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The assessment of inflammatory diseases of periodontium as cardiovascular disease risk factor

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Objective. *To study the association between inflammatory diseases of periodontium and cardiovascular diseases (CVD) in patients with different cardiovascular risk.*

Materials and methods. *Patients were divided into four groups: patients with light (n=25), moderate (n=34), severe (n=30) periodontitis and control group without inflammatory diseases of periodontium (n=20).*

Results. *Systemic inflammatory response syndrome with increased high-sensitive C-reactive protein (hs-CRP) and IL-6 are additional pathogenic factors that connects inflammatory diseases of periodontium and cardiovas-*

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cular diseases. The association between the course of somatic and dental pathology requires a joint effort from dentists and cardiologists to identify common risk factors modification.

Conclusion. *Specialists of related disciplines need to evaluate the prognostic significance of risk factors when assessing subclinical atherosclerosis and periodontium condition in order to perform preventive measures.*

Key words*: periodontitis, cardiovascular diseases, cardiovascular risk, hs-CPR, inflammation, atherosclerosis.*

Conflict of interests: none declared.

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Introduction

One of the main global medicine goals are to increase life expectancy and improve its quality. It is also important to improve the property of life itself, especially among progressively increasing number of elderly people. Since functional and morphological impairment of vascular system progress with age, the main mortality cause are cardiovascular diseases. That is why cardiovascular disease (CVD) prevention is essential. Cardiological specialists study closely, all, mainly chronic, processes in the body that affect the state of vascular wall. They mainly include local inflammation, that with the increase of its duration may significantly aggravate or cause chronic inflammatory process. In our country the association between these processes has been studied since 1920s, and has also been investigated by foreign experts [1–4].

Myocardial infarction (MI) — is the main manifestation of coronary artery wall inflammation. MI is one of the leading causes of death in the Western world. Can periodontitis or other inflammatory diseases of oral cavity cause CVD, is there a systemic relationship and association with atherosclerosis and diabetes mellitus (DM) – are the main issues of modern dentistry. Dentist's practice is associated with treatment of significant number of patients (> 30 %) with a history of somatic diseases [5]. The aging of population and the presence of risk factors contribute to the number of concomitant diseases and organism capabilities decompensation [6].

The association between chronic generalized periodontitis (CGP) and CVD is complicated. Negative impact of CVD on the development and the course of periodontal diseases has been proven in a number of studies [5, 7, 8], but the inverse effect of existing chronic periodontitis on CVD risk and their complications has not been studied enough yet. Currently, the pathogenesis of many somatic diseases is being associated with systemic inflammatory response (SIR) with both infection and aseptic inflammation [1, 2]. With severe local inflammation or failure of the mechanisms that limit its course, hs-CRP rises, cytokines enter the circulatory system and lead to the development of SIR [9].

The aim of our study was to establish the association between inflammatory periodontal diseases and the development of CVDs in patients with various cardiovascular risk (CVR).

Objective

To study the association between inflammatory diseases of periodontitis and CVDs in patients with different cardiovascular risk.

Materials and methods

We divided all the patients into four groups — with mild (n=25), moderate (n=34) and severe CGP (n=30) and the control group — without CGP (n=20).

Patients with mild CGP were aged 45.5±1.85 years, with moderate and severe CGP — 48.6±2.08 and 49.3±1.8 years, respectively. The age of patients from the control group was 45.7±2.91 years. Subgroups did not differ by age. Patients with mild CGP included 8 (32 %) men and 17 (68 %) women. Patients with moderate CGP — 10 men (29 %) and 24 women (71 %). Patients with severe CGP — 6 men (20 %) and 24 women (80 %).

The level of hs-CRP was determined by a high-sensitive immunoturbidimetric method with carboxylated polystyrene particles using Sapphire 400 biochemical analyzer, Japan, and the level of pro-inflammatory IL-6 using PW40 Microplate Washer analyzer, BIO-RAD LABORATORIES SAS, France.

CVD risk was assessed using the SCORE (Systematic Coronary Risk Evaluation) scale that determines 10-year risk of fatal cardiovascular events. Over 5 % is considered to be the high risk and 1–4 % — low risk.

Statistical analysis of obtained data was performed with descriptive statistics methods and ROC curves using STATISTICA 10 software.

Results and discussion

Patients with mild, moderate, and severe CGP, had SCORE risk 0.3±0.11, 1.4±0.41, and 1.6±0.37, respectively. Patients from the control group had 0.8±0.37 SCORE. High SCORE risk in the control group occurred in 5% of patients from the control group and in 0%, 8.8%, and 13.3% of patients with mild, moderate, and severe CGP, respectively. The significance of differences between groups was assessed using Fisher analysis of variance. Multiple comparison showed significant differences between groups: the severity of CGP directly correlated with CVD risk.

Sensitive markers that characterize SIR include hs-CRP, IL-6 and fibrinogen. The upper limit of hs-CRP blood level is 5 mg/l, of IL — 6–10 pg/ml, fibrinogen — 4 g/l. The paraments of these markers in patients included in our study are presented in table 1.

The level of blood hs-CRP increased with the severity of periodontitis. Compared with the control group, the level of hs-CRP increased by 66.7% (p <0.05), 95.2% (p <0.01) and 2.8 times (p <0.001) in patients with mild, moderate and severe periodontitis, respectively. IL-6 parameters had similar pattern. The upper limit of IL-6 increased even in patients with mild chronic periodontitis (11.0±3.38 pg/ml). During comparison with the control group, blood IL-6 level significantly increased in patients with mild (2.4 times), moderate (2.8 times) and severe (3.2 times) CGP (p <0.05). Fibrinogen significantly increased in patients with severe chronic periodontitis compared with the control group by 30.3% (p <0.05). Patients with mild and moderate periodontitis had only a tendency to fibrinogen increase. Thus, in patients with CGP, SIR markers increased with the severity of periodontitis.

Considering that CGP is an inflammatory disease, and the connection between inflammation and atherosclerosis had been studied closely recently, hs-CRP can serve as mediator [3, 4, 5]. The results of two independent researches, published in 2005, showed that hs-CRP is involved in the process of atherosclerosis and, consequently, in the occurrence of stroke and acute MI. Authors emphasize that the level of hs-CRP directly correlates with cardiovascular complications [3, 4]. According to American Heart Association (AHA), hs-CRP is recommended to be included into screening recommendations for patients with a moderate cardiovascular risk [3].

We used ROC curves in order to clarify the diagnostic significance hs-CRP blood level during CVD risk assessment. We selected patients with severe CGP and high SCORE risk. The condition of these patients was considered as «1», and we also assessed their hs-CRP blood level. The rank of patients with mild and moderate CGP and low SCORE risk was considered as 0. Obtained results are described further. The differential separation point of hs-CRP or the cut-off point was 3.4 mg/L. When this level was exceeded, patients with CGP had increased risk of severe periodontal lesion and CVD complications development with 94.4% diagnostic sensitivity and 47.8% specificity. The area under the ROC curve (AUC, Area Under Curve) was high (AUC=0.690±0.064) with p=0.0029 (z=2.98) that confirmed the prognostic significance of the risk assessment test (Figure 1).

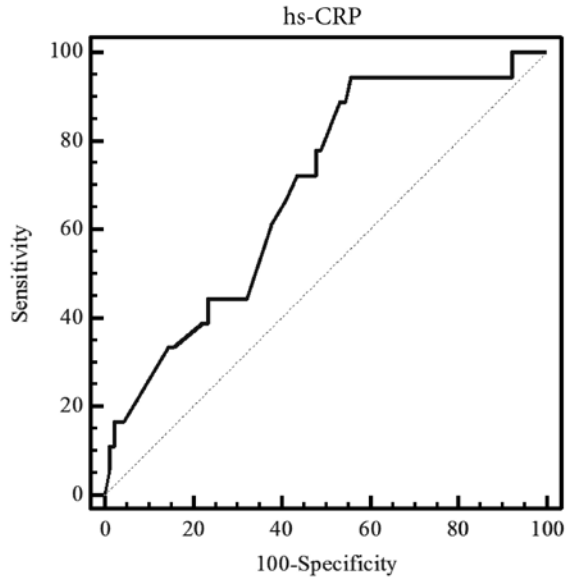

Figure 1. ROC-curve of hs-CRP level as CVD risk marker in patients with CGP

Table 1. **Sensitive SIR markers in patients with different CGP severity and the control group**

Parameters	CGP severity			Control group n=20	P*
	mild n=25	moderate n=34	severe n=30		
hs-CRP, mg/l	3.5±0.28	4.1±0.44	5.8±0.27	2.1±0.30	0.039
IL-6, pg/ml	11.0±3.38	12.8±2.62	14.5±1.40	4.6±1.96	0.016
Fibrinogen, g/l	3.2±0.1	3.4±0.12	4.3±0.08	3.3±0.13	0.64

***** significance of differences between groups was assessed using Fisher analysis of variance.

Thus, it is necessary to control hs-CRP and IL-6 blood levels in patients with CGP, in order to prevent the progression of periodontitis and the development of CVD.

Performed ROC analysis revealed that the differential separation point of apolipoprotein A1 (APO-A1) blood level or the cut-off point was 170 mg/dl. Patients with CGP and decreased APO-A1 blood level (below 170 mg/dL) had higher risk of severe periodontal lesions and CVD complications development with 74.6% diagnostic sensitivity and 72.7% specificity. The area under the ROC curve (AUC) was high (AUC=0.794±0.04) with p <0.0001 (z=6.67) that confirms the prognostic significance of the risk assessment test.

We performed multiple regression analysis in order to establish the association between systemic inflammatory markers, blood lipid spectrum and the severity of the disease in patients with CGP. Based on the results of multiple regression analysis, we obtained the following mathematical expression:

$$Z = 0{,}068 – 0{,}0004 * x + 0{,}36 * y,$$

where:

Z — disease rank: 1 — mild; 2 — moderate; 3 — severe CGP, 0 — absence of the disease;

x — APO-A1 (mg/dl), y — hs-CRP (mg/l).

β-regression coefficient that reflects the effect of APO-A1 on the disease severity, was 0.012 (p=0.028), and 0.76 (p <0.001) for hs-CRP.

The three-dimensional relationship between the severity of chronic periodontitis, the level of hs-CRP and APO-A1 blood level is the following: the blood level of hs-CRP increase and APO-A1 decrease aggravate the severity of periodontal pathology (Figure 2).

In order to reduce the systemic inflammatory response, the dentist needs to carry out effective periodontal treatment. Patients with high CVD risk are the priority group for specific preventive measures. According to modern pathogenesis of atherosclerosis theory, CVD risk factors lead to endothelial dysfunction and initiate inflammation. Subclinical inflammation is caused by sequential cascade of mutually regulated factors, including cellular, humoral immunity, as well as inflammatory mediators, including interferon, interleukins, proteins of inflammation acute phase.

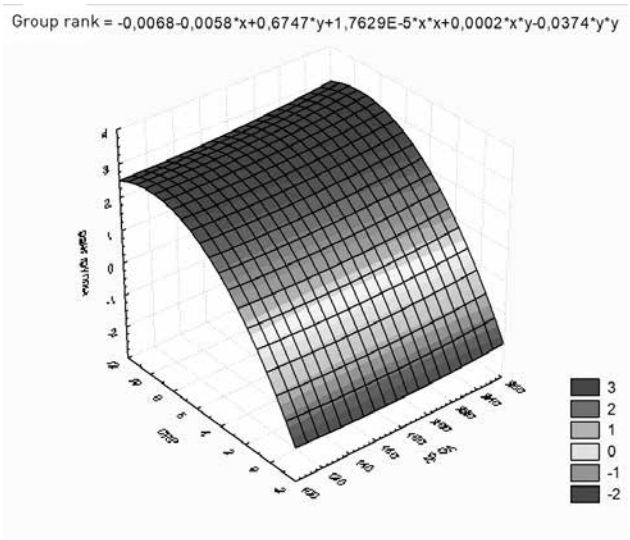

Figure 2. Three-dimensional relationship between the severity of chronic periodontitis, the level of hs-CRP and APO-A1 blood level decrease. The X axis shows the APO- A1 blood level in mg/dl, the y axis shows the hs-CRP blood level in mg/l, the Z axis shows the disease rank.

Conclusion

1. According to the results obtained in this study, we can consider inflammatory periodontal diseases as one of the additional risk factors of CVD development. This conclusion is based on the fact that cardiovascular risk (CVR) increases with the severity of chronic generalized inflammatory process, by 8.8% in patients with moderate CGP and 13.3% — with severe (p=0.04).

2. Specialists of related disciplines need to evaluate the prognostic significance of risk factors when assessing subclinical atherosclerosis and periodontium condition in order to perform preventive measures.

Thus, the presence of CGP can be considered as the aggravating factor of CVD course, and, possibly, CVD predictor. Effective preventive measures, diagnosis and treatment of inflammatory periodontal diseases can reduce CVR.

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