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Клинико-иммунологические особенности сочетанного течения ревматоидного артрита и гиперурикемии

В.И. Мазуров[1, 2], И.З. Гайдукова[1, 2], А.Ю. Фонтуренко[1, 2], Р.А. Башкинов[1, 2], М.С. Петрова[1, 2], О.В. Инамова[1, 2]

[1] Северо-Западный государственный университет им. И.И. Мечникова, Санкт-Петербург, Россия;
[2] Клиническая ревматологическая больница № 25, Санкт-Петербург, Россия

Обоснование. В настоящее время общеизвестно негативное влияние бессимптомной гиперурикемии на развитие и прогрессирование сердечно-сосудистых патологий, метаболических нарушений и хронической болезни почек. Однако в литературе недостаточно освещены особенности сочетанного течения гиперурикемии и ревматоидного артрита.

Цель работы — изучить взаимосвязь гиперурикемии и клинико-лабораторных, иммунологических, рентгенологических и функциональных характеристик ревматоидного артрита.

Материалы и методы. За период с января 2000 по апрель 2020 г. проанализированы данные 524 пациентов с ревматоидным артритом, у 262 из которых (основная группа) выявили гиперурикемию — значение уровня мочевой кислоты в сыворотке крови выше 360 мкмоль/л. Остальные 262 пациента вошли в группу сравнения. Основную группу разделили на две подгруппы пациентов с низкой (<500 мкмоль/л) и высокой (≥500 мкмоль/л) гиперурикемией. В исследование включили 440 женщин и 84 мужчины, средний возраст которых составил 60 ± 13,6 года. В статистический анализ внесли сведения о демографических особенностях (пол, возраст) пациентов, диагнозе, наличии и длительности гиперурикемии, длительности наблюдения, активности и терапии ревматоидного артрита, а также его лабораторных, иммунологических, рентгенологических и функциональных характеристиках.

Результаты. В подгруппе пациентов с высокой гиперурикемией было больше мужчин, чем в подгруппе с низкой гиперурикемией и группе сравнения. У каждого третьего пациента отмечены значимые структурные изменения суставов (III и IV рентгенологические стадии). У 98 % пациентов обнаружили умеренные и выраженные функциональные ограничения (функциональные классы II и III). Самый большой средний возраст зафиксирован в основной группе. Пациенты с гиперурикемией чаще обращались к врачу, дольше наблюдались по поводу ревматоидного артрита при его меньшей рентгенологической прогрессии и большем количестве болезненных и припухших суставов, реже и в меньшей дозе принимали метотрексат и чаще — сульфасалазин в сравнении с пациентами без гиперурикемии.

Выводы. Гиперурикемия негативно влияет на течение ревматоидного артрита. С ней ассоциированы прямые (большее количество болезненных и припухших суставов) и косвенные (большие длительность наблюдения и количество обращений к врачу) признаки его тяжелого течения. Отсутствие взаимосвязи гиперурикемии с общепризнанными маркерами активности (скоростью оседания эритроцитов, уровнем С-реактивного белка, индексом DAS28) и иммунологическим профилем (ревматоидным фактором, позитивностью по антителам к циклическому цитруллинированному пептиду) ревматоидного артрита, а также ее неоднозначная взаимосвязь с его рентгенологической прогрессией, функциональной недостаточностью суставов и темпом снижения плотности костной ткани вызваны иммуносупрессивной терапией.

Ключевые слова: ревматоидный артрит; гиперурикемия; мочевая кислота; метотрексат; лефлуномид.

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Coexistent rheumatoid arthritis and hyperuricemia: clinical and immunological features

Vadim I. Mazurov[1, 2], Inna Z. Gaydukova[1, 2], Aleksandra Yu. Fonturenko[1, 2], Roman A. Bashkinov[1, 2], Marianna S. Petrova[1, 2], Oksana V. Inamova[1, 2]

[1] North-Western State Medical University named after I.I. Mechnikov, Saint Petersburg, Russia;
[2] Clinical Rheumatology Hospital No 25, Saint Petersburg, Russia

BACKGROUND: Currently, the negative role of asymptomatic hyperuricemia (HU) in the development and progression of cardiovascular pathology, metabolic disorders and chronic kidney disease is generally recognized. There is not much data in the literature on the effect of HU on the course of rheumatoid arthritis (RA), therefore, the study of the relationship of HU with clinical, radiological and immunological features of RA seems relevant.

AIM: To study the relationship between HU with the clinical, radiological and immunological features of RA.

MATERIALS AND METHODS: The data of 262 patients with RA and HU and 262 with RA without HU (comparison group) included in the city register from January 2000 to April 2020 have been analyzed. The information included demographic features (gender, age), diagnosis, presence and duration of HU, duration of observation, disease activity, laboratory, immunological, radiological and functional parameters, therapy of the underlying disease. HU was understood as a recorded ⩾1-fold increase in the level of uric acid (UA) in the blood serum >360 mmol/l. The study has been approved by the local ethics committee.

RESULTS: The data of 524 patients with rheumatoid arthritis for the period from January 2000 to April 2020 have been analyzed. The study included 440 women and 84 men. The average age of the patients was 60.0 ± 13.6 y. The patients with HU have been divided into two subgroups: the first – with the level of UA less than 500 mmol/l, the second — with the level of UA more than 500 mmol/l. The number of males was significantly higher among the patients with high HU than among the patients with low HU and the comparison group. Every third patient had significant structural changes in the joints (radiological stage III-IV) and 98% of the patients had moderate and pronounced functional limitations (functional class 2-3). The patients with HU were older, had more follow-up visits, were observed for a longer period of time, had a lower frequency of radiological progression, a greater number of painful and swollen joints, less often and at a smaller dose had methotrexate and more often sulfasalazine in comparison with the patients without HU ($p < 0.05$).

CONCLUSIONS: 1) Thus, we can emphasize the negative impact of hyperuricemia on the course of rheumatoid arthritis: if it is present, there are direct (more PJ, SJ) and indirect signs of a more severe course (longer duration of observation and the number of visits). 2) Immunosuppressive therapy is associated with the absence of differences with the generally recognized markers of disease activity (ESR, CRP, DAS28), the immunological profile (RF, ACCP) and the ambiguous relationship with radiological progression and functional insufficiency of the joints, as well as unreliable relationship with a higher frequency of bone density reduction.

Keywords: rheumatoid arthritis; hyperuricemia; uric acid; methotrexate; leflunomide.

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BACKGROUND

The search for relationship between the hyperuricemia (HU) and course of rheumatoid arthritis (RA) has been performed for a long time both in the experimental and practical medicine. A less number of studies have found that, HU contributes to the favorable course of RA.

A. Lussier *et al*., studied the development of adjuvant-induced arthritis in rats with a HU induced by the administration of oxonic acid. The reaction after the primary adjuvant exposure in the rats with and without HU did not differ, but after the secondary exposure, the reaction in the rats with a HU was significantly less pronounced than rats without the HU [1]. With the additional administration of sodium mono-urate crystals to the rats, similar results were obtained, namely injections of crystals that preceded injections of the Freund's adjuvant increased the severity of arthritis in rats with normal uricemia, and slightly reduced in rats with the HU [2]. In the work by Y.H. Chang *et al*., adjuvant-induced arthritis did not develop in rats with the HU induced by the diet with the high oxonic acid [3].

In a study by R.A. Turner *et al*., HU enhanced the release of the azurophilic granular B-glucuronidase enzyme induced by the phagocytosis and reduced the polyclonal activation of immunocompetent cells [4].

R.D. Situnayake *et al*., showed an inverse correlation between the serum uric acid (UA) levels and oxidative changes of albumin in RA patients. This indicates the protective role of UA which scavenges free radicals that damage the protein during inflammation [5]. M. Mahajan *et al*., obtained data on a decrease in the level of UA with an increase in the duration of the RA, and associated them with the effective scavenge by the UA of free radicals [8].

C.A. Agudelo *et al*., selected 12 patients with the RA, whose UA level >450 μmol/L for ⩾6 months. In 11 of them, no exacerbations of RA were registered during the HU [6].

In their study, D. Pekhlivanov *et al*., revealed that the HU and calcemia decrease as a RA activity increases, despite their direct correlation with the severity of destructive changes [7].

Most of the researchers agree that the HU negatively affects the course of RA. R. Wang *et al*., showed the effect of sodium mono-urate crystals on synovial fibroblasts in the RA patients, induces the expression of type-1 adhesion of vascular endothelium molecules, which are responsible for the adhesion of leukocytes to the vascular wall, and subsequent activation and dysfunction of the endothelium [9].

F.S. Di Giovine *et al*., demonstrated the experiment on a dose-dependent effect of increasing production of tumor necrosis factor (TNF), the main pro-inflammatory cytokine in the pathogenesis of RA, after an exposure to sodium mono-urate crystals on the blood monocytes. At the same time, crystals of calcium pyrophosphate or hydroxyapatite did not stimulate a significant part in the production of TNF [10].

According to the NHANES III study, RA could be considered a predictor of the HU in women along with a marriage, smoking, alcohol consumption, as well as high body mass index, high levels of C-reactive protein (CRP), and increased blood pressure and glomerular filtration rate [11].

Similar data were obtained in the study by D.M. Mohammed Ali *et al*., [12], where the levels of UA, CRP, chemerin, and visfatin were significantly higher in 60 patients with a RA than in the 30 patients without it.

A. Chiou *et al*., found that the level of UA of 405–476 μmol/L, increases the risk of lethal outcome from a cardiovascular disease [13].

The study aimed to investigate the relationship between the HU and clinical, laboratory, immunological, radiological, and functional characteristics of the RA.

MATERIALS AND METHODS

For the period from January 2000–April 2020, data from the 524 patients with RA verified in accordance with the 2010 EULAR/ACR criteria, were analyzed. All patients gave the informed consent to be included in the St. Petersburg City Registry of gout and asymptomatic HU. In 262 patients (the main group), the HU was detected with a blood serum level of uric acid >360 μmol/L. The remaining 262 patients were included in the comparison group. Patients of the main group were divided into the two subgroups of patients with low (<500 μmol/L) and high (⩾500 μmol/L) HU. The study included 440 women and 84 men having the age >18 years. The mean age of the patients was 60 ± 13.6 years.

The exclusion criteria were, severe pathology of the cardiovascular system (acute myocardial infarction <6 months ago, unstable angina), oncological and/or lympho-proliferative disease (current or past), severe liver disease (fibrosis stage III/IV), stage V chronic disease (including the renal replacement therapy), chronic infectious diseases (tuberculosis, viral hepatitis B and C, HIV infection). To enter data into the register, individual numbers of the patients were indicated instead of their names.

The study was approved by the local Ethics committees of the Mechnikov Northwestern State Medical University and Clinical Rheumatology Hospital No. 25. The Statistical analysis was performed using a Statistica 8.0 software package. The nature of the data distribution was assessed by the graphical method and using the Shapiro–Wilk test. In case of a normal distribution of an attribute, it was described as M ± SD, where M is the mean value and SD is the standard deviation. When distributing the data that was different from the norm, the χ^2 test was used. Differences and relationships were considered statistically significant at $p < 0.05$.

RESULTS

Patients with the HU were distributed into two subgroups. The subgroup-1 included 152 patients with an average UA level of 435.8 ± 34.6 μmol/L, and the group-2 included 110 patients with an average UA level of >590.2 ± 92.2 μmol/L. In the comparison group, the average level of UA was 249.7 ± 62.7 μmol/L. Table 1 presents the patient characteristics' relevant to the study.

Data of therapy with the glucocorticoids and basic anti-inflammatory drugs are presented in the Table 2.

DISCUSSION

W.F. Weaver *et al.*, showed that in RA and the degenerative joint diseases, the level of UA is higher in men [14]. In their work, J.R. Lambert *et al.*, analyzed data of 48 patients with a RA. The HU was detected in 12% of the patients, and all they were male [15]. As in the above studies, according to our data, the level of UA in men is higher, and a direct relationship between the level of UA and age was observed, so that in the main group, the highest average age was registered.

Table 1. Demographic, laboratory, immunological, radiological, and functional characteristics of the patients with a rheumatoid arthritis

Таблица 1. Демографические, лабораторные, иммунологические, рентгенологические и функциональные характеристики пациентов с ревматоидным артритом

Parameter	Subgroup of patients with low hyperuricemia (*n* = 152)	Subgroup of patients with high hyperuricemia (*n* = 110)	Comparison group (*n* = 262)	*p*-level
Age, years	62.79 ± 11.24	60.97 ± 14.09	57.98 ± 14.39	$p_2 < 0.05$
Women, *n* (%)	139 (91.45)	79 (71.82)	222 (84.73)	$p_1 < 0.05$
Men, *n* (%)	13 (8.55)	31 (28.18)	40 (15.27)	$p_1 < 0.05$
Follow-up period for rheumatoid arthritis, years	2.48 ± 3.43	1.68 ± 3.53	0.58 ± 1.50	$p_2 < 0.05$
Duration of hyperuricemia, years	3.02 ± 2.84	3.13 ± 3.75	–	–
Number of seeking of medical help	2.86 ± 3.85	1.74 ± 1.35	1.35 ± 0.87	$p_2 < 0.05$
Erythrocyte sedimentation rate, mm/h	29.25 ± 14.67	28.22 ± 14.39	30.14 ± 14.43	$p \geqslant 0.05$
C-reactive protein, mg/L	21.10 ± 20.88	23.69 ± 29.93	22.48 ± 21.49	$p \geqslant 0.05$
Rheumatoid factor positivity, *n* (%)	89 (58.55)	62 (56.37)	120 (46.15)	$p_2 < 0.05$
Positivity for antibodies to cyclic citrullinated peptide, *n* (%)	55 (36.18)	35 (31.82)	102 (40.31)	$p \geqslant 0.05$
Painful joints	15.54 ± 5.87	16.35 ± 6.23	9.37 ± 4.46	$p_2 < 0.05$
Swollen joints	10.38 ± 7.21	11.68 ± 5.38	5.11 ± 3.92	$p_2 < 0.05$
DAS28	5.56 ± 1.04	5.55 ± 1.12	5.53 ± 1.16	$p \geqslant 0.05$
Rheumatoid arthritis, grade-I, *n* (%)	7 (4.61)	9 (8.18)	1 (0.38)	$p \geqslant 0.05$
Rheumatoid arthritis, grade-II, *n* (%)	55 (36.18)	36 (32.73)	102 (40.31)	$p \geqslant 0.05$
Rheumatoid arthritis, grade-III, *n* (%)	90 (59.21)	65 (59.09)	159 (60.69)	$p \geqslant 0.05$
X-ray stage-III or-IV, *n* (%)	57 (37.5)	38 (34.55)	81 (30.92)	$p \geqslant 0.05$
X-ray progression, *n* (%)	25 (16.45)	7 (6.36)	20 (33.33)	$p_2 < 0.05$
Period of radiographic progression, years	3.28 ± 2.57	1.71 ± 1.25	2.18 ± 2.21	$p \geqslant 0.05$
Functional class-2 or-3, *n* (%)	149 (98.03)	108 (98.18)	260 (99.24)	$p \geqslant 0.05$
Downgrade in functional class, *n* (%)	7 (4.61)	2 (1.82)	7 (11.67)	$p \geqslant 0.05$
Period of functional class downgrade, years	3.36 ± 2.59	4.0 ± 4.24	3.29 ± 2.87	$p \geqslant 0.05$
Osteopenia, *n* (%)	19 (12.5)	18 (16.37)	15 (5.73)	$p \geqslant 0.05$
Osteoporosis, *n* (%)	18 (11.84)	7 (6.36)	19 (7.25)	$p \geqslant 0.05$

Note: DAS28 — disease activity score 28 joints; p_1 — significant differences between patients of all three groups; p_2 — significant differences between patients of the main group and the comparison group.

Table 2. Data on treatment with the glucocorticoids and basic anti-inflammatory drugs

Таблица 2. Данные терапии глюкокортикоидами и базисными противовоспалительными препаратами

Drug	Subgroup of patients with low hyperuricemia (*n* = 152)	Subgroup of patients with high hyperuricemia (*n* = 110)	Comparison group (*n* = 262)	*p*-level
Glucocorticoids in terms of prednisolone, mg	7.54 ± 3.33	10.11 ± 4.50	8.82 ± 3.48	$p \geqslant 0.05$
Dexamethasone intravenously, mg	14.93 ± 13.81	8.86 ± 2.27	13.1 ± 9.7	$p \geqslant 0.05$
Methylprednisolone intravenously, mg	361.11 ± 131.76	333.33 ± 123.09	342.74 ± 128.97	$p \geqslant 0.05$
Prednisolone intravenously, mg	123.75 ± 31.04	131.0 ± 31.29	145.95 ± 34.76	$p \geqslant 0.05$
Methotrexate, mg	13.28 ± 4.80	10.79 ± 4.71	13.31 ± 4.23	$p_1 < 0.05$
Methotrexate therapy, *n* (%)	106 (69.74)	76 (69.09)	222 (84.73)	$p_2 < 0.05$
Leflunomide, mg	18.89 ± 3.33	20 ± 0	20 ± 0	$p \geqslant 0.05$
Leflunomide therapy, *n* (%)	9 (5.92)	6 (5.45)	12 (4.58)	$p \geqslant 0.05$
Sulfasalazine, mg	1454.55 ± 687.55	1428.57 ± 932.23	1833.33 ± 752.77	$p \geqslant 0.05$
Sulfasalazine therapy, *n* (%)	11 (7.24)	7 (6.36)	6 (2.29)	$p_2 < 0.05$
Hydroxychloroquine, mg	223.53 ± 66.42	246.15 ± 87.71	240.0 ± 84.3	$p \geqslant 0.05$
Hydroxychloroquine therapy, *n* (%)	17 (11.18)	13 (11.81)	10 (3.82)	$p \geqslant 0.05$
Cyclophosphamide, mg	250.0 ± 212.1	–	350 ± 0	$p \geqslant 0.05$
Cyclophosphamide therapy, *n* (%)	1 (0.38)	–	2 (0.76)	$p \geqslant 0.05$
Azathioprine, mg	50 ± 0	66.67 ± 28.87	75 ± 50	$p \geqslant 0.05$
Azathioprine therapy, *n* (%)	3 (1.97)	3 (2.72)	4 (1.53)	$p \geqslant 0.05$
Mycophenolate mofetil, mg	250 ± 0	–	–	$p \geqslant 0.05$
Therapy with mycophenolate mofetil, *n* (%)	1 (0.38)	0 (0)	0 (0)	$p \geqslant 0.05$
Chlorbutin, mg	4 ± 0	–	–	$p \geqslant 0.05$
Chlorbutin therapy, *n* (%)	1 (0.38)	0 (0)	0 (0)	$p \geqslant 0.05$
D-penicillamine, mg	250 ± 0	–	–	$p \geqslant 0.05$
Therapy with D-penicillamine, *n* (%)	1 (0.38)	0 (0)	0 (0)	$p \geqslant 0.05$
Genetically engineered biological products, *n* (%)	3 (1.97)	0 (0)	2 (0.76)	$p \geqslant 0.05$
Osteoporosis therapies, *n* (%)	22 (14.47)	9 (8.18)	10 (3.82)	$p \geqslant 0.05$

Note: p_1 — significant differences between patients from two subgroups; p_2 — significant differences between patients of the main group and the comparison group.

We did not evaluate the incidence of HU in the RA, as we formed the main and comparative groups equal in number of the patients. In a study by J. Ren *et al.*, a total of 28.6% out of 30 RA patients had HU, and urate deposits, according to the dual-energy computed tomography, were revealed in 6.7% of the patients in five urate deposit foci [16].

According to the results of the study by C. Petsch *et al.*, out of 100 patients with RA, high HU predominated in men and patients >60 years of age and was also registered with a longer duration of RA and its moderate activity. Urate deposits were detected in every 5th patient, and RA seronegativity was detected in 70% of the patients, the level of which correlated with urate deposition in the tissues [17].

We also recorded the relationship of HU along with the duration of RA and the number of visits to the doctor. There was no significant relationship found between HU and the levels of acute phase parameters (ESR, CRP) and the level of activity according to DAS28, however we revealed significant differences in the number of painful and swollen joints in patients with HU (regardless of the UA level) and without HU. This may be because, the patients previously received therapy with the basic anti-inflammatory drugs. Similar data on a high level of systemic inflammation in patients with the RA and HU were obtained previously [18].

A significantly higher frequency of radiological progression, and a tendency to a decrease in the functional class

with a high level of UA are of interest. The periods of a radiological progression are also longer in the HU patients than in the control group patients, but this difference did not reach the required degree of significance.

Some authors [19] suggested that chronic inflammation in the RA is directly affected by the increased levels of UA (due to an increased production of CRP, cytokines, and superoxide by neutrophils) and the accumulation of mono-sodium urate crystals, which prevents local bone remodeling due to an excessive formation of the osteoclasts and decreased differentiation of osteoblasts.

H. Zhuoran *et al*., demonstrated that in a group of male patients <50 years and premenopausal women, the diseases such as ankylosing spondylitis and systemic lupus erythematosus (SLE) affects the decrease in the bone mineral density. At the same time, the osteopenia and osteoporosis were more often noted in men >50 years of age and postmenopausal women with the RA, osteoarthritis, and SLE. HU has been recognized as a factor preventing a bone loss [20].

In another study [21], the authors revealed a positive correlation between the level of UA and bone mineral density of the thigh (not the lower back) and concluded on a possible protective role of UA in the process of a bone loss in RA in the hip area.

In our study, there were no significant differences in the incidence of the osteopenia and osteoporosis between the groups, but it is worth noting the higher incidence conditions in the group of the HU patients. Underdiagnosis of bone metabolism disorders in this group of patients cannot be ruled out. Patients with the HU received therapy for osteoporosis more often (probably due to the higher incidence of osteoporosis in the group), however, the differences from corresponding indications in the comparison group did not reach the required degree of significance.

F. Perez-Ruiz *et al*., demonstrated the urate-lowering effect of the leflunomide. In 37 patients with the RA, the blood serum levels of UA, creatinine, and phosphate, as well as their daily excretion before, during, and after treatment with the leflunomide were assessed. There was a decrease in the level of UA and phosphate in the blood serum with a parallel increase in the clearance and fractional excretion of the urates, as well as a decrease in tubular reabsorption of the phosphate. The amount of creatinine clearance in the urine was unchanged. Two weeks after the drug withdrawal, a partial return to the baseline values was noted. No cases of gouty arthritis identified [22].

Similar results were obtained by the authors of another study [23], who analyzed the metabolic syndrome and urate-lowering effect of the leflunomide in 177 patients with a RA. The levels of UA and other markers of oxidative stress in patients with and without the RA did not differ. With the intake of leflunomide, the UA levels and total antioxidant radical scavenging parameter decreased, while carbonyl protein levels and the nitric oxide ratio of metabolites to total antioxidant radical scavenging parameter increased.

J.Y. Choe *et al*., evaluated UA excretion in 172 patients treated with the methotrexate and leflunomide and in 27 patients treated with a methotrexate alone. They proved that, leflunomide reduces the blood serum concentration of UA, by increasing its excretion in the urine, which is not associated with a change in the RA activity [24].

H. Gosselt *et al*., studied predictors of response to methotrexate therapy in 82 patients with the RA from the Rotterdam cohort (tREACH study). They found that the initial concentrations of the homocysteine, taurine, adenosine triphosphate, guanosine diphosphate, and UA were significantly lower, and 1,3-/2,3-diphosphoglyceric acid, glycerol-3-phosphate, and phosphoenolpyruvate were significantly higher in the blood plasma of the patients, who did not have sufficient response to therapy [25].

Another study demonstrated in RA patients showed, 24 h after the administration of methotrexate, the levels of UA (from 205.5 ± 13.5–160.9 ± 13.5 μmol/L) and other components of the nucleotide metabolism, hypoxanthine, and uridine, significantly decrease [26].

J. Lee *et al*., studied the effect of methotrexate on UA levels based on the data from the Canadian cohort of patients with early RA (CATCH). In the main group, they noted a greater decrease in the UA levels (from 300–273 μmol/L) than in the control group of patients who did not take methotrexate (from 280–282 μmol/L). In the main group, compared with the control group, there was a greater decrease in the DAS28 index (2.37 and 3.26, respectively) after 18 months of the treatment [27].

N.A. Bileciik *et al*., showed that, in patients with a RA and metabolic syndrome have higher UA levels than the RA patients without it. The frequency of a metabolic syndrome in patients taking methotrexate was significantly lower [28].

The authors of another study examined the metabolic biomarkers that could predict response to four-week methotrexate therapy in rats with a collagen-induced arthritis. Using a nuclear magnetic resonance, a spectral analysis of the urine samples from rats with a response to therapy (n = 20) and without a response (n = 11) was performed. The UA and some other metabolites (taurine, histidine, methionine, glycine, etc) were chosen as biomarkers for predicting response to a methotrexate therapy [29].

In the research of R. Araiza-Casillas *et al*., a total of 15 RA patients received the hydroxychloroquine at a dose of 400 mg/day for three months. There were no changes in the level of UA during the therapy, but a decrease in the level of triglycerides and an increase in the insulin tolerance were noted.

According to our data, in relation to the RA therapy, HU patients received sulfasalazine significantly more often

than the methotrexate, and dose of the methotrexate was significantly lower in the subgroup of the patients with higher levels of UA.

CONCLUSIONS

HU adversely affects the course of RA. It is associated with a direct (a greater number of the painful and swollen joints) and indirect (longer follow-up period and greater number of visits to the doctor) signs of its' severe course.

The absence of a relationship between the HU and generally recognized markers of activity (ESR, CRP, DAS28 index), and the immunological profile (rheumatoid factor, positivity for antibodies to cyclic citrullinated peptide) of the RA, as well as its ambiguous relationship with its radiological progression, functional joint insufficiency, and the rate of decrease in bone density, were caused by the immunosuppressive therapy.

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AUTHORS INFO

Vadim I. Mazurov, MD, Dr. Sci. (Med.), Professor,
Honoured Science Worker, Academician of the RAS;
ORCID: https://orcid.org/0000-0002-0797-2051;
Scopus Author ID: 16936315400;
ResearcherId: A-8944-2016;
eLibrary SPIN: 6823-5482;
e-mail: maz.nwgmu@yandex.ru

Inna Z. Gaydukova, MD, Dr. Sci. (Med.);
ORCID: https://orcid.org/0000-0003-3500-7256;
Scopus Author ID: 55237525900; ResearcherId: F-6020-2013;
eLibrary SPIN: 3083-7996; e-mail: ubp1976@list.ru

Aleksandra Yu. Fonturenko;
ORCID: https://orcid.org/0000-0003-4860-0518;
eLibrary SPIN: 5613-9035;
e-mail: aleksa.fonturenko@mail.ru

Roman A. Bashkinov;
ORCID: https://orcid.org/0000-0001-9344-1304;
eLibrary SPIN: 5169-5066;
e-mail: bashkinov-roman@mail.ru

ОБ АВТОРАХ

Вадим Иванович Мазуров, д-р мед. наук, профессор,
заслуженный деятель науки РФ, академик РАН;
ORCID: https://orcid.org/0000-0002-0797-2051;
Scopus Author ID: 16936315400;
ResearcherId: A-8944-2016;
eLibrary SPIN: 6823-5482;
e-mail: maz.nwgmu@yandex.ru

Инна Зурабиевна Гайдукова, д-р мед. наук;
ORCID: https://orcid.org/0000-0003-3500-7256;
Scopus Author ID: 55237525900; ResearcherId: F-6020-2013;
eLibrary SPIN: 3083-7996; e-mail: ubp1976@list.ru

Александра Юрьевна Фонтуренко;
ORCID: https://orcid.org/0000-0003-4860-0518;
eLibrary SPIN: 5613-9035;
e-mail: aleksa.fonturenko@mail.ru

Роман Андреевич Башкинов;
ORCID: https://orcid.org/0000-0001-9344-1304;
eLibrary SPIN: 5169-5066;
e-mail: bashkinov-roman@mail.ru

AUTHORS INFO

Marianna S. Petrova, MD, Cand. Sci. (Med.);
ORCID: https://orcid.org/0000-0001-5261-6614;
e-mail: podagra@bk.ru

*** Oksana V. Inamova**;
address: 41 Kirochnaya St., Saint Petersburg, 191015, Russia;
ORCID: https://orcid.org/0000-0001-9126-3639;
eLibrary SPIN: 8841-5496;
e-mail: b25@zdrav.spb.ru

* Corresponding author / Автор, ответственный за переписку

ОБ АВТОРАХ

Марианна Семеновна Петрова, канд. мед. наук;
ORCID: https://orcid.org/0000-0001-5261-6614;
e-mail: podagra@bk.ru

*** Оксана Владимировна Инамова**;
адрес: Россия, 191015, Санкт-Петербург, Кирочная ул., д. 41;
ORCID: https://orcid.org/0000-0001-9126-3639;
eLibrary SPIN: 8841-5496;
e-mail: b25@zdrav.spb.ru