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ANALYSIS OF INFLAMMATORY CHANGES OF ENTHESES AND SYNOVIAL STRUCTURES IN PATIENTS WITH PSORIASIS AND PSORIATIC ARTHRITIS

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The study presents data on the relationship between clinical manifestations and signs of enthesitis, synovitis, and tendinitis detected during ultrasonography in patients with the cutaneous form of psoriasis and psoriatic arthritis. 56 patients with widespread psoriasis whom dermatologists first referred to a rheumatologist for joint and muscle pain were examined. The period of musculoskeletal pain in patients did not exceed 10 months. In addition to general clinical and laboratory examinations, all patients underwent ultrasonography of swollen and/or painful joints, tendons and ligaments. The study demonstrated the diagnostic capabilities of ultrasound to detect foci of inflammation in patients with psoriatic arthritis and identify groups of patients with isolated enthesitis and a combination of enthesitis with synovitis for differentiated anti-inflammatory therapy.

Key words: enthesitis, synovitis, psoriasis, psoriatic arthritis, ultrasonography.

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АНАЛІЗ ЗАПАЛЬНИХ ЗМІН ЕНТЕЗИСІВ ТА СИНОВІАЛЬНИХ СТРУКТУР У ХВОРИХ НА ПСОРИАЗ ТА ПСОРИАТИЧНИЙ АРТРИТ

У статті наведені дані щодо взаємозв'язку клінічних проявів та виявлених при ультразвуковому дослідженні ознак ентезиту, синовіїту та тендосиновіїту у хворих на шкірну форму псоріазу та псоріатичний артрит. Було обстежено 56 хворих на розповсюджений псоріаз, які були вперше направлені дерматологами на консультацію до ревматолога у зв'язку з болем у суглобах та м'язах. Тривалість періоду кістково-м'язового болю у хворих не перевищувала 10 місяців. Крім загальноклінічного та лабораторного обстежень, всім хворим проводилося ультразвукове дослідження набряклих та/або болючих при пальпації суглобів, сухожилків та зв'язок. У роботі було продемонстровано діагностичні можливості ультразвукового дослідження щодо виявлення вогнищ запалення у хворих на псоріатичний артрит та виділення груп хворих з ізольованим ентезитом та поєднанням ентезиту із синовіїтом для проведення диференційованої протизапальної терапії.

Ключові слова: ентезит, синовіїт, псоріаз, псоріатичний артрит, ультразвукове дослідження.

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Psoriasis and psoriatic arthritis (PsA) are characterized by significant clinical heterogeneity due to the possibility of developing various skin and nail plate lesions and involvement of the entheses, joints, and spine in the autoimmune inflammatory process [3]. In the clinical picture of the disease, an isolated lesion of one of the above-listed target organs and various combinations of such disorders can be observed [2]. Among the clinical manifestations of PsA, a special place belongs to inflammation of entheses, which are often the zones of primary localization of inflammation of the musculoskeletal system structures associated with psoriasis. Enthesitis can lead to the emergence of a pronounced pain syndrome, decrease patients' quality of life and contribute to the formation of refractoriness to treatment [1]. They can often be observed in patients with psoriasis in the early stages of the disease. Sometimes, they are the only manifestation of involvement in the musculoskeletal system's pathological process and are considered a risk factor for further PsA development [9, 10, 14].

Along with the clinical examination of patients, an informative method of screening diagnosis of enthesitis is ultrasonography, which allows detecting inflammatory changes in tendons and ligaments (thickening and reduction of echogenicity with loss of fibrillar structure, effusion and thickening of tendons and ligaments), and signs of structural damage in the form of calcifications in the projection of entheses, marginal bone erosions and osteophytes in the place of attachment of tendons and ligaments [6, 12]. Many studies noted the relevance of ultrasound and magnetic resonance imaging as methods of diagnosing enthesitis in spondyloarthritis and PsA, validated the standards of changes detected by ultrasound and the sonographic index of enthesitis activity in patients with PsA developed by the OMERACT Community [4, 7, 12, 13]. An important additional aspect of ultrasonography in the examination of patients with PsA can also be the identification of foci of inflammation to distinguish isolated enthesitis and its combination with inflammation of the synovial membrane of the joint, which allows for differential therapy.

The purpose of the study was to assess the relationship between clinical manifestations and signs of enthesitis, synovitis, and tendinitis detected by ultrasound in patients with psoriasis and psoriatic arthritis.

Materials and methods. The study was based on the analysis of examination data of 56 patients with psoriasis, who were first referred by dermatologists for consultation to a rheumatologist in connection with pain syndrome in joints and muscle attachment points from 2020 to 2022. The duration of musculoskeletal pain in these patients did not exceed 10 months and mean d 4 months. There were 30 women and 26 men in this group. The mean age was 46.4 years. At the time of inclusion of the patients in the study, all of them had active manifestations of psoriasis. In 14 patients, the area of skin damage when assessed by BSA (Body Surface Area) was <3 %. In the rest, it was 3 % or more, and the value of the PASI index (Psoriasis Area and Severity Index) varied from 4 to 50. Palmar and plantar aponeurosis were involved in 6 patients, inguinal and axillary skin areas – in 9, and nail damage – in 26 patients. Before consulting a rheumatologist, the following drugs were used for psoriasis: methotrexate at a dose of 10 mg per week in combination with folic acid 5 mg per week (n=6); golimumab 50 mg per month (n=4). The duration of psoriasis ranged from 3 months to 26 years.

Clinical examination of all psoriasis patients with articular and muscular manifestations included palpation of joints and entheses, determination of the amount of active and passive movements in the affected joints, and evaluation of the sensitivity of 18 sensitive zones. In addition, the content of C-reactive protein (CRP), rheumatoid factor (RF), and the presence of HLA-B27 antigen in the blood was determined, and x-rays of the joints and spine and ultrasonography were performed if required. The severity of enthesitis was evaluated according to the LEI (Leeds Enthesitis Index) index [11], arthritis activity – according to the DAS28-CRP (Disease Activity Score), and the functional activity of patients – according to the HAQ-DI (Health Assessment Questionnaire Disability Index).

All patients underwent ultrasonography of swollen and/or painful joints, tendons of the quadriceps and triceps muscles, proximal and distal ligaments of the patella, Achilles tendon, plantar aponeurosis, as well as areas of the lateral epicondyle of the humerus and the medial condyle of the femur. The Radmir Ultima PA Expert device (Radmir, Ukraine) with a linear sensor (7.5–15 MHz frequency) was used, and a Doppler energy study with a pulse frequency of 6.6 MHz was also performed. During ultrasonography, according to the definition of OMERACT, the signs of enthesitis were considered to be a decrease in the echogenicity of the tendon/ligament enthesis with loss of the normal fibrillar structure, thickening of tendons/ligaments in the enthesis zone, enthesophytes (protruding bony structures above the general level of the marginal bone in the enthesis zone), calcifications, bone erosions in the enthesis zone, the appearance of Doppler signals in the enthesis at a distance of less than 2 mm from the place of attachment of the ligament or tendon to the bone [5]. The degree of expressiveness of ultrasonographic signs of enthesitis in patients with PsA was evaluated according to the MASEI index (Madrid Sonographic Enthesitis Index), which takes into account the nature of enthesitis changes in six localizations, mainly in the lower extremities [8].

The diagnosis of PsA was established according to the CASPAR criteria [15]. A clinical sign of enthesitis was pain on palpation in the projection of the enthesis, and a sign of arthritis was pain on palpation and/or swelling of the joint.

The obtained data was processed using Statistica 6.0 (StatSoft Inc., USA). The Mann-Whitney test assessed the statistical significance of the differences. Spearman correlation analysis was used to assess the relationship between parameters. Differences and associations were considered statistically significant at $p < 0.05$. Quantitative data are presented as the median and interquartile range (Me [25th; 75th percentiles]).

Results of the study and their discussion. Based on the data of a comprehensive examination of 56 patients with psoriasis who were first referred to a rheumatologist in connection with musculoskeletal pain with a duration of no more than 12 months, the diagnosis of PsA was established in 42 (74.7 %).

Palpatory tenderness in the area of entheses was determined in 26 of 56 patients with PsA (45.8 %), the mean value of the Enthesitis Index LEI was 2.2 [1.2; 2.6], the mean number of painful joints is 3.6 [1.8; 6.0], the mean number of swollen joints is 5.2 [2.4; 7.3], the mean value of the DAS28-CRP index is 3.7 [2.8; 4.4].

During ultrasonography, enthesis changes in at least one studied area were detected in 38 out of 56 patients with PsA (67.7 %). At the same time, signs characteristic of an active inflammatory process in entheses were observed in 27 (47.9 %) patients: a decrease in tendon/ligament echogenicity with loss of fibrillar structure – in 22 (39.3 %), thickening of the tendon at the site of attachment to the bone – in 28 (49.2 %); the appearance of Doppler signals in the projection of entheses – in 12 (22.3 %).

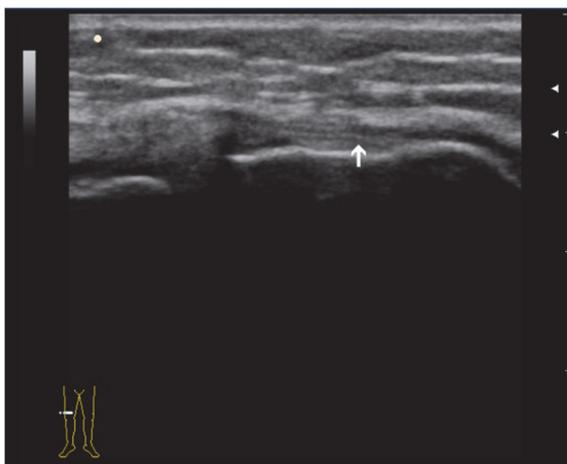


Fig. 1. Ultrasonographic signs of active enthesitis in the distal part of the bunion are presented: thickening, reduced echogenicity and loss of homogeneity, and scattered Doppler signals.

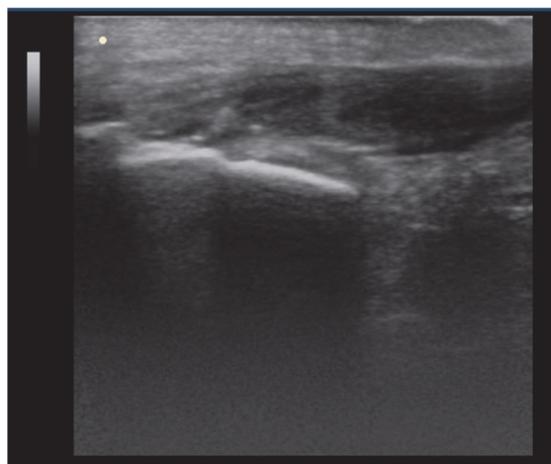


Fig. 2. Ultrasonographic signs of active enthesitis of the Achilles tendon are presented: local thickening, reduced echogenicity, and heterogeneity of the tendon at the point of attachment to the heel bone.

In 15 (24.6 %) patients, ultrasonography revealed signs of structural damage to the entheses: enthesophytes – in 5 (8.8 %), calcifications – in 10 (16.5 %), bone erosions in the place of tendon attachment – in 8 (14.4 %). The mean value of the MASEI index was 9.2 [7.6; 12.0]: inflammatory domains – 6.4 [4.4; 9.7], domains of structural damage – 3.4 [2.3; 5.9]. In all patients with palpable tenderness in the area of entheses, signs of active synovitis, including swelling, thickening, and increased blood flow, were determined by ultrasonography. In 3 patients with PsA and 5 with psoriasis, signs of active enthesitis detected by ultrasound were clinically asymptomatic. During ultrasonography, signs of structural damage in the entheses area (calcifications, enthesophytes and marginal erosions of bone at the site of entheses) were observed only in 7 patients with palpable tenderness in the area of entheses. In 9 (15.3 %) patients, the signs of structural damage of entheses detected by ultrasound were not accompanied by clinical and ultrasonographic signs of active enthesitis.

Thickening of the synovial membrane of the joints during ultrasound was detected in 23 (41.0 %) patients. Doppler signals in the projection of the synovial membrane were determined in 17 (30 %) patients, and effusion in the joint cavity – in 14 (25.4 %) patients. Tendinitis was detected in 20 (35.2 %) patients. Bone erosions of articular surfaces were found in 3 (5.8 %) and osteophytes – in 9 (15.6 %) patients.

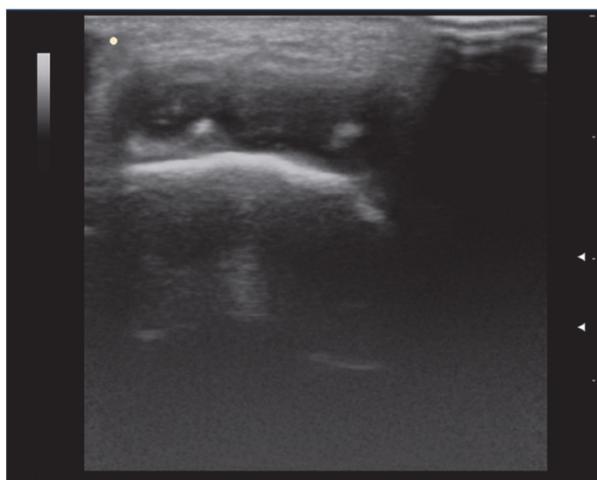


Fig. 3. Ultrasonographic signs of structural damage without signs of active enthesitis inflammation were presented: isolated scattered calcifications in the distal part of the Achilles tendon.

In 13 (23.8 %) patients, ultrasonography revealed isolated signs of an active inflammatory process in the entheses (active enthesitis), in 18 (31.5 %) patients, they were combined with synovitis, and in 11 (20.5 %) – with tendinitis. At the same time, tendinitis was accompanied by ultrasonographic signs of synovitis in all cases.

A correlation analysis of medium strength was found between the values of the MASEI ultrasonographic index and the clinical indices of arthritis activity, enthesitis and functional activity of the joints. The correlation coefficient between the MASEI and LEI indices was 0.63; between MASEI (inflammatory domains) and LEI – 0.72; between MASEI (structural damage domains) and LEI – 0.45; between MASEI and DAS28-CRP – 0.34; between MASEI and HAQ-DI was 0.47.

In patients with PsA, during ultrasonography, signs of an active inflammatory process in the entheses of tendons and ligaments, as well as in the synovial membranes of joints, were detected more often than in patients with psoriasis who did not meet the CASPAR criteria. In addition, erosions in the projection of entheses were most often observed in patients with PsA. The frequency of calcifications and enthesophyte detection in the compared groups of patients did not differ (Table 1).

Table 1

**Comparative analysis of ultrasonography results in patients with PsA
and the skin form of psoriasis**

Signs	All patients under observation (n=56)	PsA patients (n=42)	Patients with skin psoriasis (n=14)	p*
Reduced tendon/ligament echogenicity with loss of fibrillar structure n (%)	22 (39.3)	19 (45.2)	3 (21.42)	0.002
Tendon/ligament thickening at the enthesis site n (%)	27 (47.9)	23 (54.76)	4 (28.6)	0.002
Appearance of Doppler signals in the enthesis projection n (%)	12 (22.3)	11 (26.1)	1 (6.6)	0.004
Enthesophytes n (%)	5 (8.8)	4 (9.5)	1 (6.6)	0.780
Calcifications n (%)	10 (16.5)	7 (16.6)	3 (21.4)	0.988
Marginal bone erosions in the area of enthesis n (%)	8 (14.4)	7 (16.6)	1 (6.6)	0.022
MASEI index, Me [25th; 75th percentile]	9.2 [7.6; 12.0]	12.7 [8.6; 14.0]	3.4 [3.4; 6.8]	0.008
Value of the inflammation domains of the MASEI index	6.4 [4.4; 9.7]	10.3 [4.4; 14.7]	0.4 [0.2; 0.6]	0.017
Signs of active inflammation in entheses n (%)	13 (23.8)			
The value of domains of structural damage of the MASEI index, Me [25th; 75th percentiles] n (%)	3.2 [2.2; 5.6]	3.8 [1.9; 6.6]	2.6 [1.1; 3.0]	0.093
Signs of structural damage to entheses	15 (24.6)	15 (35.7)	0 (0)	0.094
Signs of enthesitis n (%)	14	13 (30.9)	1 (7.1)	0.038
Synovitis n (%)	18 (31.5)	17 (40.4)	1 (7.1)	0.001
Tendinitis n (%)	11 (20.5)	10 (23.8)	1 (7.1)	0.001

Note: PsA is psoriatic arthritis; * – statistically significant differences between groups of patients with PsA and psoriasis; MASEI – Madrid Sonographic Enthesitis Index.

In patients with active enthesitis, compared to other patients with psoriasis, signs of nail damage were observed more often, more pronounced changes and functional disorders of the joints were noted, and a higher level of C-reactive protein (Table 2). Other indices did not differ significantly.

Table 2

**Comparative analysis of clinical and laboratory data in patients depending on detecting signs
of enthesitis during ultrasonography.**

Parameters	Patients with enthesitis (n=27)	Patients without enthesitis (n=29)	p*
PASI index	28.2 [18.3; 45.5]	31.9 [19.7; 47.1]	0.348
Nail lesions n (%)	12 (44.4)	6 (20.7)	0.042
Palmar and plantar lesions n (%)	4 (14.8)	5 (17.2)	0.137
Lesions of axillary and inguinal areas n (%)	5 (18.5)	2 (6.9)	0.215
The number of painful joints, Me [25th; 75th percentile]	5.9 [2.9; 6.7]	1.7 [0.7; 3.2]	0.014
The number of swollen joints, Me [25th; 75th percentile]	4.9 [2.4; 5.8]	1.3 [0.8; 3.0]	0.055
DAS28-CRP index, Me [25th; 75th percentile]	4.5 [3.3; 5.7]	2.8 [2.1; 4.2]	0.024
HAQ-DI index, Me [25th; 75th percentile]	2.34 [1.8; 3.8]	1.26 [1.0; 1.75]	0.033
CRP (mg/L), Me [25th; 75th percentile]	9.3 [5.1; 8.9]	3.6 [2.8; 5.2]	0.027
HLA-B27+ n (%)	9 (33.3)	3 (10.34)	0.086

Note: * – statistically significant differences between groups of patients with enthesitis and without enthesitis; PASI – Psoriasis Area and Severity Index; DAS28-CRP – Disease Activity Score in modification using C-reactive protein; HAQ-DI – Health Assessment Questionnaire Disability Index; CRP – C-reactive protein

In order to determine the peculiarities of the course of the disease in patients with isolated active enthesitis, two groups of patients were selected. In the first group, ultrasound showed signs of active enthesitis without synovitis and tendinitis (n=13). In the second group, enthesitis was accompanied by synovitis (n=18).

Patients with isolated enthesitis compared to patients with a combination of enthesitis and synovitis had less pronounced clinical signs of enthesitis and functional joint disorders according to the HAQ-DI, lower values of the LEI index and lower CRP levels in the absence of differences in the features of skin and nail plate lesions, as well as in the frequency of HLA-B27 antigen detection.

In many clinical studies using ultrasonography, it has been demonstrated that enthesitis is the earliest and most common manifestation of the inflammatory process in patients with PsA. The frequency of detecting signs of active enthesitis and its consequences in osteoproliferation and calcification by ultrasonography varies from 27.8 to 90 % [12]. A feature of our patients, in contrast to patients included in other studies, is a relatively short duration of pain (the mean duration of pain before the start of the examination was 4 [0.8; 8.1] months), which in part of the patients corresponded to the early period of PsA in the absence of targeted essential therapy.

In this study, a high level of correlation between clinical and ultrasonographic signs of enthesitis was noted. The correlation coefficient between clinical and ultrasonographic enthesitis indices was 0.71 (for inflammatory domains of the MASEI index). The study results show that ultrasonography can differentiate isolated enthesitis and the combination of enthesitis with synovitis and tendinitis in patients with PsA. Significant differences in the clinical symptoms of the disease were found between these groups. Thus, patients with enthesitis combined with synovitis had more pronounced functional disorders, clinical manifestations of enthesitis, and signs of systemic inflammation. Taking into account certain differences in the recommendations for the treatment of enthesitis and arthritis, the use of ultrasonography can be of great importance for choosing the tactics of adequate differentiated therapy of PsA, in particular for deciding on the appointment of methotrexate and other primary anti-inflammatory disease-modifying drugs.

In this study, signs of structural damage to entheses (calcifications, enthesophytes, and bone erosions) during ultrasound were determined in 25.6 % of patients with a short history of clinically pronounced enthesitis and in 15.4 % of patients without clinical and ultrasonographic signs of active enthesitis. These data are consistent with the results of other studies, in which, in many patients with psoriasis without clinical symptoms of musculoskeletal inflammation, ultrasonography also revealed a violation of the structure of entheses, which was considered a consequence of the subclinical course of enthesitis in patients with psoriasis [14]. These data confirm the hypothesis about the importance of enthesitis inflammation in patients with PsA and open perspectives for studying the possibilities of preventive therapy in this category of patients with psoriasis.

Conclusion

According to our study's results, a high correlation level between clinical and ultrasonographic signs of enthesitis was noted; the correlation coefficient between clinical and ultrasonographic indices of enthesitis was 0.71 (for the inflammatory domains of the MASEI index). The results of the study show that ultrasonography can differentiate isolated enthesitis and the combination of enthesitis with synovitis and tendinitis in patients with PsA. Significant differences in the clinical symptoms of the disease were found between these groups. Thus, ultrasonography can be of great importance for choosing the tactics of adequate differentiated therapy of PsA, in particular for solving the issue of prescribing methotrexate and other essential anti-inflammatory disease-modifying drugs.

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ANXIETY, DEPRESSION, DYSFUNCTION OF THE AUTONOMIC NERVOUS SYSTEM AND THEIR CORRELATIONS DURING COVID-19 PANDEMIC

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The purpose of the study was to explore correlations between psychological and regulatory mechanisms in the development of autonomic nervous system dysfunction in response to stressors during the COVID-19 pandemic. 133 students were examined. HADS, PSS-10, State-aR questionnaires were used. Dysfunction of the autonomic nervous system was determined according to A.M. Wein and based on heart rate variability analysis. 37.0 % of respondents had symptoms of anxiety, 38.1 % had subclinical and clinical symptoms of depression, 99.1 % had a moderate and high level of subjective stress. Altered heart rate variability was noted in individuals with subclinical and clinical signs of depression. There were positive correlations between levels of anxiety and depression ($R=0.50$, $p<0.001$), anxiety and stress ($R=0.28$, $p<0.01$), anxiety and ANS dysfunction index ($R=0.23$, $p<0.01$), depression and ANS dysfunction index ($R=0.30$, $p<0.005$), negative correlations – between levels of anxiety and the total index of autonomic regulation aR ($R=-0.45$, $p<0.001$), depression and the total index of autonomic regulation aR ($R=-0.29$, $p<0.01$).

Key words: stress, anxiety, depression, autonomic nervous system, COVID-19 pandemic, international students

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ВЗАЄМОЗВ'ЯЗОК ТРИВОГИ, ДЕПРЕСІЇ ТА ДИСФУНКЦІЇ АВТОНОМНОЇ НЕРВОВОЇ СИСТЕМИ ПІД ЧАС ПАНДЕМІЇ COVID-19

Метою дослідження було вивчення взаємозв'язку психологічних і регуляторних механізмів розвитку дисфункції автономної нервової системи у відповідь на стресові фактори під час пандемії COVID-19. Було обстежено 133 студента. Використовували опитувальники HADS, PSS-10, State-aR. Дисфункцію автономної нервової системи визначали за A.M. Вейном та на основі аналізу варіабельності серцевого ритму. Серед когорти обстежених у 37,0 % відмічались прояви тривоги та 38,1 % мали субклінічні та клінічні прояви депресії. Помірний та високий рівень суб'єктивного стресу мали 99,1 % опитаних. У осіб з субклінічними та клінічними ознаками депресії відзначалась змінена варіабельність серцевого ритму. Прямі зв'язки були між рівнями тривоги та депресії ($R=0,50$, $p<0,001$), тривоги та стресу ($R=0,28$, $p<0,01$), тривоги та показника дисфункції АНС ($R=0,23$, $p<0,05$), депресії та дисфункції АНС ($R=0,30$, $p<0,005$), зворотні – між рівнем тривоги та сумарного показника автономної регуляції aR ($R=-0,45$, $p<0,001$), між рівнем депресії та сумарного показника автономної регуляції aR ($R=-0,29$, $p<0,01$).

Ключові слова: стрес, тривожність, депресія, автономна нервова система, пандемія COVID-19, іноземні студенти

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Since the beginning of the COVID-19 pandemic, there has been a deterioration in people's mental health. The prevalence of such symptoms as stress, anxiety, and depression increased by 25 % in the first year of the pandemic, according to the World Health Organization's (WHO) data [12]. During the pandemic, people faced numerous stressors, such as social isolation, restrictions on work, and communication with loved ones. Being alone, feeling a constant fear of infection, the suffering