FEATURES OF THE COURSE OF RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS IN PATIENTS WITH ASYMPTOMATIC HYPERURICEMIA

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⬥ **Introduction.** According to numerous studies, the prevalence of asymptomatic hyperuricemia has increased in most countries. Uric acid is an important biomarker of the cardiovascular system, and there are now quite a big number of sources indicating its role in the development of a some chronic metabolic conditions, cardiovascular disease and associated mortality. At present, there is no consensus on the need for urate-lowering therapy in patients with asymptomatic hyperuricemia. There is a limited number of studies examining the problem of asymptomatic hyperuricemia in patients with rheumatic diseases, the features of comorbidity in these conditions, the frequency and effectiveness of urate-lowering therapy.

Purpose. To study the peculiarities of the course of rheumatoid arthritis and osteoarthritis with associated asymptomatic hyperuricemia and compare them with the ones associated with arthragra.

Materials and methods. The analysis was performed on the basis of the data collected from the city register of the patients with arthragra and asymptomatic hyperuricemia in St. Petersburg. The data collected included the medical records of 1725 patients with arthragra, 433 patients with rheumatoid arthritis and hyperuricemia and 355 patients with osteoarthritis and hyperuricemia.

Results. The patients with rheumatoid arthritis and hyperuricemia were more likely to have increased erythrocyte sedimentation rate and C-reactive protein, the highest medium level of erythrocyte sedimentation rate; acute myocardial infarction, chronic heart failure, gallstone disease and non-alcoholic fatty liver disease were more frequently detected. The patients with osteoarthritis and hyperuricemia were more likely to have high total cholesterol, at its highest medium level; stable angina, arrhythmia, varicosity, obesity, prediabetes and type 2 diabetes mellitus were more likely to be detected. Kidney damage was detected more frequently in the patients with arthragra. In the group of rheumatoid arthritis and hyperuricemia urate-lowering therapy was started in 30.95% of the patients, in the group of osteoarthritis and hyperuricemia — in 36.06%.

Conclusions. In rheumatic diseases, hyperuricemia is a common associated condition. Their combination leads to increased risk and frequency of cardiovascular, metabolic and gastroenterological comorbidity. The prescription of urate-lowering therapy to the patients with rheumatic diseases and asymptomatic hyperuricemia with high cardiovascular risk led to the target uric acid levels in 34.58% of the patients with rheumatoid arthritis and 52.08% of the patients with osteoarthritis.

⬥ **Keywords:** hyperuricemia; gout; osteoarthritis; rheumatoid arthritis; comorbidity; urate-lowering therapy.

ОСОБЕННОСТИ ТЕЧЕНИЯ РЕВМАТОИДНОГО АРТРИТА И ОСТЕОАРТРИТА У ПАЦИЕНТОВ С БЕССИМПТОМНОЙ ГИПЕРУРИКЕМИЕЙ

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◆ **Введение.** По данным многих исследований, отмечается увеличение распространенности бессимптомной гиперурикемии в большинстве стран мира. Сывороточная мочевая кислота является важным биомаркером состояния сердечно-сосудистой системы, и в настоящее время существует достаточно большое количество источников, свидетельствующих о ее роли в развитии ряда хронических метаболических состояний, сердечно-сосудистых заболеваний и связанной с ними смертности. На данный момент нет единого мнения по поводу необходимости проведения уратснижающей терапии у пациентов с бессимптомной гиперурикемией. Проведено ограниченное количество исследований, посвященных проблеме бессимптомной гиперурикемии у пациентов с ревматическими заболеваниями, особенностям коморбидности при данных состояниях, частоте и эффективности уратснижающей терапии.

Цель — изучить особенности течения ревматоидного артрита и остеоартрита с сопутствующей бессимптомной гиперурикемией и провести сравнительный анализ с особенностями течения подагры.

Материалы и методы. Анализ выполнен на основании данных городского регистра Санкт-Петербурга пациентов с подагрой и бессимптомной гиперурикемией, сформированного из медицинских карт 1725 пациентов с подагрой, 433 больных ревматоидным артритом с гиперурикемией и 355 больных остеоартритом с гиперурикемией.

Результаты. У больных ревматоидным артритом с гиперурикемией чаще наблюдались повышенные скорость оседания эритроцитов и уровень С-реактивного белка, при этом у них зафиксирован самый высокий средний показатель скорости оседания эритроцитов; чаще встречались острый инфаркт миокарда, хроническая сердечная недостаточность, желчнокаменная болезнь и неалкогольная жировая болезнь печени. У больных остеоартритом с гиперурикемией был чаще повышен уровень общего холестерина, при этом у них зарегистрирован самый высокий средний уровень этого показателя; у этих пациентов чаще выявляли стенокардию напряжения, нарушения ритма и проводимости сердца, варикозную болезнь, ожирение, преддиабет и сахарный диабет 2-го типа. У пациентов с подагрой чаще отмечалось поражение почек. В группе больных ревматоидным артритом с гиперурикемией уратснижающая терапия была инициирована в 30,95 % случаев, в группе больных остеоартритом с гиперурикемией — у 36,06 % пациентов.

Выводы. При ревматических заболеваниях гиперурикемия является частым сопутствующим состоянием. Сочетание ревматических заболеваний и гиперурикемии приводило к повышению риска и частоты сердечно-сосудистой, метаболической и гастроэнтерологической коморбидности. Назначение уратснижающей терапии пациентам с ревматическими заболеваниями и бессимптомной гиперурикемией с высоким сердечно-сосудистым риском позволяло достичь целевых уровней мочевой кислоты у 34,58 % пациентов с ревматоидным артритом и у 52,08 % пациентов с остеоартритом.

◆ **Ключевые слова:** гиперурикемия; подагра; остеоартрит; ревматоидный артрит; коморбидность; уратснижающая терапия.

Introduction

Gout is a chronic disease associated with impaired uric acid (UA) metabolism, which results in blood UA level increase and UA sodium salt (urates) crystal deposition in the tissues, which is clinically manifested by recurrent acute arthritis and gouty node (tophi) formation [1]. Gout is associated with metabolic disorders and cardiovascular system and kidney damage [2, 3]. Its prevalence in the Russian Federation is 0.3% [4]. Although hyperuricemia (HU) is necessary for the onset of gout, only approximately 10% of patients have clinical onset of the disease during follow-up. HU occurs as a result of the interaction of many factors, including gender, age, genetics, lifestyle, and the environment. The most common rheumatic diseases (RDs) in the Russian Federation are osteoarthritis (OA)

(13%) and rheumatoid arthritis (RA; 0.61%) [4]. HU occurs quite often in various RDs. According to numerous epidemiological studies, there is an increase in HU prevalence in most countries of the world, with 19.87% in China [5] and 20.1% (47.13 million people) in the USA [6]. In Japan, the prevalence of HU is approximately 30% in men and 1%–2% and approximately 3% in women aged <50 and ≥50 years, respectively [7]. In the Russian Federation, this figure is 16.8% (14.9 million people; 25.3% among men and 11.3% among women). Thus, the prevalence of HU and gout in the Russian population does not exceed that in the United States, China, and Japan [8].

Serum UA is an important biomarker of the cardiovascular system state; a large number of

sources indicate its role in the development of several chronic metabolic conditions, cardiovascular diseases (CVDs), and associated mortality [9, 10]. According to the literature and many studies, HU is directly related to arterial hypertension (AH) [9], ischemic heart disease [11], acute myocardial infarction [12], heart failure [13], acute cerebrovascular accident [14], and cardiovascular and general mortality [15].

The complex therapy for gout includes urate-lowering therapy (ULT) to prevent exacerbations and correction of HU [16–18]. There is currently no consensus on the need for ULT in patients with asymptomatic HU. The American College of Rheumatology [16] and the Russian Association of Rheumatologists [17] do not recommend ULT in patients with asymptomatic HU. However, in several countries (e.g., Japan and Portugal), patients with asymptomatic HU receive ULT under certain conditions (pronounced comorbidity and high UA level) because of the significance of an increased UA level in the pathology development of the cardiovascular system and kidneys [19, 20]. Moreover, the European Society of Cardiology (ESC) and the Russian Society of Cardiology (RSC) recommend ULT for patients with asymptomatic HU and high cardiovascular risk [21, 22].

A limited number of studies have been conducted on the problem of asymptomatic HU in RD patients, the peculiarities of comorbidity in these conditions, and the frequency and effectiveness of ULT.

This study aimed to analyze the aspects of RA and OA courses with concomitant asymptomatic HU and to conduct a comparative analysis of the course characteristics of gout.

Materials and methods

In 2017, the teams from the Mechnikov North Western State Medical University and St. Petersburg Clinical Rheumatological Hospital No. 25 created the St. Petersburg City Registry of Patients with Gout and Asymptomatic HU, which included data from the medical records of 1725 patients with gout and 1431 patients with other RDs and asymptomatic HU, who were examined and treated at St. Petersburg Clinical Rheumatological Hospital No. 25 from 2000 to 2020. The register was formed based on the cloud-based electronic data storage system GALENOS (TexLab). The study analyzed data from 433 RA patients with HU, 355 OA patients with HU, and 1725 patients with gout based on the registry. Data about the patient's gender, age, RD, laboratory parameters, and comorbid condition presence were considered, and the drugs used to treat the underlying and concomitant diseases were registered. Asymptomatic HU was considered an increase in serum UA levels of >360 µmol/L in women and >420 µmol/L in men without signs of gouty arthritis. The data were entered into the registry in anonymized form, which did not enable us to identify the patient's personality. An individual number was assigned to each patient. The study was approved by the local ethics committee of the Mechnikov North Western State Medical University and St. Petersburg Clinical Rheumatological Hospital No. 25.

Statistical analysis was performed for all patients using STATISTICA 8.0 software package (StatSoft Inc., Tulsa, OK, USA). Data distribution was assessed graphically, and the Shapiro–Wilk test was used. The normal distribution of the trait was presented as mean ± standard deviation. If the distribution was different from the normal, the χ^2 test was used. Correlation relationships between quantitative characteristics were calculated using the Pearson or Spearman correlation coefficient. Differences and relationships were considered significant at $p \leq 0.05$.

The inclusion criterion was patient's informed consent to be in the registry. Various forms and doses of glucocorticoids were used as treatment for the underlying disease in patients with gout and RA. Prednisolone, in both tablet and parenteral forms, and parenteral methylprednisolone were prescribed to RA patients significantly more frequently, and dexamethasone was prescribed to patients with gout. Patients with gout were treated with nonsteroidal antiinflammatory drugs and colchicine. RA patients received therapy for the underlying disease using basic antiinflammatory drugs, including methotrexate (69.05%), hydroxychloroquine (11.78%), sulfasalazine (6.93%), leflunomide (4.85%), and azathioprine (3%), and genetically engineered biological agents, with four patients on rituximab, three on abatacept, and one each on adalimumab and infliximab. Courses of nonsteroidal antiinflammatory drugs and drugs with chondroprotective effect (symptomatic slow-acting drug for OA) were prescribed to OA patients.

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Results

A total of 2513 patients were included in the study and divided into three groups. Group 1 included 433 RA patients with concomitant HU, group 2 with 355 OA patients with concomitant HU, and group 3 with 1725 patients with gout. Male patients prevailed significantly in the gout and OA with HU groups, and female patients prevailed in the RA with HU group (Table 1).

Along with the demographic characteristics of patients, the laboratory parameters were compared in the study groups. The most significant differences were noted in the frequency of increase in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), total cholesterol, UA, and creatinine. The data are presented in Table 2. In the group of patients with gout, creatinine level increased more often, and the highest average values of CRP, creatinine, UA, glomerular filtration rate, and daily kidney protein loss were registered. A higher average glomerular filtration rate level, with the highest average creatinine level and the most frequent kidney damage in patients with gout, was associated with early detection of chronic kidney disease in the hyperfiltration stage and earlier initiation of nephroprotective therapy in this group of patients. In the group of RA patients with HU, ESR and CRP were more often increased, and the highest average ESR was noted. In the group of OA patients with HU, the total cholesterol level was more often increased at its highest average level.

Patients with gout, RA, and OA have a high incidence of comorbid conditions. In this regard, an analysis of the severity of concomitant diseases in the study groups was performed (Table 3). In patients with a combination of RA and HU, acute myocardial infarction, chronic heart failure of various grades, choledocholithiasis, and non-alcoholic fatty liver disease were detected significantly more often. Among OA patients with HU, there was a significantly higher prevalence of angina of effort of various grades, as well as heart rhythm and conduction disorders, varicose veins, overweight and obesity of varying severity, prediabetes, and type 2 diabetes mellitus. Patients with gout were characterized by a significantly higher incidence of urolithiasis, kidney abnormalities according to ultrasound examination, and chronic kidney disease of varying severity.

Since patients with RA and concomitant HU and patients with OA and concomitant HU had a rather high prevalence of cardiovascular system diseases (AH, angina of effort, and chronic heart failure), ULT was indicated following the ESC and RSC criteria [21, 22]. ULT was performed in 30.95% ($n = 134$) of RA patients with HU and 36.06% ($n = 128$) of OA patients with HU with average UA levels of 518.99 ± 92.26 and 524.63 ± 86.63 μmol/L, respectively. Allopurinol was predominantly used as a drug for ULT in both groups (with average doses of 100.37 ± 48.47 and 102.38 ± 41.64 mg for groups 1 and 2, respectively). The target UA value was <360 μmol/L. There were no adverse events with this therapy. It should be noted that the changes in the time of the UA levels could be assessed in 107 patients in group 1 and 48 patients in group 2 and were associated with low adherence to treatment and absence of some patients for check-up examinations (which was common among OA patients). The target UA level with a mean value of 304.76 ± 40.76 μmol/L was achieved in 34.58% ($n = 37$) of 107 RA patients with HU who received ULT. (The target value was not achieved in 65.42% [$n = 70$] of patients, and the mean UA

Table 1 / Таблица 1

Demographic characteristics of the patients in the groups under study, $n = 2513$
Демографическая характеристика пациентов исследуемых групп, $n = 2513$

Characteristic	Group			Significance, p
	1	2	3	
Women, n (%)	305 (70.44)	162 (45.63)	285 (17)	0.01 (1–3, 2–3)
Men, n (%)	128 (29.56)	193 (54.37)	1440 (83)	0.01 (1–3, 2–3)
Average age (years)	63.28 ± 11.84	60.99 ± 10.45	57.1 ± 7.9	0.05 (1–3, 2–3)
Period of follow-up of patients (years)	3.17 ± 3.25	3.53 ± 3.52	4.85 ± 3.36	0.05 (1–2)

N o t e. Group 1 consists of patients with rheumatoid arthritis and concomitant hyperuricemia, group 2 with osteoarthritis and concomitant hyperuricemia, and group 3 with gout.

level was 445.79 ± 63.26 μmol/L.) The target UA level with a mean value of 291.28 ± 64.23 μmol/L was achieved in 52.08% ($n = 25$) of 48 OA patients with HU who received ULT. (The target value was not achieved in 47.98% [$n = 23$] of patients, and the mean UA level was 411.87 ± 33.35 μmol/L.) In every third RA patient with HU and every second OA patient with HU, the average UA level was quite low, which could be a reason for reducing the dose of the urate-lowering drug in some cases. Noncompliance of drug intake, unwillingness to follow the recommended lifestyle modification and diet, an increase in body weight and obesity, and insufficient correction of comorbid metabolic conditions (dyslipidemia, prediabetes, and type 2 diabetes mellitus) were among the causes of failure to achieve the target UA levels.

Table 4 presents the therapy prescribed to patients in the study groups for correcting comorbid conditions. When analyzing drugs that affect UA exchange, data obtained showed that acetylsalicylic acid drugs were more often taken by RA patients with HU, calcium channel blockers and losartan were administered to patients with gout, and diuretics (especially indapamide and hydrochlorothiazide) and statins were prescribed to OA patients with HU. It is worth noting that diuretics and acetylsalicylic acid drugs were taken by approximately equal numbers of patients in groups 1 and 2. So, diuretics were used by 40.56% ($n = 144$) of OA patients with HU (including indapamide in 18.31% and hydrochlorothiazide in 14.93% of cases) and by 39.95% ($n = 173$) of RA patients with HU (including indapamide in 15.47% and hydrochlorothiazide in 10.85% of cases). Acetylsalicylic acid drugs were used by 25.87% ($n = 112$) and 24.51% ($n = 87$) of patients in groups 1 and 2, respectively. The data obtained are important for the selection and correction of complex therapy in patients with HU and comorbid diseases (withdrawal of acetylsalicylic acid drugs and diuretics in the absence of vital indications for taking these drug groups and use of losartan and calcium channel blockers as antihypertensive therapy).

Discussion

Experimental studies have shown that UA is a functionally active molecule that can contribute to the development of CVDs, proatherogenic processes, inflammation, endothelial dysfunction,

Table 2 / Таблица

Laboratory characteristics of the patients in the groups under study, $n = 2513$
Лабораторные показатели пациентов исследуемых групп, $n = 2513$

Groups and indices	ESR, mm/h	CRP, mg/L	Creatinine, μmol/L	UA, μmol/L	TC, mmol/L	GFR, mL/min	DPL, g/day
Normal values	1–15	0–10	44–115	280–360/420	3.0–5.5	80–120	0–0,5
Group 1	28.8 ± 14.4	22.7 ± 24.8	90.5 ± 23.9	498.6 ± 93.2	5.5 ± 1.3	74.9 ± 32.6	0.25 ± 0.4
Increase, n (%)	364 (84.06)*	259 (59.81)*	47 (10.85)*	433 (100)*	202 (46.65)*	–	82 (18.94)
Group 2	17.8 ± 9.3	9.3 ± 8.9	87.9 ± 24.6	501.5 ± 90.0	5.9 ± 1.2	87.9 ± 34.5	0.25 ± 0.5
Increase, n (%)	211 (59.44)*	78 (21.97)*	26 (7.32)*	355 (100)*	215 (60.56)*	–	54 (15.21)
Group 3	25.4 ± 15.1	23.2 ± 28.2	98.2 ± 38.9	529.6 ± 128.4	5.5 ± 1.8	92.9 ± 35.5	0.3 ± 0.4
Increase, n (%)	1203 (71.8)*	874 (52.4)*	316 (18.32)*	1544 (92.2)*	737 (44.4)*	–	363 (21.67)

N o t e. DPL was determined in 142 patients in group 1, 96 in group 2, and all patients in group 3. * Significance of differences $p = 0.01$. ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; UA, uric acid; TC, total cholesterol; GFR, glomerular filtration rate by creatinine clearance; DPL, daily protein loss.

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Table 3 / Таблица 3

Comparison of the frequency of comorbid conditions in the patients of the groups under study, *n* = 2513
Сравнение частоты коморбидных состояний у пациентов исследуемых групп, *n* = 2513

Pathology	Group		
	1, *n* (%)	**2, *n* (%)**	**3, *n* (%)**
Arterial hypertension	365 (84.29)	300 (84.51)	1461 (84.7)
Grade I–IV angina of effort	75 (17.32)*	76 (21.41)*	215 (12.46)*
Heart rhythm and conduction disorders	233 (53.81)*	209 (58.87)*	215 (12.46)*
History of AMI	33 (7.62)*	11 (3.09)*	123 (7.13)*
Grade I–IV CHF	108 (24.94)*	67 (18.87)*	278 (16.12)*
History of TEPA	6 (1.39)	4 (1.13)	11 (0.64)
Deep venous thrombosis	10 (2.31)	7 (1.97)	20 (1.16)
Varicose veins	109 (25.17)	97 (27.32)*	223 (12.93)*
History of TIA	6 (1.38)	3 (0.85)	17 (0.99)
History of ACVA	28 (6.47)	14 (3.94)	102 (5.91)
Overweight, obesity I–III degrees	237 (54.73)*	333 (90.8)*	490 (28.41)*
Prediabetes	76 (17.55)*	80 (22.53)*	147 (8.52)*
Type 2 diabetes mellitus	115 (26.56)*	115 (32.39)*	382 (22.14)*
Urolithiasis	75 (17.32)*	57 (16.06)*	655 (37.97)*
Kidney abnormalities according to ultrasound examination	126 (29.09)*	78 (21.97)*	679 (40.54)*
Grade I–V CKD	212 (48.96)*	21 (5.91)*	1223 (70.9)*
Choledocholithiasis	97 (22.4)*	71 (20)*	199 (11.54)*
NAFLD	132 (30.48)*	104 (29.29)*	189 (10.96)*

N o t e. * Significance of differences *p* = 0.01. Kidney abnormalities according to ultrasound examination: abnormal size changes, cysts, renal pelvis and calyces enlargement, hydronephrosis, and renal duplication. AMI, acute myocardial infarction; CHF, chronic heart failure; TEPA, thromboembolia of the pulmonary artery; TIA, transient ischemic attack; ACVA, acute cerebrovascular accident; CKD, chronic kidney disease; NAFLD, nonalcoholic fatty liver disease.

and oxidative stress. Reactive oxygen species produced after xanthine oxidase activation are declared as a main cause of endothelial dysfunction and vascular inflammation [23]. There is growing evidence that serum UA may be significant in CVD development in the general population. According to epidemiological studies, an increase in UA concentration is associated with AH development [9]. Moreover, the literature provides data that increased UA concentrations can be a predictor of peripheral artery disease, coronary heart disease [11], acute myocardial infarction [12], heart failure [13], acute cerebrovascular accident [14], and cardiovascular and general mortality [15]. An increase in UA levels leads to the development of both systemic and glomerular hypertension in combination with increased resistance and decreased blood flow in the renal vessels. Evidence has shown that persistent HU is a risk factor for renal fibrosis in progressive chronic kidney disease and renal failure [24]. In the experiment, HU induced AH, glomerular hypertrophy/hypertension, afferent arteriolar sclerosis, and macrophage infiltration in normal kidney of a rat; therefore, UA can be considered not only a marker but also a cause of kidney disease. Studies have demonstrated that HU is accompanied by an increase in the production of tumor necrosis factor alpha (TNF-alpha), interleukin-6, interleukin-8, and miRNA-155 and local expression of monocytic chemotactic protein 1 in the kidneys and type 2 cyclooxygenase in blood vessels [25]. It has been proven that a higher UA concentration in the blood serum is associated with hyperlipidemia, triglyceridemia, type 2 diabetes mellitus, and metabolic syndrome [10]. According to our study, in the group of patients with gout, creatinine levels were more often

Table 4 / Таблица 4

Treatment of comorbid conditions in the patients of the study groups, *n* = 2513
Лечение коморбидных состояний у пациентов исследуемых групп, *n* = 2513

Group of drugs	Group			Drug	Group		
	1, *n* (%)	2, *n* (%)	3, *n* (%)		1, *n* (%)	2, *n* (%)	3, *n* (%)
Antiplatelet agents	201 (46.42)	182 (51.27)	894 (51.83)	Acetylsalicylic acid	112 (25.87)*	87 (24.51)	326 (18.9)*
Anticoagulants	25 (5.77)	17 (4.79)	108 (6.26)	–	–	–	–
Beta adrenoreceptor antagonists	174 (40.18)	147 (41.41)	745 (43.19)	–	–	–	–
Calcium channel blockers	120 (21.71)*	96 (27.04)*	642 (37.22)*	–	–	–	–
Angiotensin-converting enzyme inhibitors	178 (41.11)	148 (41.69)	825 (47.83)	–	–	–	–
Angiotensin II receptor blockers	97 (22.4)*	101 (28.45)*	649 (37.62)*	Losartan	69 (15.94)*	70 (19.72)*	554 (32.12)*
Imidazoline receptor antagonists	27 (6.24)	17 (4.79)*	169 (9.8)*	–	–	–	–
Nitrates and nitrate-like agents	17 (3.93)	19 (5.35)	57 (3.3)	–	–	–	–
Diuretics	173 (39.95)*	144 (40.56)*	426 (24.7)*	Indapamide	67 (15.47)*	65 (18.31)*	113 (6.55)*
				Hydrochloro-tiaside	47 (10.85)*	53 (14.93)*	55 (3.19)*
Other cardiotropic drugs	24 (5.54)*	9 (2.54)	48 (2.78)*	–	–	–	–
Statins	31 (7.16)	37 (10.42)*	101 (5.86)*	–	–	–	–
Oral antihyperglycemic drugs	27 (6.24)*	27 (7.61)	184 (10.67)*	Metformin	41 (9.47)	45 (12.68)	149 (8.64)

N o t e. * Significance of differences *p* = 0.01.

increased, and the highest average levels of CRP, creatinine, and UA were registered, which may be associated with a high level of inflammatory activity during acute gouty arthritis, a longer and more persistent course of HU, and more frequent kidney damage in this pathology. In the group of RA patients with HU, increased ESR and CRP indices were more often revealed, and the highest average ESR was registered, which may be due to a chronic inflammatory process in this pathology. In the group of OA patients with HU, the total cholesterol level was more often increased at its highest average level, which may indicate pronounced metabolic disorders when these pathologies are combined.

There are several studies on asymptomatic HU in RD patients. Petsch et al. [26] revealed that deposits of sodium monourate crystals were found in every third patient with seronegative RA with HU, according to the data of dual-energy computed tomography of the hands and feet. Krasnokutsky et al. [27] reported that in patients with knee OA, an increased UA level had a prognostically unfavorable value in relation to the joint space narrowing and served as a biomarker of OA progression. In an observational study of three groups of patients with gout, OA, and RA, gout was associated with a 3.1-fold risk of primary cardiovascular events. An increase in serum UA was associated with an increased risk of CVDs in RD patients without gout than in patients with gout. Gout and high UA levels were stronger predictors of early cardiovascular events than some traditional CVD risk or inflammatory factors [28].

According to the analysis of St. Petersburg gout register, the vast majority of patients with

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gouty arthritis have increased UA level and cardiovascular and renal comorbid condition incidence compared with that of the general population, which indirectly confirms the independent role of HU as a factor of cardiovascular and renal risks [2]. In this study, patients with gout had a significantly higher incidence of urolithiasis, kidney changes according to ultrasound examination data, and chronic kidney disease of varying severity. This confirms the pronounced kidney damage in this pathology compared with not only the general population but also the RA patients with concomitant HU and OA patients with concomitant HU. In patients with a combination of RA and HU, comorbid conditions in the form of acute myocardial infarction, chronic heart failure of various grades, choledocholithiasis, and nonalcoholic fatty liver disease were significantly more frequent. The data obtained confirmed an increased risk of CVDs in RA patients and an increased risk of thrombogenesis due to the influence of systemic inflammation [29]. The increased prevalence of choledocholithiasis and nonalcoholic fatty liver disease may be due to the use of basic antiinflammatory drugs that can negatively affect the liver and other parts of the gastrointestinal tract. A significantly high prevalence of angina of effort of various grades was revealed, as well as cardiac rhythm and conduction disorders, varicose veins, overweight and obesity of various degrees of severity, and prediabetes and type 2 diabetes mellitus among OA patients with HU. It is worth noting that HU in OA was associated with diseases associated with impaired carbohydrate and lipid metabolism. Thus, according to an earlier study, diseases associated with metabolic syndrome were significantly more common in patients with gout and asymptomatic HU than in the control group [3]. Moreover, in this group of patients, the manifestations of ischemic heart disease, probably induced by atherosclerosis of the coronary arteries due to lipid metabolism disorders, were most common.

In the case of diagnosed gout, the use of ULT is a direct method for treating the disease [16–18], but there is no consensus among the world scientific community regarding asymptomatic HU. According to the Japanese National Guidelines for the Management of Patients with Gout and HU, drug therapy should be considered for asymptomatic HU of at least 9 mg/dL (535 μmol/L) despite an improved lifestyle. In addition, the possibility of drug therapy should be considered when the serum UA level reaches 8 mg/dL (475 μmol/L) or more and if the patient has concomitant diseases such as urolithiasis, chronic kidney disease, AH, ischemic heart disease, type 2 diabetes mellitus, and metabolic syndrome [19]. According to the Portuguese National Guidelines for the Management of Patients with Gout and HU, for serum UA of at least 9 mg/dL (535 μmol/L), pharmacological treatment should be considered after an individual assessment of the risk/benefit ratio, in particular for preventing gout [20]. In 2020, the RCS approved the clinical guidelines for AH, and according to which UA is a cardiovascular risk factor and its level should be determined for all AH patients [30]. Moreover, RSC and ESC adopted a consensus for patients with asymptomatic HU and high cardiovascular risk, and according to which ULT is recommended in this group of patients [21, 22]. According to the results of our study, ULT was started in 30.95% of RA patients with HU and in 36.06% of OA patients with HU. Allopurinol was predominantly used. There were no reports of adverse events with this therapy. Prospective follow-up of this group of patients continues.

It is worth noting that there are risk factors for HU in RA patients. The intake of basic antiinflammatory and genetically engineered biological drugs can advance the occurrence of UA. In an observational study, the effect of a 3-month treatment of RD with TNF-alpha inhibitors on an increase in serum UA levels was proven. In the cohort of RA patients under study, nine patients received genetically engineered biological agents. During the therapy, UA level increased in 66.6% ($n = 6$) of patients, and HU was not detected before in 44.4% ($n = 4$). On the contrary, UA level decreased in 33.3% ($n = 3$) of patients.

Conclusions

HU is a common comorbidity in RA and OA. These combinations lead to an increased risk and frequency of cardiovascular, metabolic, and gastroenterological comorbidity.

With a combination of RDs (both RA and OA) with HU, compared with the group of patients with gout, concomitant diseases in the form of angina of effort of various grades, heart rhythm and conduction disorders, chronic heart failure of various grades, overweight and obesity,

prediabetes, type 2 diabetes mellitus, choledocholithiasis, and nonalcoholic fatty liver disease are significantly more frequent. Gout is significantly more often associated with kidney damage in the form of urolithiasis and chronic kidney disease of varying severity. The prevalence of acute myocardial infarction in history is significantly higher in RA patients with HU than in patients with gout, and the prevalence of varicose veins is higher in OA patients with HU.

ULT in patients with RDs and asymptomatic HU with high cardiovascular risk enabled to achieve the target UA levels in 34.58% and 52.08% of patients with RA and OA, respectively. In the complex therapy of HU, in addition to drug treatment, it is of great importance to follow the recommendations for improving lifestyle, normalizing body weight, adhering to a low-purine diet, correcting metabolic disorders, and increasing compliance.

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