УДК 616.311:517.171.4
DOI https://doi.org/10.35220/2078-8916-2023-49-3.5

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ORAL AND INTESTINAL DYSBIOSIS IN OBESE PATIENTS WITHOUT TYPE 2 DIABETES WITH PERIODONTAL DISEASE

The purpose of research. *To study the relative activity of lysozyme and urease enzymes in oral fluid and blood serum and to determine the degree of dysbiosis of the oral cavity and intestines in patients with various degrees of obesity without type 2 diabetes with periodontal pathology, as well as the change in these indicators after therapy with antidysbiotic and hepatoprotective drugs and corrected diet.* ***Materials and methods****. During the research, 170 patients aged from 25 to 55 years with a body mass index of 27-53 were examined. 63 patients with obesity were examined for oral and intestinal dysbiosis. 53 patients with periodontal diseases underwent treatment in the form of basic periodontal tissue therapy along with general obesity treatment prescribed by an endocrinologist. 33 of these patients were additionally taking, following our recommendation, an anti-dysbiotic hepatoprotective medicinal complex of herbal origin and kept a corrected diet.* **Results***. Laboratory studies proved that, before treatment, all patients with periodontal diseases had the indicators of the relative lysozyme activity significantly reduced and the indicators of the relative urease activity significantly increased, both in the blood serum and in the oral fluid, and high degree of oral and intestinal dysbiosis, accordingly. After the treatment, the relative lysozyme activity increased significantly and the relative urease activity of decreased significantly, and the degree of dysbiosis, both in the blood serum and in the oral fluid, declined accordingly in all patients. In patients tested after the therapy with a medicinal complex and corrected diet, these indicators significantly approached the indicators of patients with healthy periodontium in the setting of obesity of various severity.* **Conclusion***. The obtained results enable to assume that there is a correlation between the oral and intestinal dysbiosis and to recommend this medicinal complex for the treatment of patients with periodontal diseases in the setting of obesity of various severity in comprehensive therapy.*

Key words: *comorbid pathology, intestinal microflora, oral microflora, periodontal disease.*

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ДИСБІОЗ РОТОВОЇ ПОРОЖНИНИ І КИШЕЧНИКА У ПАЦІЄНТІВ З ОЖИРІННЯМ БЕЗ НАЯВНОСТІ ЦУКРОВОГО ДІАБЕТУ 2 ТИПУ З ЗАХВОРЮВАННЯМИ ПАРОДОНТУ

Мета роботи. *Дослідити відносну активність ферментів лізоциму та уреази у ротовій рідині і сироватці крові та визначити ступінь дисбіозу ротової порожнини і кишечника у пацієнтів з ожирінням різного ступеня без наявності цукрового діабету 2 типу з патологією пародонту, а також зміну цих показників після прийому антидисбіотичних і гепатопротекторних препаратів та корекції харчування.* **Матеріали та методи***. В процесі роботи було оглянуто 170 пацієнтів, віком від 25 до 55 років, з ІМТ від 37-53. Обстежено щодо дисбіозу ротової порожнини та кишечника 63 пацієнта з ожирінням. Проліковано 53 пацієнта з захворюваннями пародонту, які отримували базову терапію тканин пародонту разом із загальним лікуванням ожиріння, призначеного лікарем-ендокринологом. Із цих пацієнтів 33 особи додатково застосовували запропонований нами антидисбіотичний та гепатопротекторний лікарський комплекс рослинного походження та корекцію харчування.* **Результати.** *Лабораторні дослідження довели, що у всіх пацієнтів з захворюваннями пародонту перед лікуванням були достовірно зменшені показники відносної активності ферменту лізоциму та статистично достовірно збільшені показники відносної активності ферменту уреази як у сироватці крові так і у ротовій рідині та відповідно збільшено ступінь дисбіозу ротової порожнини та кишечника. Після проведеного лікування статистично достовірно збільшилась відносна активність ферменту лізоциму та статистично достовірно знизилася відносна активність ферменту уреази та відповідно знизився ступінь дисбіозу як у сироватці крові так і у ротовій рідині у всіх пацієнтів. У пацієнтів, після прийому лікарського комплексу та корекції харчування, ці показники статистично достовірно наблизилися до показників пацієнтів зі здоровим пародонтом на тлі ожиріння різного ступеня тяжкості.* **Висновок***. На підставі отриманих результатів можна припустити, що існує кореляційний зв'язок між дисбіозом порожнини рота і кишечника та рекомендувати цей комплекс препаратів для лікування пацієнтів із захворюваннями пародонту на тлі ожиріння різного ступеня тяжкості у комплексній терапії.*

Ключові слова: *коморбідна патологія, кишкова мікрофлора, мікрофлора ротової порожнини, захворювання пародонту.*

Introduction. Inflammatory periodontal diseases are currently one of the most serious and widespread sociomedical problems and take one of the leading places in the dental morbidity structure [1].

The majority of scientists today believe that the leading role in the development of periodontal pathology is played by a microbial factor [2].

Influence of general somatic diseases is proved to be among the general factors that affect the entire organism as they lead to periodontal pathology. It is common for combined pathologies to complicate each other [3]. With various pathologies of internal organs and systems, significant functional and morphological changes occur in the periodontal complex. One of the important topics of research in periodontology has become the relationship between the etiology and pathogenesis of periodontal diseases and obesity. The promising approach to research is to consider both diseases as a comorbid pathology [4].

Obesity is among the most widespread chronic non-infectious diseases in the world. A progressive increase in the number of patients, both among adults and children, is reported in all countries [5]. According to the literature, the pathological effect of obesity on the development of comorbid pathology is stipulated with a number of mechanisms, among which the development of insulin resistance, atherogenic dyslipidemia, and secretory disorder of adipose tissue are considered to be among the most important [5]. Current literature data indicate that there is an ethiopathogenetic relationship between the development of insulin resistance and inflammatory-dystrophic changes of the periodontium, which are insulin-dependent [6].

An oral cavity is a unique ecosystem in which various microorganisms are in dynamic equilibrium and form a microbiocenosis [7]. Oral microbiocenosis is a relative 'constant' of specific microorganisms, which changes under certain conditions causing a pathological condition defined as dysbiosis [8]. Inflammatory periodontal diseases are usually accompanied by dysbiosis in the oral cavity, and its severity corresponds to the degree of periodontal tissue damage. Most often, oral dysbiosis develops in the setting of intestinal dysbiosis.

The prevailing part of the human microflora is found in the gastrointestinal tract, namely in the intestines. Colonization of human intestines begins at birth and becomes relatively stable in adulthood. Intestinal microbiota (IM) is not stable, as it is affected by numerous factors [8]. Over the past decade, several studies have evaluated the effects of diet on IM composition and its metabolic functions. L.A. David et al. (2014) demonstrated that diet has a significant effect on IM. Nutrients interact with IM, changing the microbial landscape, which results in a significant impact on human health [9]. IM contributes to obtaining the maximum calories from the consumed food. Dysbiosis may be responsible for the pathogenesis of metabolic disorders, including obesity, type 2 diabetes, and metabolic syndrome [10-11]. A high-fat diet attracts special attention in patients with obesity. It has been experimentally demonstrated that the high-fat diet can increase the levels of circulating lipopolysaccharide (LPS). In 2007 P.D. Cani et al. proposed the term "metabolic endotoxemia" to define the inflammatory condition [11], according to the hypothesis, LPS act as a trigger of inflammation that develops during metabolic disorders [12-13]. A high-fat food has been proved to increase the pool of Gram-negative bacteria, leading to plasma LPS levels sufficient to increase body weight, fasting blood glucose, and to incite inflammation. One of the important sources of LPS supply to blood is the oral cavity, which is stipulated with a high content of Gram-negative bacteria in the periodontal pockets [12-13]. In turn, the onset of dysbiosis in the oral cavity also causes changes in the composition of the general microflora.

In view of the above, timely and duly diagnostics, prevention, correction of oral and intestinal dysbiosis and the search for effective methods of treatment and prevention of periodontal diseases in patients with obesity of various severity are still of high priority. This determined the topicality of a comprehensive study to be conducted in this direction.

Purpose of the research. To study the relative activity of lysozyme and urease in oral fluid and blood serum and to determine the degree of oral and intestinal dysbiosis in patients with obesity of various severity without the type 2 diabetes with periodontal pathology, and to determine the changes in these indicators after a therapy with anti-dysbiotic and hepatoprotective drugs and corrected diet.

Materials and methods. During the research, 170 patients aged from 25 to 55 years, with a body mass index (BMI) of 27-53 were examined. Patients underwent a comprehensive clinical, laboratory and instrumental examination at the Weight Correction Center of the counselling outpatient clinic of the State University "V.Ya. Danylevskyi Institute of Endocrine Pathology of the National Academy of Medical Sciences of Ukraine". Examination by a dentist was carried out according to the generally accepted pattern for patients with periodontal pathology. The presence of obesity was assessed by BMI

(WHO, 2007). In the course of study, laboratory testing of 53 patients with periodontal diseases and 10 patients without periodontal diseases with varying severity of obesity, without type 2 diabetes, aged 25-55 years with a BMI of 27-53, was carried out. Patients with periodontal diseases were divided into the study group n=33 patients and the comparison group n=20 patients; the control group consisted of 10 patients without periodontal diseases who only receive anti-obesity treatment prescribed by an endocrinologist. All patients underwent a biochemical and immunoenzymatic analysis of oral fluid and blood for oral dysbiosis and intestinal in the certified central R&D laboratory of Kharkiv National Medical University. Laboratory tests of blood serum and oral fluid in the study group and the comparison group were performed before treatment and 3 months thereafter. The relative lysozyme activity was determined in the oral fluid to assess the state of oral non-specific immunity, and in the blood to assess the state of intestinal non-specific immunity; and the relative urease activity in oral fluid and blood as an indicator of microbial colonization of the oral cavity and intestines; based on the ratio of the relative urease and lysozyme activities, the degree of oral and intestinal dysbiosis was calculated according to the enzymatic method by A.P. Levitskyi (2011). All patients received basic therapy for alimentary-constitutional abdominal obesity of various severity prescribed by an endocrinologist. In the study group, patients received traditional therapy of the relevant periodontal pathology and additionally, on our recommendation, the medicinal complex Kvertulin of plant origin (developed by Scientific Production Association "Odesa Biotechnologies"), 1 tablet three times a day for 1.5 months, Lekvin 1 tablet 3 times a day for 1.5 months, dissolve in the mouth Lysozyme Forte before meals twice a day for 1 month, and had their nutrition corrected with a low-fat diet and vegetable oils replaced with high-oleic sunflower oil "Olyvka". In the comparison group, patients received traditional therapy for the corresponding periodontal pathology.

All examined patients signed an informed consent to participate in the study. The requirements of the Declaration of Helsinki adopted by the General Assembly of the World Medical Association, the principles and norms of the Council of Europe Convention on Human Rights and Biomedicine, the applicable law, orders of the Ministry of Health of Ukraine were observed during the study and approved by the Bioethics Commission of Sumy State University (protocol №.2/5 dated May 16, 2023).

The degree of probability was assessed according to the Student's test using parametric methods of variation statistics with the use of Statistica 6.0 statistical program package and Microsoft Excel 2010. For all indicators, the values of the arithmetic mean (M and errors of the mean (m), sample size (n)) were calculated, the confidence coefficient is less than 0.05.

Results. During the study, 170 patients were examined, and periodontal pathology was detected in 138 of them, who were aged 25-55 and had BMI of 27-53; their share was 81.1 %.

Laboratory tests proved that all patients from the study and comparison groups had significantly reduced indicators of the relative lysozyme activity before treatment (see Table 1, Figure 1 to Table I) and significantly increased indicators of the relative urease activity both in blood serum and in oral liquid (Table 2, Figure 2) and high degree of oral and intestinal dysbiosis, accordingly (Table 3, Figure 3 to Table III).

After the treatment, the relative lysozyme activity increased significantly and the relative urease activity decreased significantly, and the degree of dysbiosis, both in blood serum and in the oral fluid, declined

Table I

Lysozyme activity (U/l) in the biological fluids of patients with periodontal disease and the control group (x ± Sx)

Groups	Oral fluid		Blood serum	
	Before treatment	After n = 6	Before treatment	
Healthy (control group)	49.27 ± 2.84 (n = 5)		37.18 ± 3.74 (n = 5)	
Medication + (study group)	29.82 ± 5.26 *P < 0.05 (n = 13)	49.75 ± 4.04 (n = 6)	28.35 ± 5.84 *P < 0.05 (n = 11)	32.58 ± 3.92 (n = 6)
No medication (comparison group)	29.39 ± 4.21 *P < 0.05 (n = 6)	37.35 ± 3.83 *P < 0.05 **P < 0.05 (n = 6)	28.84 ± 5.81 *P < 0.05 (n = 6)	30.42 ± 5.89 *P < 0.05 (n = 6)

*Note: *P – significant difference relative to the Healthy group; **P – significant difference relative to the Medication + group.*

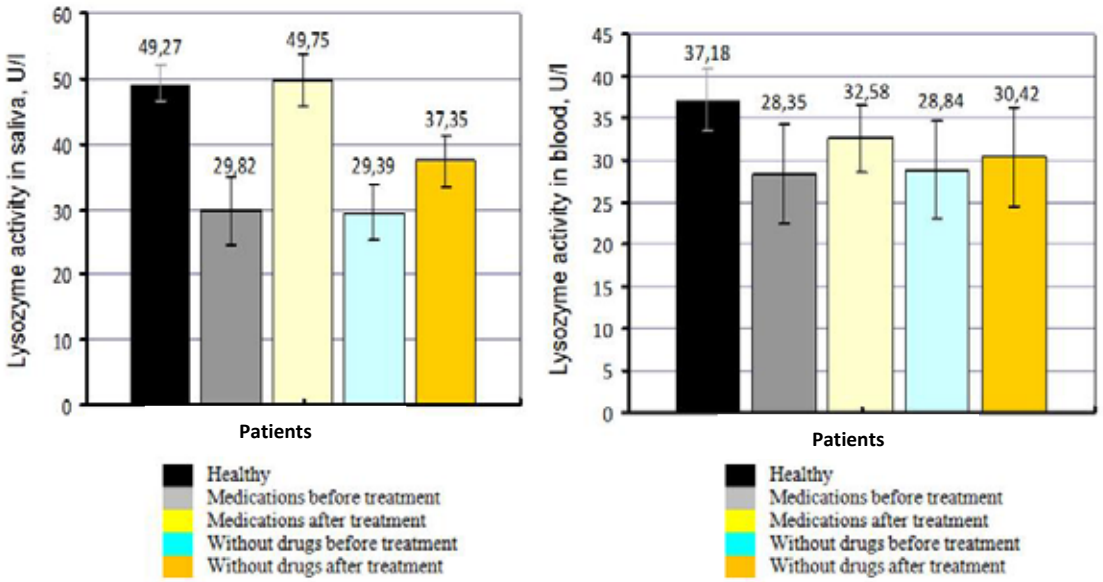

Figure 1 to Table I. Lysozyme activity (U/l) in the biological fluids of patients with periodontal disease and the control group (x ± Sx) before and after treatment.

accordingly in all patients. In the study group, after the therapy with the proposed medicinal complex and corrected diet, these indicators significantly approached the indicators of patients with healthy periodontium in the setting of obesity of various severity.

Discussion. Based on the study of the degree of dysbiosis in the biological fluids (oral fluid and blood serum) of patients with periodontal diseases in the setting of obesity without type 2 diabetes, we found the following:

– indicators of the relative lysozyme activity were significantly reduced 1.65 times in patients from the study group (P<0.05) and 1.67 times in the comparison group (P<0.05) before treatment, against the control group. After treatment, the relative lysozyme activity in the oral fluid and blood of all patients significantly increased.

In the study group, after the therapy with the proposed medicinal complex and corrected diet, the indicators of the relative lysozyme activity in the oral fluid significantly increased 1.66 times (P<0.05), and in the comparison group, it was 1.27 times (P<0.05). The relative lysozyme activity in the blood in the study group significantly increased 1.14 times (P<0.05), and in the comparison group, it was 2.05 times (P<0.05) (Table 1, Fig. 1);

– indicators of the relative urease activity were significantly high before treatment: 2.4 times in oral fluid in the study group (P<0.05), 2.37 times in the

Table 2

Urease activity (μmol/min/l) in biological fluids of patients with periodontal diseases and the control group (x ± Sx) before and after treatment

Groups	Oral fluid		Blood serum	
	Before treatment	After n = 6	Before treatment	After
Healthy (control group)	5.77 ± 0.91 (n = 5)		3.38 ± 0.62 (n = 5)	
Medication + (study group)	13.87 ± 2.53 *P < 0.01 (n = 13)	6.15 ± 0.83 (n = 6)	5.01 ± 0.77 *P < 0.05 (n = 11)	3.11 ± 0.55 (n = 6)
No medication (comparison group)	13.69 ± 1.88 *P < 0.05 (n = 6)	8.66 ± 1.28 *P < 0.05 **P < 0.05 (n = 6)	4.98 ± 0.71 *P < 0.05 (n = 6)	3.79 ± 0.57 **P < 0.05 (n = 6)

*Note:*P – significant difference relative to the Healthy group;*

***P – significant difference relative to the Medication + group.*

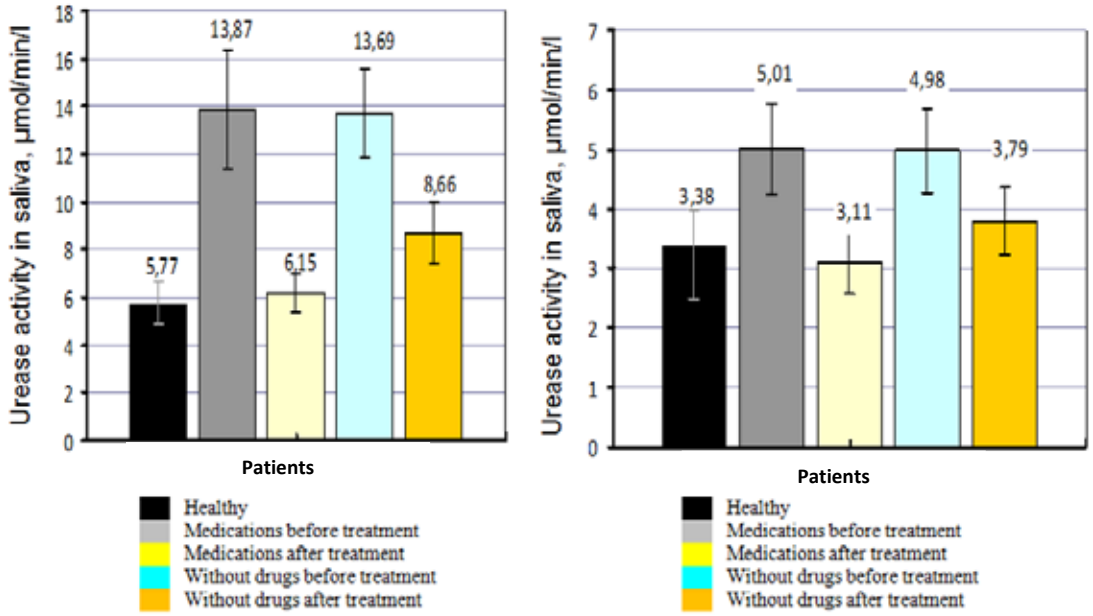

Figure 2 to Table II. Urease activity (µmol/min/l) in biological fluids of patients with periodontal diseases and the control group (x ± Sx) before and after treatment.

comparison group (P<0.05). In blood serum, 1.48 times in the study group (P<0.05), 1.27 times in the comparison group (P<0.05) against the control group.

After the treatment, these indicators significantly decreased: 2.25 times in oral fluid in the study group (P<0.05), 1.5 times in the comparison group (P<0.05). In blood serum, 1.61 times in the study group by (P<0.05), 1.31 times in the comparison group (P<0.05) (Table 2, Fig. 2);

– the degree of oral and intestinal dysbiosis was significantly high before treatment in all patients, in particular, 4 times in the oral cavity in the study group (P<0.05), 3.9 times in the comparison group (P<0.05) against the control group. After the treatment, the degree of dysbiosis in all patients significantly decreased, in particular, 4 times in the oral cavity in the study group (P<0.05), 2.04 times in the comparison group (P<0.05). The degree of intestinal dysbiosis after treatment significantly reduced 1.93 times in the study group (P<0.05), 1.3 times in the comparison group (P<0.05) (Table III, Fig. 3).

Conclusion. Based on the findings of study focused on the relative activity of enzymes in oral fluid and blood serum and the degree of oral and intestinal dysbiosis, in patients with various severity of obesity without type 2 diabetes with periodontal pathology, it can be assumed that there is a correlation between the oral and intestinal dysbiosis, and its calculation enables to assess intestinal dysbiosis using the indicator of oral dysbiosis.

Thus, we have proven through clinical and laboratory studies that the anti-dysbiotic and hepatopro-

Table 3

Dysbiosis index in biological fluids of patients with periodontal diseases and the control group (x ± Sx) before and after treatment

Groups	Oral fluid		Blood serum	
	Before treatment	After n = 6	Before treatment	After
Healthy (control group)	0.12 ± 0.02 (n = 5)		0.093 ± 0.02 (n = 5)	
Medication + (study group)	0.48 ± 0.11 *P < 0.01 (n = 13)	0.12 ± 0.02 (n = 6)	0.84 ± 0.05 *P < 0.05 (n = 11)	0.095 ± 0.01 (n = 6)
No medication (comparison group)	0.47 ± 0.07 *P < 0.05 (n = 6)	0.23 ± 0.04 *P < 0.05 **P < 0.05 (n = 6)	0.179 ± 0.04 *P < 0.05 (n = 6)	0.130 ± 0.04 *P < 0.05 **P < 0.05 (n = 6)

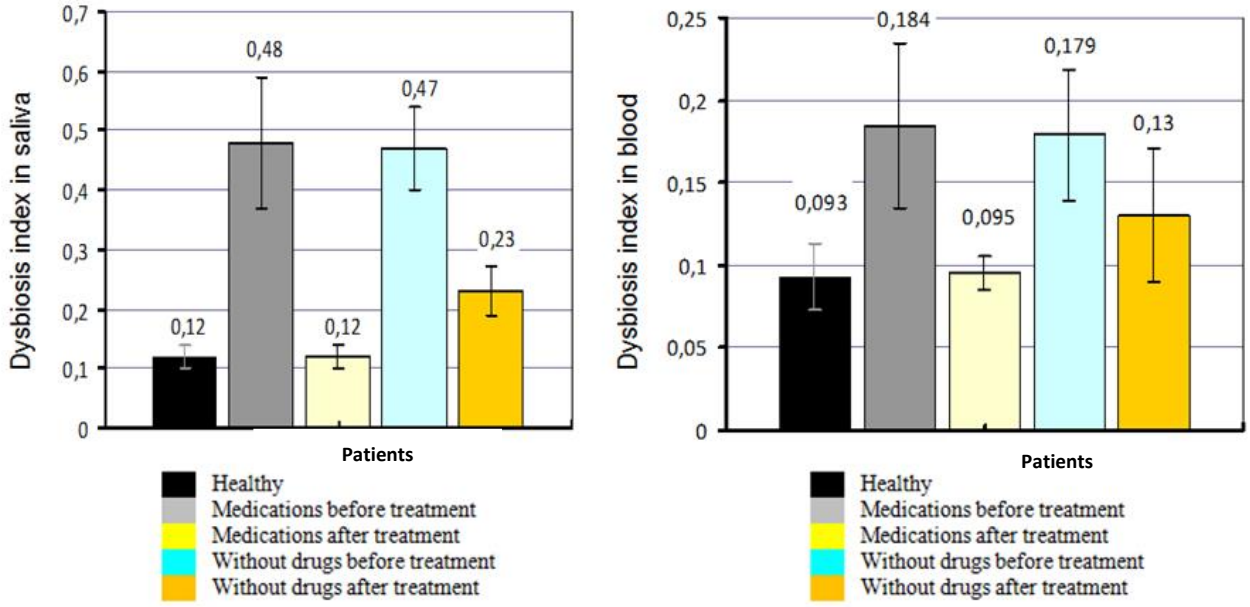

Figure 3 to Table 3. Dysbiosis index in biological fluids of patients with periodontal diseases and the control group (x ± Sx) before and after treatment.

tective medicinal complex proposed by us and the corrected diet significantly reduce the degree of oral and intestinal dysbiosis, which gives grounds for including the medicinal complex and corrected diet in the comprehensive treatment of patients with periodontal diseases in the setting of obesity of various severity.

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