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DEVELOPMENT OF ENDOGENOUS INTOXICATION AND CHANGES IN THE CONCENTRATION OF C-REACTIVE PROTEIN IN THE BLOOD IN BACTERIAL-IMMUNOID PERIODONTITIS ON THE BACKGROUND OF THE USE OF PROSTHETIC BASES

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Key words: *removable prosthetics, base materials, nylon prosthesis, acrylic prosthesis, periodontium, periodontitis, endogenous intoxication, C-reactive protein*
Ключові слова: *знімне протезування, базисні матеріали, нейлоновий протез, акриловий протез, пародонт, пародонтит, ендогенна інтоксикація, С-реактивний протеїн*

Absrtact. Development of endogenous intoxication and changes in the concentration of C-reactive protein in the blood in bacterial-immunoid periodontitis on the background of the use of prosthetic bases. Demkovych A.Ye., Poliukhovych Y.I., Piasetska L.V., Rosolovska S.O. *The purpose of this work was to determine changes in endogenous intoxication indicators and C-reactive protein levels in experimental bacterial-immune periodontitis under the conditions of using acrylic and nylon bases of removable dentures. Experimental studies were conducted on clinically healthy male white rats weighing 150-200 g, which were kept in conditions that met the requirements of sanitation and good laboratory practice (GLP). Acrylic and nylon dentures were made for rats, and bacterial-immune periodontitis was simulated by injecting Staphylococcus aureus and Streptococcus hemolyticus in egg protein into periodontal tissue. The level of endogenous intoxication was assessed by the erythrocyte index, the middle molecular weight molecules were determined by spectrophotometer, and the level of C-reactive protein was determined by enzyme-linked immunosorbent assay. The data were processed using nonparametric statistical methods in STATISTICA 10.0. Characterizing the indicators of the erythrocyte intoxication index of the experimental model of periodontitis and against the background of prosthetics with nylon bases, it should be noted that the results obtained were higher (by 1.27 times; ($p<0.001$) than the control indicators, but lower than the data of animals without prosthetics (by 1.44 times; $p<0.001$) and with acrylic prostheses (by 1.24 times; $p<0.001$), respectively. The content of C-reactive protein after fixation of acrylic bases was significantly increased compared to the intact group (by 2.50 times; $p<0.001$). The obtained data also showed that the level of this protein was by 1.60 times higher ($p<0.001$) compared to the indicators in rats with bacterial-immune periodontitis without the use of removable acrylic structures. In the blood serum of rats with inflammatory periodontal disease and prosthetics with nylon bases, the level of C-reactive protein also increased significantly: it was by 1.91 times higher ($p<0.001$) compared to the control group and by 1.22 times ($p<0.01$) compared to animals with periodontitis on 30^{th} day without dentures. The use of different types of prosthetic bases in bacterial-immune inflammation of the periodontium affects the level of endogenous intoxication, reducing the dynamics of the inflammatory process in the periodontal complex. However, the use of acrylic bases contributes to an increase in the level of C-reactive protein, which indicates a more negative effect of acrylic plastics on the main mechanisms of inflammation in periodontal tissues.*

Реферат. Розвиток ендогенної інтоксикації та зміни концентрації С-реактивного білка в крові при бактеріально-імунному пародонтиті на тлі використання протезних базисів. Демкович А.Є., Полюхович Ю.І., Пясецька Л.В., Росоловська С.О. *Метою дослідження було визначення змін показників ендогенної інтоксикації та рівня С-реактивного білка при експериментальному бактеріально-імунному пародонтиті за умов використання акрилових та нейлонових базисів знімних зубних протезів. Експериментальні дослідження проводили на клінічно здорових самцях білих щурів масою 150-200 г, яких утримували в умовах, що відповідали вимогам санітарії та належної лабораторної практики (GLP). Для щурів виготовили акрилові та нейлонові зубні протези, а бактеріально-імунний пародонтит змоделювали шляхом ін'єкцій Staphylococcus*

aureus і Streptococcus hemolyticus в яєчному білку в тканини пародонта. Рівень ендогенної інтоксикації оцінювали за еритроцитарним індексом, молекули середньої маси визначали спектрофотометром, а рівень С-реактивного протеїну – методом імуноферментного аналізу. Дані обробляли за допомогою непараметричних статистичних методів у STATISTICA 10.0. Характеризуючи показники еритроцитарного індексу інтоксикації експериментальної моделі пародонтиту та на тлі протезування нейлоновими базисами, слід зазначити, що отримані результати були вищими від показників контролю в 1,27 раза (p<0,001), але нижчими від даних тварин без протезування (в 1,44 раза; p<0,001) та з акриловими протезами (в 1,24 раза; p<0,001) відповідно. Вміст С-реактивного білка після фіксування акрилових базисів був достовірно підвищеним порівняно з інтактною групою (у 2,50 раза; p<0,001). Отримані дані також показали, що рівень цього протеїну був вищим в 1,60 раза (p<0,001) порівняно з показниками у щурів з бактеріально-імунним пародонтитом без застосування знімних акрилових конструкцій. У сироватці крові щурів із запальним процесом у пародонті та протезуванням нейлоновими базисами рівень С-реактивного білка також значно підвищився: він був вищим в 1,91 раза (p<0,001) порівняно з контрольною групою та в 1,22 раза (p<0,01) порівняно з тваринами з пародонтитом на 30-й день без протезів. Використання різних типів протезних базисів при бактеріально-імунному запаленні пародонта впливає на рівень ендогенної інтоксикації, зменшуючи динаміку запального процесу в пародонтальному комплексі. Однак застосування акрилових базисів сприяє збільшенню рівня С-реактивного білка, що вказує на більш негативний вплив акрилових пластмас на основні механізми розвитку запалення в пародонтальних тканинах.

Inflammatory processes in periodontal tissues often cause an excessive immune response to bacterial antigens, which leads to the destruction of bone and connective tissue, the progression of periodontitis and increased lipoperoxidation. This, in turn, causes the accumulation of peroxidation products and depletion of the body's antioxidant system, which leads to the development of hyperenzymemia and toxic substances [1, 2]. Endogenous intoxication is an important factor in the development of inflammatory processes in the periodontal complex [3] In case of periodontitis metabolism is disturbed, which causes the release of toxic products, in particular medium-weight molecules that destroy membrane structures. These molecules have high functional activity, which causes alteration of the body [4, 5] Periodontopathogenic microorganisms that produce endotoxins, in addition to the direct harmful effect on periodontal tissues, when entering the blood, stimulate the production of acute phase reactants of inflammation. The main periodontogenic microorganisms that produce endotoxins include *Porphyromonas gingivalis* (lipopolysaccharides, gingipains), *Aggregatibacter actinomycetemcomitans* (lipopolysaccharides, leukotoxin), *Tannerella forsythia* (lipopolysaccharides, proteases), *Prevotella intermedia* and *Fusobacterium nucleatum* (lipopolysaccharides). Their endotoxins interact with TLR-2 and TLR-4 receptors of immune system cells, stimulating macrophages and monocytes to synthesize IL-6, which, in turn, activates hepatocytes to produce C-reactive protein (CRP) [6, 7]. CRP activates the complement cascade and promotes phagocytosis of damaged cells. Its receptors on macrophages, monocytes and neutrophils enhance the local inflammatory response [8, 9].

A current direction is the study of the effect of dentures on the condition of oral tissues [10]. A response to wearing orthopedic structures can cause chronic pathologies in the periodontal complex, which is an entry gate for microorganisms and prosthetic components. Removable dentures, especially when in prolonged use, create favorable conditions for colonization by periodontogenic microorganisms, such as *Porphyromonas gingivalis*, *Aggregatib*acter actinomycetemcomitans, Tannerella forsythia, Prevotella intermedia, *Fusobacterium nucleatum*. The formation of a biofilm on the surface of orthopedic structures triggers a number of pathogenetic cascades. At the initial stage, bacterial products, in particular lipopolysaccharides and lipoteichoic acids, penetrate periodontal tissues, activate Toll-like receptors of immune system cells, stimulating the release of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α). This leads to activation of synthesis of C-reactive protein by hepatocytes, increased levels of lipoperoxidation, and the development of both local and systemic inflammation, which ultimately contributes to the destruction of periodontal tissues, with their own immune system that provides local homeostasis and protection [11, 12, 13].

Thus, tooth loss and orthodontic treatment can affect the functions of oral fluids, salivary glands and immune defense, which disturbs the balance of the oral microbiota, especially in the presence of generalized periodontitis. Despite efforts to minimize the negative impact of removable dentures, optimal methods for improving their biocompatibility and safety have not yet been found [14].

The purpose of the study was to investigate changes in endogenous intoxication indicators and C-reactive protein levels in experimental bacterial-immune periodontitis under the conditions of using acrylic and nylon bases of removable dentures.

MATERIALS AND METHODS OF RESEARCH

Experimental studies were conducted on clinically healthy male white rats weighing 150-200 g, which

were kept in vivarium conditions in compliance with sanitary and hygienic requirements and principles of good laboratory practice (GLP) [15]. The experimental animals were randomly divided into four groups: Group I – intact animals (control, n=10); Group II – rats with periodontitis on the 30th day of the study (n=8); Group III – animals with periodontitis on the 30th day, to whom acrylic bases were mounted (n=8); Group IV – rats with periodontitis on the 30th day, to whom nylon bases were mounted (n=8).

The dentures were manufactured according to generally accepted methods: acrylic bases were formed by thermal polymerization using the polymethacrylate material "Villacryl H Plus" (Zhermack, Poland) [16], and nylon bases were formed by pressure molding using the thermoplastic material "Vertex ThermoSens" (Vertex, Netherlands) [17]. The orthopedic structures were designed in such a way as not to cover the occlusal surfaces of the teeth, while ensuring reliable fixation on both central incisors of the lower jaw. Before the start of the experiment, all intact animals underwent a clinical examination of the oral cavity with an assessment of the condition of the gums and teeth, swabs from the gingival sulcus and their inoculation of nutrient media to exclude pathogenic microflora. No signs of inflammation, bleeding, hyperemia or edema of the gums were detected in the rats, which indicated the absence of periodontitis. The development of periodontitis in animals of the experimental groups was confirmed by the presence of characteristic clinical signs (redness, edema, exudate).

An experimental model of bacterial-immune periodontitis in experimental animals was created by injecting a suspension of microorganisms *Staphylococcus aureus* and *Streptococcus hemolyticus* in egg white directly into the periodontal tissue. Components of the cell wall of gram-positive bacteria, in particular lipoteichoic acids, peptidoglycan and lipoproteins, activated the inflammatory process through toll-like receptors 2, which contributed to the recognition of pathogens and the launch of innate immunity mechanisms. To enhance the immune response, experimental rats were simultaneously administered complete Freund's adjuvant. Repeated administration was carried out on the 14th day of the experiment in order to confirm the effectiveness of induction and chronicity of bacterial-immune periodontitis [18].

On the 30th day of the experiment, the experimental animals were euthanized by exsanguination under general anesthesia using sodium thiopental. After that, blood was collected from the heart of the experimental animal, serum was separated from it for further analysis of endogenous intoxication indicators (average mass molecules and erythrocyte intoxication index).

The determination of the level of middle molecules (MM) was carried out using a spectrophotometer SF-46 at a wavelength of 254 nm (for chain amino acids) and 280 nm (for aromatic amino acids) relative to distilled water. The results obtained were expressed in conventional units corresponding to extinction indices [19]. MM_{254} – the content of middle molecules with an absorption maximum at 254 nm (chain amino acids); MM_{280} – the content of middle molecules with an absorption maximum at 280 nm (aromatic amino acids). The method for determining the erythrocyte intoxication index was based on the properties of erythrocytes as universal adsorbents. It allows assessing the level of endogenous intoxication through changes in the sorption capacity of erythrocytes to methylene blue, a polar substance that almost does not penetrate their membrane. The level of C-reactive protein (CRP) in blood serum was determined by enzyme-linked immunosorbent assay according to the protocol of the company Monobind Inc. (USA) using the High Sensitivity CRP (hs-CRP) test system. All experimental procedures were performed in accordance with the provisions of the "European convention for the protection of vertebrate animals used for experimental and other scientific purposes" (Strasbourg, 1986) and the "General ethical principles of animal experiments" (Kyiv, 2001) [20]. The study was approved by the Bioethics Commission of the I. Ya. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine (protocol No. 78 dated August 18, 2024).

Data processing was carried out using nonparametric statistical methods in the STATISTICA 10.0 software (StatSoft, USA) (License AGAR909E415822FA). Analysis of variation series included calculation of the arithmetic mean (M) and its standard error (m). Statistical analysis was performed using nonparametric methods, the choice of which was due to the small sample size and greater reliability of such approaches under these conditions. To assess the reliability of differences between independent quantitative variables that had a normal distribution, the Mann-Whitney U-test was used. All statistical analyses were performed at a critical significance level of $p<0.05$ [21].

RESULTS AND DISCUSSION

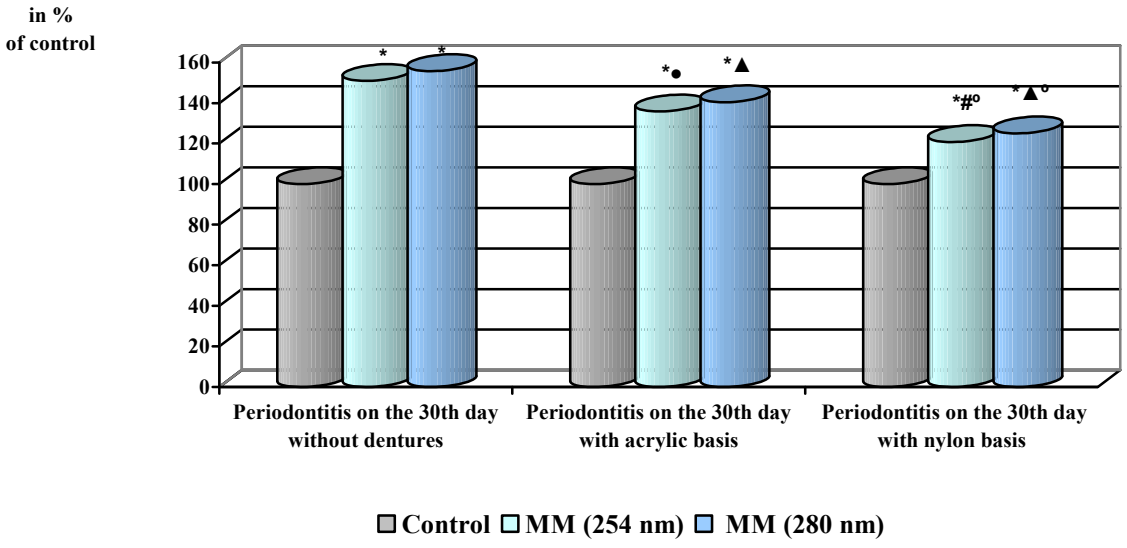
The indicators of middle molecules determined in blood serum at a wavelength of 254 nm (chain amino acids) significantly increased in periodontitis on the 30th day of the experiment (by 1.51 times; $p<0.001$) compared to the intact group (Table).

Changes in endogenous intoxication and C-reactive protein indicators in blood serum of experimental animals with experimental bacterial-immune periodontitis and under conditions of fixation of prosthetic bases (M±m)

Research conditions and indicators	Group 1	Group 2	Group 3	Gorup 4
Term of research (days)	-	30	30	30
Number of rats	10	8	8	8
MM_{254} (c.u.)	0,053±0,001	0,080±0,002 p_1<0,001	0,072±0,001 p_1<0,001; p_2<0,05	0,064±0,001 p_1<0,001; p_2<0,01; p_3<0,01
MM_{280} (c.u.)	0,052±0,001	0,081±0,001 p_1<0,001	0,073±0,001 p_1<0,001; p_2<0,001	0,065±0,002 p_1<0,001; p_2<0,001; p_3<0,01
EII (%)	46,47±0,37	85,24±0,68 p_1<0,001	73,48±0,62 p_1<0,001; p_2<0,001	59,07 0,40 p_1<0,001; p_2<0,001; p_3<0,001
C-reactive protein (mg/l)	0,32±0,02	0,50±0,02 p_1<0,001	0,80±0,03 p_1<0,001; p_2<0,001	0,61±0,02 p_1<0,001; p_2<0,01; p_3<0,01

Notes: p_1 – statistical significance of differences with the intact group of animals; p_2 – statistical significance of differences with the group of animals with bacterial-immune periodontitis on the 30th day without prosthetics; p_3 – statistical significance of differences with the group of animals with bacterial-immune periodontitis on the 30th day with the use of acrylic bases.

It is worth noting that when using acrylic bases in periodontitis on the 30th day, there was a decrease in MM_{254} in the blood serum in the same period compared to the study group without prosthetics (by 1.11 times; ($p<0.05$). However, this indicator was significantly higher compared to the control group of animals (by 1.36 times; $p<0.001$) (Fig. 1).



* – statistical significance of differences with the intact group of animals ($p<0.001$); ▲ – statistical significance of differences with the group of animals with bacterial-immune periodontitis on the 30th day without prosthetics ($p<0.001$); # – statistical significance of differences with the group of animals with bacterial-immune periodontitis on the 30th day without prosthetics ($p<0.01$); ● – statistical significance of differences with the group of animals with bacterial-immune periodontitis on the 30th day without prosthetics ($p<0.05$); ° – statistical significance of differences with the group of animals with bacterial-immune periodontitis on the 30th day using acrylic bases ($p<0.01$).

Fig. 1. Changes in the content of MM_{254} under the conditions of the development of bacterial-immune periodontitis and the use of prosthetic bases (in % of control)

When comparing the level of the above hydrophilic components of endogenous intoxication on the 30th day of the development of bacterial-immune periodontitis and using nylon bases, we found a significant increase in MM_{254} compared to the control (by 1.21 times; $p<0.001$) and a decrease by 1.11 times ($p<0.05$), compared to the 30th day of the experimental disease without prosthetics. It should be noted that this indicator was also significantly lower compared to the group of animals with acrylic prostheses (by 1.13 times; $p<0.01$).

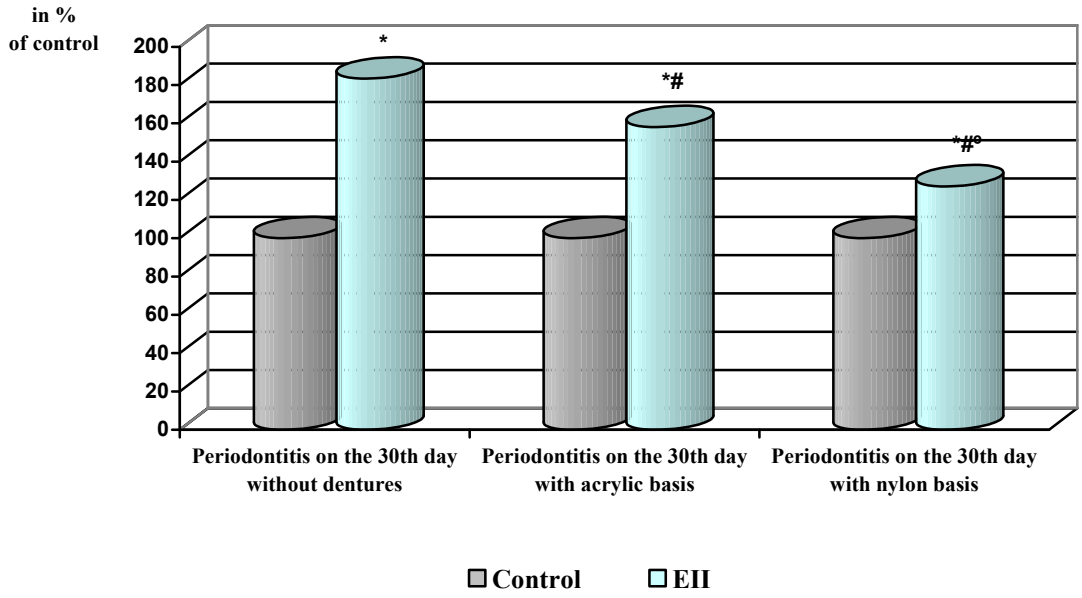
In experimental bacterial-immune periodontitis, on the 30th day, there was also observed an increase of medium molecules by 1.56 times ($p<0.001$) in the blood serum, which were examined at a wavelength of 280 nm (aromatic amino acids), as compared to the control (Table).

However, when using polymethylacrylate bases under conditions of periodontitis, this indicator decreased by 1.11 times; $p<0.001$, compared to the indicators of animals without prosthetic structures, and it was significantly higher compared to the intact group of animals (by 1.40 times; $p<0.001$).

In bacterial-immune inflammation in periodontal tissues under the condition of using thermoplastic nylon removable prosthetic structures, the concentration of aromatic amino acids in the composition of middle molecules significantly increased compared to the control (by 1.56 times ($p<0.001$). If compared with the 30th day of the experiment without prosthetics, this pool of middle molecules decreased (by 1.25 times; $p<0.001$). When comparing the level of MM_{280} relative to the group of animals with acrylic prostheses, it should be noted that it was lower (by 1.12 times; $p<0.01$) (Fig. 1).

As a result of the study of the effect of toxins on erythrocyte membranes in animals with bacterial-immune inflammation of the periodontium, significant changes were found in the level of erythrocyte intoxication index (EII). In particular, on the 30th day of periodontitis development in rats, an increase of this indicator by 1.83 times ($p<0.001$) was observed compared to the control (Table).

In animals with periodontitis on the 30th day under conditions of prosthetics with acrylic structures, an increase in the EII index (1.58 times; $p<0.001$) was also observed as compared to the intact group. However, these indicators were lower relatively animals without dentures (by 1.16 times; $p<0.001$), which indicated an increase in the adsorption capacity of erythrocytes during prosthetics and the course of inflammation (Fig. 2).



* – statistical significance of differences with the intact group of animals ($p<0.001$); # – statistical significance of differences with the group of animals with bacterial-immune periodontitis on the 30th day without prosthetics ($p<0.001$); ° – statistical significance of differences with the group of animals with bacterial-immune periodontitis on the 30th day with the use of acrylic bases ($p<0.001$).

Fig. 2. Changes in the erythrocyte intoxication index under the conditions of bacterial-immune periodontitis development and the use of prosthetic bases (in % of control)

Characterizing the indicators of the erythrocyte intoxication index in this experimental model of periodontitis and against the background of prosthetics with nylon bases, it should be noted that the results obtained were higher than the control indicators (by 1.27 times; ($p<0.001$), but lower than the

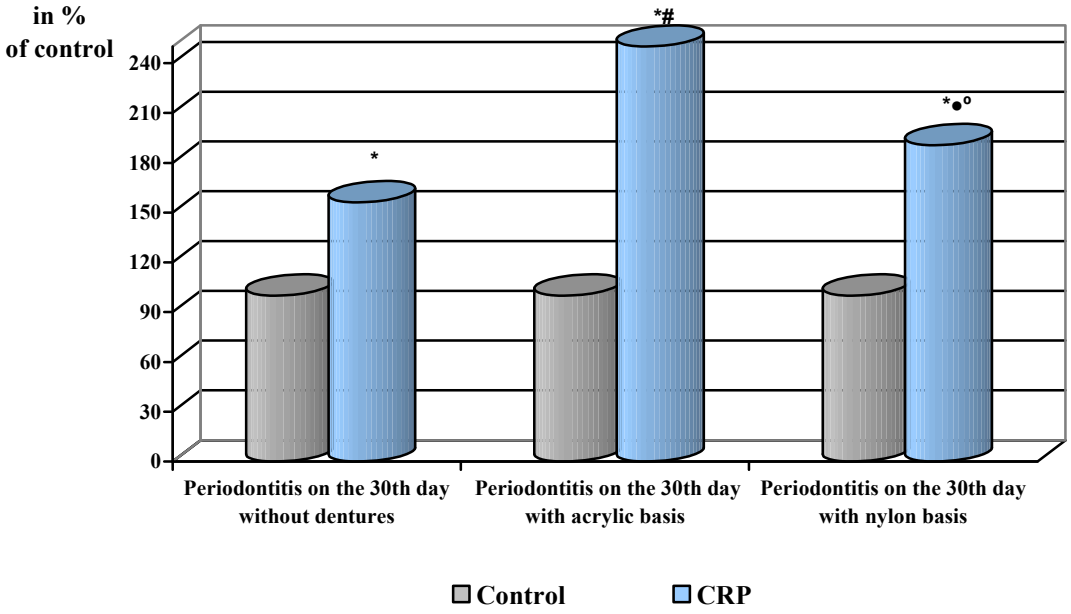
data of animals without prosthetics (by 1.44 times; p<0.001) and with acrylic prostheses (by 1.24 times; p<0.001), respectively.

The determination of the level of C-reactive protein in the blood serum of experimental animals with bacterial-immune periodontitis on the 30th day of the experiment showed that its content significantly exceeded (by 1.56 times; p<0.001) the indicators that were in intact rats.

The content of C-reactive protein after fixing acrylic bases significantly increased compared to the intact group (by 2.50 times; p<0.001). The obtained data also showed that the level of this protein was higher (by 1.60 times (p<0.001) as compared to the indicators in rats with bacterial-immune periodontitis without the use of removable acrylic structures (Table, Fig. 3).

In the blood serum of rats with inflammatory periodontal disease and prosthetics with nylon bases, the level of C-reactive protein also increased significantly (by 1.91 times; (p<0.001) compared to the control group and by 1.22 times (p<0.01) compared to animals with periodontitis on the 30th day without dentures (Fig. 3).

The use of nylon plastic bases caused a decrease in the level of CRP in the blood serum of animals with experimental bacterial-immune periodontitis compared to rats with the same pathology, but with acrylic structures (by 1.17 times; (p<0.01).



* – statistical significance of differences with the intact group of animals (p<0.001); # – statistical significance of differences with the group of animals with bacterial-immune periodontitis on the 30th day without the use of bases (p<0.001); ● – statistical significance of differences with the group of animals with bacterial-immune periodontitis on the 30th day without the use of bases (p<0.01); º – statistical significance of differences with the group of animals with bacterial-immune periodontitis on the 30th day with the use of acrylic bases (p<0.01).

Fig. 3. Changes in the content of C-reactive protein under the conditions of the development of bacterial-immune periodontitis and the use of prosthetic bases (in % of control)

Increased permeability of erythrocyte membranes is an indicator of an impairment of the functional state and structure of the plasma membranes of all cells of the body. The erythrocyte intoxication index reflects a decrease in sorption activity, which is due to changes in the lipid composition of cell membranes and a decrease in the functional activity of erythrocytes under the influence of toxic factors [22].

An increase in the level of the erythrocyte intoxication index in periodontitis indicates an impairment of the function of erythrocytes and an increase in the toxic load on the body. This may be a consequence of both systemic and local intoxication caused by bacterial infection and the inflammatory process in periodontal tissues.

Endogenous intoxication, in the context of the development and course of periodontitis, can cause general signs of intoxication, such as weakness, increased fatigue, affect the general condition of the body [23], as well as reduce the effectiveness and complicate the orthopedic treatment of dental patients.

Removable prosthetic structures can increase the risk of developing pathogenic microflora in the oral cavity due to their impact on the biofilm and the

surrounding environment. However, the data obtained, on the contrary, showed a decrease in endogenous intoxication rates in periodontitis with prosthetics. Perhaps the dentures changed the balance of the microflora, creating conditions for less aggressive bacteria, even if their total number remained high [24]. This change led to a decrease in systemic intoxication, despite the fact that local hygiene problems arose.

It should be specified that the primary one is the microbial load and the formation of endotoxins, which triggers an inflammatory reaction and leads to periodontitis. Dentures act as a factor that modifies the microbiota and enhances this process, especially in the case of acrylic materials.

The results of our studies have demonstrated a significant increase in the level of C-reactive protein in bacterial-immune inflammation of the periodontium in the blood serum, both without the use of removable dentures and with them. The increase in the concentration of CRP in the blood serum is probably due to the influence of inflammatory mediators (IL-1, IL-6), which are released in periodontitis and stimulate hepatocytes to synthesize it [25].

Comparative analysis of indicators between groups shows that prosthetics, regardless of the base material, reduces the level of endogenous intoxication in bacterial-immune periodontitis compared to the absence of prostheses. However, acrylic bases are associated with a more pronounced increase in CRP, which indicates their greater stimulating effect on systemic inflammation compared to nylon bases.

The obtained data are important for understanding the influence of dentures on the development and course of periodontitis and can be used to improve methods of treatment and prevention of periodontal diseases in patients with removable prosthetic structures.

CONCLUSIONS

1. During the development of the simulated inflammatory process in the periodontal complex, an increase in the level of endogenous intoxication is observed, which is manifested in an increase in the permeability of erythrocyte membranes and an increase in the concentration of middle molecules. The use of prosthetic bases of different types under conditions of bacterial-immune inflammation of the periodontal complex affects the level of endogenous intoxication of the body towards decrease in the dynamics of the inflammatory process in the periodontal complex.
2. Bacterial-immune inflammation of the periodontal complex in rats leads to a significant increase in the level of C-reactive protein in the blood serum by 56%, which indicates the presence of not only local inflammatory reactions in periodontitis, but also the development of a systemic inflammatory process. Fixation of prosthetic bases contributed to an increase in the level of C-reactive protein, especially under the conditions of using acrylic bases (by 60%), which indicates a more adverse effect of acrylic plastics on the key mechanisms of the development of the inflammatory process in periodontal tissues.

Contributors:

Demkovych A.Ye. – research concept and design, final approval of the article;

Poliukhovych Y.I. – article writing;

Piasetska L.V. – data collection, article editing;

Rosolovska S.O. – data analysis and interpretation.

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