FEATURES OF IMPACT OF HYPERFERRITINEMIA IN COMBINATION WITH HYPERURICEMIA ON THE COURSE OF GOUT

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Ключові слова: подагра, гіперферритинемія, артеріальна гіпертензія, ферритин, сечова кислота крові, метаболізм заліза

Ключевые слова: подагра, гиперферритинемия, артериальная гипертензия, ферритин, мочевая кислота крови, метаболизм железа
The prevalence of gout has recently increased in all countries of the world, reaching >6% in the population, with gouty arthritis remaining in the position of the most common type of arthritis among men [8].

According to modern ideas, the basis of inflammation are changes in homeostasis of iron. Serum ferritin is a biomarker of the inflammatory process. Uric acid acts as an iron chelator, on the one hand, modeling the activity of xanthine oxidase, and on the other – affecting its synthesis. According to the NHANES (USA) study, ferritin is positively associated with uric acid, and high ferritin levels increase the risk of hyperuricemia [7, 9]. It is the combination of such components that form the complex of uric acid iron crystals, through the activation of granular cells and the complement system contributes to the development of a gout exacerbation. Increase in
serum ferritin is today interpreted solely as a sign of iron overload. Ferritin is not only a depot of iron, it is also a positive protein in the acute phase of inflammation. A number of authors point out that ferritin is a marker of even a hyper-inflammatory reaction in which its level rapidly increases in the short time. The so-called hemophagocytic syndrome (HPS) associated with hyperferritinemia even threatens patients' lives. Based on the above, it is reported that serum ferritin is a sufficiently sensitive and specific marker of inflammation. Due to the cytokine storm and uncontrolled activation conditions, the capture of iron by macrophages is increased and its export to erythropoiesis is impaired. Activation of macrophages and impaired iron export from it is a leading factor in the inflammatory process. Such a massive immune response contributes to the loss of cytotoxicity by T-lymphocytes. Therefore, it should be noted that macrophages initiate the inflammation process, both in the joint cavity and phagocytate monosodium urate crystals (MSU) and participate in ferritin-MSU complexation. Macrophages then create a framework for the formation of specific proteins, so-called inflammasomes in the cytoplasm of the macrophage. Inflammasomes are a high molecular weight protein complex that triggers the mechanisms of transformation of inactive pro-interleukin-1β (pro-IL-1β) into biologically active IL-1β, which is subsequently released from the cell [1, 4].

It is known that iron is mainly a component of proteins, among which there are those that directly bind iron. The amount of iron released from the enterocytes into the bloodstream is regulated by enhancing or attenuating the synthesis of the protein apoferritin (ferritin containing no iron), which stores iron by transforming it into ferritin and retaining it internally in cells. When the iron enters the blood, its transport is carried out by the protein of the blood-transfervoın. An iron exchange regulator is hepcidin, which is capable of both blocking and enhancing iron homeostasis. Ferritin is involved in the acute phase of inflammation, even during the pre-immune response. The acute phase response is a complex defense that is aimed at a qualitative immune response. To effectively promote iron, cells of the reticuloendothelial system (KES) enhance ferritin synthesis, which is accompanied by the influence of pro-inflammatory cytokines, first of all, IL-1 and IL-6. Studies have shown that ferritin rich in the H-subunits plays a significant role in the acute phase response, as it is able to capture iron faster, than the more stable L-ferritin. It is the first protects that cells from radicals. On this basis, cells are able to regulate the amount of H-ferritin contained in them by secreting it into the plasma, thus getting rid of residues that lead to excessive iron uptake. It is possible that this is the main reason for the increase of plasma ferritin during the response in the outbreak of gouty arthritis. Prolonged circulation of proinflammatory cytokines leads to iron retention in RES cells and iron overload in ferritin composition. In this case, ferritin is gradually transformed into hemosiderin, which not only has a protective effect, but also damages the cells. The latter degrades very slowly, but at the same time binds iron firmly, breaking its secretion [5, 6, 10, 14].

In recent years, there has been an increasing interest in studying the mechanisms of iron metabolism in gout, which is accompanied by an increase in ferritin level, whose clinical and pathogenic significance has not been fully elucidated in gout. The role of uric acid and ferritin in the development of oxidative stress is being studied [15].

In tophus removed surgically, synovia and iron are detected in ionized form, which, in combination with MSU crystals, is a factor in exacerbation of gouty arthritis. The resulting iron-MSU complex leads to the activation and release of the cascade of proinflammatory cytokines, which are the main pathogenetic link of the inflammatory process in gout [11, 14].

The purpose of the study is to find out the frequency of development of hyperferritinemia in combination with hyperuricemia in patients with gout, to assess their pathogenetic significance and to outline the role in the development of joint syndrome, to identify informative prognostic criteria.

Materials and Methods of Research
The research was carried out at the clinical basis of the Department of Therapy, Cardiology and Family Medicine of Faculty of Postgraduate Education of the State Establishment "Dnipropevtovsk Medical Academy of Health Ministry of Ukraine" in the settings of the MNE "Center for primary health care N 4" of Kryvyi Rih City Council, and further examination was carried out in the Municipal Enterprise «Kryvyi Rih City Clinical Hospital N 2» of Kryvyi Rih City Council in the period from 2016 to 2018.

Permission was obtained from the Commission on Biomedical Ethics of the State Establishment “Dnipropevtovsk Medical Academy of Health Ministry of Ukraine” (protocol N 1 of January 16, 2017) the scientific research was approved, the work was in accordance with generally accepted standards of morality, the requirements of observance of rights, interests and personal dignity of research participants, there is no risk to research subjects while performing the work, laboratory and instrument research methods are generally accepted and the drugs to be used are approved.
72 patients with gout were examined. The first (main) group included 37 patients with gout with hyperuricemia combined with hyperferritinemia, whose average age was 55.9 (10.7) years. Group 2 (comparison group) included 35 patients with gout and hyperuricemia with normal levels of ferritin (average age – 52.8 (4.8) years). Group 3 (control) included 20 practically healthy individuals (average age 52.0 (2.9) years).

The average age of gout manifestation in group 1 was 49.6 (10.2) years (28 to 65 years). The duration of the disease ranged from 1 to 17 years (median – 6.0 (4.0; 8.0) years). In patients in group 2, gout developed at the age of 47.2 (8.7) years (36 to 65 years), and the median of disease duration was 4.0 (2.0; 6.0) years (1 to 14 years).

The diagnosis of gout was established according to the criteria of the American College of Rheumatology and the European Anti-rheumatic League (2015) [12]. The diagnosis of hypertension was established in accordance with the order of the Ministry of Health of Ukraine N 384 dated May 24, 2012, in accordance with the recommendations of the Ukrainian Association of Cardiology and the clinical recommendations of the European Society of Hypertension and the European Society of Cardiology (2018) [3, 13]. Clinical and anamnestic data of all patients were taken, an analysis of the previous medical documentation, laboratory and instrumental research methods was carried out.

Main inclusion criteria: patients with gout and hyperuricemia (blood uric acid level for male >420.0 μmol/L, for female >360.0 μmol/L) combined with hyperferritinemia (ferritin level >400.0 ng/mL) who gave informed consent to participate in the study; patients with gout and normal levels of ferritin who gave informed consent to participate in the study; patients aged 30-65 years.

Exclusion criteria: patients who did not give consent to participate in the study; patients who abuse alcohol or narcotic drugs; patients with cancer, psychiatric and rheumatologic diseases, diseases of the blood system, other crystalline arthropathies; cardiac insufficiency of IIB-III stage, functional class IV, chronic kidney disease of IV-V stage; viral hepatitis, tuberculosis, HIV-infected patients.

All patients with gout were given allopurinol at a starting dose of 100 mg per day, followed by titration of the dose once a month and determination of blood uric acid level to reach the target blood uric acid level <360.0 μmol/L. In exceeding the reference levels of ferritin >400.0 ng/mL deferoxamine was administered alternate days 500 mg per day to reach the target level of ferritin within 100.0-200.0 ng/mL.

Determination of the level of ferritin was carried out by immunochemical method with electrochemiluminescent detection, using the Cobas 6000 analyzer and the Roche Diagnostics test system (Switzerland). Determination of blood uric acid concentration was carried out by means of colorimetric analysis, urinary uric acid – by spectrophotometric method, SRP – by the immune enzyme method.

Methods of mathematic-statistical analysis of research materials were used: verification of normal distribution of quantitative indicators using the Shapiro-Wilk test; assessment of the reliability of the difference in mean for quantitative attributes with the normal distribution according to the Student's t-test; an abnormal distribution Mann-Whitney (U) test for unrelated samples; the probability of the difference in relative indices using the Pearson Chi-Square (χ2) test, including the Yates correction for values of the index close to 0 or 100. Comparisons of the three independent groups were performed using the Kruskal-Wallis One-Way Analysis of Variance (nonparametric tests algorithms). A correlation analysis was carried out with the calculation of the Spearman's Rank Correlation Coefficient (ρ), multiple regression analysis.

Descriptive statistics results were presented in the form of mean (M) and standard deviation (SD) for values with normal distribution and in the form of median (Me) and interquartile range (Q25; Q75) for parameters with the distribution that differs from normal.

P-values of <0.05 were determined to represent statistical significance. The statistical analysis was carried out using the Microsoft Excel 2010, data analysis program AtteStat 12.0.5, and Statistica 6.1 (StatSoft Inc.).

RESULTS AND DISCUSSION

The duration of gout averaged 4.0 (2.5; 7.0) years, the age of disease debut was 48.4 (9.5) years, the number of exacerbations of gout per year – 5.0 (4.0; 5.0), the total number of affected joints – 5.5 (2.0; 12.0), the duration of the last exacerbation of gout over the last year – 16.0 (14.0; 17.0) days, the duration of arthritis – 15.0 (14.0; 16.0) days. The first sign of gout in 97.2% (70) of patients was a joint inflammation and in 2.8% (2) – renal colic. Articular pathology in 77.6% (56) cases debuted with arthritis of the first metatarsal joints, 15.2% (11) – of ankle, 4.2% (3) – of knee. The incidence of intermittent arthritis was 22.2% (16) and chronic – 77.8% (56). Peripheral tophus was found in 13.9% (10), bone – in 34.7% (25), metabolic syndrome was diagnosed in 93.1% (67) of observations.

The duration of hypertension in patients with gout was 6.0 (3.0; 9.0) years. Hypertension debut was 48.2 (46.0; 52.0) years. The number of
exacerbations of hypertension per year is 4.0 (3.0; 5.0). The average level of systolic blood pressure (SBP) was 145.0 (140.0; 150.0) mm Hg, diastolic blood pressure (DBP) 90.0 (87.5; 100.0) mm Hg. By stages of hypertension patients were divided as follows: stage I was registered in 7 (9.7%) patients, stage II – in 63 (87.5%), III – in 2 (2.8%) patients. 1 degree of hypertension was detected in 47 (65.3%) patients, 2 – in 20 (27.8%), 3 – in 5 (6.9%) patients.

Hyperuricemia at the time of examination >360 µmol/L was established in 81.9% (59) of cases, low uraturia (<2200 µmol/L) – in 19.4% (14), metabolic type of impaired purine metabolism was in 12.5% (9), renal – in 20.8% (15), mixed – in 66.7% (48).

### Table 1

| Indicator, units of measurement | Main group (n=37) | Comparison group (n=35) | Control group (n=20) | p |
|---------------------------------|------------------|------------------------|---------------------|---|
| Gender: male, n (%)            | 36 (97.3)        | 30 (85.7)               | 16 (80.0)           | p=0.09** |
| Age, years                     | 55.9 (10.7)      | 52.8 (4.8)              | 52.0 (2.9)          | p=0.11** |
| The clinical stage, n (%)      |                  |                        |                     |   |
| - acute gouty arthritis;       | 1 (2.7)          | 1 (2.9)                 |                     | p=0.97†† |
| - intermittent gouty arthritis;| 5 (13.5)         | 9 (25.7)                |                     | p=0.19†† |
| - chronic gouty arthritis;     | 24 (64.9)        | 22 (62.9)               |                     | p=0.86†† |
| - chronic tophaceous arthritis | 7 (18.9)         | 3 (8.6)                 |                     | p=0.20†† |
| Radiological stage of the disease, n (%) |  |                       |                     |   |
| - no changes                   | 4 (10.8)         | 6 (17.1)                |                     | p=0.65†† |
| - I                            | 9 (24.3)         | 17 (48.6)               |                     | p=0.03† |
| - II                           | 23 (62.2)        | 10 (28.6)               |                     | p=0.01† |
| - III                          | 1 (2.7)          | 2 (5.7)                 |                     | p=0.83†† |
| functional insufficiency of the joints, n (%) |  |                       |                     |   |
| - absent                        | 3 (8.1)          | 9 (25.7)                |                     | p=0.04† |
| - I                            | 19 (51.4)        | 22 (62.9)               |                     | p=0.41†† |
| - II                           | 15 (40.5)        | 4 (11.4)                |                     | p=0.03† |

Note: * – Significant difference between the main and control group, † – Significant difference between the main and comparison group, ‡ – Significant difference between the comparison and control group, ** – There is no significant difference between the main and control group, †† – There is no significant difference between the main and comparison group, ‡‡ – There is no significant difference between the comparison and control group.

In patients of group I (main), acute gouty arthritis was established in 1 (2.7%) patient, intermittent gouty arthritis – in 5 (13.5%), chronic gouty arthritis – in 24 (64.9%), chronic tophaceous arthritis – in 7 (18.9%), and in group II (comparison) – 1 (2.9%), 9 (25.7%), 22 (62.9%), 3 (8.6%), respectively, Table 1. In the radiological stage of the disease, patients in group I were divided as follows: no changes – 4 (10.8%), stage I – 9 (24.3%), II – 23 (62.2%), III – 1 (2.7%), and in group II – the following data: 6 (17.1%), 17 (48.6%), 10 (28.6%), 2 (5.7%), respectively. There was no functional insufficiency of the joints in 3 (8.1%), stage I – in 19 (51.4%), stage II – in 15 (40.5%) patients compared with patients with normal ferritin level – 9 (25.7%), 22 (62.9%), 4 (11.4%), respectively. That is, among the patients in the main group, there is a high proportion of patients with a more severe course of gout, as well as with marked changes in the radiograph and a higher degree of functional insufficiency of the joints than in the comparison group.

The general characteristics of the groups are shown in Table 2. The average level of blood uric acid was significantly different (p=0.0254) in the main group and the comparison group and amounted to 464.5 (122.5) µmol/L and 403.8 (403.8; 403.8), respectively. The value of ferritin in the main group was significantly higher 410.2 (356.2; 415.2), p<0.01) ng/mL, than in the comparison group 132.1 (20.5) ng/mL, as well as C-reactive protein values (hs-CRP) (p=0.0001) 8.2 (6.0; 8.2) and 5.8 (6.1) mg/L, respectively. Values of urine uric acid differed significantly (p=0.0028) in both groups and amounted to 2509.0 (630.6) µmol/L in the main group and 2408.5 (2193.0; 2469.0) µmol/L in the comparison group. It should be noted that statistically significant difference and lower values of laboratory parameters in the control group were
registered compared to the main group and patients with gout and normal ferritin level.

Patients with gout and high levels of ferritin, unlike patients with normal levels of ferritin, have the following clinical anamnestic signs: greater number of exacerbations of gout per year (p=0.002), duration of gout (p=0.008), duration of the last exacerbation of gout (p=0.005), duration of arthritis in exacerbation (p=0.003), total number of affected joints (p=0.03), pain intensity during exacerbation by scale VAS (p=0.03). There was no significant difference between the groups regarding the age of gout debut (p=0.25).

**Clinical and laboratory characteristics of patients in the main, control and comparison groups, M (SD), Me (25%; 75%)**

| Indicator, units of measurement | Main group (n=37) | Comparison group (n=35) | Control group (n=20) | p       |
|--------------------------------|------------------|-------------------------|----------------------|---------|
| Ferritin, ng/mL                | 410.2 (356.2; 415.2) | 132.1 (20.5) | 113.5 (60.4) | p<0.01*  |
|                                |                   |                         |                      | p<0.01†  |
|                                |                   |                         |                      | p=0.0002‡ |
| Blood uric acid, μmol/L        | 464.5 (122.5) | 403.8 (403.8; 403.8) | 281.9 (63.5) | p<0.01*  |
|                                |                   |                         |                      | p=0.0254†  |
|                                |                   |                         |                      | p<0.01‡  |
| Uric acid in urine, μmol/L     | 2509.0 (630.6) | 2408.5 (2193.0; 2469.0) | 2114.1 (547.2) | p=0.0002*  |
|                                |                   |                         |                      | p=0.0028†  |
|                                |                   |                         |                      | p=0.0003‡  |
| hs-CRP, mg/L                   | 8.2 (6.0; 8.2)  | 5.8 (6.1)               | 1.0 (0.0; 2.9) | p=0.01*  |
|                                |                   |                         |                      | p=0.0001†  |
|                                |                   |                         |                      | p=0.01‡  |
| The number of exacerbations of gout per year | 5.0 (5.0; 5.0) | 4.0 (4.0; 6.0) | - | p=0.04†  |
| Duration of gout, years        | 6.0 (4.0; 8.0)  | 4.0 (2.0; 6.0) | - | p=0.008‡  |
| Gout debut age, years          | 49.6 (10.2)      | 47.2 (8.7)              | -                    | p=0.25    |
| Duration of the last exacerbation of gout, days | 16.0 (16.0; 17.0) | 14.0 (12.0; 16.0) | - | p<0.01†  |
| Duration of arthritis with exacerbation, days | 15.0 (15.0; 16.0) | 14.0 (13.0; 16.0) | - | p=0.004†  |
| Total number of joints affected | 8.0 (4.0; 14.0) | 2.0 (2.0; 12.0) | - | p=0.03†  |
| Exacerbation by VAS scale, mm  | 41.0 (16.0)      | 30.0 (30.0; 40.0) | -                    | p=0.03†  |

Note: * – Significant difference between the main and control group, † – Significant difference between the main and comparison group, ‡ – Significant difference between the comparison and control group, †† – There is no significant difference between the main and comparison group.

A direct, moderate, significant correlation (r=0.30; p<0.05) was found in the main group between blood uric acid and ferritin, and a significant correlation was found between blood uric acid and duration of gout (r=0.41; p<0.05), total number of affected joints (r=0.35; p=0.03), severity of gout (r=0.36; p<0.05), as well as between the level of ferritin and the number of gout outbreaks (r=0.44; p<0.05).

We have analyzed the relationship between ferritin and hs-CRP in patients with gout. In group I, high levels of ferritin were accompanied by significantly higher levels of hs-CRP than in patients in group II. In our view, both hs-CRP and ferritin may participate in separate pathogenesis links in gout patients. However, ferritin and hs-CRP were not risk factors for hyperuricemia. Both levels were significantly elevated in patients with gout. Of course, the increase in the level of ferritin and hs-CRP can be explained by the development of chronic inflammatory process in gout, but recent studies indicate that the association of ferritin with uric acid and gout is independent of the level of hs-CRP [6].

Iron exchange rates and excessive deposition of MSU crystals affect the severity and form of gouty
arthritis, the nature of bone-destructive signs (including erosions) of articular syndrome, the presence of peripheral and bone tophus.

Exacerbation of gouty arthritis was accompanied by mono-articular lesions of foot joints (especially the first metatarsal joints) or ankle joints; rapid onset of severe pain (by VAS scale activity reaching values of varying severity) and swelling of the joints (within 24 hours), erythema, synovitis.

In the lesion of the first metatarsal foot joints in patients with gout accompanied by hyperferritinemia in combination with high levels of uric acid, according to ultrasound diagnostics of the joint, lesions of the surrounding soft tissues, synovitis, and in some patients – tophus were revealed. Half of the patients of group I and one third of group II reported the deposition of MSU crystals on the surface of the cartilage of the joint as a "double contour" sign.

The association between hyperferritinemia and hyperuricemia was accompanied by a more pronounced outbreak of gouty arthritis. It can be assumed that high level of ferritin not only enhances the formation of uric acid, but also promotes the crystallization of MSU. The latter is confirmed by the presence of MSU crystals in the synovial fluid aspirate, as well as by imaging diagnostic methods for finding the deposition of MSU crystals (ultrasound, dual-energy computed tomography - DECT).

Chronic tophaceous arthritis according to radiographic examination of the joints was characterized by the soft tissue compaction, the presence of erosion, periarticular deposition of MSU crystals. Tissue edema, granulomatous response to MSU crystals were located both intra- and extra-articularly.

In patients with gout the combination of hyperuricemia with hyperferritinemia is closely associated with the severity of joint syndrome (p<0.01), the degree of narrowing of the joints gaps (p<0.05), the severity of subchondral sclerosis (p<0.05), the development of erosions (p<0.05), which have prognostic significance as revealed by multiple regression analysis.

All patients with gout received allopurinol starting with a dose of 100 mg monthly, determining the level of blood uric acid and increasing the dose of allopurinol by 100 mg to reach the target level of blood uric acid <360 µmol/L. On average, reaching the target uric acid level in patients in the main group occurred in 4 (3; 4) months, and in the comparison group – in 3 months at an average dose of allopurinol 300 (268; 300) mg in both groups.

In exacerbations of gout, colchicine was administered at a starting dose of 1 mg on the first day, then 0.5 mg in hour, on day 2 – 0.5 mg three times a day. Supportive therapy for patients in remission was performed with colchicine at a preventive dose (0.5 mg per day) to reduce the risk of exacerbation.

Separate studies have shown possible random connections between iron and the frequency of gout outbreaks. It is suggested that even the exclusion of iron-rich food can help to prevent gout outbreaks [14].

Complex therapy for patients in both groups included antihypertensive drugs (Figure): angiotensin II receptor blocker and angiotensin-converting enzyme inhibitors: 18 (48.6%) received losartan and 19 (51.4%) – ramipril; beta-blockers: bisoprolol – 3 (8.1%), nebivolol – 2 (5.4%), carvedilol – 2 (5.4%); calcium channel blockers: amlodipine – 21 (56.8%), lercanidipine – 4 (10.8%); nonthiazide diuretics – indapamide 7 (18.9%). Acetylsalicylic acid was prescribed to 21 (56.8%) patients and clopidogrel – 2 (5.4%) patients as antithrombotic agents. All patients with gout were prescribed atorvastatin at a starting dose of 20 mg daily and subsequent dose titration (40, 60 mg) according to lipidograms. That is, the selected drug groups are in line with the recommendations of the European League Against Rheumatism (2016), i.e. patients with gout and comorbid hypertension were prescribed losartan and calcium antagonists, and in hyperlipidemia statins were given preference.

If the reference levels of ferritin >400.0 ng/mL are exceeded, the preparation of deferoxamine was administered 500 mg on alternate days to reach the target level of ferritin within 100.0-200.0 ng/mL. An analysis of treatment efficacy in patients with hyperferritinemia during a gout outbreak showed a significant improvement in the overall condition (halving the VAS pain intensity) after the first injection of deferoxamine. Course treatment with the use of the drug deferoxamine in the complex therapy of gouty arthritis among patients of group I (1500-2000 mg) reduced the serum ferritin level to the target level (100.0-200.0 ng/mL), and was more effective (reducing the period of joint syndrome to 7 days) than in patients in the comparison group (duration of joint syndrome – 14 days). At the same time, the visualization data were changing, namely the disappearance of the "double contour" sign according to the ultrasound data, which indicated a regression of changes related to the deposition of urate in the joints. In addition, ultrasound imaging clearly showed the disappearance of synovitis and resorption of doughy tophus by the 7th day. In the comparison group, this process was longer and affected the period of restoration of the functional state of the joints.
The main groups of antihypertensive drugs prescribed to the patients with gout

CONCLUSIONS

1. Hyperferritinemia in combination with hyperuricemia is found in 51.0% of patients with gout, significantly worsening the course of the inflammatory process. Patients with gout and high levels of ferritin, unlike patients with normal levels of ferritin, have the following clinical anamnestic signs: greater number of exacerbations of gout per year, duration of gout, and last exacerbation of arthritis, for total number of affected joints, pain intensity during exacerbation by scale VAS.

2. In patients with gout, the severity of the course and the form of gouty arthritis, which are determined according to imaging methods (erosion, peripheral and bone tophus, the sign of "double contour", the degree of narrowing of the joint gaps and the severity of subchondral sclerosis), have prognostic significance.

3. Increased levels of ferritin and hs-CRP in gout patients are factors that are involved in the development of inflammation but are not personally risk factors for hyperuricemia. The association of ferritin with blood uric acid in gout does not depend on the level of hs-CRP.

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