УДК 616.314.18-002.4-002.2-092.11
https://doi.org/10.20538/1682-0363-2026-1-54-60

The Role of IL-1β and RANK-L in the Pathogenesis of Chronic Periodontitis

Davidovich N.V., Galieva A.S., Sabanaev M.A., Solovieva N.V., Bazhukova T.A.

Northern State Medical University of the Ministry of Healthcare of the Russian Federation
51 Troitskiy Ave., 163000 Arkhangelsk, Russian Federation

ABSTRACT

Aim. To establish the role of interleukin 1β (IL-1β) and receptor activator of nuclear factor κB ligand (RANK-L) in combination with microbial invasion in chronic periodontitis.

Materials and methods. The clinical material was the gingival fluid of patients with chronic periodontitis (60 people) and with an intact periodontium (28 people). The content of IL-1β and RANK-L was determined using enzyme-linked immunosorbent assay (ELISA). Markers of periodontopathogenic bacteria were isolated during real-time polymerase chain reaction (PCR). Statistical data processing was carried out using the STATA v.14 software package.

Results. In the group of patients with chronic periodontitis, the levels of IL-1β and RANK-L were significantly higher than in individuals with intact periodontium (median 37.1 [32.9; 41.3] pg/ml versus 2.5 [1.9; 3.4], $p < 0.001$) and median 6.3 [4.2; 10.4] pg/ml versus 0.0 [0.0; 0.7], $p < 0.001$), respectively). In patients with chronic periodontitis, periodontopathogens were detected in 100.0% of the cases (*A. actinomycetemcomitans* – 81.7%, *P. gingivalis* – 76.7%, *T. forsythia* – 70.0%, associations – 60.0%), while in the group with intact periodontium, periodontopathogenic bacteria were isolated in only 32.1%. In the group of patients with periodontitis, the quantitative content of IL-1β and RANK ligand positively correlated with all periodontopathogens of the first order, while the strongest correlations were found with an average degree of destruction of periodontal tissues.

Conclusion. The presence of relationships between *A. actinomycetemcomitans, P. gingivalis,* and *T. forsythia* with an increased content of the proinflammatory cytokine IL-1β and the immune mediator RANK-L and the severity of bone tissue destruction may indicate a key synergistic effect of these cytokines in the inflammatory and bone-plastic events of the pathogenesis of chronic periodontitis.

Keywords: cytokines; periodontopathogenic bacteria; chronic periodontitis

Conflict of interest. The authors declare the absence of obvious and potential conflict of interest related to the publication of this article.

Source of financing. This work was supported by the "Internal Grant Competition for Young Scientists in Priority Development Areas of the Federal State Budgetary Educational Institution of Higher Education, Northern State Medical University, Arkhangelsk" No. 162 dated February 5, 2021, for the project "Monitoring the Development of Antibiotic Resistance in Oral Microbial Biotopes and Optimization of Pathogenetic Approaches in the Treatment of Inflammatory Periodontal Diseases".

Conformity with the principles of ethics. All patients signed a voluntary informed consent to participate in the study. The study was approved by the local Ethics Committee at Federal State Budgetary Educational Institution of Higher Education Northern State Medical University (Arkhangelsk) of the Ministry of Healthcare of the Russian Federation (Minutes No. 8/11 dated November 28, 2018).

For citation: Davidovich N.V., Galieva A.S., Sabanaev M.A., Solovieva N.V., Bazhukova T.A. The Role of IL-1β and RANK-L in the Pathogenesis of Chronic Periodontitis. *Bulletin of Siberian Medicine.* 2026;26(1):54–60. https://doi.org/10.20538/1682-0363-2026-1-54-60.

✉ *Davidovich Nataliia V.,* nvdavidovich@gmail.com

Роль IL-1β и RANK-L в патогенезе хронического пародонтита

Давидович Н.В., Галиева А.С., Сабанаев М.А., Соловьева Н.В., Бажукова Т.А.

Северный государственный медицинский университет (СГМУ)
Россия, 163000, г. Архангельск, пр. Троицкий, 51

РЕЗЮМЕ

Цель. Установить роль интерлейкина 1β (IL-1β) и лиганда активатора рецептора ядерного фактора κB (RANK-L) на фоне микробной инвазии в патогенезе хронического пародонтита.

Материалы и методы. Клиническим материалом послужила десневая жидкость пациентов с хроническим пародонтитом (60 человек) и с интактным пародонтом (28 человек). С помощью иммуноферментного анализа определяли содержание IL-1β и RANK-L. Маркеры пародонтопатогенных бактерий выделяли в ходе полимеразной цепной реакции в режиме реального времени. Статистическая обработка данных проведена с помощью пакета программ STATA v. 14.

Результаты. В группе пациентов с хроническим пародонтитом уровни IL-1β и RANK-L были значительно выше, чем у лиц с интактным пародонтом (37,1 [32,9; 41,3] пг/мл против 2,5 [1,9; 3,4], $p < 0,001$) и 6,3 [4,2; 10,4] пг/мл против 0,0 [0,0; 0,7], $p < 0,001$) соответственно). У пациентов с хроническим пародонтитом частота выявления пародонтопатогенов составила 100,0% (*A. actinomycetemcomitans* – 81,7%, *P. gingivalis* – 76,7%, *T. forsythia* – 70,0%, ассоциации – 60,0%), тогда как в группе с интактным пародонтом пародонтопатогенные бактерии выделялись лишь у 32,1%. В группе пациентов с пародонтитом количественное содержание IL-1β и лиганда RANK положительно коррелировало со всеми пародонтопатогенами I порядка, при этом наиболее сильные корреляции были выявлены при средней степени деструкции тканей пародонта.

Заключение. Наличие взаимосвязей между выделением пародонтопатогенов *A. actinomycetemcomitans, P. gingivalis, T. forsythia* с повышенным содержанием провоспалительного цитокина IL-1β и иммунного медиатора RANK-L, а также выраженностью степени деструкции костной ткани может свидетельствовать о ключевом синергидном эффекте данных цитокинов в воспалительных и деструктивных процессах патогенеза хронического пародонтита.

Ключевые слова: цитокины, пародонтопатогенные бактерии, хронический пародонтит

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Работа выполнена при финансовой поддержке «Внутреннего конкурса грантов для молодых ученых по приоритетным направлениям развития ФГБОУ ВО СГМУ г. Архангельск» № 162 от 05.02.2021, проект «Мониторинг формирования антибиотикорезистентности микробных биотопов полости рта и оптимизация патогенетических подходов в лечении воспалительных заболеваний пародонта».

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено локальным этическим комитетом СГМУ (протокол № 8/11 от 28.11.2018).

Для цитирования: Давидович Н.В., Галиева А.С., Сабанаев М.А., Соловьева Н.В., Бажукова Т.А. Роль IL-1β и RANK-L в патогенезе хронического пародонтита. *Бюллетень сибирской медицины.* 2026;26(1):54–60. https://doi.org/10.20538/1682-0363-2026-1-54-60.

INTRODUCTION

The multifactorial etiology of periodontal diseases determines the complexity of their pathogenesis and requires a systematic approach to study the mechanisms driving pathology development. A key link in the pathogenic chain is an imbalance in the immune response system, which leads to an inappropriate inflammatory response to the invasion of periodontopathogenic microbiota [1]. Cytokines play a central role in the pathogenesis of periodontal diseases, acting as the main mediators of intercellular interactions and the activation of immune and stromal cells, leading to local inflammation and tissue damage, including the destruction of periodontal ligaments, gingiva, and alveolar bone resorption [2].

Immunopathological mechanisms of periodontitis development are characterized by a response to microbial invasion by periodontopathogenic microorganisms (mainly *P. gingivalis, A. actinomycetemcomitans,* and *T. denticola*) and by an imbalance between pro- and anti-inflammatory cytokines, which leads to the development of chronic inflammation [3]. A number of studies have demonstrated that interleukin 1β (IL-1β), IL-6, and tumor necrosis factor-alpha (TNFα) may play a key role in the mechanisms driving periodontitis development [4, 5].

Chronic periodontitis is characterized by alveolar bone resorption caused by the proliferation of immature osteoclast precursors and their differentiation into mature osteoclasts, which promotes the degradation of organic and inorganic bone components. Osteoclast differentiation is primarily regulated by the receptor activator of nuclear factor κB (RANK), RANK ligand (RANK-L), and osteoprotegerin. RANK-L, also known as osteoclast differentiation factor, osteoprotegerin ligand, and TNF-associated activating cytokine, is the most potent known inducer of osteoclastogenesis [6].

Although IL-1β was one of the first cytokines proposed as a relevant biomarker for the early diagnosis of periodontitis [2], its relationship with RANK-L, periodontopathogenic microflora, and the degree of periodontal tissue destruction remains poorly understood. Therefore, the aim of this study was to establish the role of IL-1β and RANK-L in the pathogenesis of chronic periodontitis caused by microbial invasion.

MATERIALS AND METHODS

The analysis included data from clinical and laboratory examinations of 88 patients (men and women aged 18–45 years) who visited a periodontist at the Severodvinsk Dental Polyclinic, State Autonomous Healthcare Institution of the Arkhangelsk Region. These included 60 patients with a confirmed diagnosis of chronic periodontitis (according to ICD-10 – K05.3) and 28 patients with clinically healthy periodontium. The study was cross-sectional in design.

In accordance with the World Medical Association Declaration of Helsinki (last revision at WMA General Assembly, Fortaleza, Brazil, October 2013), each patient provided a written voluntary informed consent to participate in the study. A positive conclusion was received from the local Ethics Committee of Northern State Medical University (Arkhangelsk) (Minutes No. 8/11dated November 28, 2018).

The study inclusion criteria were as follows: a signed written informed consent, "young age" according to the WHO, a diagnosis of "K05.3 – chronic periodontitis," and no antimicrobial use in the past six months. Exclusion criteria were lack of a signed informed consent, age under 18 or over 45 years, and orthodontic treatment at the time of the study. Participants were excluded from the study if they had other inflammatory oral diseases, any concomitant somatic-symptom pathology in the decompensation stage, pregnancy or lactation, or received antibacterial therapy in the past six months.

The clinical material consisted of periodontal pocket fluid collected using a paper absorbent point during a dental examination. The resulting samples were centrifuged at 1,500 rpm for 20 minutes. Aliquots of the samples were frozen and stored at –80°C until molecular genetic and immunological testing were conducted.

The Russell's Periodontal Index (PI, 1956) was used to assess the presence and depth of the periodontal pocket, the degree of tooth mobility, and the severity of gum inflammation. The technique included the assessment of each tooth using a periodontal probe. The result was entered into the periodontogram as a score: 0 points – no inflammation; 1 point – mild degree, inflammation does not surround the entire tooth; 2 points – inflammation surrounds the tooth, without damage to the epithelial attachment; 4 points – initial degree of resorption of the apices of the interdental septa; 6 points – presence of a periodontal pocket, the tooth is stable; 8 points – severe destruction of periodontal tissues, the tooth is mobile. The index is calculated using the formula: PI = sum of teeth / n; where n is the number of examined teeth. The index value of 0.1–1.5 points is stage 1 of the disease, 1.5–4.0 points is stage 2 and 4.0–8.0 points is stage 3.

Bone density was assessed using the Fuchs Index (FI). By analyzing orthopantomograms, the root of each tooth was assessed, divided into three parts, and a score was assigned according to the following formula: 0 points – the tooth is outside the bone or was removed due to periodontal disease; 1 point – bone loss exceeding two-thirds of the root length; 2 points – from one-third to two-thirds of the root length; 3 points – up to one-third of the root length; and 4 points – no bone loss detected, or the tooth was removed due to complicated caries. The result was calculated using the formula: sum of the scores / n * 4, where n is the number of teeth in the oral cavity. An FI value of 0 points indicates bone tissue resorption up to the root

tips, 0.25–0.5 points corresponds to resorption at 2/3 of the root length, 0.5–0.75 implies resorption at half of the root length, > 0.75 corresponds to resorption at 1/3 of the root length, and 1 point indicates normal bone tissue condition.

The RANK-L and IL-1β levels in gingival fluid were determined using enzyme-linked immunosorbent assay (ELISA) in thawed samples according to the kit instructions provided by Wuhan Fine Biotech Co., Ltd. (China). The optical density of the wells was measured and recorded using a Multiscan EX photometer (Thermo Fisher Scientific, USA). The results were evaluated according to the kit instructions using calibration curves constructed based on standard measurements. Molecular genetic methods included the determination of marker periodontal pathogens Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, and Tannerella forsythia (periodontopathogens of the first order), Treponema denticola and Prevotella intermedia (periodontopathogens of the second order), and Candida albicans fungi using the real-time polymerase chain reaction (RT-PCR) in accordance with the instructions for the manufacturer's kits (ParodontoScreen, DNA-Technology LLC, Russia).

Statistical processing of the obtained results, assessment of the distribution of indicators, and comparative analysis of samples were performed using the STATA v.14 software package for statistical data processing (College Station, TX: StataCorp LP., USA). The normality of distribution was assessed using the Shapiro–Wilk test. Quantitative data for normal distribution were presented as the arithmetic mean and standard deviation $M \pm SD$, and in the case of abnormal distribution, as the median and interquartile range Me $[Q_{25};Q_{75}]$. For statistical comparison of RANK-L and IL-1β levels in two independent groups, the nonparametric Mann–Whitney test was chosen. Spearman's rank correlation coefficient was used to search for intragroup relationships between the levels of individual parameters. The critical level of significance at all stages of the statistical analysis was taken as $p \leq 0.05$.

RESULTS

In a study of gingival fluid samples from patients with chronic periodontitis and a control group with intact periodontium, the levels of the proinflammatory cytokine IL-1β and the receptor activator of nuclear factor kappa-B ligand were determined (Table 1). Thus, in patients with chronic periodontitis, a significant increase in IL-1β content was found compared to those in the control group (median – 37.1 [32.9; 41.3] pg/ml versus 2.5 [1.9; 3.4], $p < 0.001$). The concentration of RANK-L in gingival fluid was also higher in patients with chronic periodontitis (median 6.3 [4.2; 10.4] pg/ml versus 0.0 [0.0; 0.7], $p < 0.001$).

In a group of patients with chronic periodontitis, the levels of bone destruction varied among individuals. The average FI was 0.83 ± 0.03 in patients with mild chronic periodontitis and 0.71 ± 0.05 in those with moderate chronic periodontitis.

Analysis of IL-1β concentrations in patients with chronic periodontitis showed that in the subgroup with a moderate degree of bone tissue destruction, its content was 3.7 ($p = 0.042$) times higher than in the subgroup of patients with a mild degree. Similarly, the RANK-L indicator in patients with a moderate degree of destruction was 2.5 times higher than in patients with a mild degree ($p = 0.037$). Correlations were established between the content of IL-1β and RANK-L with the degree of bone tissue destruction: $r = 0.562$ ($p = 0.025$) and $r = 0{,}408$ ($p = 0.033$), respectively.

Table 1

The Levels of IL-1β and RANK-L (pg/ml) in Individuals with Chronic Periodontitis and Intact Periodontium, Me $[Q_{25}; Q_{75}]$

Parameter	Chronic periodontitis	Intact periodontium
IL-1β	37.1 [32.9; 41.3]	2.5 [1.9; 3.4]
RANK-L	6.3 [4.2; 10.4]	0.0 [0.0;0.7]

$p < 0.001$

A study of the frequency of periodontopathogenic microbiota in gingival fluid samples obtained from examined people revealed significant group differences. Thus, in patients with chronic periodontitis, the frequency of detection of one or more periodontopathogens was 100.0% (60 individuals), whereas in the group of subjects with an intact periodontium, periodontopathogenic bacteria were isolated in only 32.1% (9 individuals). In the chronic periodontitis group, the following first-order periodontopathogens were isolated with the highest frequency: *A. actinomycetemcomitans* (81.7%), *P. gingivalis* (76.7%), *and T. forsythia* (70.0%), and associations of periodontopathogens (60.0%). Periodontopathogenic species of the second order were isolated with a lower frequency: *T. denticola* (63.3%), *P. intermedia* (56.7%), and *C. albicans* (30.0%). While periodontopathogens of the first order were not isolated in the examined individuals of the control group, periodontopathogenic bacteria of the

second order predominated: *T. denticola* – 17.8% and *P. intermedia* – 10.7%. The fungi *C. albicans* were also isolated in one examined individual.

In order to identify the relationships between the gingival microbiota and cytokines, a correlation analysis was performed, with statistically significant correlations being found only in the group with chronic periodontitis (Table 2).

The quantitative content of both proinflammatory cytokines IL-1β and RANK ligand positively correlated with all representatives of the group of periodontopathogenic bacteria of the first order, with the strongest correlations being found at the moderate degree of periodontal tissue destruction. For periodontopathogenic bacteria of the second order, direct correlations of weak strength were revealed, with the exception of a correlation between *T. denticola* and RANK-L (r = 0.452, p = 0.029) at the moderate degree of periodontal tissue destruction. Associations of periodontopathogens positively correlated with the content of both cytokines at both degrees of periodontal tissue destruction, but the moderate strength of correlations was established at the moderate degree of destructive changes.

Table 2

Correlation Matrix of Cytokines IL-1β, RANK-L and Periodontopathogenic Bacteria of Gingival Fluid in Patients with Chronic Periodontitis with Varying Degrees of Bone Tissue Destruction

Parameter	IL-1β		RANK-L	
	Mild degree of destruction (Fuchs index)	Moderate degree of destruction	Mild degree of destruction	Moderate degree of destruction
P. gingivalis	r = 0.548* (p = 0.003)	r = 0.618* (p = 0.008)	r = 0.232 (p = 0.04)	r = 0.612* (p = 0.016)
A. actinomycetemcomitans	r = 0.485* (p = 0.032)	r = 0.539* (p = 0.002)	r = 0.342 (p = 0.028)	r = 0.553* (p = 0.042)
T. forsythia	r = 0.188 (p = 0.052)	r = 0.423* (p = 0.037)	r = 0.118 (p = 0.048)	r = 0.618* (p = 0.006)
T. denticola	r = 0.267 (p=0.035)	r = 0.231 (p = 0.04)	r = 0.152 (p = 0.029)	r = 0.452* (p = 0.029)
P. intermedia	r = 0.278 (p = 0.047)	r = 0.134 (p = 0.026)	r = 0.243 (p = 0.0212	r = 0.243 (p = 0.034)
C. albicans	r = 0.218 (p = 0.48)	r = 0.175 (p = 0.041)	r = 0.134 (p = 0.016)	r = 0.168 (p = 0.013)
Periodontopathogenic associations	r = 0.318 (p = 0.006)	r = 0.452* (p = 0.042)	r = 0.288 (p = 0.034)	r = 0.589* (p = 0.002)

*moderate strength of correlation r at $p < 0.05$

DISCUSSION

Destruction of periodontal tissues is caused by a non-specific inflammatory response, leading to a shift in the dynamic balance of inflammatory mediators, among which cytokines play a leading role [7].

IL-1β belongs to the family of proinflammatory cytokines and has potent immunoregulatory functions in chronic periodontitis [8, 9]. Released during periodontal cell damage and immune cell activation, IL-1β is involved in innate immunity mechanisms, inflammasome activation processes, and the T-cell-mediated immune response mechanism. This cytokine ensures control of the spread of inflammation to deeper areas of connective tissue; high levels of IL-1β are associated with loss of connective tissue attachment, osteoclast activation, and subsequent alveolar bone loss [8].

Our study revealed an increased content of the cytokine IL-1β in the gingival fluid of patients with chronic periodontitis, as compared to those in the control group with an intact periodontium, which may indicate increased activity of immunocompetent cells and a shift in the immune homeostasis of periodontal tissues with a predominant production of proinflammatory cytokines, which is consistent with data from previous studies [10, 11].

RANK-L, a member of the TNF family of cytokines, plays a key role in bone resorption: when it binds to the NF-κB receptor activator, a membrane receptor primarily produced by osteoclasts and their progenitor cells, it both induces the differentiation of progenitor cells into osteoclasts and stimulates the activity of mature osteoclasts.

Previous studies have shown that RANK-L levels are the highest in patients with severe periodontitis compared with those with moderate to mild periodontitis or with an intact periodontium [1]. In our study, RANK-L concentrations in gingival fluid were also higher in patients with chronic periodontitis compared to those with an intact periodontium (median 6.3 [4.2;10.4] pg/ml vs. 0.0 [0.0; 0.7], $p <$ 0.001). It is worth noting the correlations identified in our study: IL-1β and RANK-L positively correlated with the degree of bone tissue destruction in patients with chronic periodontitis. These cytokines likely control key pleiotropic pathways that are crucial for the homeostasis of bone and connective tissue in the periodontium.

However, the microbial component, namely the imbalance of the gingival microbiota with a predominance of periodontopathogenic flora, may be a key link in the development of the initial nonspecific inflammatory process, which deepens into the gingival sulcus, subsequently forming a periodontal pocket [2, 12]. In our study, in patients with chronic periodontitis, the frequency of detection of one or more periodontopathogens was 100.0%, whereas in the group of subjects with an intact periodontium, periodontopathogenic bacteria were isolated in only 32.1%.

In the chronic periodontitis group, periodontopathogens of the first order were isolated with the highest frequency: *A. actinomycetemcomitans, P. gingivalis, T. forsythia,* and associations of periodontopathogens. The periodontopathogenic bacteria isolated by us exhibit the greatest bone-resorptive activity. Thus, *P. gingivalis* is one of the key pathogens that activates osteoclasts via the TLR4 system and enhances the production of proinflammatory cytokines, including IL-1β and RANK-L, as well as TNFα and IL-6. *T. forsythia* promotes increased osteoclast activation and suppression of bone formation, and *A. actinomycetemcomitans* stimulates the production of matrix metalloproteinases and proinflammatory factors, which also leads to bone resorption [13].

The presence in our study of a large number of positive correlations of moderate strength between the content of both the proinflammatory cytokine IL-1β and the RANK ligand with a group of periodontopathogenic bacteria of the first order, identified in the group of patients with a moderate degree of bone tissue destruction, may indicate that these bacteria trigger a cascade of inflammatory reactions leading to increased secretion of proinflammatory cytokines, activation of osteoclastogenesis, suppression of osteogenesis, and increased destruction of bone tissue [14].

These periodontopathogens probably do not act in isolation, but as part of a biofilm, where their combined effect significantly enhances the destructive potential, and the presence of correlations between the isolated associations of periodontopathogens with cytokines confirms this assumption. The presence of these correlations may also indicate an imbalance between bone formation and resorption in favor of the latter, which leads to progressive bone loss in periodontitis. Also, the identified correlation of the second-order periodontopathogen *T. denticola* with RANK-L of moderate strength ($r = 0.452$, $p = 0.029$) with an average degree of periodontal tissue destruction may reflect the presence of many virulence factors in this bacterium, such as the production of proteolytic enzymes (oligopeptidase, dentipain, dentilisin, etc.), which also have a destructive effect on periodontal tissues.

CONCLUSION

The pathogenesis of chronic periodontitis is determined by a number of factors, with a key role played by the interaction of periodontopathogenic bacteria and their aggressive factors with gingival epithelial cells, which leads to the stimulation of mediator production in the inflammatory zone. Mediators detected in gingival crevicular fluid are primarily proinflammatory cytokines, including IL-1β and the immune mediator RANK-L, which are central to soft tissue destruction and periodontal bone resorption.

These mediators likely acting in synergy participate in the cytokine cascade, promoting the degradation of collagen and other extracellular matrix components enhancing osteoclast activation and differentiation, and binding to the RANK receptor on the osteoclast surface, thereby leading to increased alveolar bone resorption and disrupting bone remodeling processes. Conversely, proteolytic bacterial enzymes (oligopeptidases, dentipains, dentilisins) and endotoxins can directly disrupt periodontal tissue homeostasis by suppressing periodontal ligament cell function and inducing nitric oxide secretion by macrophages, which promotes bone resorption.

Thus, the associations between the periodontopathogenic bacteria *A. actinomycetemcomitans, P. gingivalis*, and *T. forsythia*, and their associations with elevated cytokine levels and the severity of bone tissue destruction, may indicate a key joint role of the proinflammatory cytokine IL-1β and the immune mediator RANK-L in the inflammatory and bone-destructive processes in the pathogenesis of chronic periodontitis. RANK-L in combination with IL-1β may also serve as a valuable diagnostic biomarker for periodontitis, reflecting the progression of the pathological process.

REFERENCES

1. Chen B., Wu W., Sun W., Zhang Q., Yan F., Xiao Y. RANKL expression in periodontal disease: where does RANKL come from? *Biomed. Res. Int.* 2014;2014:731039. DOI: 10.1155/2014/731039.
2. Neurath N., Kesting M. Cytokines in gingivitis and periodontitis: from pathogenesis to therapeutic targets. *Front. Immunol.* 2024;26(15):1435054. DOI: 10.3389/fimmu.2024.1435054.

3. Nagasawa T., Kiji M., Yashiro R., Hormdee D., Lu H., Kunzeet M. et al. Roles of receptor activator of nuclear factor-κB ligand (RANKL) and osteoprotegerin in periodontal health and disease. *Periodontology.* 2007;43(1):65–84. DOI: 10.1111/j.1600-0757.2006.00185.x.
4. Kawai T., Matsuyama T., Hosokawa Y., Makihira S., Seki M., Karimbux N.Y. et al. B and T lymphocytes are the primary sources of RANKL in the bone resorptive lesion of periodontal disease. *Am. J. Pathol.* 2006;169(3):987–998. DOI: 10.2353/ajpath.2006.060180.
5. Walsh N.C., Alexander K.A., Manning C.A., Karmakar S., Wang J.F., Weyand C.M. et al. Activated human T cells express alternative mRNA transcripts encoding a secreted form of RANKL. *Genes Immun.* 2013;14(5):336–345. DOI: 10.1038/gene.2013.29.
6. Huang S.J., Li R., Xu S., Liu Y., Li S.H., Duan S.Z. Assessment of bidirectional relationships between circulating cytokines and periodontitis: Insights from a mendelian randomization analysis. *Front. Genet.* 2023;14:1124638. DOI: 10.3389/fgene.2023.1124638
7. Galieva A.S., Davidovich N.V., Opravin A.S., Kharkova O.A., Polivanaya E.A., Bazhukova T.A. The Role of Inflammatory Biomarkers of Crevicular fluid Involved in Modulating of Immune Protection Mechanisms in Chronic Periodontitis. *I.P. Pavlov Russian Medical Biological Herald.* 2023;31(3):451–458. (In Russ.). DOI: 10.17816/PAVLOVJ321217.
8. Graves D.T., Cochran D. The contribution of interleukin-1 and tumor necrosis factor to periodontal tissue destruction. *J. Periodontol.* 2003;74:391–401. DOI: 10.1902/jop.2003.74.3.391.
9. Teixeira Q.E., Ferreira D.C., da Silva A.M.P., Goncalves L.S., Pires F.R., Carrouel F. et al. Aging as a risk factor on the immunoexpression of pro-inflammatory IL-1beta, IL-6 and TNF-alpha cytokines in chronic apical periodontitis lesions. *Biol. (Basel).* 2021;11:14. DOI: 10.3390/biology11010014.
10. Van Dyke T.E., Bartold P.M., Reynolds E.C. The nexus between periodontal inflammation and dysbiosis. *Front. Immunol.* 2020;11:511. DOI: 10.3389/fimmu.2020.00511.
11. Wei Y., Shi M., Nie Y., Wang C., Sun F., Jiang W. et al. Integrated analysis of the salivary microbiome and metabolome in chronic and aggressive periodontitis: A pilot study. *Front. Microbiol.* 2022;13:959416. DOI: 10.3389/fmicb.2022.959416
12. Davidovich N.V., Galieva A.S., Opravin A.S., Gagarina T.Yu., Malygina O.G., Leikhter S.N. et al. Correlation of Marker Periodontopathogenic Bacteria with the Immune Component SCD14 Secretion Level in Inflammatory Periodontal Diseases. *Russian Clinical Laboratory Diagnostics.* 2022;67(8):471–475. (In Russ.). DOI: 10.51620/0869-2084-2022-67-8-471-475.
13. Tsaryov V.N., Nikolaeva E.N., Ippolitov E.V. Periododontopathogenic Bacteria of the Main Factors of Emergence and Development of Periodontitis. *Journal of Microbiology, Epidemiology and Immunobiology.* 2017;5:101–112. (In Russ.).
14. Guo Y., Xu C., Wu X., Zhang W., Sun Y., Shrestha A. Leptin regulates OPG and RANKL expression in gingival fibroblasts and tissues of chronic periodontitis patients. *Int. J. Med. Sci.* 2021;18(11):2431–2437. DOI: 10.7150/ijms.56151.

Author Contribution

Davidovich N.V., Solovieva N.V., and Bazhukova T.A. – conception and design. Sabanaev M.A. and Galieva A.S. – collection and processing of material.Sabanaev M.A.. – figure preparation. Galieva A.S. and Sabanaev M.A. – statistical processing of data. Davidovich N.V. and Sabanaev M.A. – drafting of the manuscript. Solovieva N.V. and Bazhukova T.A. – editing of the manuscript. All coauthors – final approval of the manuscript, responsibility for the integrity of all parts of the manuscript .

Author Information

Davidovich Nataliia V. – Cand. Sci. (Med.), Associate Professor; Associate Professor of the Deptartment of Clinical Biochemistry, Microbiology and Laboratory Diagnostics, Northern State Medical University, Arkhangelsk, nvdavidovich@gmail.com, https:orcid.org/0000-0002-6414-9870

Galieva Aleksandra S. – Cand. Sci. (Med.), Associate Professor, Deptartment of Therapeutic Dentistry, Northern State Medical University, Arkhangelsk, alexgalieva@yandex.ru, https://orcid.org/0000-0002-7037-7730

Sabanaev Mikhail A. – Assistant, Department of Clinical Biochemistry, Microbiology and Laboratory Diagnostics, Northern State Medical University, Arkhangelsk, mix.sabanaeff@gmail.com, https://orcid.org/0000-0001-5642-3019

Solovieva Natalia V. – Dr. Sci. (Med.), Associate Professor, Head of the Department of Pathological Physiology, Northern State Medical University, Arkhangelsk, patophiz@yandex.ru, https://orcid.org/0000-0002-0664-4224

Bazhukova Tatiana A. – Dr. Sci. (Med.), Professor, Head of the Department of Clinical Biochemistry, Microbiology and Laboratory Diagnostics, Northern State Medical University, Arkhangelsk, tbazhukova@yandex.ru, https://orcid.org/0000-0002-7890-2341

(✉) **Davidovich Nataliia V.,** nvdavidovich@gmail.com

Received on September 15, 2025;
approved after peer review on September 24, 2025;
accepted on October 16, 2025