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Improvement of the psycho-emotional state and cytokine profile of patients with rheumatoid arthritis and hepatic steatosis after therapy with thioctic (lipoic) acid and methotrexate

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Abstract

Background. The social significance of such inflammatory diseases as rheumatoid arthritis is growing all over the world, which determines the need to find new ways to optimize the ongoing standard therapy.

Aim. Evaluation of the effect of combined use of thioctic (lipoic) acid with methotrexate in comparison with methotrexate and meloxicam therapy on the psycho-emotional state of patients with rheumatoid arthritis and hepatic steatosis.

Material and methods. The study included 60 women diagnosed with rheumatoid arthritis and hepatic steatosis. By the beginning of the observation, patients divided into two groups were comparable according to all criteria for inclusion in the study. The first group took methotrexate and thioctic (lipoic) acid, the second group — methotrexate and meloxicam daily for a month. The psycho-emotional state of the patients according to the Spielberger tests modified by Yu.L. Khanin and depression according to Beck were assessed. Determination of pro-inflammatory cytokines was carried out by enzyme immunoassay. The research results were subjected to statistical processing.

Results. An intergroup analysis showed that the use of thioctic acid and methotrexate led to a significant decrease in the level of anxiety in patients, in contrast to women taking methotrexate and meloxicam (the level of reactive anxiety decreased by 2.7 times compared with baseline data; p=0.03). It is also important to note the revealed correlation between the degree of decrease in the level of tumor necrosis factor α and the severity of anxiety 1 month after taking the cytostatic and the hepatoprotector (Kendal's Tay-b correlation coefficient, r=0.732, p=0.046).

Conclusion. The inclusion of thioctic (lipoic) acid in the basic therapy with methotrexate in patients with rheumatoid arthritis and hepatic steatosis improves their psycho-emotional state in the form of a decrease in anxiety-depressive spectrum disorders, practically normalizing the level of pro-inflammatory tumor necrosis factor α, the degree of reduction of which correlates with the degree of reduction in the level of anxiety.

Keywords: thioctic acid, rheumatoid arthritis, tumor necrosis factor α, psycho-emotional state.

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Background

The global significance of inflammatory diseases, such as rheumatoid arthritis (RA), is increasing, necessitating the search for new methods to optimize the current standard therapy [1]. The development of safe drug combinations to enhance the efficacy of RA therapy is a multifaceted process with numerous alternatives and overlapping pathways. In this regard, impacting only one of the targets of pathogenesis either does not produce a sufficient pharmacological effect or results in several side effects [2].

The prevalence of anxiety–depressive disorders in patients with RA and the antianxiety and antidepressant properties of thioctic acid that we previously identified in an animal experiment on an experimental model of RA (adjuvant arthritis) [3] served as a basis for evaluating the effect of thioctic acid on anxiety–depressive disorders in patients with RA.

RA is a rheumatic autoimmune disease that causes chronic erosive arthritis and systemic damage to internal organs. Patients with RA often experience chronic pain, limited daily activity, and a loss of ability to work and maintain social relationships. These issues can lead to changes in financial status and deterioration in quality of life [2]. Over the past decade, studies have established an association between RA and psychiatric disorders. Data show that more than 60% of patients

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with RA have been diagnosed with psychiatric disorders, with anxiety–depressive spectrum disorders being more prevalent than many other chronic somatic diseases [4].

Studying the clinical–pathogenetic relationships between RA and anxiety–depressive spectrum disorders in patients can help identify patterns, influence treatment tactics, and increase effectiveness.

Aim

This study aimed to assess the impact of combining thioctic (lipoic) acid with methotrexate compared with therapy with methotrexate and meloxicam on the psychoemotional state of patients with RA and hepatic steatosis.

Materials and methods

Data from 150 patients diagnosed with RA at the Republican Clinical Hospital (Kazan) between 2016 and 2017 were analyzed before treatment. The clinically randomized, simple blinded, continuous study included 60 women.

The inclusion criteria for the study are as follows:

– A confirmed diagnosis of RA according to the American College of Rheumatologists/European League Against Rheumatism RA Classification Criteria (2013) and Russian Clinical Guidelines for Rheumatology [2, 5];

– Signed informed consent for the study;

– Presence of concomitant liver pathology (steatosis) [6];

– Absence of allergic diseases;

– Unchanged therapy for comorbidities 6 months;

– Stable dose of methotrexate for 3 months.

This study randomized patients into two groups using the envelope method [7].

Group 1 consisted of women who received methotrexate at a mean dose of 10.3 ± 2.4 mg/week and thioctic (lipoic) acid at a daily dose of 150 mg (50 mg, three times a day) daily for 1 month as a hepatoprotector.

Group 2 consisted of patients who received methotrexate at a mean dose of 11.08 ± 2.2 mg/week and meloxicam at a mean daily dose of 9.5 ± 3.4 mg daily for 1 month.

The patients were similar in age, gender, and disease stage and had comparable severity and quantified clinical manifestations of joint syndrome (Table 1).

This study examined the psychoemotional state of patients with RA by assessing anxiety using the Spielberger Personality and Reactive Anxiety Self-Assessment Scale modified by Khanin [8, 9]. The term "personality anxiety" refers to a stable individual characteristic that reflects a certain level of anxious perception of a particular situation. Reactive anxiety is characterized by an emotional response to stressful situations. Patients categorized as highly anxious tend to perceive a threat to their well-being in various situations and react with a pronounced state of anxiety. The results, evaluated in scores, are interpreted as follows: up to 30 points indicate low anxiety, 31–45 points indicate moderate anxiety, and 46 points or more indicate high anxiety [8, 9].

This study used the Beck Depression Inventory [10] to identify the presence of depression. The results were interpreted as follows: 0–9 points indicate an absence of depressive symptoms, 10–15 points indicate mild depression (subdepression), 16–19 points indicate moderate depression, 20–29 points indicate marked depression (moderate severity), and 30–63 points indicate severe depression [10].

The levels of interleukin (IL)-1β and IL-6, as well as tumor necrosis factor α (TNFα), were determined using an enzyme immunoassay (ELISA-BEST Reagent Kit, Russia).

The results of the study were subjected to statistical processing. The data were presented as arithmetic mean values, considering the standard error of the mean value. The data distribution was evaluated using the Shapiro–Wilk criterion and presented graphically. Signs with normal distribution were expressed as M ± SD, whereas signs with non-normal distribution were expressed as Me [Q_1–Q_3]. The independent *t* test, Mann–Whitney and Wilcoxon criteria, and Kendall's tau-b correlation coefficient were used to test the statistical hypotheses at a critical level of significance of ≤0.05.

This study was approved by the local ethical committee of the Kazan State Medical University of the Ministry of Health of the Russian Federation on February 24, 2015 (Protocol No. 2).

Results

This study assessed the quantitative characteristics of personality and reactive anxiety in the context of anxiety using the Spielberger–Khanin questionnaire. In Group 1, the level of reactive anxiety was 57.8 ± 8.4 points and that of personal anxiety was 55.9 ± 8.6 points. In Group 2, the level of reactive anxiety was 55.1 ± 9.6 points and that of personal anxiety was 56.5 ± 9.9 points.

One month after therapy, patients in Group 1 who received methotrexate and thioctic acid showed a 2.7-fold decrease in reactive anxiety levels ($p = 0.03$) compared with the initial data, with levels amounting to 21.4 ± 5.3 points. In Group 2, patients who received methotrexate and meloxicam had reactive anxiety levels of 53.3 ± 7.6 points, which did not significantly differ from

Table 1. Clinical characteristics of patients with rheumatoid arthritis (RA)

Characteristics		Group 1 (n = 30)	Group 2 (n = 30)	p
Average age, years (M ± SD)		54,1±2,7	54,7±3,3	0,1
Average body weight, kg (M ± SD)		71,7±5,2	75,1±7,3	0,4
Average height, cm (M ± SD)		161,16±3,2	158,4±2,5	0,6
Average duration of RA, years (Me [Q_1–Q_3])		7 [6–8]	7 [6–8]	0,1
Seropositivity		28 (93,3%)	27 (90%)	0,5
Seronegativity		2 (6,7%)	3 (10%)	0,5
Presence of antibodies against cyclic citrullinated peptide		25 (83,3%)	24 (81%)	0,3
Clinical stage	Advanced	27 (90%)	26 (86,7%)	0,1
	Late	3 (10%)	4 (13,3%)	0,3
Degree of RA activity	II degree	28 (93,3%)	27 (90%)	0,1
	III degree	2 (6,7%)	3 (10%)	0,4
Radiologic stage	II degree	22 (73,3%)	25 (83,3%)	0,5
	III degree	8 (26,7%)	5 (16,7%)	0,1
Functional class	I	8 (26,6%)	5 (16,7%)	0,1
	II	17 (56,7%)	20 (66,6%)	0,3
	III	5 (16,7%)	5 (16,7%)	0,5
Disability		4 (13,3%)	2 (6,6%)	0,08
Average number of painful joints (Me [Q_1–Q_3])		6 [5–7]	6 [5–7]	0,5
Average number of swollen joints (Me [Q_1–Q_3])		4 [3–5]	4 [3–4]	0,5
Assessment of disease activity on a visual analog scale, mm (Me [Q_1–Q_3])		3 [3–4]	3,5 [3–4]	0,3
Average Disease Activity Score-28 index score (Me [Q_1–Q_3])		4,96 [4,82–5,07]	5,01 [4,9–5,11]	0,1

the pretherapy values. The data on anxiety levels related to personality after therapy showed no significant changes in either group and remained within the same range as before the study.

When analyzing the level of depression using Beck's questionnaire, both groups exhibited severe depression (medium severity), with a depression level of 20.9 ± 2.8 points in Group 1 and 21.9 ± 2.9 points in Group 2. Following therapy, the severity of depression in the group of women receiving methotrexate and thioctic acid decreased from marked to moderate in 73.5% of patients (p = 0.043 compared with the baseline), with a depression level of 18.3 ± 2.1 points. In the group treated with methotrexate and meloxicam, the level of depression did not differ significantly from the baseline and amounted to 21.5 ± 2.8 points (p = 0.082 compared with the baseline). After therapy, the combined use of methotrexate and thioctic acid led to a significant decrease in the concentration of TNFα in serum. The level of TNFα in this group was 6.49 ± 3.1 pg/mL, which was significantly lower than the initial value of 10.04 ± 5.7 pg/mL (normal value = 0–6 pg/mL). Furthermore, a correlation was detected between the degree of TNFα level reduction and anxiety levels in this group of patients (Kendall's tau-b correlation coefficient, r = 0.732, p = 0.046).

The levels of IL-1β and IL-6 did not show significant changes in either group during the study and remained within normal physiological values.

Discussion

Psychoemotional disorders in patients with RA are caused by disorders of the autonomic nervous system. Prolonged exposure to a pathological factor leads to strain, which can deplete the central and peripheral nervous system regulatory mechanisms. This disturbance of vegetative balance can cause changes in the psychosomatic state [11]. Vegetative disorders are usually associated with emotional and depressive disorders, with anxiety being the most common psychopathological syndrome associated with autonomic dysfunction [12]. Anxiety–depressive disorders can also exacerbate inflammation, affecting the course and outcome of RA and patient compliance with medical recommendations.

The high initial levels of anxiety and depression observed in both study groups can be attributed to psychological discomfort and anxious anticipation

of the future resulting from dissatisfaction with their current life situation.

The initial high value of the reactive anxiety indicator detected in the patients indicates pronounced psychoemotional stress. This indicator characterizes subjective emotional feelings, such as anxiety, concern, and nervousness about a situation.

Personality anxiety is a stable tendency to perceive various situations as threatening and to react to such situations with anxiety. The initial high level of personal anxiety indicates the formation of a stable character trait in patients characterized by constant anxiety.

Our findings are consistent with those of Lysenko, who showed that patients with RA and chronic pain syndrome exhibit high levels of personal and reactive anxiety, as well as pronounced depression [13]. The results of this study are also consistent with those of another scientific study, which determined that more severe joint destruction is associated with longer RA duration and anxiety–depressive syndrome [14].

The significant decrease in reactive anxiety observed in the group of patients with RA who received thioctic acid therapy, as opposed to the group treated with methotrexate and meloxicam, provides clinical evidence of the anxiolytic properties of thioctic acid. These properties were previously identified in experiments [3, 15, 16].

Research has shown that patients with chronic somatic diseases who also have anxiety–depressive spectrum disorders are three times more likely to be noncompliant with therapy [17]. The diagnosis of anxiety–depressive disorders can be challenging because of overlapping symptoms with RA, such as fatigue, decreased appetite and weight, insomnia, and motor limitations. Research indicates that the presence of depression in patients with RA under observation for 18 years leads to a twofold increase in the probability of premature death [18].

Following therapy, the severity of depression decreased from marked to moderate in 73.5% of patients receiving methotrexate and thioctic acid. However, therapy with methotrexate and meloxicam did not affect the severity of depression in women with RA.

The decrease in the severity of anxiety–depressive disorders with the inclusion of thioctic acid in RA therapy can be attributed to the improvement of brain metabolic processes. Thioctic acid inhibits lipid peroxidation and improves the transfer of acetate and fatty acids from the cytosol to the mitochondrial matrix for further oxidation by increasing the synthesis of coenzyme A [19]. Thioctic acid increases acetylcholine formation in the brain by activating choline acetyltransferase and increasing the production of acetyl coenzyme A. Moreover, thioctic acid reduces cerebral oxidative stress and the synthesis of inducible nitric oxide synthase, which serves as a basis for its neuroprotective efficacy [20, 21].

The treatment of patients with RA and hepatic steatosis using methotrexate and thioctic acid improved their emotional and psychoemotional states by reducing anxiety–depressive spectrum disorders and normalized the level of the proinflammatory cytokine TNFα. The degree of TNFα level reduction correlated with the degree of anxiety reduction. This circumstance indicated that thioctic acid effectively reduces the severity of anxiety–depressive disorders in patients with RA. These disorders develop as cytokine-dependent conditions in the long-term course of the disease and contribute to the effectiveness of therapy in general. Korshunov et al. reported that RA activity indices decrease during therapy when depression is absent or when it is corrected with antidepressants [22].

The use of the low-toxicity hepatoprotector thioctic (lipoic) acid in the complex therapy of RA can contribute to the optimization of therapy and the recovery of the psychoemotional state of patients with RA, considering the side effects of drugs, including antidepressants, used for RA treatment.

Conclusions

The addition of thioctic (lipoic) acid to the current standard therapy with methotrexate in patients with RA and hepatic steatosis has been shown to improve their psychoemotional state by reducing anxiety–depressive spectrum disorders. This improvement is associated with the normalization of the level of proinflammatory TNFα, which correlates with the degree of anxiety reduction.

Authors' contribution. A.N.G., collection and processing of the materials, statistical analysis of the results, and writing of the text; L.N.Z. and D.I.A., supervision of the work, conception and design of the study, discussion of the results, and editing of the article.

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