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EFFECT OF A THERAPEUTIC AND PREVENTIVE COMPLEX ON THE BIOCHEMICAL INDICATORS OF THE MUCOUS MEMBRANE OF RATS' GUMS UNDER CONDITIONS OF A CARIES-INDUCING DIET AND DIETARY VITAMIN D DEFICIENCY ON THE BACKGROUND OF JAW BONE TISSUE DESTRUCTION

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The study was devoted to assessing the effect of the proposed therapeutic and prophylactic regimen on the biochemical parameters of the gingival mucosa in rats under conditions of a cariogenic diet and dietary vitamin D deficiency against a background of jawbone destruction. Experimental studies were conducted on 30 four-month-old Wistar rats. During the experiment, the animals were divided into three groups of 10 rats each: Group 1 – intact; Group 2 – trauma to the lower jaw region in the projection of the molar roots and modeling of dietary vitamin D deficiency against a background of a high-sugar cariogenic diet; Group 3 – pathology model and application of a therapeutic-preventive complex. Gingival homogenates were prepared, and levels of biochemical markers of systemic inflammation were determined: elastase activity and malondialdehyde content, as well as urease, lysozyme, and catalase activity. The therapeutic and preventive use of the proposed complex in rats contributes to the inhibition of the identified disorders, normalizing the studied parameters to the levels of intact animals, which indicates the pronounced antioxidant, anti-inflammatory, and antimicrobial properties of the complex.

Key words: bone destruction, rats, vitamin D deficiency, dental caries, biochemical parameters of the gums, experiment.

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ВПЛИВ ЛІКУВАЛЬНО-ПРОФІЛАКТИЧНОГО КОМПЛЕКСУ НА БІОХІМІЧНІ ПОКАЗНИКИ СЛИЗОВОЇ ОБОЛОНКИ ЯСЕН ЩУРІВ ЗА УМОВ КАРІЄСОГЕННОЇ ДІЄТИ ТА АЛІМЕНТАРНОГО ДЕФІЦИТУ ВІТАМІНУ D НА ТЛІ ДЕСТРУКЦІЇ КІСТКОВОЇ ТКАНИНИ ЩЕЛЕП

Робота була присвячена оцінці впливу запропонованого лікувально-профілактичного комплексу на біохімічні показники слизової оболонки ясен щурів за умов карієсогенної дієти та аліментарного дефіциту вітаміну D на тлі деструкції кісткової тканини щелеп. Експериментальні дослідження були проведені на 30 чотиримісячних щурах лінії Wistar стадного У ході експерименту тварини були поділені на три групи, по 10 щурів у кожній: 1 група – інтактні; 2 група – травма ділянки нижньої щелепи в проекції коренів молярів та моделювання аліментарного гіповітамінозу D на тлі високосахарозної карієсогенної дієти; 3 група – модель патології та застосування лікувально-профілактичного комплексу.. Готували гомогенати ясен та визначали рівень біохімічних маркерів системного запалення: активність еластази та вміст малонового діальдегіду, а також активність уреази, лізоциму та каталази. Лікувально-профілактичне застосування у щурів запропонованого комплексу сприяє гальмуванню виявлених порушень, нормалізуючи досліджувані показники до рівня інтактних тварин, що свідчить про виражені антиоксидантні, протизапальні та протимікробні властивості комплексу.

Ключові слова: деструкція кістки, щури, дефіцит вітаміну D, карієс, біохімічні показники ясен, експеримент.

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Improving the effectiveness of treatment for chronic apical periodontitis is a priority area in dentistry, as periodontal disease ranks third among periodontal conditions, following caries and pulpitis [4, 10]. Apical periodontitis is an inflammatory process that develops around the apex of the tooth root as a complication of caries and pulpitis. The chronic course of the disease results in bone destruction. As early as 1965, S. Kakehashi et al. demonstrated in an experiment that microorganisms infecting the pulp of root canals are the etiological factor in the development of a periapical inflammatory focus [12] Currently, the generally accepted concept holds that the development of inflammation and subsequent destruction of bone tissue around the apex of the tooth root are stimulated not by the bacteria themselves, but by their antigens, including components of the cell membrane. Local inducers of bone tissue destruction include: prostaglandins, pro-inflammatory cytokines (IL-1, IL-6, TNF), growth factors, products of bacterial origin (lipopolysaccharides; teichoic acids; lipid A-associated proteins), bacterial cell wall components (membrane proteins of A. actinomycetemcomitans, P. gingivalis, E. corrodens, Staphylococcus aureus, and Staphylococcus epidermidis), membrane polysaccharides, and others [11].

The primary objectives in the treatment of destructive forms of periodontitis are not only to eliminate the source of periodontal infection and

address the microflora of the root canals, but also to actively influence the granulation tissue in order to stimulate reparative processes at the site of destruction [8].

Vitamin D influences virtually all mechanisms of nonspecific defense against infectious agents and the immune response system [3]. Noteworthy is the link between vitamin D deficiency and musculoskeletal disorders, particularly osteoporosis, developmental defects of oral cavity structures, oxidative stress, and other processes related to dental pathology [5, 6]. Therefore, there is a need for relevant experimental and clinical studies, as well as the development of a well-founded therapeutic and preventive regimen.

The purpose of the study was to evaluate the effect of the proposed therapeutic and preventive regimen on the biochemical parameters of the gingival mucosa in rats under conditions of a cariogenic diet and dietary vitamin D deficiency against a background of jawbone destruction.

Materials and methods. Experimental studies were conducted using 30 male Wistar rats of herd breeding, 4 months old with an average body weight of 214.8±3.2 g. Inclusion criteria were: confirmed Wistar strain and male sex; age exactly 16±1 weeks (verified from breeding records); body-weight falling within cohort mean at baseline (214.8±3.2 g); absence of visible injury, malocclusion, or systemic/oral pathology on veterinary inspection; no previous exposure to experimental procedures or pharmacological agents. Exclusion criteria, applied immediately prior to random assignment, included: clinically detectable disease or behavioral abnormalities; weight outside the predefined range; wounds or oral lesions; aggressive behavior; modeling errors; and failure to adapt during the 7-day acclimatization period. Only male Wistar rats were enrolled to minimize biological variability introduced by sex-specific endocrine cycles.

The study was conducted from July 1, 2025, to August 2, 2025. All animals were maintained in the accredited barrier-type vivarium of SE "ISMFS NAMS" under the husbandry conditions specified in the institute's standard operating procedure, which fulfils both Ukrainian legislation and ARRIVE 2.0 recommendations. Briefly, rats were group-housed (4–5 per cage) in individually ventilated Euro-Type IV polycarbonate cages (floor area ≈ 1500 cm²; internal dimensions 425×266×185 mm) fitted with stainless-steel wire lids and placed on ventilated racks delivering 12±2 air changes h^{-1}. Cages contained 3 cm of autoclaved aspen-wood shavings (LIGNOCEL® Hygienic Animal Bedding, JRS GmbH) that were replaced twice weekly. Environmental enrichment was provided ad libitum and comprised shredded paper nesting material (Nestlets), hardwood gnawing blocks (2×2×6 cm), and a cardboard tunnel (⌀ 9 cm, length 12 cm) per cage; items were refreshed at each cage change.

The room was held at 21±2 °C with 55–75 % relative humidity and a 12:12 h light/dark cycle (lights on 07:00–19:00). Noise was <50 dB SPL outside scheduled stress-exposure periods. Reverse-osmosis-filtered water was supplied in polycarbonate bottles with stainless-steel sipper tubes and replaced thrice weekly.

Daily husbandry included visual health checks and removal of soiled enrichment; full cage sanitisation (hot-water wash and autoclave) was performed weekly.

Each rat was weighed, assigned an individual code, and allocated to an experimental arm by simple computer-generated randomisation carried out with Microsoft Excel software. Animals were assigned to three experimental groups:

1. Intact group – rats that underwent no surgical procedures and received no drug administration; they were fed a complete balanced diet, n=10;

2. Pathology (TDK) – trauma to the lower jaw region in the projection of the molar roots and modeling of dietary hypovitaminosis D against the background of a high-sugar cariogenic diet (CD), n=10;

3. Treatment (TDK+TPC) – trauma to the mandibular region in the projection of the molar roots, administration of a therapeutic and prophylactic complex (TPC) against a background of simulated dietary hypovitaminosis D using a high-sugar cariogenic diet, n=10.

No animal met any exclusion criterion, and there were no deaths or withdrawals after group allocation. consequently, the composition of all three groups remained unchanged throughout the 33-day observation period, and data from every animal were included in the final analysis.

Experimental studies were conducted at the "Laboratory of Biochemistry and Vivarium" of the SE "The Institute of stomatology and maxilla-facial surgery National academy of medical sciences of Ukraine" (SE "ISMFS NAMS"). All experiments on rats were conducted according to standard operating procedures approved by SE "ISMFS NAMS", developed in accordance with the Guidelines of the Pharmacological Committee of the Ministry of Health of Ukraine, the "General Ethical Principles of Animal Experiments" adopted by the Seventh National Congress on Bioethics (Kyiv, 2019) and was guided by the recommendations of the European Convention for the Protection of Vertebrate Animals for Experimental and Other Scientific Purposes (Strasbourg, 1985). Studies recommended by the Commission on Bioethical Expertise (conclusion of the bioethics commission of the ONMedU, protocol No. 26 of 23/10/2024).

Injuries to the lower jaw were induced in a laboratory setting using a portable dental drill and a sterile carbide bur under thiopental anesthesia.

To study the effect of cariogenic factors on the recovery of the injured jaw, the cariogenic diet developed by M.S. Bugayova and S.A. Nikitin, as modified by I.V. Khodakov et al. (2023) [7], was used.

The reduction of oil content by 0.5 % was justified by the use of this oil for dosing retinol acetate (34.4 mg (100,000 IU)/ml. Manufacturer: PJSC "Technolog," Uman, Ukraine). Vitamin A was administered to rats at a rate of 0.048 ml per 100 g of feed (48,000 IU). The removal of "Undevit" from the diet was justified by the use of vitamins A and D3 in the study. The reduction in oil content in the feed was compensated for by increasing the content of breadcrumbs by 0.5 %, resulting in the following composition of the cariogenic diet: refined sugar (57 %); skimmed cow's milk cheese (18.5 %); white wheat bread crumbs (19 %); unrefined sunflower oil (4.5 %); table salt (1 %).

Animals first received "Mumie" gel (centaury infusion + echinacea infusion + sage infusion + mumie + 0.05 % chlorhexidine), developed by the Laboratory for the Development and Research of Oral Hygiene Products of the State Establishment "The Institute of Stomatology and Maxillofacial Surgery of the National Academy of Medical Sciences of Ukraine" (State Sanitary and Epidemiological Expertise Conclusion No. 1378/16 dated 10 December 2019): 0.3 mL per 200 g of body weight, administered per os once daily, to provide anti-inflammatory, adaptogenic, regenerative, osteotropic, anticoagulant, antibacterial, haemostatic, and immunomodulatory effects, as well as to increase salivation rate. Immediately afterwards, the animals received "Osteovit" (glucosamine sulfate + chondroitin sulfate + Boswellia sarca extract + vitamin D3 + calcium carbonate; LLC "Elite-Pharm", Dnipro, Ukraine): 150 mg/kg of body weight, administered to reduce inflammation, support cartilage and bone tissue regeneration, provide calcium required for bone mineralisation, and promote calcium and phosphorus absorption while supporting immune function. The animals also received Aquadetrim Vitamin D3 water solution (INN Cholecalciferol; Medana Pharma S.A., Poland): 0.000297 mL per 100 g of body weight (4.45 IU of vitamin D3), administered per os to regulate calcium and phosphate metabolism, promote proper skeletal mineralisation and growth, and participate in immune-system function. In addition, the animals received "Forteza" 0.15 % oral spray (INN Benzydamine hydrochloride; Abdi Ibrahim Ilaç Sanayi ve Ticaret A.Ş., Istanbul, Türkiye): 0.3 mL per 200 g of body weight, administered for its analgesic, anti-inflammatory, antiexudative, and disinfectant properties, as benzydamine penetrates the epithelial layer and reaches effective concentrations in inflamed tissues.

At the conclusion of the experiment, the animals were euthanized on the 33rd day of the study under thiopental anesthesia (20 mg/kg) by total exsanguination from the heart. Gingival homogenates were prepared at a concentration of 20 mg/mL in 0.05 M Tris-HCl buffer, pH 7.5, and levels of biochemical markers of systemic inflammation were determined: the activity of the proteolytic enzyme elastase and the content of the end product of lipid peroxidation – malondialdehyde (MDA), as well as the activity of urease (an indicator of microbial contamination) and the antioxidant enzyme catalase, and the level of lysozyme (an indicator of nonspecific immunity). The degree of dysbiosis was calculated based on the ratio of the relative activities of urease and lysozyme using the method of A. P. Levitsky. In addition, the antioxidant-prooxidant index (API) was calculated based on the ratio of catalase activity to MDA concentration [2].

Data processing was carried out with MS Excel 2010. Prior to parametric testing, the Shapiro-Wilk normality test was applied to each continuous variable; none showed significant deviation from a Gaussian distribution ($p>0.05$). Therefore, inter-group comparisons were performed with the two-tailed Student's t-test. When pair-wise contrasts were required (Control × Comparison, Control × Intervention, Comparison × Intervention), the family-wise type-I error rate was controlled with the Bonferroni adjustment. [1].

Results of the study and their discussion. The studied indicators were selected as integral biochemical characteristics of the functional state of the gingival mucosa under the modeled pathological conditions. Their assessment made it possible to determine the direction and severity of metabolic disturbances developing in response to jawbone injury in combination with a cariogenic diet and dietary vitamin D deficiency. Table 1 presents data on the biochemical parameters of rat gums under conditions of a cariogenic diet and dietary vitamin D deficiency against a background of jawbone destruction.

The data show that in the gums of the second group of animals, in which jawbone destruction was simulated under conditions of a cariogenic diet and dietary vitamin D deficiency, there was an intensification of inflammatory processes and lipid peroxidation: MDA levels increased significantly by 34.9 % ($p<0.002$), and the activity of elastase, one of the most important markers of inflammation, significantly increased by 21.8 % ($p<0.001$) compared to the intact group, indicating an intensification of inflammatory processes in the gingival mucosa. Administration of TPC for 33 days in animals of the third group contributed to an

effective reduction in the intensity of lipid peroxidation and a reduction in inflammatory processes. Thus, in the gums of rats in the third group, there was a tendency toward a 17.4 % decrease in elastase activity ($p_1<0.002$) and a significant 29.1 % reduction in MDA levels ($p_1<0.01$) compared to the parameters in the second group. Thus, the use of the TPC indicates a significant reduction in inflammation in the gingival mucosa of rats against the background of jawbone destruction under conditions of a cariogenic diet and dietary vitamin D deficiency, and therefore, the pronounced anti-inflammatory effect of the complex.

Table 1

Biochemical parameters of rat gums under conditions of a cariogenic diet and dietary vitamin D deficiency against a background of jawbone destruction, M±m

Indices / Group	Catalase activity, mkat/kg	MDA content, mmol/kg	API	Elastase activity, mU/kg
1. Intact group, n=10	8.15±0.46	17.96±1.65	4.54±0.21	49.84±1.87
2. Pathology + CD, n=10	6.82±0.32 p<0.05	27.57±2.50 p<0.002	2.47±0.16 p<0.001	63.75±2.14 p<0.001
3. Pathology + CD + TPC, n=10	7.85±0.38 p>0.6 $p_1<0.05$	19.58±1.70 p>0.5 $p_1<0.01$	4.0±0.25 p>0.2 $p_1<0.001$	52.70±2.10 p>0.3 $p_1<0.002$

Note: p – significance relative to the intact group; p_1 – significance relative to the group 2.

The activity of the antioxidant defense marker catalase decreased by 16.3 % (p<0.05) in the pathological group. Long-term administration of the proposed TPC for 33 days led to the normalization of catalase activity in rats of group 3 to a level practically equivalent to that of the intact animal group. The intergroup difference between the indicators of groups 2 and 3 was 13.1 % in males ($p_1<0.05$). The functional state of the gums and their resistance capacity are most objectively characterized by the ratio of antioxidant enzyme activity to lipid peroxidation products in tissues – the antioxidant-prooxidant index. The API was significantly elevated by 38.3 % (p<0.001) in animals of the "Pathology + CD + TPC" group compared to the group of rats with simulated pathology.

Urease activity reflects the degree of contamination by opportunistic microbiota that synthesize this enzyme in the oral cavity. The level of microbial colonization can be indirectly assessed based on urease activity (Table 2).

Table 2

Effect of TPC on urease and lysozyme activity in the gingival mucosa of rats under conditions of a cariogenic diet and dietary vitamin D deficiency against a background of jawbone destruction, M±m

Indices / Group	Urease activity, μkat/kg	Lysozyme activity, units/kg	Degree of dysbiosis (DD),
1. Intact group, n=10	0.420±0.010	342±23	1.0±0.09
2. Pathology + CD, n=10	0.730±0.024 p<0.001	256±15 p<0.002	2.32±0.11 p<0.001
3. Pathology + CD + TPC, n=10	0.442±0.012 p>0.2 $p_1<0.001$	327±19 p>0.7 $p_1<0.02$	1.09±0.09 p>0.8 $p_1<0.001$

Note: p – significance relative to the intact group; p_1 – significance relative to the group 2.

A statistically significant 1.7-fold increase was observed in rats with simulated pathology (p<0.001). In animals of the 3rd group, against the background of pathology modeling and TPC administration, urease activity decreased, approaching the level of the intact group. The intergroup difference between the 2nd and 3rd groups was 39.4 % ($p_1<0.001$).

Thirty-three days after TPC administration, lysozyme activity in the gums of experimental animals remained virtually unchanged compared to the intact group. The 1.3-fold increase in the activity of the antimicrobial enzyme lysozyme in rats of group 3 can be considered an adaptive response to the development of pathology and the result of TPC administration.

The state of the "antimicrobial defense and opportunistic microbiota" system in the oral cavity is clearly reflected by the dysbiosis index. In animals of group 2, the DD exceeded the corresponding indicator in animals of the intact group by 2.3 times. After the application of the TPC, the degree of oral dysbiosis in rats corresponded to normal values.

Thus, the results of the experimental studies indicate inflammation, contamination with opportunistic bacteria, a decrease in antioxidant defense, and an increase in lipid peroxidation processes in the study material under conditions of a cariogenic diet and dietary vitamin D deficiency against a background of jawbone destruction, as well as inhibition of inflammation of the oral mucosa, which justifies the use of the proposed TPC in clinical practice for patients with destructive periodontal lesions.

The obtained results confirm that the modeled pathology, which combined mandibular bone injury, a cariogenic diet, and dietary vitamin D deficiency, was accompanied by a pronounced inflammatory and oxidative shift in the gingival mucosa. This interpretation is consistent with the general concept of apical and periapical inflammation described in the cited literature, according to which microbial antigens and their structural components initiate cytokine-dependent tissue destruction and support chronic inflammatory reactions in periapical tissues [10–12]. In our study, this pathogenic pattern was reflected by a significant increase in elastase activity and malondialdehyde content, together with a decrease in catalase activity and the antioxidant-prooxidant index. These changes indicate activation of proteolysis and lipid peroxidation with simultaneous weakening of antioxidant defense, which agrees with the view that destructive periodontal lesions are associated not only with infection itself, but also with secondary oxidative damage of surrounding tissues [8]. Our data also support the assumption that vitamin D deficiency aggravates inflammatory changes in oral tissues. This is in line with the publications included in the reference list, where vitamin D is considered an important regulator of immune responsiveness, mineral metabolism, and oral tissue homeostasis [3, 5, 6]. In the present experiment, vitamin D deficiency combined with a cariogenic diet and jawbone destruction was associated with increased MDA and elastase levels, reduced catalase activity, increased urease activity, decreased lysozyme activity, and a 2.3-fold elevation in the dysbiosis index. Thus, our findings extend the positions formulated in earlier reviews and observational studies [3, 5, 6] by demonstrating, in an experimental model, that vitamin D deficiency is associated not only with impaired mineral metabolism, but also with deterioration of local antioxidant protection, nonspecific antimicrobial defense, and microbial balance in the gingival mucosa. These findings are also concordant with the current concept that vitamin D insufficiency promotes gingival inflammation and periodontal vulnerability through immune dysregulation and impaired control of microbial challenge. The corrective effect of the therapeutic and preventive complex in our study was manifested by a decrease in elastase and MDA, restoration of catalase activity, normalization of the antioxidant-prooxidant index, reduction of urease activity, preservation of lysozyme activity close to intact values, and normalization of the dysbiosis index. Such multidirectional improvement is pathogenetically justified, since the treatment strategy for destructive periodontal lesions should include not only suppression of infection, but also stimulation of reparative processes in the lesion area [8]. The favorable shifts observed in the treatment group are likewise in agreement with the literature data indicating that local inflammatory lesions of the oral cavity may be reduced by agents with anti-inflammatory, antimicrobial, and tissue-protective activity. In particular, the anti-inflammatory component of the complex is supported by the known pharmacological properties of benzydamine, whereas the osteotropic and immunomodulatory orientation of the regimen corresponds to the role of vitamin D and calcium-containing support in maintaining bone and mucosal homeostasis [3, 5, 6]. A relevant experimental study demonstrated that apical periodontitis in rats induces significant alterations in oxidative stress parameters, thereby confirming the importance of oxidative imbalance in periapical tissue pathology and indirectly supporting the biological plausibility of the antioxidant effects observed in our work [9].

Limitations. A limitation of this study is that the experimental design was focused on biochemical assessment of gingival homogenates; therefore, the findings characterize mainly the metabolic, inflammatory, antioxidant, and antimicrobial components of the modeled pathology and its correction.

Conclusions

1. Analysis of the results of biochemical studies of rat gingival mucosa homogenates showed that the administration of a cariogenic diet against a background of dietary vitamin D deficiency and destruction of jawbone tissue led to a disruption of the LPO-AOS system, characterized by an increase in lipid peroxidation processes (a 34.9 % increase in MDA content, a 16.3 % decrease in catalase activity), an increase in inflammatory processes in the gingival mucosa (a 21.8 % increase in elastase activity), and an increase in microbial colonization (by 42.5 %).

2. Therapeutic and prophylactic use of the proposed complex in rats helps to inhibit the identified disorders under conditions of a cariogenic diet and dietary vitamin D deficiency against a background of jawbone destruction, normalizing or bringing the studied parameters closer to the levels of intact animals, which indicates the complex's pronounced antioxidant, anti-inflammatory, and antimicrobial properties.

3. Further study of the proposed TPC's effect on oral health will enable dentists to positively influence the healing process of bone and mucosa in the area of damage. The effectiveness of these measures depends, first and foremost, on early diagnosis, which will allow for the correction of abnormalities, ensure normal physiological regeneration of bone tissue, and improve the patient's oral health.

Prospects for further research lie in the development of an effective method for preventing complications and accelerating healing in chronic destructive periodontitis, depending on serum vitamin D levels, using an appropriate therapeutic and preventive regimen.

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Conflict of interest. The authors have no conflicts of interest to declare.

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