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I.V. Kovach [1],
O.V. Kopchak [2],
K.A. Buniatian [1 *],
L.V. Kriachkova [1],
N.V. Alieksieienko [1],
O.Yu. Bindiugin [1]

PROGNOSTIC MODEL OF EARLY INFLAMMATION DEVELOPMENT IN PERIODONTAL TISSUES BY BIOCHEMICAL PARAMETERS OF ORAL FLUID IN PATIENTS WITH ORTHODONTIC APPLIANCES

Dnipro State Medical University [1]
V. Vernadskyi str., 9, Dnipro, 49044, Ukraine
[*]*e-mail: kristinabunyatyan@gmail.com*
Kyiv medical university [2]
Boryspilska str., 2, Kyiv, 02099, Ukraine
Дніпровський державний медичний університет [1]
вул. В. Вернадського, 9, Дніпро, 49044, Україна
ПВНЗ «Київський медичний університет» [2]
вул. Бориспільська, 2, Київ, 02099, Україна
e-mail: terdent@kmu.edu.ua

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Ключові слова: *хронічний катаральний гінгівіт, раннє запалення, ортодонтичне лікування, ротова рідина, прогнозування*
Ключевые слова: *хронический катаральный гингивит, раннее воспаление, ортодонтическое лечение, ротовая жидкость, прогнозирование*

Abstract. Prognostic model of early inflammation development in periodontal tissues by biochemical parameters of oral fluid in patients with orthodontic appliances. Kovach I.V., Kopchak O.V., Buniatian K.A., Kriachkova L.V., Alieksieienko N.V., Bindiugin O.Yu. *One of the main etiological risk factors and pathogenetic mechanisms for the development of inflammatory diseases of the periodontal disease is a bite pathology or dentofacial anomalies. Therefore, in recent years, scientists make attempts to find new markers that would allow to predict the course of the disease at the preclinical stage of its diagnostics, which would allow to take preventive treatment. In recent years, individual proteins of the mouth, which include matrix metalloproteinases (MMP-8), which can hydrolyze the main proteins in extracellular space and lactoferrin, catelitsidine, KLOTHO protein should be considered leading markers. The purpose is to predict the emergence of early inflammation in periodontal tissues in patients with non-removable orthodontic appliance by studying protein content in the oral fluid in the dynamics of treatment. Among the 113 patients surveyed by us, which underwent orthodontic treatment with non-removable appliance, according to clinical and laboratory studies, 82 people (72,57%) had signs of early inflammation of periodontal tissues. All examined young people were students or students of educational institutions who appealed for advice and treatment to a dental clinic. Biochemical studies of oral fluid and their analysis was conducted at the beginning of orthodontic treatment and 3 and 6 months after the delivery of non-removable orthodontic appliance. The oral fluid was collected in the morning, and the quantitative determination of proteins in it was carried out by the IFA method. In order to assess the probability of prognostication of early inflammation in patients with orthodontic appliance, there was made rank correlation analysis with the determination of the correlation coefficients of the disparity (rs), ROC analysis with the determination of Optimal Cut-Off Point (OCP) – the value of the indicator for prediction and simple and multiple logistic regressions with the calculation of the odds ratio and the construction of a prognostic model (logistics regression equation). For the analysis of factors, on the basis of which it is possible to predict early inflammation of periodontal tissues in patients with orthodontic appliance, a correlation analysis was performed, which showed that the largest changes were in the biochemical parameters of the mouth, namely: MMP-8 (rs=0.58; p<0.001), lactoferin (rs=0.45; p<0.001), catelitsidine (rs= -0.59; p<0.001) and KLOTHO protein (rs= -0.58; p<0.001), with which statistically significant correlations were established. ROC analysis was used to evaluate the discriminatory capacity of the markers investigated, which showed the presence of statistically significant correlations with early signs of inflammatory process in periodontal tissues. As a result of the correlation analysis, it has been found that the most significant changes in the inflammatory process in periodontal tissues were in the biochemical parameters of the mouth, such as MMP-8 (rs=0.58; p< 0.001), lactoferin (rs=0.45; p< 0.001), catholicidine (rs= -0.59; p< 0.001) and*

Klotho protein (rs= -0.58; p< 0.001), with which statistically significant correlations of average force were detected. The chances of patients with non-removable orthodontic appliance for the development of inflammation in the periodontal tissues are increased by 4.2 times.

Реферат. Прогностическая модель возникновения раннего воспаления в тканях пародонта у пациентов с ортодонтическими конструкциями в полости рта по биохимическим показателям ротовой жидкости. Ковач И.В., Копчак О.В., Бунятян К.А., Крячкова Л.В., Алєксєєнко Н.В., Биндюгин А.Ю. *Одним из основных этиологических факторов риска и патогенетических механизмов развития воспалительных заболеваний пародонта является патология прикуса или зубочелюстные аномалии. Поэтому в последние годы ученые предпринимают попытки поиска новых маркеров, которые позволили бы прогнозировать течение заболевания на доклиническом этапе его диагностики, что позволило бы заниматься превентивным лечением. В последние годы ведущими маркерами следует считать отдельные белки ротовой жидкости, к которым относятся матриксные металлопротеиназы (ММР-8), которые могут гидролизовать основные белки во внеклеточном пространстве, и лактоферрин, кателицидин, белок Klotho. Цель – прогнозирование возникновения раннего воспаления в тканях пародонта у пациентов с несъемной ортодонтической аппаратурой путем изучения содержания белков в ротовой жидкости в динамике лечения. Среди 113 обследованных нами пациентов, которым проводилось ортодонтическое лечение с помощью несъемных конструкций, по данным клинического и лабораторного исследований, у 82 человек (72,57 %) имелись признаки раннего воспаления в тканях пародонта. Все обследованные молодые люди были учениками или студентами учебных заведений и обратились за консультацией и лечением в стоматологическую клинику. Биохимические исследования и их анализ проводились в ротовой жидкости пациентов в начале ортодонтического лечения и через 3 и 6 месяцев после установки несъемной ортодонтической аппаратуры. Ротовую жидкость собирали утром натощак, а количественное определение белков в ней проводили методом ИФА. Для предсказания вероятности раннего воспаления в тканях пародонта у пациентов с ортодонтическими конструкциями был проведен ранговый корреляционный анализ с определением коэффициентов корреляции Спирмена (r_s), ROC-анализ с определением оптимальной точки отсечения (Optimal cut-off point – OCP) – значение показателя для прогноза, и простую и множественную логистические регрессии с расчетом отношения шансов и построением прогностической модели (уравнения логистической регрессии). Для анализа факторов, на основании которых можно прогнозировать раннее воспаление тканей пародонта у пациентов с ортодонтическими конструкциями в полости рта, был проведен корреляционный анализ, показавший, что наибольшие изменения имели следующие биохимические показатели ротовой жидкости, а именно: ММР-8 (rs=0 ,58; p<0,001), лактоферрин (rs=0,45; p<0,001), кателицидин (rs =-0,59; p<0,001) и белок Klotho (rs=-0,58; p<0,001), с которыми были установлены статистически значимые корреляционные связи. ROC-анализ применялся для оценки дискриминационной способности исследованных маркеров, показавших наличие статистически значимых корреляционных связей с ранними признаками воспалительного процесса в тканях пародонта. В результате корреляционного анализа установлено, что наиболее значимые изменения при воспалительном процессе в тканях пародонта имеют такие биохимические показатели ротовой жидкости, как ММР-8 (rs=0,58; p<0,001), лактоферрин (rs=0,45; г<0,001), кателицидин (rs=-0,59; г<0,001) и белок Klotho (rs=-0,58; г<0,001), с которыми были обнаружены средней силы, статистически значимые корреляционные связи . Шансы у пациентов с несъемными ортодонтическими конструкциями в полости рта по поводу развития воспаления в тканях пародонта увеличиваются в 4,2 раза.*

At the beginning of the 20th century scientists considered general pathology and abnormal occlusion to be the cause of the development of periodontal diseases. However, accumulated epidemiological and clinical data led to the formation of a hypothesis about the significant role of certain risk factors in the development and progression of periodontal tissue diseases [1-2].

One of the main etiological risk factors and pathogenetic mechanisms of the development of periodontal inflammatory processes is bite pathology or dentofacial anomalies [3-4]. It is known that a high percentage of complications, namely the development of inflammatory diseases in periodontal tissues, are detected during or after orthodontic treatment [5-6].

In recent years in numerous studies scientists have tried to find new markers that would allow predicting the course of the disease at the stage of its diagnosis, which would allow to conduct preventive treatment [7]. Recently, individual proteins of the oral fluid should be considered leading markers, which include matrix metalloproteinases (MMP-8), which can hydrolyze the main proteins in the extracellular space, and lactoferrin, cathelicidin and Klotho protein [8-13] .

The purpose of the work is to predict the occurrence of early inflammation in the periodontal tissues in patients with non-removable orthodontic appliances by studying the protein content in the oral fluid in the dynamics of treatment.

MATERIALS AND METHODS OF RESEARCH

Among the 113 patients examined, who underwent orthodontic treatment with the help of fixed orthodontic appliances, according to the data of clinical and laboratory studies, 82 individuals (72.57%) were found

to have signs of early inflammation in the periodontal tissues. All the examined were pupils or students of educational institutions and applied for consultation and treatment to the dental clinic. Biochemical studies and their analysis were carried out in the oral fluid of patients at the beginning of treatment, 3 and 6 months after the installation of fixed orthodontic appliances. Oral fluid was collected in the morning on an empty stomach, and quantitative determination of proteins in it was carried out by the ELISA method. To predict the probability of early inflammation in the periodontal tissues in patients with orthodontic appliances in the oral cavity, a rank correlation analysis was performed with determination of Spearman's correlation coefficients (rs). To assess the discriminatory ability of the studied markers, which showed the presence of statistically significant correlations with early signs of the inflammatory process, ROC analysis was used to determine the optimal cut-off point (OCP) – the value indicator for prediction and simple and multiple logistic regression with the calculation of the odds ratio and the construction of a prognostic model (logistic regression equation).

The procedure strictly complied with the generally accepted standards of morality, the requirements for observing the rights, interests and personal dignity of the research participants. There was no risk to the research subjects during the performance of the work. The research was conducted in accordance with the principles of bioethics set forth in the Helsinki Declaration "Ethical Principles of Medical Research Involving Humans" and the "General Declaration on Bioethics and Human Rights (UNESCO)". Research participants were informed about all aspects related to the purpose, tasks, methods and expected benefit of the research. Laboratory and instrumental research methods were generally accepted. Experimental studies on humans were not used.

Statistical processing of research results was carried out using biostatistics methods implemented in Microsoft Excel software packages (Office Home Business 2KB4Y-6H9DB-BM47K-749PV-PG3KT) and STATISTICA 6.1 (StatSoftInc., serial number AGAR909E415822FA). ROC analysis was performed in the software package MedCalc Statistical Software trial version 19.2.6 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2020).

RESULTS AND DISCUSSION

In order to analyze the factors on the basis of which it is possible to predict early inflammation in the periodontal tissues in patients with orthodontic apploiances, a correlation analysis was conducted, which showed that the most significant changes against the background of the inflammatory process had the following biochemical indicators of the oral fluid, namely: MMP-8 ($rs=0.58$; $p<0.001$), lactoferrin ($rs=0.45$; $p<0.001$), cathelicidin ($rs= -0.59$; $p<0.001$) and Klotho protein ($rs= -0, 58$; $p<0.001$), with which statistically significant correlations of medium strength were found.

The value of the area under the ROC curve was interpreted as indicators of diagnostic accuracy (Šimundić A-M., 2009): 0.9-1.0 – excellent, 0.8-0.9 – very good, 0.7-0.8 – good, 0.6-0.7 – average, 0.5-0.6 – unsatisfactory; a value of 0.5 indicated the prognostic unsuitability of the marker. The ROC analysis data were presented as the average value of the area under the ROC curve (AUC) with its 95% confidence interval (95% CI), indicators of sensitivity (Sensitivity – Se) and specificity (Specificity – Sp) corresponding to the discriminatory points

The results of the ROC analysis are shown in Table 1 and Figures 1-4.

Table 1

Evaluation of the possibilities of predicting early inflammation in patients with orthodontic appliances in the oral cavity by biochemical indicators of oral fluid (the results of ROC analysis and simple logistic regression analysis)

Indicators	AUC	95% CI AUC	*p*	Se	Sp	COP	OR (95% CI)
MMP-8, ng/ml	**0.830**	**0.748- 0.894**	***<0.001***	**73.17**	**96.77**	**>3.56**	**4.22 2.15-8.31**
Lactoferin, ng/ml	**0.801**	**0.715- 0.870**	***<0.001***	**63.41**	**93.55**	**>75.38**	**1.23 1.12-1.35**
Cathelicidin, μM	**0.851**	**0.772- 0.911**	***<0.001***	**69.51**	**100.0**	**>0.45**	**2.22 1.56-3.45**
Klotho protein, ng/ml	**0.833**	**0.751- 0.896**	***< 0.001***	**69.51**	**96.77**	**> 4.53**	**5.26 2.63-11.11**

Notes: AUC (Area Under Curve) – area under ROC-curve; Se (Sensitivity); Sp (Specificity); OCP – Optimal cut-off point.

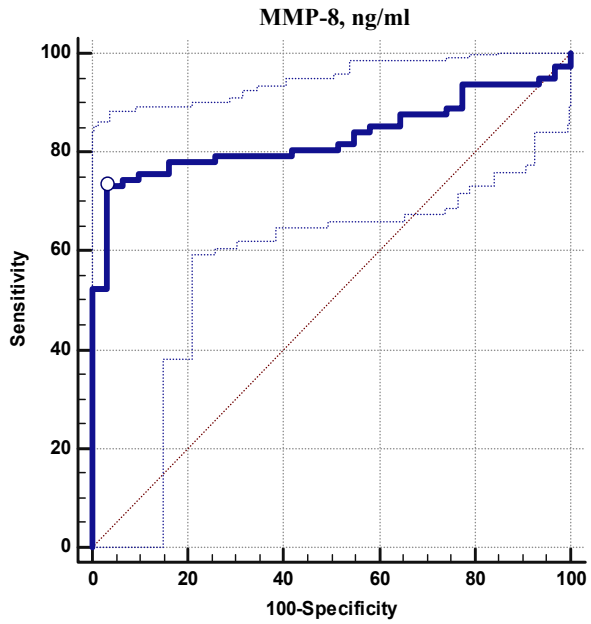

Fig. 1. ROC curve for predicting early inflammation in patients with orthodontic appliances in the oral cavity according to the level of MMP-8 (ng/ml)

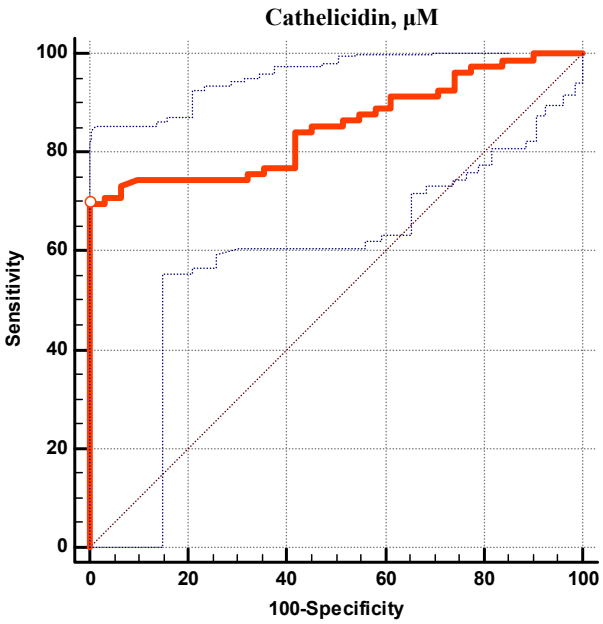

Fig. 3. ROC curve for predicting early inflammation in patients with orthodontic appliances in the oral cavity according to the level of cathelicidin

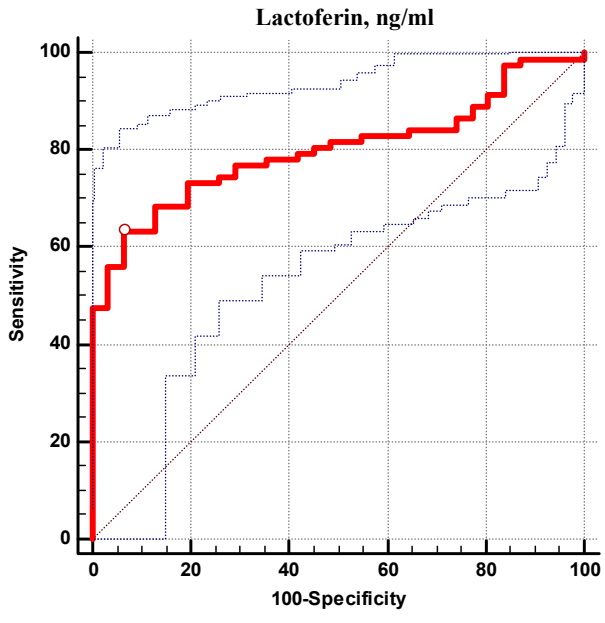

Fig. 2. ROC curve for predicting early inflammation in patients with orthodontic appliances in the oral cavity according to the level of lactoferrin (ng/ml)

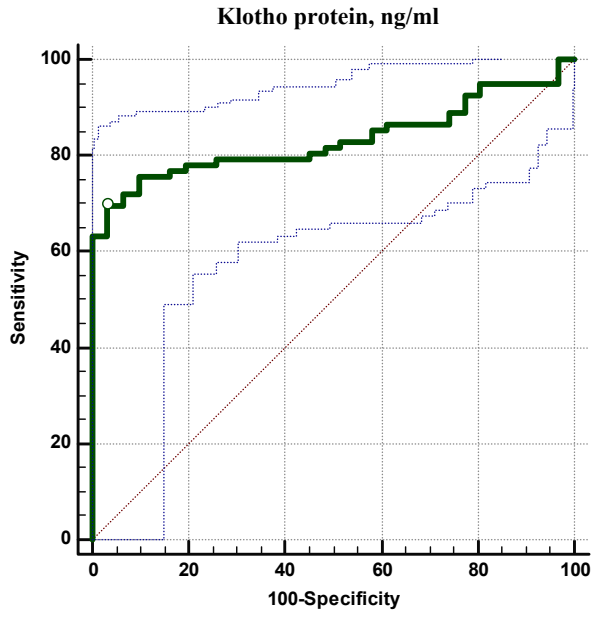

Fig. 4. ROC curve for predicting early inflammation in patients with orthodontic appliances in the oral cavity according to the level of Klotho protein (ng/ml)

The operational characteristics of the areas under the ROC curves of all the investigated biochemical indicators reached a statistically significant level ($p<0.001$) and ranged from 0.800 to 0.900, which, according to the generally accepted classification, indicates their very good proognostic value in predicting early manifestations of inflammation in periodontal tissues in the presence of orthodontic appliances in the oral cavity.

Statistically significant discriminative abilities with regard to the prognosis of early manifestations of inflammation are revealed by all investigated biochemical markers, the pairwise comparison of which did not show the presence of statistically significant ($p>0.05$) differences between them (Fig. 5), however, it was determined that the best operational characteristics are Klotho protein AUC=0.833 (95% CI 0.751-0.896), sensitivity 69.51%, specificity 96.77%, and cathelicidin AUC=0.851 (95% CI 0.772-0.911), sensitivity 69,51%, specificity 100.0%.

Multiple logistic regression analysis was performed to assess the probability of inflammation in the periodontal tissues of patients at the stage of treatment with orthodontic appliances in the oral cavity. As a basis, the logistic regression equation was used, which assumes that the acquired effect (inflammation) is related to the level of the studied factors according to the formula:

$$y = \exp(b_0 + b_{1\text{-}n} \times x_{1\text{-}n}) / [1 + \exp(b_0 + b_{1\text{-}n} \times x_{1\text{-}n})] \quad (1)$$

where y – result (probability of inflammation); b_0 – a coefficient indicating the value of the result in the case when the predictor is equal to 0; b1-n – regression coefficients showing how much the logarithm of the chance of developing the inflammation effect will change on average when the independent variable changes by one unit of its measurement; x1-n – predictor variables, indicators of each individual patient for whom the prognosis is calculated.

For the determined predictors, the indicator is introduced into the equation in the obtained values of the measurement units. The obtained result -y- varies in the range from 1 (inflammation present in the oral cavity) to 0 (inflammation absent).

Table 2 presents the predictors that were included in the developed model for predicting the early occurrence of periodontal tissue inflammation in patients with orthodontic appliances in the oral cavity by multiple logistic regression analysis with stepwise inclusion of independent variables. Among the investigated factors, two biochemical indicators were included in the model – cathelicidin and Klotho protein. Taking into account the obtained data (Table 2), the equation for predicting the occurrence of early inflammation in the periodontal tissues in patients with orthodontic appliances in the oral cavity based on the biochemical parameters of the oral fluid will have the following form:

$$y = \frac{\exp(5{,}275 - 0{,}736 \times x_1 - 0{,}249 \times x_2)}{1 + \exp(5{,}275 - 0{,}736 \times x_1 - 0{,}249 \times x_2)} \quad (2),$$

where – y – the probability of inflammation; x_1 – the level of cathelicidin (in μM) of a patient, for which the prognosis is calculated; x_2 – Klotho protein level (in ng/ml) of a patient, for which the prognosis is calculated; 5.275 – coefficient b_0, which indicates the value of the result in the case when the variables x_1 and x_2 will be equal to 0; -0.736 and -0.249 are regression coefficients b, which show how much the logarithm of the chance of the development of the inflammatory effect will change on average when the variables of cathelicidin and Klotho protein are changed, respectively, per unit of measurement (Table 2).

The share of correct prediction (concordance level) according to the results of the logistic regression model is 82.57%. This is a sufficient degree of agreement between the real distribution of observations and the distribution based on the logistic regression equation.

The predicting equation built on the basis of logistic regression (logistic model) turned out to be adequate. Evaluation of the logistic regression equation by the Chi-square value showed its adequacy, as its statistically significant level was determined: $\chi 2 = 46.73$ ($p<0.001$).

The overall assessment of the agreement of real and calculated data based on the Hosmer-Lemeshov test showed their significant coincidence as $p=0.385$, which allows us to assert the consistency of real and calculated results.

Based on the shape of the ROC curve and the area under it (AUC), the prognostic accuracy of the logistic regression equation was evaluated (Fig. 5). It was determined that the prognostic model in the form of a logistic regression equation has very good operational characteristics: sensitivity 70.73%, specificity 96.77%, area under the ROC curve – 0.846 (95.0% CI 0.766-0.907; $p<0.001$).

Regardless of the values of x, the predicted value of the result (y) in this model will always be in the range from 0 to 1. If the calculated probability has a value greater than 0.5, it can be assumed that the event will occur – inflammation will develop and vice versa. Clarification of these values was carried out on the basis of ROC analysis. The cut-off point on the ROC curve was 0.56, which makes it possible to accurately establish the predicting criteria based on the result obtained on the basis of the equation. If the calculated probability is less than the cut-off point of 0.56, it can be assumed that the event will not occur (inflammation will not develop); in the opposite case (the value according to the equation is greater than 0.56), the early development of inflammation is predicted in patients with orthodontic appliances in the oral cavity.

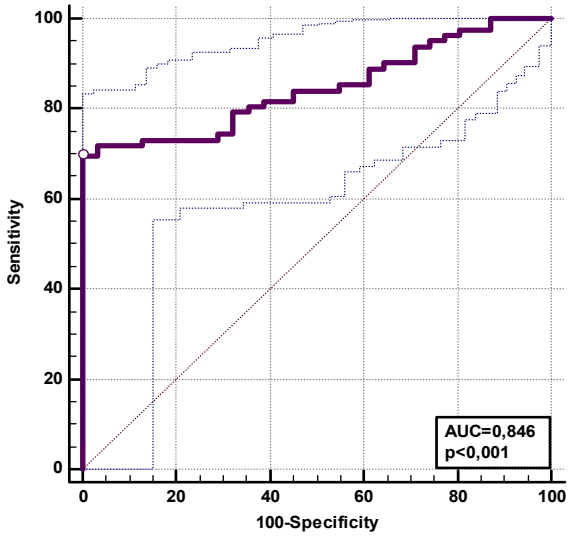

Fig. 5. ROC curve for predicting the early development of inflammation in patients with orthodontic appliances in the oral cavity based on the results of logistic regression analysis

The Nigelker coefficient of determination – R^2=0.490, obtained from the results of the regression equation, shows the share of influence of the predictors of the model on the variance of the dependent variable. This means that the share of the combined effect of the level of cathelicidin and Klotho protein, included in the model, on the early development of inflammation in patients with orthodontic appliances in the oral cavity is 49%. Another share is due to other factors that were not taken into account in the model.

Thus, the chances of developing inflammation in patients treated with non-removable orthodontic appliances in the oral cavity increase by 4.2 times (95% CI 2.15-8.31) with an MMP-8 level greater than 3.56 ng/ml; by 1.2 times (95% 1.12-1.35) with a lactoferrin level greater than 75.38 ng/ml; by 2.2 times (95% 1.56-3.45) with a cathelicidin level greater than 0.45 μM; by 5.3 times (95% 2.63-11.11) with Klotho protein level greater than 4.53 ng/ml.

Table 2

Prediction of the occurrence of early inflammation in patients with orthodontic appliances in the oral cavity by biochemical indicators of oral fluid (based on multiple logistic regression analysis)

Prediction variables	Regression coefficient β	Standard error of coefficient β	Wald χ^2	Wald p-value χ^2
Free term of equation	5.275			
Cathelicidin (x_1)	-0.736	0.361	4.151	0.004
Klotho protein (x_2)	-0.249	0.315	4.116	0.007
Logistic equation (model)		$y=\exp(5.275 - 0.736 \times x_1 - 0.249 \times x_2)/[1+ \exp(5.275- 0.736 \times x_1 - 0.249 \times x_2)]$		
Xi-square		$\chi^2= 46.73$ ($p<0.001$)		
Percentage of concordance		82.57 %		
Operational characteristics of predicting according to ROC-analysis data				
Sensitivity, %		70.73		
Specificity, %		96.77		
AUC		0.846		
95% CI AUC		0.766-0.907		
p-level		<0.001		
Qualitative evaluation of the model		Very good		

CONCLUSIONS

1. A model for predicting the early occurrence of periodontal tissue inflammation in patients with orthodontic appliances in the oral cavity has been developed.
2. As a result of the correlation analysis, it was established that the development of the inflammatory process in the periodontal tissues occurs against the background of changes in such biochemical indicators of the oral fluid as MMP-8 (rs=0.58; p & lt; 0.001), lactoferrin (rs=0.45; p & lt; 0.001), cathelicidin (rs= -0.59; p & lt; 0.001) and Klotho protein (rs= -0.58; p & lt; 0.001), with them statistically significant correlations of average force were revealed.
3. The level of concordance according to the results of the logistic regression model is 82.57%.
4. The chances of developing periodontal tissue inflammation in patients with fixed orthodontic appliances in the oral cavity increase by 4.2 times (95% CI 2.15-8.31) with an MMP-8 level greater than 3.56 ng/ml; by 1.2 times (95% 1.12-1.35) with a lactoferrin level greater than 75.38 ng/ml; by 2.2 times (95% 1.56-3.45) with a cathelicidin level greater than 0.45 μM; by 5.3 times (95% 2.63-11.11) with Klotho protein level greater than 4.53 ng/ml

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

Prospects for further research are in more in-depth diagnosis of early inflammation in periodontal tissues in patients with fixed orthodontic appliances in the oral cavity, in order to prevent complications from the dentofacial system.

REFERENCES

1. Borysenko AV, Antonenko MYu, Lynovytska LV, Sidelnikova LF, Nesyn OF, Dikova IH, et al. [Stomatological diseases: therapeutic stomatology]. AV Borysenko, editor. VSV «Medytsyna»; 2017. Ukrainian.
2. Jenkins WM, Papapanou PN. Epidemiology of periodontal disease in children and adolescents. Periodontology 2000. 2001;26(1):16-32. doi: https://doi.org/10.1034/j.1600-0757.2001.2260102.x
3. Albandar JM. Global risk factors and risk indicators for periodontal diseases. Periodontology 2000. 2002;29(1):177-206. doi: https://doi.org/10.1034/j.1600-0757.2002.290109.x
4. Neely AL, Holford TR, Löe H, Anerud A, Boysen H. The Natural History of Periodontal Disease in Man. Risk Factors for Progression of Attachment Loss in Individuals Receiving No Oral Health Care. Journal of Periodontology. 2001;72(8):1006-15. doi: https://doi.org/10.1902/jop.2001.72.8.1006
5. Fábián TK, Fejérdy P, Csermely P. Salivary Genomics, Transcriptomics and Proteomics: The Emerging Concept of the Oral Ecosystem and their Use in the Early Diagnosis of Cancer and other Diseases. Current Genomics. 2008;9(1):11-21. doi: https://doi.org/10.2174/138920208783884900
6. Madhwani T, McBain AJ. Compositional modification of nascent in vitro dental plaques by human host-defence peptides. FEMS Immunology & Medical Microbiology. 2012;64(3):374-81. doi: https://doi.org/10.1111/j.1574-695X.2011.00922.x
7. Yao Y, Berg EA, Costello CE, Troxler RF, Oppenheim FG. Identification of Protein Components in Human Acquired Enamel Pellicle and Whole Saliva Using Novel Proteomics Approaches. The Journal of Biological Chemistry. 2003;278(7):5300-8. doi: https://doi.org/10.1074/jbc.M206333200
8. Ogawa Y, Miura Y, Harazono A, Kanai-Azuma M, Akimoto Y, Kawakami H, et al. Proteomic Analysis of Two Types of Exosomes in Human Whole Saliva. Biological and Pharmaceutical Bulletin. 2011;34(1):13-23. doi: https://doi.org/10.1248/bpb.34.13
9. Boman HG. Antibacterial peptides: basic facts and emerging concepts. Journal of Internal Medicine. 2003;254(3):197-215. doi: https://doi.org/10.1046/j.1365-2796.2003.01228.x
10. Melekhin VV, Makeyev OG. [Klotho gene: modern view on the structure and function. Possible mechanisms of antitumor action]. Vestnik uralskoi meditsinskoi akademicheskoi nauki; 2018;15(3):393-404. Russian. doi: https://doi.org/10.22138/2500-0918-2018-15-3-393-404
11. Imura A, Tsuji Y, Murata M, Maeda R, Kubota K, Iwano A, et al. α-Klotho as a Regulator of Calcium Homeostasis. Science. 2007;316(5831):1615-8. doi: https://doi.org/10.1126/science.1135901
12. Franco C, Patricia HR, Timo S, Claudia B, Marcela H. Matrix Metalloproteinases as Regulators of Periodontal Inflammation. International Journal of Molecular Sciences. 2017;18(2):Article 440. doi: https://doi.org/10.3390/ijms18020440
13. Markelova EV, Zdor VV, Romanchuk AL, Birko ON. [Matrix metalloproteinases: on their relationship with cytokine system, diagnostic and prognostic potential]. Immunopatologiya, allergologiya, infektologiya. 2016;(2):11-22. Russian. doi: https://doi.org/10.14427/jipai.2016.2.23

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