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CONDITION OF DYSLIPIDEMIA AND CYTOKINE PROFILE IN PATIENTS WITH GOUT: THE ROLE OF IL-6, IL-18 AND THE PLACE OF HYPERURICEMIA IN THE DEVELOPMENT OF METABOLIC DISORDERS

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Evaluation of the correlation of immunological and biochemical values with clinical manifestations of gout, as well as the role of hyperuricemia in comorbid states is important for the search for therapeutic targets.

Objective: *to investigate the relationship between indexes of dyslipidemia and immunological changes in patients with tophaceous gout and asymptomatic hyperuricemia.*

Patients and methods. *The study included 85 male patients: 1st group – 49 patients with primary chronic gout according to Wallace S.L. criteria, 2nd (control) group – 36 patients with asymptomatic hyperuricemia. The levels of uric acid (UA), C-reactive protein (CRP), fasting glycemia, lipid profile – total cholesterol (TC), triglycerides (TG), high-density (HDL), low density (LDL), very low density (VLDL) lipoproteins, atherogenic ratio (AR); cytokine concentrations: interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), IL-4, IL-6, IL-8, IL-10 and IL-18 in the blood serum using enzyme-linked immunosorbent assay.*

Results. *UA values positively correlated with the number of affected joints (r=0.64, p=0.058), presence of tophi (r=0.73, p=0.042), glycemic level (r=0.74; p=0.038). An increase in TC by 11.85%, LDL by 22.51%, VLDL by 21.43% and a decrease in HDL by 20.9% in patients with gout was observed. AR was higher in the group of patients with gout by 25.8% (p=0.0088). An increase in the production of cytokines IL-6 (p=0.0012) and IL-18 (p=0.0008) was observed in patients with gout with UA level above 0.420 mmol/l. There was no significant increase in IL-1β (+0.36, p=0.0154),*

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TNF-α (+0.21, p=0.0944), IL-4 (+0.02, p=0.0028). There was no relationship between IL-6 and CRP (r=0.26, p=0.0122). In the 1st group strong correlations between IL-6 and AR (r=0.762, p=0.0018), IL-18 and AR (r=0.766; p=0.0052) were shown. In the 2nd group correlation between IL-6 and CA was weaker (r=0.292, p=0.0127), with a weak negative correlation between IL-18 and AR (r=-0.366, p=0.0049).

Conclusion. *The exceptional role of hyperuricemia in the development of dyslipidemia in patients with gout has not been confirmed. TC, LDL, VLDL and AR are significantly elevated, while HDL is significantly lower in patients during the intercritical period of gout. The increase of IL-6 and IL-18 is accompanied by more prominent indexes of dyslipidemia and clinical manifestations of gouty arthritis.*

Keywords: *gout; hyperuricemia; dyslipidemia; interleukins; cytokine profile.*

Gout, a chronic inflammatory disorder of purine metabolism, is known to be the most common cause of inflammatory arthritis in males over 40 years of age. The incidence of gout has increased many times over the past decades (up to 1-6% in developed countries) and continues to grow steadily against the backdrop of a tense epidemiological situation for non-communicable diseases, such as metabolic syndrome, hypertension (AH), coronary heart disease (CHD), diabetes mellitus type 2 and their complications [1–4]. The current evidence base indicates that gout is an autoimmune inflammatory disease, the main characteristic of which is the activation of the innate immune response against the background of the deposition of crystals of sodium monourate salts (MUN) in various tissues [2-4].

So, Martinon F. et al. in 2002, it was experimentally confirmed that the presence of uric acid (UA) crystals causes oligomerization and dysfunctional activity of specific macromolecules, NLRP3 inflammasomes, which are accompanied by hyperactivity of the pro-inflammatory caspase-1 enzyme. This process causes increased secretion of the inflammatory cytokines IL-1β and IL-18. These cytokines belonging to the same family, in turn, initiate an inflammatory cascade, causing endothelial activation and accumulation of a pool of leukocytes [5–6]. It is generally accepted that the main cytokines with secondary involvement in this process are IL-4 (recruitment and activation of neutrophils), IL-6 (maintenance of the inflammatory process, direct damage to the connective tissue) and TNFα (pro-inflammatory activation, maturation and increase in the transformation of monocytes to macrophages) [7]. In the studies of Martin W.J. et al. (2010), Conforti-Andreoni C. et al. (2011) and a number of others provide quite extensive information on the role of macromolecules induced by MUN salts and involved in the activation of innate immunity, which is accompanied by hyperproduction of IL-1β, IL-6, and IL-17A [5–8].

Through proteomic and immunohistochemical studies in vitro, it was revealed that MUN crystals have a direct pro-inflammatory effect, inducing the production of cytokines, by incorporating the toll-like receptor family and a number of NLRP3 inflammasomes into the inflammatory cascade. There is also evidence of a role for the MRP8/MRP14 myeloid-associated protein complex, also known as calgranulin A/B (S100A8/A9), which is a toll-like TLR-4 receptor agonist, in increasing the risk of cardiovascular events and diabetes mellitus 2- type in patients with hyperuricemia and the

development of non-alcoholic fatty liver disease (NAFLD) in them [9-10]. In addition, MUN crystals are responsible for the induction of the production of the cytosolic protein cryopyrin NALP3, the main component of the pro-inflammatory caspase-1-activating inflammasomes of the same name, which trigger the production of active cytokines IL-1β, IL-6, IL-8, IL-18, etc. [11] These data suggest the presence of targeted inflammatory biomarkers in patients with gout, which determine not only the pathogenesis of the underlying gouty arthritis, but also the development of comorbid conditions.

However, in recent years, a number of researchers have considered hyperuricemia (HU), a metabolic disorder underlying gout, not only as an obligate factor involved in the development of nephropathy in patients with gout, but also as an independent predictor of the development of atherosclerosis, mortality from cardiovascular diseases. complications and development of NAFLD.

Krishnan E. et al. conducted a 17-year study (1991-2008) of cardiovascular disease (CVD) mortality among middle-aged males with gout. They found that gouty arthritis, accompanied by an increase in the level of UA, increases the risk of death from CVD [12]. However, like most studies at that time, GU was considered, according to the definition of Polskaya I.I. and Marusenko I.M., as a "by-product", i.e. concomitant aggravating factor of common risk factors — arterial hypertension (AH), renal failure, insulin resistance and obesity [13]. However, consideration of HU in isolation from gout made it possible to expand the existing understanding of the role of HU and its primacy in cardiovascular and hepatic lesions. Zhang J. et al. in a study on 324 male respondents revealed a positive correlation between hypertension and hyperuricemia, namely, an increase in systolic blood pressure by 27 mm Hg. Art. with an increase in the concentration of UA for every 1.0 mg/dL [14]. From recent studies in the meta-analysis Jaruvongvanich V. et al. (2017) 5 observational studies involving 777 patients clearly demonstrated a significant increase in the risk of CVD, NAFLD and histologically confirmed liver damage in patients with HU [15].

Based on the foregoing, a clear understanding of the correlation of immunological and biochemical mechanisms of the disease with clinical changes, as well as the priority of hyperuricemia in comorbid conditions in patients with gout, is necessary not only to determine effective therapeutic targets for influencing the course of gout, but also to correct existing metabolic changes.

The aim of our study was to study the relationship between dyslipidemia and immunological changes in patients with tofus gout and asymptomatic hyperuricemia.

Material and methods. The study included 85 males who were admitted to the rheumatology department and the polyclinic of specialized course outpatient treatment of the 1st clinic of the Tashkent Medical Academy in the period from April 2014 to April 2017, and distributed into 2 groups.

Group 1 included 49 patients with a clinically verified diagnosis of primary chronic gout according to the criteria of Wallace S.L. (1977) [3]. The average age of patients was 57.21±6.14 years, the age of onset of gouty arthritis averaged 42.74±8.12 years (from 34 to 55 years), the average duration of the disease at the time of treatment was 4.7 (3.0– 10.0) years. In the first 5 years of the disease, 23 (46.94%) patients consulted a rheumatologist. All patients of the 1st group were examined during the interictal period of gout. In 27 (55.10%) cases, a diagnosis of gout with tophi was made, in 22 (44.90%) cases, non-tophi gout was diagnosed. The number of affected joints averaged 5.5 joints

(1.0–12.0). According to the frequency of exacerbations, an average of 2.52 (1.0-5.0) exacerbations per year was noted, 25 (51.02%) patients stated > 3 exacerbations per year.

In the interictal period of gouty arthritis, there is a more frequent use of uricosuric drugs (allopurinol at a dose of 100–300 mg/day, febuxostat at a dose of 80–120 mg/day) according to indications, as well as glucocorticosteroids, mainly for arthralgia resistant to non-steroidal anti-inflammatory drugs (Table 1). 1). The intake of these drugs for the period of immunological and biochemical studies was suspended in order to obtain reliable results. As maintenance therapy, 29 (59.18%) patients took aspirin at a dose of 75-150 mg/day, 4 (8.16%) - thiazide diuretics (indapamide 2.5 mg/day), 6 - combined antihypertensive drugs (indapamide + amlodipine + perindopril in dosages of 5 mg + 2.5 mg + 10 mg and 5 mg + 1.25 mg + 5 mg). Group 2 (control) included 36 male patients with asymptomatic hyperuricemia (not accompanied by arthritis, joint deformity, tophi at the time of the study and history) as a control group. As maintenance therapy, 26 (72.22%) patients took aspirin at a dose of 75-150 mg/day, 5 (13.89%) - thiazide diuretics, 3 (8.33%) - loop diuretics (furosemide up to 80 mg/day). days).

Table 1

Phenotypic and clinical characteristics of the study groups

	Patients with gout (n = 49)	**Patients with asymptomatic hyperuricemia (n = 36)**
Age, years	57,21±6,14	54,2±8,22
Disease duration, years	4,7±1,5	-
Exacerbation frequency	2,52±0,73	-
Body mass index, kg/m2	28,2±4,3	27,9±4,6
Waist circumference, cm	92,4±2,1	94,6±1,6
Arterial hypertension (%)	20 (40,82)	17 (47,22)
Cardiovascular pathology (%)*	12 (24,49)	8 (22,22)
Chronic kidney disease (%)**	7 (14,29)	4 (11,11)
Non-alcoholic fatty liver disease (%)	18 (36,73)	12 (33,33)
Allopurinol (%)	29 (59,18)	12 (33,33)
Febuxostat (%)	7 (14,29)	4 (11,11)
Colchicine (%)	1 (2,09)	-
Glucocorticosteroids (%)	4 (8,16)	-
Non-steroidal anti-inflammatory drugs (%)	32 (65,31)	6 (16,67)

*Note: * Including transient ischemic attack, myocardial infarction, peripheral vascular disease, arrhythmias, ischemic heart disease and/or heart failure. ** When glomerular filtration rate is below 60 ml/min.*

According to the clinical indicators of the presence of the metabolic syndrome, subjects with similar parametric data (weight, body mass index (BMI), waist circumference (WC)) were selected in the main group and the control group. The discrepancy in parametric indicators did not exceed 4.0%: in the 1st group, BMI was 28.2±4.3 kg/m2, in the 2nd group this indicator was 27.9±4.6 kg/m2. According to WC measurements — 92.4±2.1 cm and 94.6±1.6 cm in the group of patients with gout and the control group, respectively.

Exclusion criteria for the study were the presence of chronic foci of infection and active infectious diseases. The use of any lipid-lowering (statins, fibrates, niacin), antibacterial, antiviral, antifungal and antiprotozoal drugs, prebiotic and probiotic agents was also excluded during the entire study period.

In all patients, the level of UA, CRP, fasting glycemia, and lipid spectrum indicators were determined. The content of lipids in venous blood was determined by photocolorimetry on a biochemical analyzer Vitros SYSTEM Chemistry DT 60 (Austria). The optimal level was considered to be the level of total cholesterol (CHC) <5.2 mmol/l (<200 mg%) in the blood, triglycerides (TG) 1.7 mmol/l (150 mg%). High-density lipoprotein cholesterol (HDL-C) was determined in the supernatant after precipitation of lipoproteins of other classes with dextran sulfate; low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein cholesterol (VLDL-C) were calculated using the formula of Friedwald W., the distribution of cholesterol between atherogenic and antiatherogenic lipoproteins was studied using the lipid coefficient of atherogenicity (CA), which is the ratio "ChS - HDL-C / HDL-C. ALT, AST, urea, creatinine, total protein in the blood were determined spectrophotometrically on SF-46 (Russia). The determination of the level of uric acid in the blood serum was carried out using a reaction with a phosphorus-tungsten reagent.

In all 85 patients selected in both groups, the concentrations of cytokines were determined: interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10) interleukin-18 (IL-18) in blood serum by enzyme-linked immunosorbent assay on an automatic immunochemiluminescent analyzer Immulite 2000XPi (Germany).

Statistical analysis was performed using the OpenEpi 3.03 software package (Centers for Disease Control and Prevention, USA, 2014). The results are presented as means and standard deviations (M±SD) for quantitative traits. In the process of statistical data processing, descriptive statistics methods were used, the Mann–Whitney test was used to compare two independent groups, and the nonparametric Wilcoxon T-test was used to assess the significance of changes in indicators and compare correlations with metabolic indicators. The degree of correlation (r) was estimated as: $0 < r \leq 0.35$ — weak correlation; $0.35 < r \leq 0.67$ — average correlation; $0.67 < r \leq 1$ — strong correlation. Adjusted p values were calculated automatically upon reaching the limits of the confidence interval.

Research results. The studied indicators of hyperuricemia, glycemia and lipid profile are shown in Table 2. The level of UA in patients with gout varied from 0.357 to 0.760 mmol/l (mean value 0.564±0.098 mmol/l), in the group of patients with asymptomatic hyperuricemia the values were distributed with a lower threshold from 0.426 mmol / l to 0.615 mmol / l, but at the same time with a

lower average level - 0.462 ± 0.036 mmol / l, i.e. the level of sUA significantly (p=0.008; <0.01) differed downward by 14.04% compared with the main group.

In the main group, the level of sUA significantly correlated with a more severe course of gout. Higher MC values caused an increase in the frequency and duration of exacerbations. It should be noted that in 12 cases in the group of patients with gout who noted prolonged exacerbations (more than 4 weeks), the level of UA was higher than 0.5 mmol/l (value range 0.512–0.760 mmol/l; median Me=0.574 mmol/l). The number of affected joints increased with an increase in the level of UA (correlation coefficient r=0.64; p=0.058). In addition, in patients with recurrent gouty arthritis, the level of UA in the blood serum was significantly higher in the presence of tophi (r=0.73; p=0.042).

Violation of carbohydrate metabolism was assessed by the severity of fasting hyperglycemia. Blood glucose levels were higher in patients with asymptomatic hyperuricemia, and averaged 6.080±0.025 mmol/l, while in the main group the average value was 5.873±0.081 mmol/l, which apparently reflects the primacy of impaired tolerance to glucose and insulin resistance in combination with metabolic syndrome. The severity of hyperuricemia in this category of patients positively correlated with the level of glycemia (r=0.74; p=0.038).

Table 2

Uric acid levels and lipid profile (M ± SD)

Index	Patients with gout (n = 49)	Patients with asymptomatic hyperuricemia (n = 36)
Uric acid, mmol/l	0,564 ± 0,098	0,462 ± 0,036*
Fasting glucose level, mmol/l	5,873 ± 0,081	6,080 ± 0,025*
Total cholesterol, mmol/l	6,922 ± 0,016	6,104 ± 0,072*
Low density lipoproteins, mmol/l	5,022 ± 0,116	3,892 ± 0,078*
High density lipoproteins, mmol/l	1,066 ± 0,052	1,347 ± 0,045*
Very low density lipoproteins, mmol/l	0,844 ± 0,017	0,660 ± 0,009*
Triglycerides, mmol/l	1,741 ± 0,150	1,866 ± 0,183^
Atherogenic coefficient	4,831 ± 0,072	3,576 ± 0,098*

*Note: * p<0.01 — significant difference between the indicators of the control and compared groups.*
^ p>0.05 — significance of differences between groups below the established limit.

In terms of the lipid spectrum, there was a tendency to dyslipidemia and an increase in the titer of atherogenic fractions in patients in the interictal period of gout. The content of total cholesterol in the main group was significantly higher than in the control (+0.818; p=0.0054). Differences in the content of LDL-C were more pronounced compared to the level of cholesterol (p=0.0067). As for the content of VLDL-C in the blood serum of patients with gout, a significant increase in the titer of VLDL-C (above 1.04 mmol/l) was detected in 8 patients with gout and 4 subjects in the control group.

The mean values of VLDL-C did not exceed the upper limit of normal values both in the main group (0.844±0.017; p=0.0032) and in the group of patients with asymptomatic hyperuricemia (0.660±0.009; p=0.0016), which is apparently associated with low rates of clinical signs of the metabolic syndrome in both groups (BMI 28.2±4.3 kg/m2 in the 1st group and 27.9±4.6 kg/m2 in the 2nd group; waist circumference 92.4±2.1 cm and 94.6±1.6 cm in the 1st and 2nd groups, respectively).

At the same time, there was a significant decrease in HDL levels compared to the values in the hyperuricemia group without gouty arthritis (-0.281; p=0.0041), which reflects a decrease in the level of atheroprotective fractions in gout. The coefficient of atherogenicity was 4.831±0.072 in the 1st group and 3.576±0.098 in the 2nd group of the study.

Thus, the detected hypercholesterolemia was associated in patients with gout with more pronounced dyslipidemia. In the lipid profile, there was an increase in cholesterol in patients with gout by 11.85%, LDL-C by 22.51% and a decrease in HDL-C by 20.9%. The level of VLDL-C in the group of patients with gout was higher by 21.43%. Hypertriglyceridemia was observed in both groups of observation, while in the group of patients with gout, the level of TG was lower by 6.4%, however, the reliability of this indicator was insufficient due to the small sample and high variation in values (V=46.71%, p=0.097). The coefficient of atherogenicity was higher in the group of patients with gout by 25.8% (p=0.0088).

Table 3

Cytokine profile of the studied groups according to enzyme immunoassay data

Parameter, pg/ml	Patients with tophi gout (n = 49)	Patients with asymptomatic hyperuricemia (n = 36)	p
IL-1β	2,57 ± 0,81	2,21 ± 0,45*	0,0154
TNF-α	3,08 ± 1,84	2,87 ± 1,01*	0,0044
IL-4	1,38 ± 0,47	1,26 ± 0,40*	0,0028
IL-6	38,08 ± 9,82	17,18 ± 5,65*	0,0012
IL-8	14,92 ± 2,26	13,75 ± 0,53^	0,0542
IL-10	7,21 ± 2,18	7,45 ± 1,61*	0,0051
IL-18	361,75 ± 14,61	167,12 ± 20,71*	0,0008

*Note: * p<0.01 — significant difference between the indicators of the control and compared groups.*
^ p>0.05 — significance of differences between groups below the established limit.

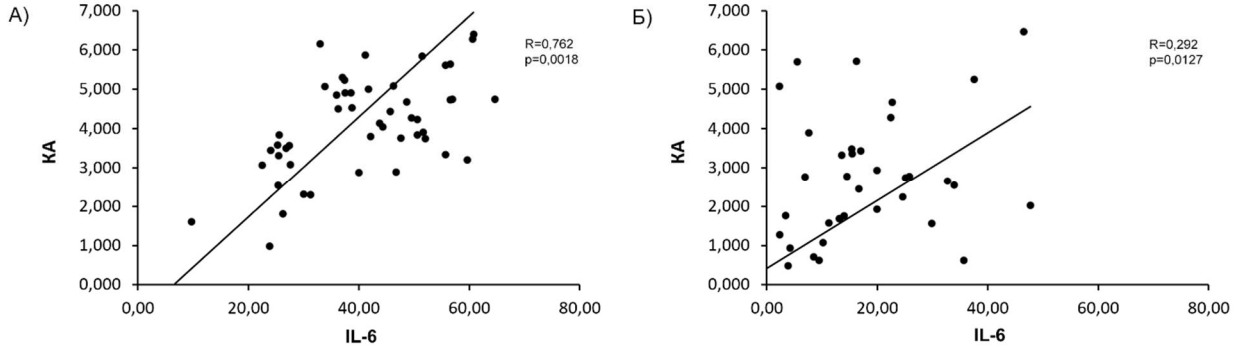
Compared with subjects with asymptomatic hyperuricemia, in patients in the interictal period of gout, there is a significant increase in the production of key pro-inflammatory cytokines IL-6 (p=0.0012) and IL-18 (p=0.0008). At the same time, there was no expected and significant increase in IL-1β (+0.36; p=0.0154), TNF-α (+0.21; p=0.0944), as well as IL- 4 (+0.02; p=0.0028). There was also no positive correlation between elevated levels of circulating IL-6 and acute-phase indicators of inflammation - C-reactive protein and erythrocyte sedimentation rate (r=0.26; p=0.0122). The results

for TNF-α, IL-8, IL-10 titers varied widely and exceeded the established confidence interval, apparently due to the absence of a prognostically significant trend in indicators.

In both study groups, no linear relationship was found between the levels of uric acid and cytokines, which correlates with the severity of clinical manifestations of gout and comorbid pathology with variable levels of uric acid in the blood serum. However, IL-6 and IL-18 were significantly elevated in gout patients with uric acid levels above the target of 0.420 mmol/L compared with controls (p=0.0004). Assessment of cytokine levels in blood serum in relation to clinical data showed a positive relationship between IL-6 titer and the presence of joint deformities (p=0.0021), IL-6 and gouty tophi (p=0.0154), and IL-18 and ultrasound signs of non-alcoholic fatty liver disease (p=0.037) in the group of patients with gout. Since in the group of subjects with asymptomatic hyperuricemia there were a small number of patients (n=3) with IL-8 levels exceeding the detection limit, the reliability and degree of correlation were not assessed for this cytokine.

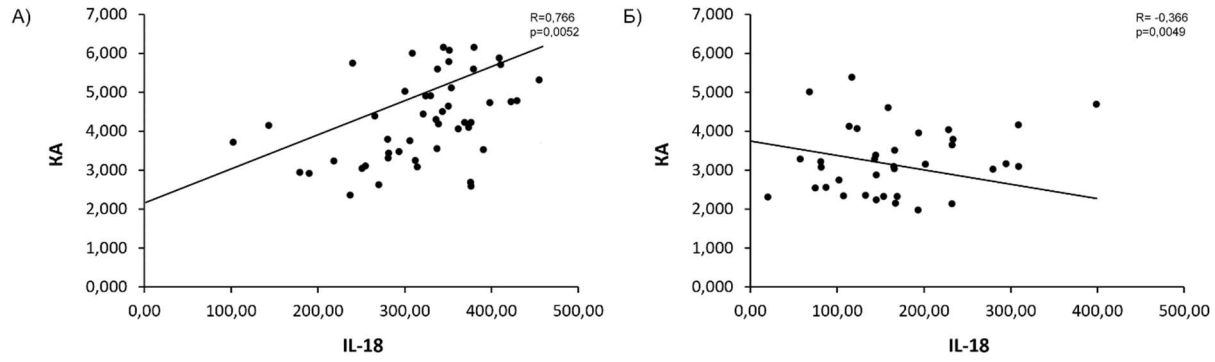
When studying the cytokine profile, the presence of a relationship between the levels of various groups of interleukins was also determined. In the main group, an average correlation was found between the levels of IL-6 and IL-18 (r=0.61; p=0.0233), and there was also a weak correlation between IL-18 and IL-1β (r=0.27 ; p=0.012).

Based on the obtained results, as well as literature data on the study of mediators of immune inflammation in gout, it was assumed that an increase in titers of IL-6 and IL-18 in patients with gout is pathognomonic for this disease. We have analyzed the dependencies of the titer of these interleukins with the most representative indicator of the lipid spectrum - the index (coefficient) of *atherogenicity.*



Rice. 1. Graphs of the correlation of IL-6 and atherogenic coefficient (CA) in the main (A) and control (B) groups. R – correlation coefficient, differences are significant at p<0.05

According to the results, in the 1st group, subjects with high levels of IL-6 had a significantly higher value of the specific coefficient of atherogenicity (r=0.762; p=0.0018) (Fig. 1, A), which reflects more pronounced deviations of the lipid profile with an increased titer of this inflammatory mediator. In the 2nd group, the correlation between IL-6 and CA was significantly weaker (r=0.292; p=0.0127) and, despite a positive relationship, did not reflect a clearly defined association between these indicators (Fig. 1, B).



Rice. 2. Graphs of the correlation of IL-18 and atherogenic coefficient (CA) in the main (A) and control (B) groups. R – correlation coefficient, differences are significant at p<0.05

The results in terms of IL-18 were similar to IL-6 in the main group, a strong correlation was demonstrated between IL-18 and CA (r=0.766; p=0.0052) (Fig. 2, A), with a total of 7 patients out of 49 in the group of gout patients had CA below 3.0 mmol/l with a range of IL-18 values equal to 179.15–381.0 pg/ml. In the comparison group, there was a weak negative relationship between the titer of IL-18 and CA (r= -0.366; p=0.0049) (Fig. 2, B), which, with a detailed analysis of the clinical data of patients in this group, can be explained by an increase in the titer of IL- 18 in 6 subjects against the background of recent respiratory viral infections and a relatively small sample.

Discussion. At the moment, experimental material has been accumulated on a number of studies aimed at studying the molecular substrate and trigger factors of chronic inflammatory diseases, and their relationship with clinical manifestations. Thus, it has been proven that attacks of gouty arthritis occur with the rapid release of crystalline MUN in the joint fluid and the initiation of the inflammatory cascade. Back in 1991, Pascual E. et al. demonstrated that MUN crystals persist in the synovial fluid, maintaining the inflammatory background during the interictal period of gout. TNF-α and other pro-inflammatory cytokines, in turn, induce the release of free oxygen radicals by macrophages, as well as inhibit antioxidant enzymes such as paraoxonase 1 (PON1) and promote the transformation of HDL into oxidized pro-inflammatory HDL. Pro-inflammatory HDL, despite the high titer in blood serum, is unable to counteract cholesterol transport and loses its antioxidant properties, which leads to the accumulation of oxidized LDL and VLDL [8, 16]. In turn, in the works of Kappelle P.J. (2011) et al., Jiang X. et al. (2013) showed that an increased concentration of oxidized LDL in blood plasma leads to an increase in the titer of IL-6, IL-8, and TNF-α, which closes the vicious circle of oxidative stress and supports the inflammatory process [17–18].

According to the results obtained in our study, the main indicators of the lipid profile in patients with gout, namely cholesterol, LDL-C, VLDL-C and the associated CA indicator, were significantly increased, while HDL was significantly reduced in patients in the interictal period. gout, which reflects a lipid profile typical of type IV dyslipidemia. These data are confirmed by Tsutsumi Z. et al. (2004),

Meek I.L. et al. (2014) regarding dyslipidemia in patients with gout. However, as noted in these studies, a high concentration of LDL, especially their oxidized fractions, correlates with the titer of proinflammatory mediators IL-1β, IL-6, and TNF-α, which increase in patients during periods of exacerbation of gouty arthritis. At the same time, in the acute inflammatory phase, these cytokines are responsible for the decrease in triglycerides and lipoprotein fractions, which then increase after the episode of acute inflammation is relieved [18–20]. This phenomenon, apparently, determined the high values of the lipid profile in patients in the interictal period of gout with relatively moderate values of TNF-α, IL-1β, IL-4 in our study.

On the other hand, a meta-analysis of large-scale clinical trials (Afzali A. et al., 2010; Viazzi F. et al., 2014; Lonardo A., 2015, etc.), as well as a number of comparative studies in vivo, indicate not only association of hyperuricemia with dyslipidemia, arterial hypertension, obesity, metabolic syndrome, but also recent studies with the development of histologically confirmed NAFLD in individuals with a persistent increase in the level of sUA [17, 21, 22]. Thus, in animal models, it was found that hyperuricemia can initiate an inflammatory cascade in adipocytes by increasing the production of monocyte chemotactic protein-1 (MCP-1), and the suppressive effect on adiponectin (GBP-28), known as an anti-inflammatory and anti-atherogenic hormone. It has also been demonstrated that under conditions of elevated levels of UA in hepatocytes, mitochondrial disorders develop and accelerated lipogenesis is noted [18, 23].

In various studies involving immunological studies, there are, as a rule, pronounced discrepancies in the results and their interpretation - varying sampling methods, low standardization of commercial sera kits for research, circadian rhythm, small sample of material, as well as measurement of cytokines in blood serum samples, rather than in the synovial fluid of patients, can lead to wide variability in the results obtained. Nevertheless, the presence of a strong correlation between the parameters, as well as the selection of patients according to the criterion of low variability of clinical signs of the metabolic syndrome (BMI and WC) allow us to state with high certainty the presence of multifactorial metabolic disorders in patients with gout.

In our study, an increase in the titer of IL-6 and, to a lesser extent, IL-18, was accompanied by more pronounced indicators of dyslipidemia and clinical manifestations of gouty arthritis. Available from Tsai et al., 2008, Yang W.H. et al., 2013 that leptin-induced dysregulation of IL-6 and its receptors in gout leads to the development of inflammation along the monocytic pathway, which leads to a more pronounced local inflammatory response and damage to the articular cartilage and periarticular structures. In addition, IL-6 correlates with an increase in acute phase parameters, more frequent cardiovascular complications and CVD mortality both in patients with gout and rheumatoid arthritis and in the general population [24–25]. IL-18, as previously stated, is a pro-inflammatory and immunoregulatory cytokine that is produced by NLRP3 inflammasomes by activating caspase-1. In addition to the interferon-stimulating function, IL-18, together with IL-23, activates T-helper type 17 (Th17) with the release of IL-17A and its accumulation in the synovial fluid and maintaining the inflammatory cascade. The relationship of IL-18 with hyperuricemia and its direct role in the course of gout is poorly understood, but according to our data, the titer of IL-18 is maintained at a high level in the period between attacks of gout and correlates with dyslipidemia in patients with frequent

relapses of gouty arthritis. It should be especially noted that an increase in the activity of IL-1β and its production is manifested at the beginning of an attack of gouty arthritis, followed by a sharp decrease, which could be the reason for the low levels of IL-1β in the subjects during the period between attacks and in individuals with asymptomatic hyperuricemia [8, 11].

Conclusions. The "primary" and exclusive role of hyperuricemia in the development of dyslipidemia, metabolic syndrome and cardiovascular disorders in patients with gout was not confirmed by the results of a correlation analysis with the main markers of inflammation and cytokine profile indicators. The main indicators of the lipid profile in patients with gout - cholesterol, LDL-C, VLDL-C and the associated CA indicator are significantly increased, while HDL is significantly reduced in patients in the interictal period of gout. In our study, an increase in the titer of IL-6 and, to a lesser extent, IL-18, was accompanied by more pronounced indicators of dyslipidemia and clinical manifestations of gouty arthritis.

At the moment, the molecular mechanisms underlying the relationship between UA, components of the lipid spectrum, the inflammatory cascade and their influence on the development of cardiovascular disorders, insulin resistance and worsening prognosis in patients with gout, as well as the possible protective role of individual cytokines, require further study, since, of course, early detection of metabolic changes and their complex correction have a positive effect on the course of the disease and reduce the risk of possible fatal complications.

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