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The complex treatment of generalized periodontitis in patients with stable angina by additional use of immunomodulators

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Abstract
The purpose of study was to evaluate of dynamics of tumor necrosis factor –alfa (TNF-α) and soluble platelet-endothelial cell adhesion molecule -1 (sPECAM-1) in oral fluid of patients with generalized periodontitis with or without CHD during treatment.
Material and Methods: 193 patients with generalized periodontitis were observed (63 without and 130 with chronic CHD – stable angina, FC II-III (CCS)). The levels of TNF-α and sPECAM-1 in gingival fluid were detected by ELISA method.
Results: The level of TNF-α in gingival fluid of patients with stable angina was higher for 22.13% and for 32.29% in observed patients with generalized periodontitis I and II stage relatively ($p<0.05$). Its concentration was significant decreased after treatment in all groups, but more strong in patients with additional use of immunomodulators. In patients with angina pectoris normalization of TNF-α levels was more slowly compared group without coronary atherosclerosis. Similar results were obtained accordance of levels of sPECAM-1 in gingival fluids of observed patients.
Conclusion: Additional prescription of immunomodulator Immuno-Ton and extratemporal gel with "Enterosgel" and herbal concentrate "Dzherelo" caused more significant normalizing of local inflammation activity in patients with generalized periodontitis.

Keywords: *generalizing periodontitis, stable angina, TNF, sPECAM-1, immunomodulators*

1. Introduction
Coronary heart disease (CHD) is a major cause of death and disability in developed countries. Although CHD mortality rates worldwide have declined over the past four decades, CHD remains responsible for about one-third or more of all deaths in individuals over age 35 [1, 2]. It has been estimated that nearly one-half of all middle-aged men and one-third of middle-aged women in the United States will develop some manifestation of CHD [3]. The 2016 Heart Disease and Stroke Statistics update of the American Heart Association (AHA) has recently reported that 15.5 million persons ≥20 years of age in the USA have CHD, whilst the reported prevalence increases with age for both women and men and it has been estimated that approximately every 42 seconds, an American will suffer for an MI [4].
Periodontitis is a disease of the supporting tissues of the teeth, which are naturally inflammatory. It's a multifactorial disease causing destruction of the periodontium. Not only does it affect general health, it also forms a component of the global burden of chronic diseases. Geographical variations are found in the prevalence of periodontal disease and they are mainly attributed to variations in socioeconomic conditions, behavioural factors, systemic conditions of people and oral hygiene patterns [5]. The National Health and Nutrition Examination Survey III (NHANES III) between 1988 and 1994 demonstrated that gingival inflammation occurs in 50% of the adult population [6]. According to the WHO, in Germany, nearly one in five people suffers from periodontitis. The economic burden of this disease can be estimated from various reports. One such report indicates that periodontal and preventive procedures totalled 14.3 billion dollars, of which, 4.4 billion dollars was spent on periodontal services to directly treat the disease [7].
The association between periodontitis and cardiovascular diseases is now well established. The explanations for the development and exacerbation of atherosclerotic plaques in periodontitis patients include: (1) bacteremia, (2) a pro-inflammatory state, (3) a prothrombotic state, (4) an overactive immunity, (5) dyslipidemia, and (6) common genetic risk factors. Most likely, these plausible mechanisms play all simultaneously a role [8]. Obviously, much more fundamental and clinic research is needed to further study the associations between periodontitis and atherosclerotic diseases.

Some immunological factors are involved in the development and control periodontitis, such as: the participation of inflammatory cells in local inflammation, the synthesis of chemotaxis proteins with activation of the complement system and a range of antimicrobial peptides, such as defensins, cathelicidin and saposins. The integration of pathogen-associated molecular patterns (PAMPs) from microorganisms with their surface receptors in the immune cells, induces the production of several cytokines and chemokines that presents either a pro- and/or anti-inflammatory role by stimulating the secretion of a great variety of antibody subtypes and the activation of mechanisms of controlling the disease, such as the regulatory T cells [9]. Although several studies have tried to clarify some of the immune mechanisms involved in periodontal disease, more studies must be conducted to understand its development and progression and consequently to discover new alternatives for the prevention and treatment of this severe inflammatory disease.

The purpose of study was to evaluate of dynamics of tumor necrosis factor –alfa (TNF-α) and soluble platelet-endothelial cell adhesion molecule -1 (sPECAM-1) in oral fluid of patients with generalized periodontitis with or without CHD during treatment.

Material and Methods

193 patients with generalized periodontitis were observed (63 without and 130 with chronic CHD – stable angina, FC II-III (CCS)). The diagnosis of periodontitis was verified in accordance of last recommendation [10]. Stable angina was verified due European Cardiology Society (2013) guidelines. All patients signed of Informed consent; design of this trial was approved by local ethic committee.

All observed patients were divided into following groups: 1A (16 persons) – patients with generalized periodontitis I stage which received standard treatment; 1C (32 persons) – patients with generalized periodontitis I stage and stable angina FC II-III which received standard treatment of both diseases and additional instillation to periodontal pockets of extratemporal gel with "Enterosgel" and herbal concentrate "Dzerelo"; 2A (16 persons) – patients with generalized periodontitis II stage which received standard treatment; 2C (32 persons) – patients with generalized periodontitis II stage and stable angina FC II-III which received standard treatment of both diseases and additional instillation to periodontal pockets of extratemporal gel with "Enterosgel" and herbal concentrate "Dzerelo"; 1B (15 persons) – patients with generalized periodontitis I stage which received standard treatment and immunomodulator "Imuno-ton" (GalychPharm, Ukraine); 1D (33 persons) – patients with generalized periodontitis I stage and stable angina FC II-III which received standard treatment of both diseases and additional instillation to periodontal pockets of extratemporal gel with "Enterosgel" and herbal concentrate "Dzherelo", and and immunomodulator "Imuno-ton"; 2B (15 persons) – patients with generalized periodontitis II stage which received standard treatment and immunomodulator "Imuno-ton"; 2D (33 persons) – patients with generalized periodontitis II stage and stable angina FC II-III which received standard treatment of both diseases and additional instillation to periodontal pockets of extratemporal gel with "Enterosgel" and herbal concentrate "Dzerelo", and and immunomodulator "Imuno-ton". All patients were observed before and on 1, 3, 6, 12 months of treatment period.

The levels of TNF-α and sPECAM-1 in gingival fluid were detected by ELISA method with use of TNF-α ELISA kit (Vector-Best, Russia) and sPECAM-1 ELISA BMS229 kit (Bender MedSystems, Austria).

Statistical analysis was performed with Statistica system software, version 12.0. Categorical variables are presented as percentages, whereas continuous variables are presented as mean (M) and standart error of mean (m) if normally distributed, or as median and interquartile range (Me [IQR]), if not. Categorical variables were compared by the χ^2 test and continuous variables by the t test or the Mann–Whitney U test. A p value of <0.05 was considered statistically significant. All tests were 2-sided.

Results and Discussion

The level of TNF-α in gingival fluid of patients with stable angina was higher for 22.13% and for 32.29% in observed patients with generalized periodontitis I and II stage relatively ($p<0.05$). Its concentration was significant decreased after treatment in all groups, but more strong in patients with additional use of immunomodulators (see table 1). In patients with angina pectoris normalization of TNF-α levels was more slowly compared group without coronary atherosclerosis.

Similar results were obtained accordance of levels of sPECAM-1 in gingival fluids of observed patients (see table 2).

It's known, TNF-α is a pleiotropic pro-inflammatory cytokine released by a variety of different cell types in response to various stimuli, including bacteria, parasites, viruses, cytokines and mitogens. It is involved in systemic and local inflammation via different signal pathways, inducing a broad range of genes. TNF-α regulates a host response to infection and its deregulation is implicated in the pathogenesis of numerous complex diseases, including periodontitis. This cytokine was shown to drive several biological processes such as induction of inflammatory mediators, for instance, matrix metalloproteases, chemokines and prostaglandins, endothelial cell activation and endothelial-leukocyte interactions, monocyte adhesion, mediating bone remodelling, and oxidative processes [11]. TNF-α induce bone resorption and up-regulate prostaglandin E_2 (PGE_2) and collagenases secretion and is produced by many cell types including macrophages, neutrophils, keratinocytes, fibroblasts, NK cells, T and B cells in the periodontium. Thise cytokine induces the up-regulation of adhesion molecules on leucocytes and endothelial cells, stimulating the production of chemokines that recruit circulating leucocytes to sites of inflammation, and inducing expression of other inflammatory mediators that potentiate inflammatory responses [12].

PECAM-1/CD31is a 130-kD vascular cell adhesion and signaling molecule of the immunoglobulin (Ig) superfamily that is expressed on the surface of circulating platelets, monocytes, neutrophils, and selected T-cell subsets. It is also a major constituent of the endothelial cell intercellular junction and plays a role in neutrophil recruitment at inflammatory sites. There is good evidence to suggest that PECAM-1 is a key participant in the adhesion cascade leading to extravasation of leukocytes during the inflammatory process [13]. Many studies suggest that chronic periodontitis is an independent risk factor for systemic vascular disease and may result in stimulation of the synthesis of acute phase protein by cytokines released by periodontal high endothelial cells [13]. However, tissue expression of adhesion molecules has not been substantially evaluated in the gingiva of patients with chronic periodontitis. This is significant in relation to potential therapy targeting expression of the adhesion molecules [14].

Table 1: Dynamics of gingival fluid levels of TNF-α (pg/ml) in patients with generalized periodontitis

period	Groups of observed patients							
	1A, n=16	**1C, n=32**	**2A, n=16**	**2C, n=32**	**1B, n=15**	**1D, n=33**	**2B, n=15**	**2D, n=33**
Before treatment	41.56±2.45	54.63±3.41	51.24±2.97	67.44±2.31	44.33±2.67	55.67±3.47	52.47±2.95	69.76±2.54
1 month	32.99±3.52 P<0.01	41.14±2.91 P<0.01	43.14±3.23 P<0.01	53.67±2.77 P<0.01	27.35±2.21 P<0.01	37.57±2.89 P<0.01	39.77±3.12 P<0.01	51.47±3.32 P<0.01
3 month	31.47±2.78 P<0.01 P_1>0.05	39.97±3.11 P<0.01 P_1>0.05	41.11±2.54 P<0.01 P_1>0.05	51.23±3.14 P<0.01 P_1>0.05	25.67±2.78 P<0.01 P_1>0.05	36.77±2.91 P<0.01 P_1>0.05	35.67±3.11 P<0.01 P_1>0.05	46.77±3.98 P<0.01 P_1>0.05
6 month	29.46±3.71 P<0.01 P_1>0.05 P_2>0.05	36.82±3.23 P<0.01 P_1>0.05 P_2>0.05	37.79±3.45 P<0.01 P_1>0.05 P_2>0.05	49.67±2.23 P<0.01 P_1>0.05 P_2>0.05	26.14±3.22 P<0.01 P_1>0.05 P_2>0.05	31.54±3.43 P<0.01 P_1<0.05 P_2<0.05	32.13±3.34 P<0.01 P_1<0.05 P_2>0.05	47.14±3.37 P<0.01 P_1>0.05 P_2>0.05
12 month	30.47±2.87 P<0.01 P_1>0.05 P_2>0.05 P_3>0.05	38.91±2.11 P<0.01 P_1>0.05 P_2>0.05 P_3>0.05	38.11±3.31 P<0.01 P_1>0.05 P_2>0.05 P_3>0.05	48.45±3.11 P<0.01 P_1>0.05 P_2>0.05 P_3>0.05	26.74±2.31 P<0.01 P_1>0.05 P_2>0.05 P_3>0.05	30.89±2.78 P<0.01 P_1<0.05 P_2<0.05 P_3>0.05	32.76±2.98 P<0.01 P_1<0.05 P_2>0.05 P_3>0.05	43.56±2.99 P<0.01 P_1<0.05 P_2<0.05 P_3<0.05

Notes: p – significance in compared groups during follow-up period

Table 2: Dynamics of gingival fluid levels of sPECAM-1 (ng/ml) in patients with generalized periodontitis

period	Groups of observed patients							
	1A, n=16	**1C, n=32**	**2A, n=16**	**2C, n=32**	**1B, n=15**	**1D, n=33**	**2B, n=15**	**2D, n=33**
Before treatment	104.45 [91.34; 119.54]	128.77 [111.43;136.74]	107.87 [93.45; 121.42]	147.45 [121.23; 167.42]	107.11 [94.75; 129.25]	135.78 [121.47; 147.98]	114.45 [91.42; 135.87]	146.21 [120.12; 165.32]
1 month	75.78 [55.34; 99.67] P<0.01	97.56 [87.45; 117.32] P<0.01	91.21 [75.45; 108.23] P<0.01	107.67 [89.78; 114.11] P<0.01	61.45 [48.78; 87.98] P<0.01	91.78 [79.54; 103.22] P<0.01	90.42 [74.74; 106.23] P<0.01	91.45 [78.79; 102.12] P<0.01
3 month	74.23 [56.34; 96.45] P<0.01 P_1>0.05	93.52 [83.41; 112.34] P<0.01 P_1>0.05	89.78 [76.45; 107.54] P<0.01 P_1>0.05	106.35 [91.25; 112.74] P<0.01 P_1>0.05	54.45 [38.44; 74.11] P<0.01 P_1<0.05	81.78 [65.47; 92.23] P<0.01 P_1<0.05	79.79 [64.51; 91.88] P<0.01 P_1<0.05	76.51 [54.89; 98.14] P<0.01 P_1<0.05
6 month	71.23 [55.76; 98.34] P<0.01 P_1>0.05 P_2>0.05	92.44 [85.42; 109.85] P<0.01 P_1>0.05 P_2>0.05	87.34 [72.45; 105.15] P<0.01 P_1>0.05 P_2>0.05	104.12 [92.12; 11.85] P<0.01 P_1>0.05 P_2>0.05	53.74 [39.78; 73.45] P<0.01 P_1<0.05 P_2>0.05	79.89 [66.45; 91.74] P<0.01 P_1<0.05 P_2>0.05	78.14 [63.61; 90.45] P<0.01 P_1<0.05 P_2>0.05	75.16 [56.14; 98.27] P<0.01 P_1<0.05 P_2>0.05
12 month	69.34 [49.34; 80.34] P<0.01 P_1>0.05 P_2>0.05 P_3>0.05	83.78 [63.45; 105.15] P<0.01 P_1<0.05 P_2<0.05 P_3<0.05	88.78 [73.87; 104.75] P<0.01 P_1>0.05 P_2>0.05 P_3>0.05	105.57 [93.45; 113.75] P<0.01 P_1>0.05 P_2>0.05 P_3>0.05	54.87 [38.78; 73.45] P<0.01 P_1<0.05 P_2>0.05 P_3>0.05	80.42 [67.45; 94.77] P<0.01 P_1<0.05 P_2>0.05 P_3>0.05	80.11 [66.63; 93.14] P<0.01 P_1<0.05 P_2>0.05 P_3>0.05	74.58 [53.71; 95.98] P<0.01 P_1<0.05 P_2>0.05 P_3>0.05

Notes: p – significance in compared groups during follow-up period

Conclusion

Additional prescription of immunomodulator Immuno-Ton and extratemporal gel with "Enterosgel" and herbal concentrate "Dzherelo" caused more significant normalizing of local inflammation activity in patients with generalized periodontitis.

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