8 years, 35% smoked at the time of the study) [8].

Based on all the obtained results, the authors concluded that among smokers in all age groups, most cases of CHD are caused by smoking.

In addition, it is noted that with CAD, intracellular protection against reactive oxygen species (ROS) is reduced, primarily due to a decrease in the level of the key enzyme of the antioxidant system superoxide dismutase (SOD) [9].

Changes in the balance between pro- and antioxidant systems lead to the formation of the earliest markers of cell damage, oxidized modified proteins (OMP), which can lead to endothelial integrity disruption [10, 11].

There is a number of risk factors that have been shown to influence the development of atherosclerosis, also have an effect on the formation of endothelial dysfunction. One of these factors is homocysteine. Homocysteine has a direct damaging effect on the vascular endothelium, which leads to the development of endothelial dysfunction, stimulates thrombosis, and also increases the mitotic activity of smooth muscle cells [12].

Thus, the search and study of specific markers make great interest, as well as their relationship with smoking in patients with coronary artery disease.

The aim of the study was to study the changes in clinical and biochemical parameters in patients with coronary artery disease with different smoking status.

MATERIALS AND METHODS:

The material for the study was a examination of 354 patients with a diagnosis of coronary artery disease, verified by standardized validated criteria and clinical and functional methods, including 175 women and 179 men from 47 to 75 years old, average age 61.8 ± 8.1 years, being treated in the cardiology department №2 of City Clinical Emergency Hospital №1.

All patients in the hospital underwent a full range of examinations with the definition of lipid profile: total cholesterol, low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), triglycerides (TG). The presence of coronary atherosclerosis in patients was confirmed by conducting a coronary angiography by the method of Judkins (1967). The study was conducted using the "General Electric Innova 3100" angiographic system (GE Healthcare, USA). Access was provided by the right transfemoral access via Seldinger. The severity of coronary atherosclerosis was determined on the basis of the Gensini index. The Gensini index is defined as the sum of the products of the index of the severity of each stenosis and the index of the functional value calculated for each segment of the coronary arteries [13]. The sample was continuous. According to the Gensini index, the patients were divided into 3 groups: GS0 (0 points on the Gensini index) - 152 patients without signs of coronary atherosclerosis, GS1 (1-15 points) - 124 patients with hemodynamically insignificant coronary atherosclerosis; GS2 (> 15 points) - 78 patients with hemodynamically significant coronary atherosclerosis.

Depending on the use of lipid-lowering therapy, the patients were divided into 2 groups: those who did not receive statins for 6 months before the study began - 185 people; received lipid-lowering therapy for 6 months before the start of the study - 169 people.

According to smoking status, patients were divided into 2 groups: 1 group - non-smokers - 188 people, 2 group - smokers - 166 people.

The determination of the oxidative modification of proteins in serum was carried out according to the method of Dubinina [14]. The optical density of 2,4 - dinitrophenyl hydrazones was collected on the instrument with an SF-36 spectrophotometer: at a wavelength of 356 nm and 370 nm, the content of aldehyde and ketone derivatives of dinitrophenyl hydrazones of a neutral character (ADPHn and

KDPHn) was determined, at a wavelength of 430 nm 530 nm - aldehyde and ketone derivatives of dinitrophenyl hydrazones of a basic character (ADPHb and KDPHb).
SOD activity was determined by spectrophotometric method.

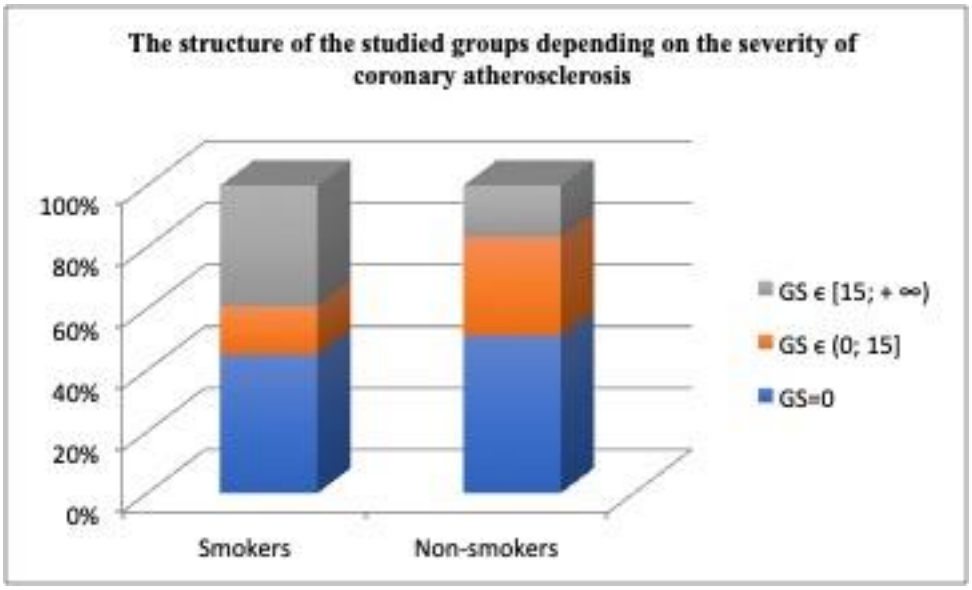
To determine the level of homocysteine, a test system was used to quantify the total L-homocysteine in human serum or plasma (manufacturer is "Axis-Shield", supplier is "BioHimMak", Russia).

The level of highly sensitive C-reactive protein (hsCRP) was determined using the High-sensitive Elisa Kit for C reactive protein kit (manufactured by Cloud-Clone Corp.).

Statistical processing of the research results was carried out using the SPSS Statistics 20 software packages.

Differences between groups were determined using the Mann-Whitney test (significant differences at $p < 0.05$). The description of features with a distribution other than normal is presented in the form Me [Q_{25}; Q_{75}], where Me is the median, Q_{25} and Q_{75} are the 25th and 75th quartiles. For comparison of qualitative signs χ^2 - Pearson criterion was used. To assess the correlations between the parameters, the Spearman criterion was used. The correlation coefficient was considered significant at $p < 0.05$.

The results of the study and their discussion:
All patients were matched for age ($p = 0.320$). In the smoking group, 71 patients were found with a Gensini index of 0, 40 patients - with a Gensini index from 0 to 15, 55 patients - with a Gensini index higher than 15. In the non-smoking group, 81 patients had a Gensini index of 0, 84 patients were with a Gensini index from 0 to 15, 23 patients were with the Gensini index higher than 15.



A statistical relationship was found between a group of patients separated by the Gensini index and smoking status (χ^2 (df = 2) = 12.889, $\phi = 0.277$, $p = 0.002$). Non-smokers with a Gensini 0-15 index were 2.1 times more than smokers. The reverse trend was found in the GS2 group: there were 2.4 times more smokers than non-smokers. In the GS0 group, in 46.9% of cases, patients smoked, in 53.1% they did not smoke.

Among non-smoking patients, the average value of the Gensini index was 9 [0.5; 13.5] points, among smoking patients - 20.25 [10; 29.75] points. When evaluating clinical and anthropometric indices, significant differences in BMI were established ($p = 0.034$): in the group of smokers, BMI was 27.8 [26.55; 29.72] kg/m2, in the non-smoking group - 25.7 [24.45; 28.05] kg/m2; waist circumference ($p = 0.045$): in the smoking group, waist circumference was 90 [84; 101.75] cm, in the group of non-smokers - 82 [79; 97.5] cm; the level of systolic blood pressure ($p = 0.022$): in the group of smokers - 160 [142.5; 180] mm Hg, in the group of non-smokers - 140 [132,5; 160] mm Hg; diastolic blood pressure ($p = 0.015$):): in the group of smokers - 90 [90; 100] mm Hg, in the group of non-smokers - 90 [80; 90] mm Hg.

When assessing the lipid profile, significant differences were found between the studied groups in

terms of cholesterol levels (p = 0.01): in the group of smokers - 6.05 [5.25; 6.87] mmol/l, in the non-smoking group - 5 [4.5; 5.85] mmol/l. There were no significant differences in the level of TG, LDL and HDL levels (p = 0.167, p = 0.120, and p = 0.452).

When conducting a correlation analysis of clinical and anthropometric melon in patients, significant interrelations were found between smoking and the Gensini index (r = 0.365, p = 0.007), BMI (r = 0.294, p = 0.033), WC (r = 0.278, p = 0.044), the level of total cholesterol (r = 0.356, p = 0.009), systolic blood pressure (r = 0.318, p = 0.02), diastolic blood pressure (r = 0.339, p = 0.013), as well as taking statins (r = -0.311 , p = 0.024).

Further, the indicators of oxidative stress, hsCRP and homocysteine were compared in the studied groups depending on the smoking status (Table 1). A significant difference was found in the level of homocysteine and some markers of oxidative stress.

Table 1: The level of biochemical markers in patients with coronary artery disease with different smoking status

Index	Group 1	Group 2	p
Homocysteine (mmol/l)	10,36 [8,74; 11,5]	11,62 [10,16; 12,33]	0,004
hsCRP (mg/ml)	0,03 [0,01;0,21]	0,12 [0,01; 0,7]	0,27
SOD (%)	35,74 [33,01; 40,55]	34,96 [31,83; 38,76]	0,095
ADPHn IU/mg	24,33 [22,01; 25,71]	25,69 [24,29; 27,31]	0,015
KDPHn IU/mg	20,58 [19,80; 21,75]	21,88 [20,43; 22,74]	0,05
ADPHb IU/mg	10,87 [10,38; 11,38]	11,18 [10,79; 11,79]	0,033
KDPHb IU/mg	6,76 [5,42; 8,11]	6,81 [6,34; 8,75]	0,308

During the correlation analysis, patients found significant relationships between smoking and homocysteine values (r = 0.403, p = 0.003), ADPHn (r = 0.337, p = 0.013), ADPHb (r = 0.295, p = 0.032), KDPHb (r = - 0.237, p = 0.027).

The increased concentration of homocysteine in the blood of smokers is probably due to the emerging deficiency of vitamin B6, as well as their decreased activity of liver enzymes involved in the metabolism of homocysteine [15].

High doses of homocysteine, enhancing oxidative processes, modify LDL, turning them into neoantigens, thereby stimulating the response of the immune system. The consequence of this is the emergence of autoantibodies against o-LDL and the formation of immune complexes, which are fixed on endotheliocytes, a decrease in antioxidant protection. This, in turn, leads to the activation of antibody-dependent phagocytosis and antibody-dependent cellular cytotoxicity, aimed at eliminating the immune complex, which causes damage to endotheliocytes and involves atherogenesis mechanisms. It has been shown that in nicotine-dependent individuals, the number of circulating endotheliocytes is 7 times higher than in the non-smoking group, with a significant increase in the percentage of dead CEC. Imbalance between the pro- and antioxidant systems leads to the accumulation of products of oxidative modification of proteins.

CONCLUSION:

The relationship between smoking status, severity of coronary atherosclerosis and the studied risk factors has been established. Thus, the correction of risk factors for CHD remains at a suboptimal level, and a significant proportion of patients are not committed to their correction. There was a low commitment to quitting smoking in patients with signs of coronary atherosclerosis. In this regard, there remains the need to search for residual risk markers, taking into account the significance of risk factors.

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Abbreviation.

ADPH, aldehyde derivative of DNPH; **CHD,** coronary heart disease; **CAG,** coronary angiography; **DNPH**, 2.4-dinitrophenylhydrazine; **HDL-C**, high-density lipoprotein cholesterol; **KDPH,** ketone derivative of DNPH; **LDL-C,** low-density lipoprotein cholesterol; **OMP**, oxidative modification of proteins; **ROS**, reactive oxygen species; **SOD,** superoxide dismutase; **TC,** total cholesterol; **TG,** triglycerides.

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