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**STATE OF COLLAGENOLYSIS
 IN EXPERIMENTAL PERIODONTITIS
 OF BACTERIAL-IMMUNE GENESIS
 AND ITS CORRECTION WITH FLAVONOL**

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Abstract. *State of collagenolysis in experimental periodontitis of bacterial-immune genesis and its correction with flavonol. Demkovych A.Ye., Bondarenko Yu.I., Fastovets O.O., Hrad A.O., Hasiuk P.A., Denefil O.V.* The article presents an assessment of the dynamics of changes in the content of the marker of collagenolysis – free oxyproline in the homogenate of soft tissues and bone in experimental bacterial-immune periodontitis and elucidation of the effect of flavonol quercetin on these indicators. The aim of this study was to determine the role of cytokinogenesis and the effect of flavonol on it in the pathogenesis, development and course of experimental periodontitis. During the experiment, a fragment of the mandible was taken from the animals, from which the soft tissues and bone were carefully separated. The state of collagen was determined by the content of free oxyproline in the soft and bone tissues. The concentration was determined according to the calibration graph and expressed in $\mu\text{mol/g}$. The results of studies of the indicators of the state of biopolymers of connective tissue structures of periodontium on the 7th, 14th and 30th day of experimental bacterial-immune periodontitis and after its correction with flavonol (from the 7th to the 14th day of the experiment) are presented. The data on the nature of changes in the content of collagen monomers in the process of formation of the inflammatory focus in the periodontal complex are given. During the acute phase of the inflammatory process in rats there was revealed a slight increase in blood free oxyproline in bone homogenate and homogenate of soft periodontal tissues, on the 14th day the dynamics continued to increase, at a later stage of the experiment, namely on the 30th day, increase in bone resorption continued as compared to the 7th and 14th day. During the correction of disorders resulted from the development of this pathological process there was a decrease in the level of free oxyproline in the bone homogenate and homogenate of soft tissues of mandibular periodontium, as compared to the same indicators of animals who did not receive quercetin on the 14th day. The use of flavonol quercetin, which, by affecting immune processes, limited the inflammatory response in periodontal tissues and stabilized collagenolysis processes in periodontal tissues was manifested by a decrease in free oxyproline in bone and soft tissue homogenates of experimental animals.

Реферат. Стан колагенолізу при експериментальному пародонтиті бактеріально-імунного генезу та корекція його флавонолом. Демкович А.Є., Бондаренко Ю.І., Фастовець О.О., Град А.О., Гасюк П.А., Денефіль О.В. У статті показана оцінка динаміки змін вмісту показника маркера колагенолізу – вільного оксипроліну в гомогенаті м'яких тканин та кістки при експериментальному бактеріально-імунному пародонтиті та з'ясування впливу флавонолу кверцетину на ці показники. Метою цього дослідження було визначення ролі цитокіногенезу та ефекту на нього флавонолу в патогенезі, розвитку та перебігу експериментального пародонтиту. Під час експерименту для дослідження відбирали у тварин фрагмент нижньої щелепи, від якого ретельно відокремлювали м'які тканини та кістку. Стан колагену визначали за вмістом у м'яких і кістковій тканинах вільного оксипроліну. Концентрацію визначали за калібрувальним графіком і виражали в мкмоль/г. Наведені результати досліджень показників стану біополімерів сполучнотканинних структур пародонта на 7-у, 14-у та 30-у добу експериментального бактеріально-імунного пародонтиту і після корекції його флавонолом (з 7-ї по 14-у добу досліду). При цьому наводяться дані про характер змін вмісту мономерів колагену в процесі формування запального вогнища в пародонтальному комплексі. У щурів у період гострої фази запального процесу виявлено незначне підвищення в крові вмісту вільного оксипроліну в кістковому гомогенаті та гомогенаті м'яких тканин пародонта, на 14-у добу динаміка продовжувала зростати, на пізнішій стадії експерименту, а саме на 30-у добу дослідження продовжилося збільшення резорбції кісткової тканини порівняно з показниками на 7-у та 14-у добу. При корекції порушень у результаті розвитку цього патологічного процесу відбувалося зниження рівня вільного оксипроліну в кістковому гомогенаті та гомогенаті м'яких тканин пародонта нижньої щелепи, порівняно з такими показниками на 14-у добу, які не отримували кверцетину. Застосування флавонолу кверцетину, який, впливаючи на імунні процеси, обмежував запальну реакцію в тканинах пародонта і призводило до стабілізації процесів колагенолізу в тканинах пародонтального комплексу, що приводило до зниження вільного оксипроліну в гомогенаті кістки та м'яких тканин піддослідних тварин.

The paper is a part of the RSW "Systemic and organic disorders due to actions of extraordinary factors on the body, mechanisms of their development and pathogenetic correction" (registration number 0116 U003390).

In recent years, there has been a general trend of increasing severity of diseases associated with the development of inflammatory processes in the periodontal complex, and a significant predominance of periodontal disease (gingivitis and periodontitis) among adults and a sharp increase among young people [6]. It should be noted that in adults (after 35 years) generalized periodontitis increases the risk of concomitant systemic pathology, including cardiovascular, respiratory infections, rheumatoid arthritis, osteoporosis, diabetes, gastrointestinal diseases and others. The most important means in planning surgery or orthodontic treatment is the condition of the bone structures of the maxilla and mandible and, finally, it is the pathological resorption of the bone tissue of the jaw in periodontal disease, regardless of age that leads to premature loss of intact teeth. Plaque microorganisms, as a result of active secretion of various enzymes, contribute to the development of microcirculation disorders in the periodontium, cause a number of inflammatory reactions, depolymerization of glycosaminoglycans, proteins of periodontal tissues, especially collagen. This mechanism of development of the pathological process occupies an important place in the pathogenesis of inflammatory and dystrophic-inflammatory periodontal diseases [10, 13].

Despite the increase in recent years in the arsenal of drugs for the treatment of periodontitis (new antiseptics and other powerful local antimicrobials, herbal medicines, anti-inflammatory and wound healing agents, etc.), the problem of periodontal diseases and their treatment remains topical and timely for theoretical and practical medicine.

The modern concept of treatment and prevention of generalized periodontitis is based on both local effects on the tissues of the dental apparatus, and on a system-wide approach. Traditional antimicrobial and anti-inflammatory treatment does not always provide correction of dystrophic changes in the cellular process, so it is important to find drugs that would help normalize metabolic processes in periodontal tissues, have antioxidant, adaptogenic and immunomodulatory properties [4]. It has been established that some polyphenols and flavonols of plant origin are able to show powerful antioxidant properties in many inflammatory and degenerative diseases [2, 14], which indicates the feasibility of their study in periodontitis.

Objective of the study: to determine the role of collagenolysis in the pathogenesis of experimental periodontitis and the use of flavonol quercetin in its correction.

MATERIALS AND METHODS OF RESEARCH

The study was performed on white outbred clinically healthy male rats weighing 150-200 g in vivarium setting. The experiments were performed in accordance with the general rules and provisions of the European Convention for the Protection of Vertebrate Animals Used for Research and Other

Scientific Purposes (Strasbourg, 1986) and the General Ethical Principles for Animal Experiments (Kyiv, 2001).

Experimental animals were divided into 5 groups: I – intact animals (n=10); II – animals with simulated experimental periodontitis, 7th day of the study (n=8); III – animals with simulated experimental periodontitis, 14th day of the study (n=8); IV – animals with simulated experimental periodontitis, 30th day of the study (n=8); V – animals with simulated experimental periodontitis, 14th day of the study, treated with quercetin (corvitin) (n=8).

Experimental bacterial-immune periodontitis in experimental animals was induced by introducing a mixture of microorganisms diluted with egg protein into the tissues of the periodontal complex [3]. In order to enhance the immune response, a complete Freund's adjuvant was injected into the rat's paw at the same time. On the 14th day of the study the pathogen was re-injected and the adjuvant was injected into the tissues. On the 7th, 14th and 30th days the experimental animals were killed by bloodletting under thiopental anesthesia. Tissue of the mandible was selected for further study.

To correct periodontitis, the animals were injected with a water-soluble preparation of quercetin (corvitin, manufactured by Borschahivsky CPF) at a dose of 100 mg/kg of animal weight for 7 days (from the 7th to the 14th day). The preparation of the bone homogenate was carried out in the conventional manner from the soft and bone tissues of the fragment of the mandible of the animal, which was carefully separated. Preparation of bone tissue

homogenate was performed by the conventional method, by separating tissues from the fragment of the animal's mandible. After taking a fragment of the animal's mandible, the mandible was thoroughly cleaned out of soft tissues. All processes involving bone isolation and preparation of the homogenate were performed at a low temperature (on an ice tray) to store enzyme activity. The state of collagen was determined by the content of free oxyproline in the soft and bone tissues. The concentration of the latter was determined by the method of Tetyanets SS [5], which is based on the reaction of pyrrolidine-2 carboxylic acid formed during the oxidation of oxyproline with paradimethylaminobenzaldehyde. The concentration was determined on a calibration graph and expressed in $\mu\text{mol/g}$. The obtained data were statistically processed using non-parametric statistical methods using STATISTICA 6.1 software (Statsoft, USA) (License AGAR909E415822FA). The reliability of the difference between the values between the independent quantitative values was determined in the normal distribution by the U-test Mann-Whitney [1].

RESULTS AND DISCUSSION

In rats with experimental bacterial-immune periodontitis during the acute phase of the inflammatory process, namely on the 7th day of the study, we found a slight increase in blood (by 1.19 times; $p < 0.05$) of content of free oxyproline in bone homogenate, taken from the mandible, relative to the intact group (Table).

The content of free oxyproline in the bone homogenate and soft tissues of experimental animals in different periods of development of experimental periodontitis and the use of quercetin ($M \pm m$)

Conditions of experiment and study indicator	Control, intact animals	White rats with experimental periodontitis			
		7	14	14 (after correction with quercetin)	30
Duration of experiment (days)	-	7	14	14 (after correction with quercetin)	30
Number of rats	10	8	8	8	8
Free oxyproline in bone homogenate, mkmol/g	3.40 ± 0.20	4.05 ± 0.21 $p_1 < 0.05$	5.35 ± 0.17 $p_1 < 0.01;$ $p_2 < 0.01$	4.73 ± 0.17 $p_1 < 0.01; p_3 < 0.05$	6.04 ± 0.20 $p_1 < 0.01; p_2 < 0.01;$ $p_3 < 0.05$
Free oxyproline in homogenate of soft tissues, mkmol/g	3.63 ± 0.15	4.49 ± 0.17 $p_1 < 0.01$	5.84 ± 0.17 $p_1 < 0.01;$ $p_2 < 0.01$	5.17 ± 0.24 $p_1 < 0.01;$ $p_3 < 0.05$	6.60 ± 0.22 $p_1 < 0.01; p_2 < 0.01;$ $p_3 < 0.05$

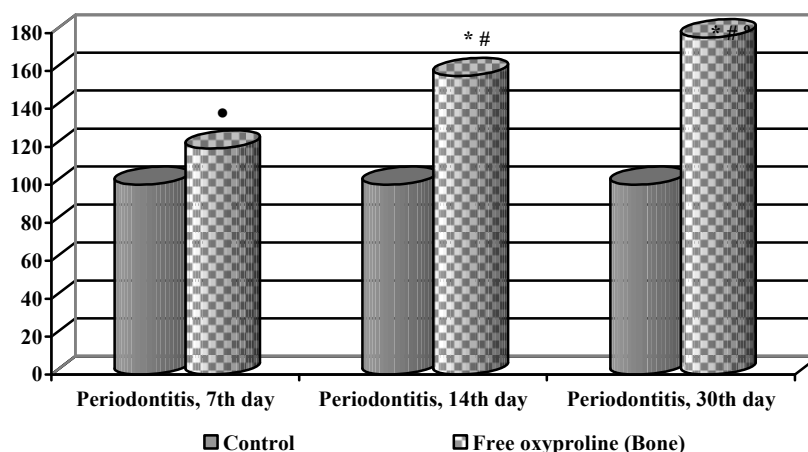
Notes: p_1 – the significance of differences relative to intact animals; p_2 – the significance of differences in animals with experimental periodontitis on the 7th day of the study; p_3 – the significance of differences in animals with experimental periodontitis on the 14th day of the study.

In the subsequent period, on the 14th day, the dynamics of the content of this marker of bone resorption continued to increase (Fig. 1), its indicator increased by 1.32 times ($p<0.01$), compared with animals on the 7th day of the experiment. Compared with the values of the intact group of animals, the content of free oxyproline in the bone homogenate was by 1.57 times higher ($p<0.01$).

A detailed analysis of the results of collagenolysis study revealed that the content of the marker of bone resorption in animals with experimental

bacterial-immune periodontitis on the 30th day of the study increased, compared with the 7th (by 1.49 times; $p<0.01$) and the 14th day (by 1.13 times; $p<0.05$). If we compare this indicator with the indicators of the control group, its level remained at a fairly high level, i.e. it was increased (by 1.78 times; $p<0.01$).

In the study of the marker of collagenolysis by the content of free oxyproline [7] in the homogenate of soft tissues of the periodontium, it was found that its relative content was by 1.24 times higher ($p<0.01$) compared with the control group of animals (Table).

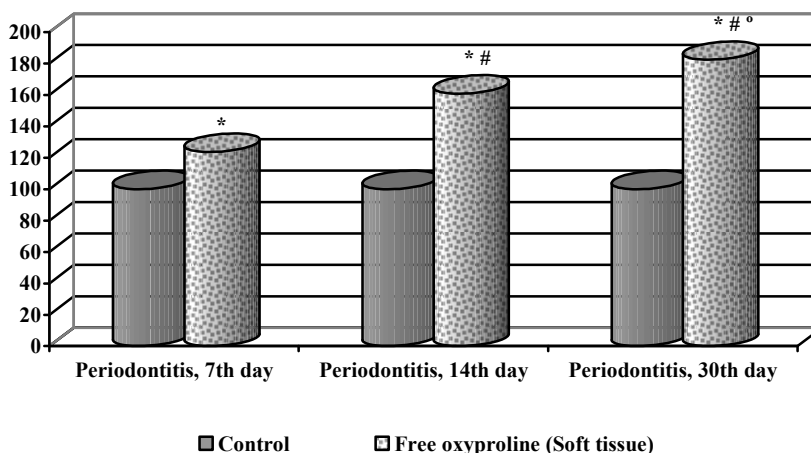


Notes: * – the significance of differences relative to intact animals ($p<0.01$); • – significance of differences relative to intact animals ($p<0.05$); # – significance of differences in animals with periodontitis on the 7th day of the experiment ($p<0.01$); ° – the significance of differences in animals with periodontitis on the 14th day of the experiment ($p<0.05$).

Fig. 1. The dynamics of free oxyproline content in the bone homogenate of rats under conditions of experimental periodontitis (in % of the control)

On the 14th day of the study, there was a statistically significant increase in these indicators (by 1.30 times; $p<0.01$) compared to the previous study period (Fig. 2). It should be noted that at this time

the indicator of resorption of connective tissue structures of the periodontium was higher than the control values (by 1.61 times; $p<0.01$).



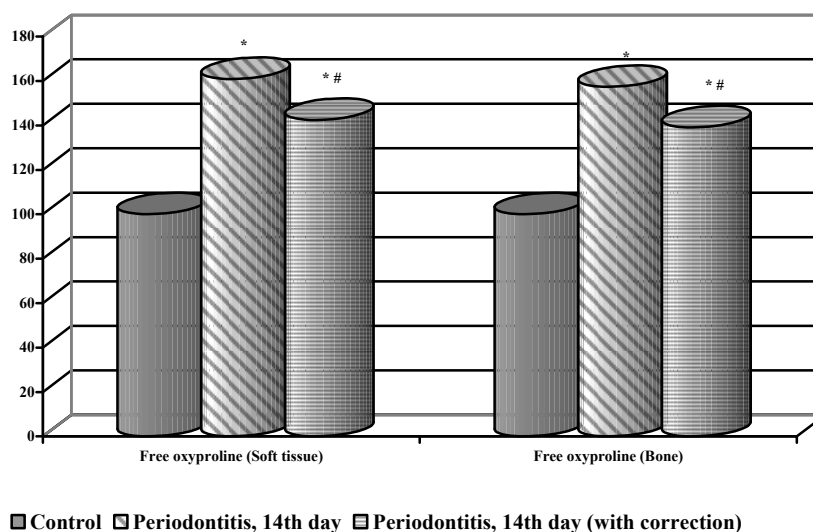
Notes: * – the significance of differences relative to intact animals ($p<0.01$); # – significance of differences in animals with periodontitis on the 7th day of the experiment ($p<0.01$); ° – the significance of differences in animals with periodontitis on the 14th day of the experiment ($p<0.05$).

Fig. 2. Dynamics of free oxyproline content in the soft tissue homogenate of white rats under the conditions of experimental periodontitis (in% of control)

The study of the above indicator of collagen resorption on the 30th day of development of experimental periodontitis revealed an increase in free oxyproline in the homogenate of soft tissues (by 1.30 times; $p < 0.05$) compared with the 14th day, and relative to the 7th day of the experiment – an increase by 1.47 times ($p < 0.01$). It should also be noted that its content was significantly higher relative to the control group of animals (by 1.82 times; $p < 0.01$).

It should be noted that in the correction of disorders as a result of the development of this

pathological process, there was also a decrease in the level of free oxyproline in the bone homogenate of the mandible by 1.13 times ($p < 0.05$), compared with the following groups of animals with experimental periodontitis on the 14th day who did not receive quercetin; this reflected a decrease in the manifestations of collagen destruction of bone tissue, which is part of the periodontal complex (Fig. 3). However, it was still higher than the control group of rats (by 1.39 times; $p < 0.01$).



Notes: * – the significance of differences relative to intact animals ($p < 0.01$); # – significance of differences in animals with periodontitis on the 14th day of the experiment without correction with quercetin ($p < 0.05$).

Fig. 3. Effect of quercetin on the content of free oxyproline in the homogenate of soft tissues of the periodontium and bone of white rats under conditions of experimental bacterial-immune periodontitis (in% of control)

Regarding the effect of this flavonol on the concentration of free oxyproline in the soft tissues of the periodontium adjacent to the central incisors of the mandible, then comparing the data of the day 14th in rats not receiving the drug, this figure was lower by 1.13 times ($p < 0.05$). However, its level still remained increased relative to the control group of animals (by 1.42 times; $p < 0.01$).

Connective tissue plays an important role in ensuring the functional state of the periodontium [12]. The intercellular matrix of connective tissue consists of three most important components – the main substance or gel-forming medium, collagen, reticular and elastic fibers, which provides rapid diffusion of substances and structural materials between blood and connective tissue cells [15]. Its components, such as collagen fibers and the main substance – proteoglycans and glycoproteins - are characterized by high sensitivity to the effects of endogenous and exogenous pathogens [11]. The leading place in the protective function of the gum epithelium, especially in preventing the

penetration of infection and toxins into adjacent tissues belongs to glycosaminoglycans, which, being "supporting" structures, can form complexes with other molecules that can retain and release various substances. Thus, the structural disorganization of glycosaminoglycans can lead to the disturbance of the barrier properties of connective tissue. The synthesis of glycosaminoglycans and proteoglycans always precedes the synthesis of collagen [8]. Collagen in the absence of glycosaminoglycans is a homogeneous mass, in the presence of chondroitin sulfate it has a clear striation characteristic of collagen fibers [9]. To assess the state of biopolymers of connective tissue structures of the periodontium, we determined the content of collagen monomers.

The introduction of egg white with a mixture of microorganisms reproduced the experimental model of periodontitis, which led to changes in its most important components of periodontal connective tissue – the main substance and protein structures. The destruction of the main substance of the

intercellular matrix of connective tissue led to the partial degradation of glycosaminoglycans, which in turn led to the destruction of gum collagen in both bone and soft periodontal tissues. Analysis of markers of connective tissue metabolism showed that the level of free oxyproline in the homogenates of bone tissue and soft tissues during the experiment increased, compared with the control group. The results of studies after the correction of this pathology with quercetin confirm the feasibility of using this flavonol.

CONCLUSIONS

1. Inflammation in the periodontal complex, which is caused by a combined effect of bacterial

and immune etiological factors, is accompanied by disorganization of connective tissue due to activation of collagenolysis in its bone and soft tissues with resorption of alveolar processes of the jaws.

2. Flavonol quercetin stabilizes the processes of collagenolysis in periodontal tissues, which is manifested by a decrease in the content of free oxyproline in the homogenate of soft tissues and bone tissue in experimental periodontitis of bacterial-immune origin.

Conflict of interests. The authors declare no conflict of interest.

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