Spectrum Journal of Innovation, Reforms and Development
Volume 27, May - 2024 | ISSN (E): 2751-1731
Website: www.sjird.journalspark.org

T-CELL IMMUNE DISORDERS IN CASE OF EARLY SYSTEMIC SCLERODERMA

Ergashova Madina Muxtorovna
PhD., Assistant of Samarkand State Medical University

Shichenko Olga Alexandrovna
Assistant of Samarkand State Medical University

Xusanov Temurbek Bobirjonovich
Student of Samarkand State Medical University
Samarkand State Medical University, Samarkand, Uzbekistan

Abstract
The genesis of pathological fibrosis in systemic scleroderma (SSD) remains unclear, but T-cell immune disorders are given important importance in the development and maintenance of this process.
Goal. A parallel study of T-lymphocytic reactions in the blood and tissues of patients with early SSD, their quantitative assessment and study of the relationship with the activity of the disease.
Material and methods. The content of the main marker of T-lymphocyte activation - The interleukin-2 receptor (rIL-2P) in the blood was quantified by ELISA in 68 patients with SSD, as well as in dynamics in 40 patients receiving glucocorticoids and/or D-penicillalmin at doses adequate to the activity of the disease. In parallel, 45 skin biopsies were morphologically examined, including immunohistochemical phenotyping of the cellular composition of infiltrates.
Results. The early stage of SSD was characterized by the greatest severity of T-lymphocytic activation processes, represented by CD 4+ T-cell infiltration of the skin and elevated levels of rIL-2P in the blood. Serological and morphological signs of T-lymphocytic activation positively correlated with connective tissue fibroplastic reaction in situ and the rapidly progressive course of the disease. The relationship between the concentration of rIL-2P and the severity of lymphocytic infiltration of the skin has been established, which indicates the possibility of quantifying immuno-inflammatory processes in tissues based on the determination of rIL-2P in the blood. The study of the content of rIL-2P in dynamics confirmed its connection with the activity of SSDs.
Conclusion. T-cell activation is characteristic of the initial stages of SSD and is closely related to
It is associated with the progression of the fibrous process. The level of rIL-2P in the blood can serve as a highly sensitive marker of the activity and prognosis of SSD*.

Keywords: systemic scleroderma, immunomorphology, T lymphocytes, cytokines.

Introduction

Systemic scleroderma (SSD) is one of the most severe rheumatic diseases characterized by a steadily progressive course and a high mortality rate. The
disease is based on connective tissue damage with a predominance of fibrosis and vascular pathology by the type of obliterating endarteriolitis, which is clinically manifested by characteristic changes in the skin, musculoskeletal system, internal
organs (lungs, heart, digestive tract, kidneys) and widespread vasospastic disorders. Among the different views on The nature of the fibrous process and microvascular damage is currently given great importance to T-cell immune disorders. Immune cell mediators, cytokines, are considered as the main factors in the pathophysiology of scleroderma fibrosis. In vitro studies have established their ability to alter the functional activity of fibroblasts, including growth, proliferation and production of intercellular matrix components. T-cell Immune disorders play an important role in the induction of genetically determined fibroblast pathology and clonal selection of their subpopulation, characterized by increased production of matrix proteins. The development of generalized vascular pathology in SSD is also associated with the cytolytic effect on endothelial cells of activated blood T-lymphocytes (subtype V5 1+ y/5 TCR) present at an early stage of the disease. T-cell autoreactivity has also been proven in relation to the components of the microvascular basement membrane. At the same time The presented experimental data have not received convincing clinical confirmation, the significance of T-cell immune disorders in the formation of the clinical symptom complex of early SSD remains unclear, the relationship of local immuno-inflammatory disorders in tissues with serological markers of Tlymphocytic activation has not been clarified. From a clinical point of view, the study of immune disorders in SSD and their connection with the processes of fibrosis and vascular pathology may be important
to develop serological markers of disease activity. Currently, this is one of the priority areas of research, due to the low information content of available clinical and laboratory indicators in assessing the condition of a patient with SSD.

The aim of this study was to quantify the indicators of T-lymphocytic activation in early SDS and to assess their relationship with the clinical and immunomorphological picture of the disease.

MATERIALS AND METHODS OF RESEARCH

Grade I (58% of patients) - initial signs of lung damage (radiological manifestations of basal pneumofibrosis, decreased FVC up to 70% of the norm), esophagus (slight, up to 20 seconds slowdown in the progress of barium sulfate through the esophagus in combination with symptoms of the absence of an epiphrenal ampoule), heart (ECG signs of impaired conduction, left ventricular ejection fraction (LVEF) not lower than 45%, echocardiography signs of compaction and separation of pericardial leaflets), kidneys (proteinuria up to 1500 mg/day, blood creatinine <180 mmol/l);

• Grade 2 (42% of patients) - severe lung damage (FVC <70% of normal and/or presence of pulmonary hypertension), heart (arrhythmia, LVL <40%), gastrointestinal tract (prolonged, >20 sec retention of barium sulfate in the esophagus, enlargement of the esophageal lumen, change in the relief of the mucous membrane, clinical and radiological signs of malabsorption), kidneys (blood creatinine >180 mmol/l, glomerular filtration < 60 ml/min). Determination of the level of the soluble receptor Interleukin-2 (rIL-2P) in blood serum was performed by quantitative enzyme immunoassay using commercial kits from EuroClon. Based on the manufacturer's

recommendations, the upper limit of the norm was determined as M ± 25 and amounted to 4950 pg/ml. Morphological examination of skin biopsies from the lower third of the forearm was performed in 45 patients (30 with early and 15 with late SSD) and included an assessment of the localization and composition of inflammatory cell infiltration, severity connective tissue fibroplastic reaction, activation of endothelial cells. The number of cells in a square was recorded. 0.002mm2 at x400 magnification. The number of fibroblasts was determined on a similar area separately in the presence of a vessel (histione region) and in a non-vascular space. Depending on the number of cells, we have identified 4 degrees of infiltration: 1 st. - from 10 to 19 cells, 2 st. - from 20 to 29 cells, 3 st. - from 30 to 39 cells and 4 st. - 40 cells or more. Immunophenotyping of lymphocytic The infiltrate composition was carried out using monoclonal antibodies from DAKO (Denmark) against common markers of T - (CD3) and B-lymphocytes (CD20), as well as CD4+ and CD8+ T-lymphocytic markers. Monoclonal antibodies from Sorbent LLC were used to identify the intercellular adhesion molecule-1 (ICAM-1). The control group consisted of 10 people who did not suffer from rheumatic or skin diseases (2 men and 8 women, average age - 47+11 years) and was comparable to the main group in age (p=0.3) and gender (p=0.5).

THE RESULTS AND THEIR DISCUSSION

The clinical symptom complex of these patients served as the basis for conducting clinical and morphological comparisons and clarifying the role of the immune factors studied by us in the pathogenesis of the initial stages of SSD.

The pathomorphological picture of the onset of the disease was characterized by actively occurring immuno-inflammatory and fibroplastic processes: pronounced perivascular infiltration consisting of T lymphocytes, macrophages and activated mast cells, expression of ICAM-1 on the vascular endothelium, accumulation of fibroblasts in perivascular spaces. Perivascular infiltrates were found in the skin of 81% of patients with rCCD. The severity of infiltration at the initial stages was significantly higher than at the later stages (31±22 cells/0.002mm2 versus 17±9 cells/0.002mm2, p<0.001). The lymphohistiocytic composition of infiltrates with a significant predominance of lymphocytes was established. Immunophenotyping of the lymphocytic component showed predominantly CD 4+T-cell composition of infiltrates at an early stage of the disease (100% vs. 33%, p<0.0005) and mixed T and B-cell composition at a late stage. Therefore, the distinctive feature of the rSSD was not not only is the infiltration significantly more pronounced, but also its qualitatively different composition is the predominance of CD4+ T lymphocytes.

The immuno-inflammatory changes characteristic of rSSD also included morphological signs of activation of endothelial and mast cells. In 73% of patients, there were clusters of mast cells in the perivascular spaces, in 88% - the presence of ICAM-1 on the vascular endothelium. These changes were significantly more common in rSSD compared with late SDS and the control group. In parallel with pronounced immuno-inflammatory changes in the skin of patients with rSSD, an active fibroplastic reaction was observed. Thus, in the majority of patients with rCCD (86%), a cluster of fibroblasts was found in the perivascular zone - an average of 26+17 cells per unit area (0.002mm2), which was 2.7+1.8 times higher than their number in the non-vascular space. For comparison, in the control group, the number of fibroblasts around the vessels and in the non-vascular areas was

the same and amounted to 8.6+2.6 cells (p<0.001). In case of late SSD fibroplastic reaction It was also poorly expressed (16±7 cells, p<0.02). A reliable relationship between immuno-inflammatory and fibroplastic changes in the skin of patients with SSD was established. Thus, there was a topographic proximity of the location of T-lymphocytes, mast cells and fibroblasts in the perivascular zone and a direct correlation of the number of mast cells and lymphocytes in the infiltrates with the number of fibroblasts (g=0.59, p <0.0001, g=0.6, p< 0.0001 accordingly), which indicates the interaction of these cells and the participation of mast and immune cells in the development of the fibrous process. The connection we found between the presence of ICAM-1 on endothelium and perivascular inflammatory infiltration (x2=6.12, p<0.01) indicates the important role of adhesion molecules in the formation of lymphocytic infiltrates in SSD. High activity and severity of the disease course were associated with significantly more pronounced inflammatory infiltration of the skin (3219 cells/0.002mm2, p<0.02), accumulation of fibroblasts in perivascular spaces (23±12 cells/0.002mm2, p<0.007) and ICAM-1 expression
on endothelial cells (100%, p<0.03). In general, morphological examination demonstrated an important pathogenetic value T-lymphocytic infiltration of the skin: its reliable relationship with the initial stages of the disease, the severity of the course of SSD and the activity of the connective tissue fibroplastic reaction was revealed. A quantitative assessment of T-cell activation in SSD and its role in the development of individual visceral localization of the process was carried out by determining rIL-2P in the blood, the main marker of T-lymphocyte activation.

The content of rIL-2P was significantly higher in patients with rSSD compared with later stages (7410+4420 pg/ml versus 4285+1790, p<0.0005) and generally had an inverse correlation with the duration of the disease. The relationship of rIL-2P with the severity of the course and activity of SSD was established (Table. 4, 5). Thus, the highest levels of this factor were found in patients with acute SSD (8870+4295pg/ml) and a maximum, 3rd degree of activity (8925+3945 pg/ml), as well as in patients with severe internal organ damage (8765+4430 pg/mlml, p<0.05) and a diffuse form of the disease (8855 5070 pg/ml, p<0.04), which indicates a connection between the process of T-lymphocytic activation and the rapidly progressive course of SSD. There was also a direct correlation of rIL-2P levels with the main clinical manifestations of cutaneous and visceral fibrosis: the amount of skin count, skin edema, progression of cutaneous and visceral pathology at the time of examination, as well as the severity of muscle damage, the severity of common symptoms, ESR, hypergamma globulinemia and ANF titer. Investigation of the content of rIL-2P in the dynamics of 40 patients with SSD confirmed its connection with the activity of the disease. Decrease in SSD activity
(n=20) was accompanied by a significant decrease in the level of rIL-2P in the blood (7055+3620 pg/ml and 3975±2275 pg/ml, p <0.003). The content of this factor in the blood did not change with consistently high (5570±3625 pg/ml and 5225+2550 pg/ml, p=0.4) or low (3175±835 pg/ml and 2640+745 pg/ml, p=0.2)

SSD activity. Therefore, the level of rIL is 2P blood levels correlate with the dynamics of the condition of patients and can be used to assess the effectiveness of therapy. The adequate reproducibility of this indicator in stabilizing the condition of patients proves its reliability in monitoring the activity of the SSD in each individual case. It is especially important to emphasize that the level of rIL2P reliably reflected the activity of immuno-inflammatory and fibroplastic processes in tissues. Thus, a high direct correlation was found between the content of rIL-2P in the blood and the number of T-lymphocytes (g=0.52, p<0.01) and fibroblasts (g=0.6, p<0.001) in the

skin.A parallel study of local and systemic immuno-inflammatory processes in patients with SSD allowed us to establish the activation of the T-cell link of immunity in the early period of SSD and its a clear connection with the severity of the disease and individual clinical and laboratory activity indicators. The relationship established in the study between the severity of T-cell infiltration and the expression of ICAM-1 on endothelial cells is consistent with the idea of the important role of adhesion molecules in leukocyte migration through the endothelium, their tissue localization and cellular interaction during the immune response. Connection ICAM-1 with SSD activity is also confirmed by the data of S. Sollberg et al. the presence of this molecule only in places of active fibrosis. A common marker of T-lymphocytic activation (soluble IL-2 receptor), according to our data, positively correlated with the severity of inflammatory infiltration in the skin, as well as with the main clinical indicators of activity SSD. Its content in the blood was increased in half of the patients with SSD, mainly at the beginning of the disease. The dependence of the concentration of rIL-2P in the blood on the duration of the disease, noted in our and a number of other works, indicates the participation of activated T-lymphocytes in the initial processes of fibrosis in SSD. The association of T-cell activation with a rapidly progressive course of the disease is also confirmed by a significant increase in serum levels
of rIL-2P with the development of diffuse skin lesions and severe visceral pathology in the early period of SSD. The study of the content of rIL-2P in dynamics demonstrated the sensitivity of this factor to changes in the clinical status of patients, which makes it possible to recommend its use in monitoring the activity of SSDs. This is consistent with the results of the work of V.D. Steen et al., in which, based on the serial determination of the level rIL-2P in the blood of 38 patients with SSD, its correlation with the dynamics of the skin process and the clinically assessed activity of the disease was established. Similar data were obtained in the study by P.G. Vlachoyiannopoulos et al. The high sensitivity of rIL-2P as an indicator of T-cell activation has been confirmed experimentally. Thus, it has been proven that the synthesis and expression of a highly affinity receptor for IL-2, as well as the release of a soluble receptor, are early signs of T-lymphocytic activation and give an idea of its duration.

CONCLUSIONS

Thus, this study proved the important pathogenetic significance of T-lymphocytic activation in the progression of the fibrous process in SSD: its reliable relationship with the initial stages and severity of the disease, connective tissue fibroplastic reaction in situ. The early stage of SSD was characterized by the greatest severity of T-lymphocytic activation processes, represented by CD4+T lymphocytic infiltration of the dermis and an increase in the level of the common marker of T-lymphocyte activation, rIL-2P, in the blood. The direct correlation between concentration established in the study rIL-2P and the intensity of lymphocytic infiltration of the skin indicates the possibility of quantifying immuno-inflammatory processes in tissues based on the determination of rIL-2P in the blood. At the same time, the close relationship of morphological and serological signs of Tlymphocytic activation with active fibrosis in tissues and the rapidly progressive course of the disease makes it possible to recommend a quantitative determination of serum levels rIL-2P for a more complete and adequate characterization of the immune process associated with fibrosis, as well as for evaluating the effectiveness of immunosuppressive and antifibrosis therapy.

References

1. Исламова, К. А. (2023). Факторы Риска Раннего Развития Остеоартроза. Journal of Science in Medicine and Life, 1(3), 1-7.
2. Исламова, К. А., & Хамраева, Н. А. (2023). Факторы Риска И Качество Жизни Больных Остеартрозом. Central Asian Journal of Medical and Natural Science, 4(6), 268-273.
3. Хусинов, А. А., Исламова, К. А., & Зиядуллаев, Ш. Х. (2023). Поражение Желудочно-Кишечного Тракта У Больных Коронавирусной Инфекцией. Central Asian Journal of Medical and Natural Science, 4(6), 580-585.
4. Исламова, К. А., & Тоиров, Э. С. (2019). Значение факторов риска на качество жизни больных остеоартрозом. In Актуальные вопросы современной медицинской науки и здравоохранения: сборник статей IV Международной научно-практической конференции молодых учёных и студентов, IV Всероссийского форума медицинских и фармацевтических вузов «За качественное образование»,(Екатеринбург, 10-12 апреля 2019): в 3-х т.-Екатеринбург: УГМУ, CD-ROM.. Федеральное государственное бюджетное образовательное учреждение высшего образования «Уральский государственный медицинский университет» Министерства здравоохранения Российской Федерации.
5. Исламова, К., & Карабаева, Г. (2020). ОСОБЕННОСТИ КЛИНИЧЕСКОГО ТЕЧЕНИЯ ЗАБОЛЕВАНИЙ СЕРДЕЧНО-СОСУДИСТОЙ СИСТЕМЫ НА ФОНЕ САХАРНОГО ДИАБЕТА. Журнал кардиореспираторных исследований, 1(3), 59-62.
6. Islamova, K. A., Olimdjanova, F. J. Q., Ziyadullaev, S. K., & Kamalov, Z. S. (2022). RISK FACTORS FOR EARLY DEVELOPMENT OF OSTEOARTHROSIS.
7. Akramovna, I. K., & Rustamovna, A. K. (2023, November). ULTRATOVUSH TEKHIRUV USULINING ERTA RIVOZHLANGAN OSTEOARTHROSIS KASALLIGIDAGI DIAGNOSTIC AHAMIYATI. In International Conference on Medicine and Life Sciences (pp. 72-75).
8. Akramovna, I. K., & Rustamovna, A. K. (2024). Peculiarities of Rheumatoid Arthritis with Hereditary Predisposition. American Journal of Bioscience and Clinical Integrity, 1(1), 11-17.
9. Akramovna, I. K., Rafikovna, U. K., & Ergashevna, E. N. (2024). Current Perceptions of Chronic Pancreatitis. International Journal of Alternative and Contemporary Therapy, 2(1), 12-16.
10. Ибадова, О. А., & Шодикулова, Г. З. (2022). ОЦЕНКА ПРОГНОСТИЧЕСКОЙ ЗНАЧИМОСТИ ИНТЕНСИВНОСТИ И ЧАСТОТЫ КАШЛЯ У ПАЦИЕНТОВ С ИНТЕРСТИЦИАЛЬНЫМ ПОРАЖЕНИЕМ ЛЕГКИХ. Journal of cardiorespiratory research, 1(2), 56-61.
11. Ибадова, О. А., & Аралов, Н. Р. (2020). Диагностические трудности и различия в терминологии идиопатической фиброзирующей болезни легких (литературный обзор). Достижения науки и образования, (2 (56)), 63-67.
12. Ибадова, О. А., Аралов, Н. Р., & Курбанова, З. П. (2020). Роль сурфактантного белка D (SP-D) в иммунном ответе при неспецифической интерстициальной пневмонии. Достижения науки и образования, (4 (58)), 45-49.
13. Ибадова, О. А., Махматмурадова, Н. Н., & Курбанова, З. П. (2020). ПОТЕНЦИАЛЬНЫЕ ФАКТОРЫ РИСКА В РАЗВИТИИ И ПРОГРЕССИРОВАНИИ НЕСПЕЦИФИЧЕСКОЙ

ИНТЕРСТИЦИАЛЬНОЙ ПНЕВМОНИИ. Journal of cardiorespiratory research, 1(1), 72-76.
14. Махматмурадова, Н. Н., Ибадова, О. А., & Закирьяева, П. А. (2020). ДИФФЕРЕНЦИАЛЬНАЯ ДИАГНОСТИКА НЕСПЕЦИФИЧЕСКОЙ ИНТЕРСТИЦИАЛЬНОЙ ПНЕВМОНИИ. Journal of cardiorespiratory research, 1(2), 50-52.
15. Махматмурадова, Н. Н., Ибадова, О., & Шодиев, О. О. (2021). Факторы риска в развитии неспецифической интерстициальной пневмонии. Вопросы науки и образования, (13 (138)), 54-64.
16. Ибадова, О. А., Курбанова, З. П., & Шодиев, О. О. (2021). ФАКТОРЫ РИСКА В ПРОГРЕССИРОВАНИИ НЕСПЕЦИФИЧЕСКОЙ ИНТЕРСТИЦИАЛЬНОЙ ПНЕВМОНИИ. Достижения науки и образования, (8 (80)), 101-107.
17. Ибадова, О. А., Шодикулова, Г. З., & Нажмиддинов, А. Ш. (2021). ТРУДНОСТИ Дифференциальной Диагностики Неспецифической Интерстициальной Пневмонии. Достижения науки и образования, (8 (80)), 50-55.
18. Ибадова, О. А., & Шодикулова, Г. З. (2022). РОЛЬ СУРФАКТАНТНОГО ПРОТЕИНА А (SP-A) В ПРОГНОЗЕ ПРОГРЕССИРОВАНИЯ И ИСХОДА НЕСПЕЦИФИЧЕСКОЙ ИНТЕРСТИЦИАЛЬНОЙ ПНЕВМОНИИ. Достижения науки и образования, (1 (81)), 66-72.
19. Khusainova, M. A., Ergashova, M. M., Eshmamatova, F. B., & Khayitov, S. M. (2023). Features of quality of life indicators in patients with pneumonia. Science and Education, 4(2), 138-144.
20. Shodikulova, G. Z., Pulatov, U. S., Ergashova, M. M., Tairova, Z. K., & Atoev, T. T. (2021). The Correlation among Osteoporosis, Calcium-Phosphore Metabolism and Clinical Symptoms of Main Disease in Patients with Rheumatoid Arthritis. Annals of the Romanian Society for Cell Biology, 4185-4190.
21. Zikriyaevna, S. G., & Muhtorovna, E. M. (2019). The features of the early diagnostics of osteoporosis in patients with rheumatoid arthritis. Достижения науки и образования, (12 (53)), 110-112.
22. Alexandrovna, I. O., Muxtorovna, E. M., & Shodikulova, G. Z. (2023). COMMUNITY-ACQUIRED PNEUMONIA AND CHRONIC HEART FAILURE. Open Access Repository, 4(2), 744-754.
23. Alexandrovna, I. O., Shodikulova, G. Z., & Muxtorovna, E. M. (2023). QUALITY OF LIFE OF ELDERLY PATIENTS WITH OSTEOARTHRITIS. Spectrum Journal of Innovation, Reforms and Development, 12, 145-155.
24. Zikiryayevna, S. G., Muxtorovna, E. M., Mamadiyarovich, S. A., & Jurayevich, M. E. (2022). EVALUATION OF 12-WEEK URATE-REDUCING THERAPY WITH ALLOPURINOL IN COMBINATION WITH THE NONSTEROIDAL ANTI-INFLAMMATORY DRUG MELOXICAM IN PATIENTS WITH GOUT. Galaxy International Interdisciplinary Research Journal, 10(6), 140-148.
25. Zikiryayevna, S. G., Zohirovna, M. G., Muxtorovna, E. M., & Bahromovich, S. S. (2022). Kidney Damage in Patients with Chronic Cardiac Insufficiency and Obesity. Texas Journal of Medical Science, 13, 72-78.

26. Zikiryayevna, S. G., Muxtorovna, E. M., Mamadiyarovich, S. A., & To'raqulovna, Q. S. (2022). KIDNEY DAMAGE IN RHEUMATOID ARTHRITIS: RELATIONSHIP WITH CARDIOVASCULAR RISK FACTORS. Galaxy International Interdisciplinary Research Journal, 10(5), 857-862.
27. Palvanovna, K. Z., & Muxtorovna, E. M. (2022). THE PREVALENCE OF LESIONS OF THE DISTAL BRONCHIAL TREE (BRONCHIOLITIS) IN PATIENTS WITH RHEUMATOID ARTHRITIS. Galaxy International Interdisciplinary Research Journal, 10(5), 1044-1051.
28. Muxtorovna, E. M., & Alexandrovna, S. O. (2023). Myocardial Condition Right Ventricle in Patients with Bronchial Asthma. Texas Journal of Medical Science, 27, 17-23.
29. Xudoyberdiyevna, S. N., Muxtorovna, E. M., & Shodikulova, G. Z. (2023). THE EFFECTIVENESS OF THYROSTATICS IN THE TREATMENT OF. Spectrum Journal of Innovation, Reforms and Development, 12, 219-228.
30. Muxtorovna, E. M., & Mamadiyarovich, S. A. (2023). New Opportunities in the Diagnosis of Anemia of Chronic Diseases. Genius Repository, 27, 24-30.
31. Alisherovna, K. M., Ismatullayevich, M. A., & Nuriddinovna, E. N. (2024). FEATURES OF HEART FAILURE IN PATIENTS WITH CORONARY HEART DISEASE AND THYROTOXICOSIS. Ta'lim innovatsiyasi va integratsiyasi, 19(4), 52-61.
32. Alisherovna, K. M., Habibulloyevna, I. M., & Voxidovna, R. F. (2024). STRUCTURAL AND FUNCTIONAL FEATURES OF THE LEFT VENTRICLE IN PATIENTS WITH HEART FAILUREIN ISCHEMIC HEART DISEASE AND THYROTOXICOSIS. Ta'lim innovatsiyasi va integratsiyasi, 19(4), 71-81.
33. Alisherovna, K. M., Erkinovna, S. D., Yazdonkulovna, X. M., & Zafarovna, C. M. M. (2024). ATRIAL FIBRILLATION IN THYROTOXICOSIS–DETERMINANTS OF DEVELOPMENT AND CONSERVATION. Ta'lim innovatsiyasi va integratsiyasi, 19(4), 103-113.
34. Alisherovna, K. M., Yaxshiboyevich, U. M. R., & Yigitaliyevich, B. A. (2024). EVALUATION OF A NATRIURETIC PEPTIDE TO OPTIMIZE THE MANAGEMENT OF COMORBID PATIENTS WITH THYROTOXICOSIS AND HEART FAILURE. Ta'lim innovatsiyasi va integratsiyasi, 19(4), 62-70.
35. Alisherovna, K. M., Akramovna, I. K., & Yorkinovna, E. N. (2024). CLINICAL AND MORPHOLOGICAL CRITERIA OF COLITIS IN PATIENTS WITH CHRONIC ISCHEMIC DISEASE OF THE DIGESTIVE SYSTEM. Ta'lim innovatsiyasi va integratsiyasi, 18(6), 6-13.
36. Alisherovna, K. M., Akramovna, I. K., & Baxtiyorovna, O. K. (2024). THE COURSE OF CHRONIC ISCHEMIC PANCREATITIS IN PATIENTS WITH CORONARY HEART DISEASE. Ta'lim innovatsiyasi va integratsiyasi, 18(5), 231-239.
37. Khabibovna, Y. S., Alisherovna, K. M., Nizamitdinovich, K. S., Tashtemirovna, E. M. M., Abdukadirovna, A. S., & Jasurovna, J. S. (2023). DEPRESSION, ANXIETY AND QUALITY OF LIFE IN PATIENTS WITH ATRIAL FIBRILLATION. Journal of new century innovations, 39(1), 185-189.
38. Alisherovna, K. M., Akramovna, I. K., & Kairatovna, R. A. (2024). THE EFFECTIVENESS OF TREATMENT OF PATIENTS WITH OSTEOARTHRITIS WITH CARDIOVASCULAR DISORDERS IN METABOLIC SYNDROME. Ta'lim innovatsiyasi va integratsiyasi, 18(5), 223-230.

39. Alisherovna, K. M., Erkinovna, S. D., Duskobilovich, B. S., & Samandarovich, T. H. (2024). ARTERIAL HYPERTENSION IN THYROTOXICOSIS AND REMODELING OF THE LEFT VENTRICLE OF THE HEART. Ta'lim innovatsiyasi va integratsiyasi, 19(4), 114-121.
40. Alisherovna, K. M., Davranovna, M. K., & Erkinovna, K. Z. (2024). CORONARY HEART DISEASE AND OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN. Spectrum Journal of Innovation, Reforms and Development, 26, 40-45.
41. Alisherovna, K. M., Mansurovna, M. D., Erkinovna, N. D., Farxodovna, X. R., Toxirovna, M. M., Tolibovna, R. D., & Yorkinovna, E. N. (2024). ARTERIAL HYPERTENSION AND THYROID STATUS IN PATIENTS OF DIFFERENT AGES. Ta'lim innovatsiyasi va integratsiyasi, 19(4), 122-129.
42. Davranovna, M. K. D. K., Alisherovna, K. M., & Erkinovna, K. Z. (2024). CARDIAC ARRHYTHMIAS IN PATIENTS WITH RHEUMATOID ARTHRITIS. Spectrum Journal of Innovation, Reforms and Development, 26, 65-71.
43. Erkinovna, K. Z., Alisherovna, K. M., & Davranovna, M. K. (2024). ARTERIAL HYPERTENSION AND ARRHYTHMIA. Spectrum Journal of Innovation, Reforms and Development, 26, 72-78.
44. Alisherovna, K. M., Erkinovna, K. Z., Davranovna, M. K., & Pulotovna, Z. D. (2022). Positive Effect of Sorbitol in Patients with Chronic Renal Insufficiency. Miasto Przyszłości, 30, 214-217.
45. Alisherovna, K. M., Akmalovna, K. N., & Mamasoliyevna, D. N. (2022). Kidney dysfunction in chronic heart failure. Texas Journal of Medical Science, 13, 104-109.
46. Baxtiyorovich, U. J., Alisherovna, K. M., & Mamasoliyevna, D. N. (2023). Features of cognitive impairment in patients with chronic kidney disease at predialysis stages. World Bulletin of Public Health, 22, 49-54.
47. Khabibovna, Y. S., & Alisherovna, K. M. (2024). STRESS TESTING IN PATIENTS WITH CORONARY HEART DISEASE. Journal of new century innovations, 45(3), 28-33.
48. Akramovna, I. K., & Alisherovna, K. M. (2024). CAUSES OF ARRHYTHMIA DURING PREGNANCY. Journal of new century innovations, 45(3), 34-41.
49. Yarmatov, S., Khusainova, M., & Djabbarova, N. (2023). STUDY OF QUALITY-OF-LIFE INDICATORS IN PATIENTS WITH CORONARY HEART DISEASE USING THE SF-36 QUESTIONNAIRE. Бюллетень студентов нового Узбекистана, 1(7), 58-64.