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МАТЕРИАЛЫ НАУЧНО-ПРАКТИЧЕСКОЙ КОНФЕРЕНЦИИ
С МЕЖДУНАРОДНЫМ УЧАСТИЕМ
«ГОФУНГОВСКИЕ ЧТЕНИЯ»
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Збірка наукових праць присвячена 210-річчю Харківського національного медичного університету. У ній представлені матеріали науково-практичної конференції з міжнародною участю «Гофунговскі читання» у рамках святкування 210-річчя ХНМУ та міжнародного Дня стоматолога (10.02.2015 р.). Збірка включає останні результати наукових досліджень по актуальних проблемах стоматології та щелепно-лицьової хірургії з різних країн. У випуск включено праці фахівців, які виконані на кафедрах стоматологічного профілю та суміжних дисциплін медичних ВНЗ і установ післядипломної освіти лікарів, а також в практичній охороні здоров'я. У них відбіті експериментальні, теоретичні і клінічні питання сучасної стоматології та щелепно-лицьової хірургії. Представлені роботи з питань профілактики, діагностики, лікування і реабілітації стоматологічних захворювань у дорослих і дітей; педагогіки, історії стоматології, медичного краснавства та огляди літератури.

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to immunohistochemically detect some p53-positive cells. This same effect is shown on patient’s gingival in the group I. Our study supports the Ki-67 protein expression as an absolute requirement for progressive growth of cell division [9].

Conclusions. Proliferative gene Ki-67 expression among patients with not atherosclerotic conditions was low. Patients, who had died from complications of atherosclerosis with cellular hyperplasia, since it is merely an adaptive process, indicated an increased Ki-67 Gene and p53 expression. Among patients with atherosclerosis it is linked to cell’s arrests in the G1 phase of the cell cycle and that provides time for repair of the damaged DNA before entry into S or induction of apoptosis.

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Ryabokon, E. N., Khudiakova, M. B.
CORRECTION OF CYTOKINE MISBALANCE IN PATIENTS WITH CHRONIC GENERALIZED PERIODONTITIS OF INITIAL-I DEGREES OF SEVERITY BY MEANS OF LOCAL APPLICATION OF QUERCETINUM GRANULES AND LIPOSOMAL QUERCETINUM-LECITHIN COMPLEX
Kharkiv National Medical University, Kharkiv, Ukraine

Introduction. Efficiency of local application of medical drugs in periodontal tissues depends on the display of substances in the periodontal pocket (PP), choice of medical substances, method of his application, contact with the gingival oral mucosa and maintainance of this concentration. Therefore it is necessary advantage to give to the forms and pathways of medications with the controlled and long action [5, 6]. Development and application high-efficiency and safe facilities of drug therapy of chronic generalized periodontitis (HGP) the last years legally considered one of priority directions of native and foreign researchers [1, 2, 3]. Medical local therapy is inalienable part of complex treatment of HGP [4].

Liposomes, owing to their small size, penetrate regions that may be inaccessible to other systems. It is noteworthy that only liposomes have been largely exploited for drug delivery because the methods of preparation are generally simple and easy to scale-up. The aim of using liposomal carriers is generally, to increase the specificity towards cells or tissues, to improve the bioavailability of drugs by increasing their diffusion through biological membranes, to protect them against enzyme in-
activation. These systems reduce the frequency of administration, further provide a uniform distribution of the active agent over an extended period of time [7, 11].

Cytokines play a major role in inflammatory and immune responses in periodontal tissues the patients with HGP. The misbalance between pro-inflammatory (IL-1β, TNF-α, IL-8) and anti-inflammatory (IL-4) mediators as being the cytokines for which there is the most substantial evidence for having a central role in cytokine networks in periodontal diseases [9, 10].

Anti-inflammatory properties of «Lipoflavon» (JSC „Biolek”, Kharkov), which contained lecithin liposomes and quercetin are conditioned by his expressed anti-leukotrienes activity. Quercetin inhibits production of inflammation-producing enzyme 5-lipoxygenase (LOX). The immunomodulating action of Quercetinum is known. Quercetinum differentiated regulates expression genes of Th-1 (IFNγ) and Th-2 (IL-4) of cytokines by the normal mononuclear cells of peripheral blood. Quercetinum increased of phenotypical expression of IFNγ mononuclear cells of peripheral blood and suppressed IL-4 are positive mononuclear cells of peripheral blood, that is compared with the results of determination of mRNC/protein [8].

Therefore the comparative study of changes of pro-inflammatory IL-8, IL-1β, TNF-α and anti-inflammatory IL-4 cytokines presents considerable theoretical and practical interest for local treatment the patients with HGP of initial-I degrees of severity with gel from the granules of Quercetinum (GQ) and liposomal Quercetinum-lecithin complex (LQLC).

The purpose of study was to increase of efficiency of complex treatment the patients with HGP of initial-I degrees of severity with gel from the granules of GQ and liposomal LQLC due to the correction of cytokine levels.

Material and Methods. The 35 patients with HGP of initial-I degrees of severity were observed. In accordance to treatment all patients were divided into 2 groups: I group – basic treatment with local application LQLC (18 patients) with the use of individual periodontal delivery tray; II group (group of comparison) – basic treatment with local application of gel from GQ (17 patients) with the use of individual periodontal delivery tray. The control group (C) included 14 healthy subjects without systemic inflammatory disease.

The patients of basic group was conduct base therapy with the local application LQLC (injection form of «Lipoflavon») as a suspension, prepared ex tempore, containing 137,5 mgs of lecithin and 3,75 mgs of Quercetinum. This suspension prepared at a premix 1/4 parts of content of small bottle with 5 ml 0,9% solution of natrium chloride, warmed-up to 38°. The patients of comparison group was conduct base therapy with local application of gel from GQ with the use of individual periodontal delivery tray during 40 minutes 2 times per a day to 10 days.

All observed patients in the morning were conducted of mouth liquid (ML) before treatment and through 1, 6 and 12 months after treatment for immunological researches. Through 6 months of patients examined, inspected the condition of periodontal tissues and conducted supporting therapy, which included the professional hygiene of mouth cavity and local treatment using of individual periodontal delivery tray with gel from GQ and LQLC during 10 days for 40 minutes 2 times per a day, and also reception inward during 1 month of 1 g «Granules of Quercetinum» 2 times per a day.
**Results and discussion.** The patients of control group was mean IL-1β - 64.44 ± 6.2 pg/ml, IL-8 - 61.62 ± 7.69 pg/ml, TNF-α - 21.71 ± 2.95 pg/ml, and anti-inflammatory IL-4 - 243.5 ± 17.48 pg/ml. As such, numerous GCF constituents have been characterized to identify biomarkers that may be used to monitor the initiation and progression of gingival inflammation and the immune response.

The first mediators to have their role related to HGP pathogenesis were innate immunity cytokines produced after microbial recognition, such as TNF-α, IL-1β. These cytokines are produced by both resident cells (i.e. epithelial cells and fibroblasts) and phagocytes (i.e. neutrophils and macrophages) in periodontal environment. While the exact contribution of each cell type remains to be elucidated, previous studies described that a hyper-reactive phenotype of phagocytes is related to increased pro-inflammatory cytokines production in HGP [12].

Recent evidence also points to important roles of resident cells in periodontal bone loss, since the periodontal ligament fibroblasts and osteoclast precursors contact synergistically increases the expression of genes related to osteoclastogenesis, such as TNF-α and IL-1β [13].

IL-1β is produced by a wide range of periodontal tissues and immune cells and, as such, is considered to have multiple roles in innate and adaptive immune responses to plaque bacteria which feature in the pathogenesis of periodontitis. IL-1β acts (often in synergy with TNF-α and prostaglandin E2 (PGE2)) to induce many of the vascular changes associated with inflammation and in particular to regulate neutrophil emigration from the circulation into the periodontium. In adaptive immunity, IL-1β stimulates antigen presentation by APCs and influences T-cell development and phenotype. Studies of the expression of IL-1β, TNF-α, and PGE2 in oral fluids and periodontal tissues in periodontal disease endorse the important role of these mediators in pathogenesis and, critically, this is supported by the results of investigations of their effect in animal models (including key studies using cytokine antagonists). Thus, IL-1β, TNF-α, and PGE2 will all activate osteoclast activity, MMP secretion,
and alveolar bone resorption in chronic periodontitis [14, 15].

TNF-α is responsible for cell migration process at multiple levels, inducing the upregulation of adhesion molecules and the production of chemokines, which are chemotactic cytokines involved in cell migration to infected and inflamed sites. TNF-α is present at high levels in gingival crevicular fluid (GCF) in HGP. Supporting the data from human studies, experimental HGP in the in rats and primates clearly demonstrated that TNF-α plays a central role inflammatory reaction, alveolar bone resorption and in the loss of connective tissue attachment [16, 17].

TNF-α is produced mainly by macrophages in response to antigens, such as lipopolysaccharides. TNF-α is present in serum and inflammatory tissues; its levels correlate with disease activity and the degree of tissue damage. TNF-α can also induce the expression of other mediators that amplify or sustain the inflammatory response (e.g., prostaglandins), stimulate the production of lytic enzymes (e.g., collagenase), and enhance bacterial killing and phagocytic activity [18, 19].

IL-8 is an inflammatory chemokine which functions mainly as a neutrophil chemotactant and activating factor. IL-8 is able to upregulate the expression of adhesion molecules on the surface of neutrophils, enhancing leukotriene B4 (LTB4) production, inducing neutrophil chemotaxis and increasing neutrophils adherence to endothelial and epithelial cells. IL-8 is found at higher levels in gingival crevicular fluid prior to clinical signs of inflammation. Moreover, IL-8 has a direct effect on osteoclast differentiation and activity by signaling through the specific receptor. Analysis of the chemokines IL-8, in an experimental model of PD in mice, revealed their expression in diseased tissues, preferentially in the junctional epithelium, and their correlation with the migration of PMNs. Furthermore, there was a significant increase in the expression of IL-8 by epithelial cells from periapical granulomas, suggesting that those cells also could increase vascular permeability and leukocyte chemotaxis [20, 21, 22, 23, 24, 25].

During the past decade numerous investigators have shown altered cytokine production in periodontitis and attempted to elucidate their role in periodontal diseases. For example, several studies have demonstrated that localized absence of IL-4 in diseased periodontal tissues is associated with periodontal disease activity and progression. Th2 cells commitment and action is primarily dependent of IL-4, the prototypical Th2 cytokine, which also acts as a B cell stimulatory factor. In addition to IL-4 is further believed to contribute to B cell differentiation and antibody production. Some studies propose that the Th2-type cytokine IL-4 may attenuate periodontitis progression, in contrast to its putative destructive role previously discussed. IL-4 has been associated to control other inflammatory diseases, such as periodontitis. In addition, there is a relative absence of IL-4-producing T cells at sites of inflammation. This imbalance is progressive, with decreasing levels of IL-4 correlated with loss of collagen and with increasing clinical severity. In addition, polymorphisms in the IL-4 promoter and intron that are associated with decreased serum levels of IL-4 are also associated with increased susceptibility to early onset periodontitis. It has been suggested that correcting this cytokine imbalance in chronic inflammatory conditions might be therapeutic [26-29].

The patients with initial-I degrees of severity in the basic group before treatment
was mean IL-1β - 123.2 ± 4.94 pg/ml, that was upper than 91 % in the C groups; IL-8 - 86.17 ± 1.84 pg/ml, that was upper than 40 % in the C groups; TNF-α - 44.91 ± 3.63 pg/ml, that was upper than 107 % in the C groups and anti-inflammatory IL-4 - 220.9 ± 11.89 pg/ml, that was lower than 9 % in the C groups. The patients in the comparison group before treatment was mean IL-1β - 122.6 ± 5.2 pg/ml, that was upper than 92 % in the C groups; IL-8 - 86.92 ± 3.54 pg/ml, that was upper than 41 % in the C groups; TNF-α - 45.29 ± 2.95 pg/ml, that was upper than 109 % in the C groups and anti-inflammatory IL-4 - 219.1 ± 7.74 pg/ml, that was lower than 10 % in the C groups.

The patients with initial-I degrees of severity in the basic group after treatment through 1 month was mean IL-1β - 63.44 ± 3.03 pg/ml; IL-8 - 65.52 ± 1.31 pg/ml, TNF-α - 25.46 ± 1.28 pg/ml and anti-inflammatory IL-4 - 316.2 ± 10.73 pg/ml, that was lower than 30 % in the C groups. The patients in the comparison group after treatment through 1 month was mean IL-1β - 76.65 ± 5.21 pg/ml; IL-8 - 70.36 ± 1.31 pg/ml; TNF-α - 29.36 ± 2.61 pg/ml and anti-inflammatory IL-4 - 359.9 ± 10.36 pg/ml, that was lower than 48 % in the C groups.

The patients with initial-I degrees of severity in the basic group after treatment through 6 month was mean IL-1β - 73.09 ± 6.97 pg/ml, that was upper than 15 % in the C groups; IL-8 - 69.35 ± 5.6 pg/ml, that was upper than 22 % in the C groups; TNF-α - 27.51 ± 2.57 pg/ml, that was upper than 107 % in the C groups and anti-inflammatory IL-4 - 292.2 ± 20.77 pg/ml, that was lower than 19 % in the C groups. The patients in the comparison group after treatment through 6 month was mean IL-1β - 85.22 ± 4.75 pg/ml, that was upper than 11 % in the C groups; IL-8 - 75.96 ± 4.31 pg/ml, that was upper than 38 % in the C groups; TNF-α - 32.72 ± 3.56 pg/ml, that was upper than 109 % in the C groups and anti-inflammatory IL-4 - 261.7 ± 16.25 pg/ml, that was lower than 17 % in the C groups.

The patients with initial-I degrees of severity in the basic group after treatment through 12 month was mean IL-1β - 68.57 ± 5.07 pg/ml, that was lower than 1 % in the C groups; IL-8 - 67.3 ± 4.95 pg/ml, that was upper than 9 % in the C groups;
TNF-α - 24.82 ± 1.6 pg/ml, that was lower than 10% in the C groups and anti-inflammatory IL-4 - 289.9 ± 10.91 pg/ml, that was upper than 1% in the C groups. The patients in the comparison group after treatment through 12 month was mean IL-1β - 84.04 ± 4.17 pg/ml, that was lower than 6% in the C groups; IL-8 - 72.45 ± 3.62 pg/ml, that was upper than 18% in the C groups; TNF-α - 31.44 ± 2.43 pg/ml, that was lower than 4% in the C groups and anti-inflammatory IL-4 - 244.8 ± 16.53 pg/ml, that was lower than 6% in the C groups.

Conclusions. The research in question demonstrates lipoflavon capability to normalize homeostasis of the oral cavity, normalize misbalance of cytokines in periodontal tissues, thus retarding process of inflammation and destruction of tissues and improving reparation of periodontal structures. High therapeutic efficiency of the liposomal quercetin-lecithin complex for patients with chronic generalized periodontitis, especially that of initial-I degrees of severity was shown to be determined by anti-inflammatory, immunomodulating and periodontoprotecting effects. This allows to recommend lipoflavon for local application as pathogenetically substantiated drug in treatment of generalized periodontitis.

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