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Dyslipidaemia and Cytokine Profile in Patients with Gout: The Role of IL-6, IL-18 and Hyperuricemia in the Development of Metabolic Disorders

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

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 an important for the search of therapeutic targets.

Objective: Investigation of the relationship between features of dyslipidaemia and immunological changes in patients with tophaceous gout and asymptomatic hyperuricemia.

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

Results: Values of UA have positively correlated with the number of affected joints (r=0.64, p=0.058), presence of tophi (r=0.73, p=0.042), glycaemic level (r=0.74; p=0.038). An increase of TC to 11.85%, LDL to 22.51%, VLDL to 21.43% and a decrease of HDL to 20.9% in patients with gout was observed. AR was higher in the group of patients with gout to 25.8% (p=0.0088). An

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increase of the production of cytokines IL-6 (p=0.0012) and IL-18 (p=0.0008) was observed in patients with gout whose level of UA was above 0.420 mmol/l. There was no significant increase of IL-1β (+0.36, p=0.0154), 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). Strong correlation was shown in the 1st group between IL-6 and AR (r=0.762, p=0.0018), IL-18 and AR (r=0.766; p=0.0052). Correlation between IL-6 and AR was weaker (r=0.292, p=0.0127), as well as a weak negative correlation was observed in the 2nd group between IL-18 and AR (r=-0.366, p=0.0049).

Conclusion: The exceptional role of hyperuricemia in the development of dyslipidaemia 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 features of dyslipidaemia and clinical manifestations of gouty arthritis.

Keywords: Gout; hyperuricemia; dyslipidaemia; interleukins; cytokine profile.

1. INTRODUCTION

Gout is a chronic inflammatory disease with deterioration of the purine metabolism, is known as the most common cause of inflammatory arthritis in men older than 40 years. The incidence of gout has increased over the past decade (up to 1-6% in developed countries) and continues to grow steadily with tense epidemiological situation by non-infectious diseases, such as metabolic syndrome, essential hypertension (EH), coronary heart disease (CHD), 2 type of diabetes mellitus and their complications [1-4]. Current evidential base of gout has proved that, gout is an autoimmune inflammatory disease. The main characteristic feature of this disease is the activation of innate immune response against the crystals of monosodium urate (MSU) in various tissues [2-4].

Martinon F. et al. in 2002 experimentally confirmed that the presence of the crystals of the uric acid (UA) causes oligomerization and dysfunctional activity of specific macromolecules called inflammasomes NLRP3 accompanied by hyperactivity of proinflammatory enzyme - caspase-1. This process causes increased secretion of inflammatory cytokines IL-1β and IL-18. These cytokines has belonged to the same family of cytokine, in turn, trigger an inflammatory cascade, causing activation of the endothelium and leukocytes pool accumulation [5,6]. It is assumed that the main cytokines with secondary participation in this process are IL-4 (recruitment and activation of neutrophils), IL-6 (maintenance of the inflammatory process, direct damage to connective tissue) and TNFα (proinflammatory activation, maturation and enhancing of transformation of monocytes to macrophages) [7]. Studies by Martin WJ, et al. [7], Conforti-Andreoni C, et al. [8] and others described quite extensive information about role of macromolecules, induced by salts of MSU and involved in the activation of innate immunity, which associated with overproduction of IL-1β, IL-6 and IL-17A [5–8].

Proteomic and immune histochemical studies *in vitro* have revealed that crystals of MSU have a direct proinflammatory effect, inducing the production of cytokines by recruiting of family of toll-like receptors and several NLRP3 inflammasomes into the inflammatory cascade. There is also evidence on the role of complex myeloid-associated MRP8/MRP14 proteins, also known as calgranulin A/B (S100A8/A9), which is the agonist of toll-like receptors TLR-4, increasing the risk of cardiovascular complications and 2 type of diabetes mellitus in patients with hyperuricemia and development of non-alcoholic fatty disease of liver (NAFDL) [9,10]. In addition, crystals of MSU are responsible for induction of cytosole protein named cryopirin NALP3, the basic component of proinflammatory caspase-1-initiated inflammasomes, launching the production of active cytokines IL-1β,IL-6,IL-8, IL-18, etc. [11]. These data suggest the presence of target biomarkers of inflammation in patients with gout, contributing not only to the primary pathogenesis of gouty arthritis, but also to the development of comorbid states.

However, in recent years several researchers consider hyperuricemia (HU) as a metabolic disorder occurring by gout, not only as an obligatory factor involved in the development of nephropathy in patients with gout, but also as an independent predictor of atherosclerosis and cardiovascular mortality.

Krishnan E, et al. [12] have conducted a 17-year-study (1991-2008) of mortality from cardiovascular diseases (CVD) among middle-aged male patients with gout. The study has revealed that gouty arthritis, accompanied by increased levels of UA has increased risk of death from CVD [12]. However, as most of the researches at that time, HU was considered as a by-product, i.e. the collateral factor aggravating the generally accepted risk factors — arterial hypertension (AH), renal failure, insulin resistance and obesity [13]. However, consideration of HU, which isolated from gout, has increased the conceptualization of the role of HU and its priority in cardiovascular and hepatic lesions. The study of Zhang J, et al. [14] has involved 324 male respondents revealed a positive correlation between AH and hyperuricemia, namely increase of systolic AP to 27 mm hg with elevation of concentration of UA to each 1.0 mg/dl. From recent studies of meta-analysis by Jaruvongvanich V et al. [15] and 5 observational studies have involved 777 patients. They has clearly demonstrated a significantly increased risk of CVD, and histologically confirmed damage of liver in patients with HU.

Based of the above information, a clear conception of the correlation of immunological and biochemical mechanisms of disease with clinical changes, as well as priority of hyperuricemia in comorbid conditions of patients with gout are necessary to determine the effective therapeutic targets to the pathological process in gout, and correction of existing metabolic disorders.

2. OBJECTIVE

The objective of our research is study of the correlation of values of dyslipidaemia with immunological changes in patients with tophaceous gout and asymptomatic hyperuricemia.

3. PATIENTS AND METHODS

The study has included 85 men, who admitted to the department of rheumatology and outpatient department of specialized treatment course in the 1st Clinic of Tashkent Medical Academy from April 2014 to April 2017. Patiens were divided into 2 groups.

1st group (main) has included 49 patients with clinically verified diagnosis of primary chronic gout by criteria of Wallace S.L. (1977) [3]. Average age of the patients was 57.21±6.14 years, initial age of gouty arthritis was 42.74±8.12 years (from 34 to 55 years), average duration of disease at the time of reference to the doctor was 4.7 (3.0–10.0) years. Rheumatologist consulted 23 (46.94%) patients in the first 5 years of the disease. All patients of the 1st group were examined in the intercritical period of gout. Tophaceous gout was diagnosed in 27 (55.10%) cases, gout without tophi in 22 (44.90%) cases. An average number of the affected joints was 5.5 (1.0–12.0) joints. Frequency of acute conditions was 2.52 (1.0–5.0), attacks >3 per year were observed in 25 (51.02%) patients.

More frequent intake of uricosuric drugs (allopurinol in dose of 100-300 mg/day, febuxostat in dose of 80-120 mg/day) according to indications, as well as glucocorticosteroids predominantly with arthralgia, resistant to nonsteroidal anti-inflammatory drugs was indicated during intercritical period of gouty arthritis (Table 1). Intake of those medications for a period of immunological and biochemical studies was suspended in order to obtain reliable results. 29 (59.18%) patients received aspirin in dose of 75-150 mg/day, 4 (8.16%) patients — thiazide diuretics (indapamide 2.5 mg/day), 16 (32,65%) patients — combined antihypertensive drugs (indapamide + amlodipine + perindopril in dosages of 5 mg+ 2.5 mg+10 mg and 5 mg+1.25 mg+5 mg) as a maintenance therapy.

2nd group (comparison) has included 36 male patients with asymptomatic hyperuricemia (not accompanied by the presence of arthritis, deformed joints, tophi at the moment of examination) as a control group. 26 (72.22%) patients in this group were administered aspirin in dose of 75-150 mg/day, 6 (16,6%) patients — thiazide diuretics, 4 (11,1%) — loop diuretics (furosemide (lasix) up to 80 mg/day) as maintenance therapy.

Patients in main and control group were elected with reference by clinical parameters of the presence of metabolic syndrome with concordant parametric data (weight, body mass index (BMI), waist circumference (WC)). The divergence of parametric data has not exceed 4.0%: in the 1st group BMI has averaged to 28.2±4.3kg/m^2, this value has averaged to 27.9±4.6 kg/m^2 in 2nd group. WC was 92.4±2.1 cm in patients with gout, and 94.6±1.6 cm in the control group, respectively.

Table 1. Phenotypic and clinical characteristics of the studied groups

	Patients with gout (n = 49)	Patients with asymptomatic hyperuricemia (n = 36)
Age, years	57.21±6.14	54.2±8.22
Duration of the disease, years	4.7±1.5	-
Frequency of exacerbations	2.52±0.73	-
index of body mass, kg/m^2	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 disease (%)*	12 (24.49)	8 (22.22)
Chronic kidney disease (%)**	7 (14.29)	4 (11.11)
Non-alcoholic fatty disease of liver (%)	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, impairment of peripheral vessels, arrhythmia, coronary heart disease and/or heart failure. ** Glomerular filtering rate lower than 60 ml/min*

Exclusionary criteria to the recruitment for study were the presence of chronic foci of infection and active infections. Also any admission of hypolipidemic (statins, fibrates, niacin containing), antibacterial, antiviral, antifungal and antiprotozoal drugs, prebiotic and probiotic supplements were excluded throughout the study period.

All patients were tested by UA, CRP levels, fasting glycaemia and lipid spectrum. Lipid content in venous blood was determined by the photo colorimetric method on Vitros SYSTEM Chemistry DT 60 (Austria) by biochemical analyzer. Optimal considered blood level of total cholesterol (TC) was <5.2 mmol/l (<200 mg%), triglycerides (TG) level <1.7 mmol/l (<150 mg%). High density lipoprotein (HDL) level was determined in the cell culture supernatant after precipitation of the lipoproteins of other classes by dextran sulphate sodium. Levels of low density lipoprotein (LDL), very low density lipoprotein (VLDL) were counted in accordance with formula of Friedwald W., distribution of TC between atherogenic and antiatherogenic lipoproteins was determined using the atherogenicity ratio (AR), represented by formula [TC - HDL/HDL]. ALT, AST, urea, creatinine, total protein levels in blood was determined using SF-46 spectrophotometer (Russia). Determination of uric acid in serum was conducted using the reaction with phosphoric tungstic reagent.

Concentrations of cytokines: interleukin-1β (IL-1β), tumour 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 with solid-phase immunosorbent analysis were tested in all 85 selected patients in both groups by using automated Immulite 2000XPi (Germany) analyser.

Statistical analysis was performed using Open Epi 3.03 software package (Centres for Disease Control and Prevention, United States, 2014). The results were presented as medians and averages of quadratic deviation (M±SD) for quantitative values. In the course of statistical data processing descriptive statistical methods were used for comparing two independent groups — criteria of Mann-Whitney, to assess the significance of the values changes and comparing correlation with metabolic rates a non-parametric Wilcoxon T-test. 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 interval of confidence limits.

4. RESULTS OF THE STUDY

Studied features of hyperuricemia, glycaemia and lipid profile parameters are listed in Table 2. Level of UA in patients with gout has ranged from 0.357 to 0.760 mmol/l (average 0.564±0.098 mmol/l), values were distributed with lower threshold from 0.426 mmol/l to 0.615 mmol/l in the group of patients with asymptomatic hyperuricemia, however they have indicated a lower average level 0.462±0.036 mmol/l,

Table 2. Levels of uric acid and parameters of lipid profile (M±SD)

Score	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, 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 ratio	4.831 ± 0.072	3.576 ± 0.098*

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

i.e. level of UA was significantly (p=0.008; <0.01) lower to 14.04% in comparison with the main group.

Level of UA has reliably correlated with more severe course of gout in the main group. Higher values of UA have led to increased frequency and duration of exacerbations. It is necessary to point out that in 12 cases of gout, patients have marked protracted exacerbations (over 4 weeks), level of UA was recorded above 0.5 mmol/l (range 0.512–0.760 mmol/l; median Me=0.574 mmol/l). The number of affected joints has increased with level of UA (correlation coefficient r=0.64; p=0.058). Furthermore, level of UA in blood serum was significantly higher in the presence of tophi in patients with recurrent gouty arthritis (r=0.73; p=0.042).

Disturbance of metabolism of carbohydrate was assessed by the symptoms of fasting hyperglycaemia. Levels of glucose in blood were higher in patients with asymptomatic hyperuricemia, and averaged to 6.080±0.025 mmol/l, while in the main group average value was 5.873±0.081 mmol/l, which apparently reflected the primacy of glucose tolerance violation and insulin resistance in combination with the metabolic syndrome. Level of hyperuricemia among this category of patients positively correlated with the level of glycaemia (r=0.74; p=0.038).

Values of lipid spectrum have tended to dyslipidaemia and increased titre of atherogenic fractions in patients with intercritical period of gout. The content of TC in the main group was significantly higher compared to the control values (+0.818; p=0.0054). Differences in content of LDL were more pronounced compared to levels of TC (p=0.0067). As the content of VLDL in serum of patients with gout, a significant increase in titre of VLDL (above 1.04 mmol/l) was detected in 8 patients with gout and 4 patients in the control group. Average levels of VLDL have not exceed the upper limit of normal values 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) that appears to be associated with low rates of the clinical signs of metabolic syndrome in both groups (BMI 28.2±4.3 kg/m^2 in 1st group and 27.9±4.6 kg/m^2 in 2nd group; waist circumference was 92.4±2.1 cm, and 94.6±1.6 cm in 1st group and 2nd group, respectively).

At the same time, level of HDL was significantly reduced compared to the group with hyperuricemia without gouty arthritis (-0.281; p=0.0041), which reflects the reduced level of atheroprotective fractions in gout. The atherogenic ratio has averaged to 4.831±0.072 in 1st group and 3.576±0.098 in 2nd group. As can be seen from Table 2, figures of AR was higher in patients of 1st group than 2nd due to level of UA was higher in 1st group than patients of 2nd group. As a result, a positive correlation was connected between UA and AR, which is elevation of UA can be cause of increase of AR.

In summary, hypercholesterolemia in patients with gouty arthritis was associated with more prominent dyslipidaemia. Level of TC was increased in patients with gout to 11.85%, LDL to 22.51% and a decrease of HDL to 20.9% in lipid panel. Level of VLDL in the group of patients with gout was higher to 21.43%. Hypertriglyceridemia was observed in both groups, however level of TG was lower to 6.4% in the 1st group. Ultimately, the accuracy of this index was inadequate due to low-scale sampling and high variability of values (V=46.71%, p=0.097). The atherogenic ratio was higher in the group of patients with gout by 25.8% (p=0.0088).

Comparison of patients with asymptomatic hyperuricemia and patients with intercritical gout has demonstrated a significantly increased production of key pro-inflammatory cytokines such as IL-6 (p=0.0012) and IL-18 (p=0.0008). There was no expected and reliable elevation of IL-1β (+0.36; p=0.0154), TNF-α (+0.21; p=0.0944), as well as IL-4(+ 0.02; p=0.0028) produced by activated CD4+ T-lymphocytes. No positive correlation revealed between elevated levels of circulating IL-6 and indicators of inflammation of acute phase — C-reactive protein and erythrocyte sedimentation rate (r=0.26; p=0.0122). Values of TNF-α, IL-8, IL-10 have ranged widely and exceeded established confidence intervals, apparently owing to the absence of significant trend of prognostic indicators.

Both of the groups have not shown a linear relationship between uric acid and cytokines that relates to the manifestation of clinical manifestations of gout and co-morbid pathology with variable level of uric acid in the serum. However, IL-6 and IL-18 were significantly elevated in 1st group with levels of uric acid above the target value (0.420 mmol/l) in comparison with control group (p=0.0004). According to the results, a positive correlation was connected between UA and IL-6, IL-12, that is elevation of UA can be cause of increase of concentration of IL-6 and IL-12 (Table 3).

Evaluation of serum cytokines levels in relation to clinical data has showed a positive relationship between the titres of IL-6 and the presence of deformities of joints (p=0.0021), IL-6 and gouty tophi (p=0.0154), as well as IL-18 and ultrasonic characteristics of non-alcoholic fatty disease of liver (p=0.037) in the group of patients with gout. Since a group of surveyed with asymptomatic hyperuricemia has included a small number of patients (n=3) with levels of IL-8 above the detection limit, the reliability and degree of correlation for this cytokine were not assessed.

The relationship between the levels of various interleukin groups was defined during the study of profile of cytokine. The main group was characterized with an average correlation between the levels of IL-6 and IL-18 (r 0.61; p=0.0233), as well as a weak correlation was detected between IL-18 and IL-1β (r=0.27; p=0.012).

Based on the obtained results, as well as data of literature, it was assumed that increase of IL-6 and IL-18 titres in patients with gout is pathognomonic for this disease. Dependencies were analysed in these interleukins with most representative indicator of lipid spectrum, i.e. atherogenic ratio (coefficient).

For the results in 1st group, patients with high levels of IL-6 had reliably higher atherogenic ratio (r=0.762; p=0.0018) (Fig. 1, A), which reflect the more pronounced deviations of lipid profile with high titres of IL-6. In 2nd group correlation between IL-6 and AR was much weaker (r=0.292; p=0.0127) and, despite the positive correlation, it has not reflect clearly defined association between those parameters (Fig. 1, B).

Results of the values of IL-18 were similar with IL-6 in the main group, a strong correlation was demonstrated between IL-18 and AR (r=0.766; p=0.0052) (Fig. 2, A). Only 7 of 49 patients in the group of patients with gout had AR below 3.0 mmol/l, with a range of values of IL-18 equal to 179.15—381.0 pg/ml. There was a weak negative relationship between the titres of IL-18 and AR in comparison group (r=-0.366; p=0.0049) (Fig. 2, B), which during the detailed

Table 3. Cytokine profile of the studied groups according to enzyme immune analysis

Index, pg/ml	Patients with 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 control and the compared groups. ^ p>0.05 — reliability of differences between the groups below the set limit*

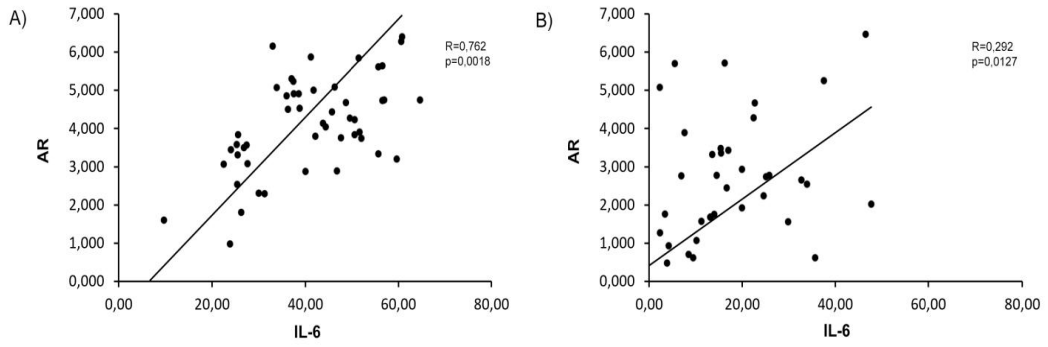

Fig. 1. Correlation charts of IL-6 and atherogenic ratios (AR) in main (a) and control (b) groups. R — correlation coefficient, differences are valid on p<0.05

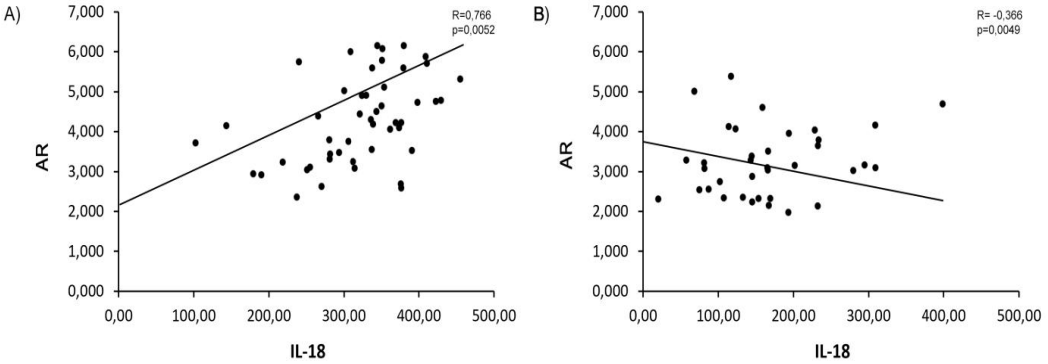

Fig. 2. Correlation charts of IL-18 and atherogenic ratios (AR) in main (a) and control (b) groups. R — correlation coefficient, differences are valid on p<0.05

parsing of clinical data of the patients in this group can be explained by the increase of IL-18 in 6 patients on the background of recent respiratory viral infections and relatively small sampling.

5. DISCUSSION

In 1991, Pascual E, et al. [16] have revealed that crystals of MSU persist in the synovial fluid, supporting the inflammatory background in the intercritical period of gout. TNF-α and other proinflammatory cytokines, in turn, induce a release of free radicals of oxygen by macrophages, and inhibit antioxidant enzymes, such as paraoxonase1 (PON1) and contribute to the transformation of HDL to oxidized proinflammatory HDL. Proinflammatory HDL, despite the high serum titre, unable to oppose the transport of cholesterol and loses its antioxidant properties, which in turn leads to the accumulation of oxidized LDL and VLDL [8,16]. Further, in researches of Kappelle PJ, et al. [17] Jiang X, et al. [18], it was shown that elevated oxidized LDL in plasma leads to higher titre of IL-6, IL-8 and TNF-α, which encloses the "vicious circle" of oxidative stress and supports the inflammatory process.

Based on the obtained results in our study, the main indicators of lipid profile in patients with gout, particularly TC, LDL, VLDL and AR were increased significantly, while HDL has reduced reliably in patients with intercritical period of gout that reflects the lipid profile, typical of the IV type of dyslipidaemia. Tsutsumi Z, et al. [19] confirm these data, Meek IL et al. [20] in relation to dyslipidaemia in patients with gout. However, as noted in those investigations, the high concentration of LDL, especially their oxidized fractions correlate with levels of proinflammatory mediators IL-1β, IL-6 and TNF-α, which elevation occurs in patients during periods of exacerbation of gouty arthritis. While in the acute inflammatory phase, these cytokines are responsible for lowering triglycerides and lipoprotein fractions, which increase further after relief of the episode of acute inflammation [18–20]. This phenomenon

apparently led to higher parameters of lipid profile in patients with intercritical period of gout with relatively moderate values of TNF-α, IL-1β, IL-4 in our study.

Conversely, a meta-analysis of large-scale clinical trials (Afzali A et al. [22]; Viazzi F et al. 2014; Lonardo A. [21] etc.), as well as a number of comparative *in vivo* studies indicate the association of hyperuricemia with dyslipidaemia, arterial hypertension, obesity, metabolic syndrome, and recent studies — with the development of histologically confirmed NAFLD in persons with persistently increased levels of UA [17,21,22]. Likewise, in animal models, it was found that hyperuricemia is capable of triggering the inflammatory cascade mainly by improving production of monocytic chemotactic protein-1 (MCP-1) and suppressive action onadiponectin (GBP-28), known as anti-inflammatory and antiatherogenic hormone. It was also demonstrated that the increased level of UA in hepatocytes lead to mitochondrial violations and accelerated lipogenesis [18,23].

In various papers based on immunological researches, generally there are expressed variations in results and their interpretation. Variable sampling techniques, low standardization of commercial serum sets viable for a research, circadian rhythm, a small sampling of subjects, as well as the measurement of cytokines in samples of serum, rather than in the synovial fluid of the patients can lead to a wide variability of results. However, a strong correlation between values, as well as the selection of patients based on low variability of clinical signs of metabolic syndrome (BMI and WC) permits a high confidence of the availability of multifactor nature of metabolic disorders in patients with gout.

In our study, increase of IL-6 and, to a lesser extent, IL-18, was accompanied by more expressed values of dyslipidaemia and clinical manifestations of gouty arthritis. There are data by Tsai et al. [24], Yang WH. et al. [25], 2013 that leptin-induced dysregulation of IL-6 and its receptors in gout leads to the development of monocytic inflammatory pathway that leads to more expressed local inflammatory reaction and damage to the articular cartilage and articular structures. In addition, IL-6 correlates with elevated acute-phase parameters, more frequent cardiovascular complications and mortality from CVD as in patients with gout and rheumatoid arthritis, as well as in the general population. IL-18, as previously stated, is proinflammatory and immune regulatory cytokine, which is produced by NLRP3 inflammasomes by activation of caspase-1. In addition to the interferon stimulating functions, IL-18, conjointly with IL-23, activates T-helper type 17 (Th17) leukocytes with a release of IL-17A and its accumulation in the synovial fluid and maintaining the inflammatory cascade. Association of IL-18 with hyperuricemia and its direct role during in gout was not studied thoroughly, but our data suggests that IL-18 persists at a high level in the intercritical period of gout and correlates with dyslipidaemia in patients with frequent recurrences of gouty arthritis. It should be emphasized that the increase in activity of IL-1β and its production are evident at the onset of gouty arthritis attack, with its subsequent rapid decline which could serve as the reason of low values of IL-1β in the intercritical period and in subjects with asymptomatic hyperuricemia [8,11].

6. CONCLUSION

"Primacy" and the exclusive role of hyperuricemia in the development of dyslipidaemia, metabolic syndrome and cardiovascular disorders in patients with gout has not been confirmed by the results of correlation analysis with key markers of inflammation and cytokine profile parameters. Main indexes of lipid profile in patients with gout — TC, LDL, VLDL and its associated index of AR are considerably increased, whereas HDL has reliably reduced in patients with intercritical period of gout. In our study, increase of IL-6 and, to a lesser extent, IL-18, was accompanied by more expressed values of dyslipidaemia and clinical manifestations of gouty arthritis.

At the moment, molecular mechanisms underlying the correlation of UA, components of lipid spectrum, inflammatory cascade and their effect on the development of cardiovascular disorders, insulin resistance and deterioration of prognosis in patients with gout, as well as possible protective role of cytokines requires further investigation, whereas early detection of metabolic disorders and their complex correction favourably changes the course of the disease, and reduce the risk of fatal complications.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

All experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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