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Reduction of depressive symptoms among patients with inflammatory bowel disease and rheumatic diseases treated with biological therapy: a cross sectional study

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Abstract

Introduction. Previous studies suggest that one of the possible reasons of depression is the autoimmune inflammation that causes increased interleukins and cytokines levels and thus affects the mood and behavior.

Aims. To compare the depression and anxiety symptoms among the patients with chronic systemic diseases (inflammatory bowel diseases and rheumatic diseases) receiving biological therapy and patients receiving different medical treatment.

Methods. Quantitative cross-sectional study design was used. Instruments: Ulcerative colitis activity index, Crohn's disease activity index, the Hospital anxiety and depression scale (HADS) and the Visual Analogue Scale (VAS). Patients diagnosed with active inflammatory bowel disease or rheumatic disease and not using antidepressants were included into study. Participants were divided into an experimental group (receiving biological therapy treatments) and a control group (receiving treatments as usual).

Results. 132 patients' data were analyzed. The disease activity index was not significantly different between the experimental group and the control group (9,42 vs 11,45, p>0,05). The mean scores of the Hospital anxiety and depression scale were significantly different between the both groups (7,96 vs 13,68, p< .001), which indicates less depression symptoms in the experimental group. The mean anxiety and depression subscales scores were also significantly lower in the experimental group (anxiety subscale - 5,46 vs 9,39, p< 0.001; depression subscale - 2,44 vs 3,91, p=0,001).

Conclusions. Participants treated with biological therapy experienced fewer depression symptoms than participants showing similar disease activity but receiving treatment as usual.

Keywords: Tumor necrosis factor - α inhibitor, IL-6 inhibitor, autoimmune depression, inflammatory bowel disease, rheumatic disease.

3. Introduction

Major depressive disorder (MDD) is a common mental disorder affecting 3 million people worldwide. Depression not only causes the burden of illness, but also has the high suicidal rates of almost 800 000 sufferers every year. By a considerable part of the medical society and the public MDD is perceived as the whole of the changes in the mood, emotions, cognitive functions and motivation. One of the most important MDD's etiopathogenetic theories is claimed to be the monoamines theory. (1) However, many more less known explanations for the development of MDD are described in various medical articles. Not only psychological factors, but also the everyday life stress, negative and shocking life events and the changes in the circadian rhythm function are claimed to contribute to the development of MDD (2,3). In spite of the possibility of the different depression etiopathogenesis among patients, the recommended treatment for major depression consists of cognitive behavioral therapy (CBT) or interpersonal therapy (IPT) and antidepressant medication. (4) This treatment does not necessarily work for every patient. Thus, in the past decade the question of the unknown depression pathogenetic ways and the other MDD treatment approaches as well as the individualized treatment possibilities emerged. The evidence of the associations between depression and inflammation began to build up and the theory of the individual anti- inflammatory treatment arose. (5) This theory has developed when the link between depression symptoms and the autoimmune inflammatory systemic diseases with the stormy reaction of cytokines was noted. (6) Such cytokines as tumor necrosis factor-α (TNF- α), interleukin 1 (IL-1) and interleukin 6 (IL-6) are the warning molecules that control the inflammatory response during the invasion of the pathogens. They are important not only in the gastrointestinal tract but also in the central nervous system (CNS). The acute inflammation instigates the increase of the cytokines and thus the brain is protected. However, during the chronic inflammation, the microglia produces excessive cytokines which disturb the circulation of the neurotransmitters in the brain and the integrity of the neurons. (7) The autoimmune inflammatory diseases with the increased concentrations of the bodily cytokines (such as rheumatic diseases, allergies, multiple sclerosis and inflammatory bowel diseases) are thought to be connected to the high occurrence of the neuropsychiatric symptoms. (6) HIV patients with the increased concentration of the cytokines in the body often experience such neuropsychiatric complications as depression and fatigue. (8) Furthermore, the increased concentration of the cytokines and the inflammatory phase proteins was observed in the patients with treatment resistant depression. (9)

This study investigates the difference of the major depression symptoms among the inflammatory bowel disease (Chron's disease and ulcerative colitis) and rheumatic diseases patients (rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis) receiving biological therapy medication and just as active diseased patients with no biological therapy and is claimed to contribute to the evidence of the depression and inflammation association.

The hypothesis of this study is that the patients treated with biological therapy experience less depressive and anxiety symptoms because of the biological therapy positive effects for such putative depression pathogenetic factors as tumor necrosis factor alpha.

4. Methods

4.1 Participants

One part of the study population consisted of inpatients of the Department of Hepatology and Gastroenterology of the Center of Vilnius University Hospital Santaros Clinics diagnosed with inflammatory bowel disease and the other part of population was comprised of outpatients with inflammatory bowel disease (Crohn's disease or/with ulcerative colitis). Criteria for inclusion of patients with inflammatory bowel disease:

- Confirmed diagnosis of Chron's disease or ulcerative colitis.
- At the time of inclusion, patient received uninterrupted treatment of biological therapy (TNF-α inhibitors) or non-biological treatment (non-steroidal inflammatory drugs, glucocorticoids and/or immunomodulators) for at least 12 weeks.
- Patient did not use antidepressants at the time of inclusion.
- Patient is 18-73 years old.
- Patient is fluent enough in Lithuanian, therefore understands the concept of the research.

Afterwards, the research was centered around the patients in the Center of Rheumatology of Vilnius University Santaros Clinics. During the research, inpatients and outpatients with rheumatological diseases (rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis) were investigated. Criteria of the inclusion of the patients with rheumatological conditions:

- Confirmed diagnosis of rheumatoid arthritis or psoriatic arthritis or ankylosing spondylitis.
- At the time of inclusion, patients received uninterrupted treatment of biological therapy (TNF-α inhibitors or IL-6 inhibitors) or non-biological treatment (non-steroidal inflammatory drugs, glucocorticoids and/or immunomodulators) for at least 12 weeks.
- Patient is 18-65 years old.
- Patient is fluent enough in Lithuanian, therefore understands the concept of the research.

The data was collected through an interview and by filling the questionnaires. The permission of the research in the Department of Hepatology and Gastroenterology of the Center of Vilnius University Hospital Santara Clinics was granted on 2017 October 25th by Vilnius University Ethics committee Clinic's Nr. 17CR-16278. The permission of the research in the Center of Rheumatology of Vilnius University Santaros Clinics was granted on 2019 November 7th by Vilnius University Santaro Clinic's Ethics committee Nr. 1R-3774.

The quantitative section study model was chosen and data was collected from 2017 September to 2019 March and also from 2019 October to 2021 March. The research did not take place during SARS-CoV2-19 lockdown during the pandemics from 2020 March 16th till June 14th and from 2020 November 4th until the end of January. The investigation was resumed during the internship and data was collected in February and March of 2021st. Instruments used to assess the subjects with the inflammatory bowel disease were ulcerative colitis activity index, Chron's disease activity index and Hospital Anxiety and Depression Scale (HADS). Instruments used to investigate patients with

rheumatic conditions were Visual disease's activity scale and HADS. Inpatients were interviewed in the hospital, outpatients were interviewed during the outpatient visit.

The subjects were divided according to their treatment. The study group was comprised of the patients diagnosed with inflammatory bowel disease or rheumatic disease and receiving biological therapy treatment (TNF-α inhibitors or IL-6 inhibitors). The control group consisted of patients diagnosed with inflammatory bowel disease or rheumatic disease and receiving non-steroidal inflammatory drugs, glucocorticoids and/or immunomodulators.

In total, 132 patients were analyzed (59,8% - women, 40,2% - men). 88 patients had the diagnosis of the inflammatory bowel diseases (57,9% - women, 42,1 % - men) and 44 patients were diagnosed with the rheumatological disease (63,6% - women, 36,4% - men). The age varied from 18 to 73 years old. Among patients with the inflammatory bowel disease, 33% comprised Chron's disease and 67% ulcerative colitis. Among patients with rheumatological conditions, 56,8% comprised rheumatoid arthritis, 13,6% psoriatic arthritis and 29,6% ankylosing spondylitis. The mean duration of the inflammatory bowel disease was 8,5 years (from 1 to 33 years) and the mean duration of the rheumatological disease was 10,8 years (from 1 to 41 years). The mean duration of the disease in general population was 9,3 years. 66 of the patients (50 %) received biological therapy and 66 of the patients (50%) received non-biological therapy. 44 patients (50%) diagnosed with inflammatory bowel disease received biological therapy and 44 (50%) of inflammatory bowel disease patients were treated with non-biological therapy. 22 patients (50%) of the rheumatic diseases group received biological treatment and 22 (50%) of rheumatic disease patients were treated with the non-biological medication.

Table 1. The characteristics of the inflammatory bowel disease population

	Study group	Control group
Sex		
Male	23 (52,27%)	14 (31,82%)
Female	21 (47,73%)	30 (68,18%)
Age	39,00 ± 12,87	32,09 ± 8,99
Ulcerative colitis	22 (50%)	37 (84,09%)
Chron's disease	22 (50%)	7 (16,01%)
Mean duration of inflammatory bowel disease	9,75 ± 5,94	7,30 ± 5,95

Table 2. The characteristics of the rheumatic disease population

	Study group	Control group
Sex		
Male	7 (31,82%)	9 (40,91%)
Female	15 (68,18%)	13 (59,09%)
Age	51,55 ± 8,60	49,36 ± 12,37
Rheumatoid arthritis	13 (59,09%)	12 (54,55%)
Ankylosing arthritis	7 (31,82%)	6 (27,27%)
Psoriatic arthritis	2 (9,09%)	4 (18,18%)
Mean duration of rheumatological disease	14,59 ± 10,96	7,05 ± 9,99

Table 3. The characteristics of general study population

	Study group	Control group
Sex		
Male	30 (45,45%)	23 (34,85%)
Female	36 (54,55%)	43 (65,15%)
Age	43,18 ± 13,00	37,85 ± 13,05
Inflammatory bowel disease	44 (66,67%)	44 (66,67%)
Rheumatological disease	22 (33,33%)	22 (33,33%)
Mean duration of disease	11,36 ± 8,21	7,21 ± 7,46

4.2 Procedure

Patients were introduced with the concept of the research concept and have given the written consent. Outpatients were interviewed and filled the questionnaires during the outpatient visit. Inpatients were interviewed by the researchers and filled the questionnaire during the ward rounds. The patients with diagnosis of the the inflammatory bowel disease filled HAD scale and inflammatory bowel disease activity questionnaires. The patients diagnosed with the rheumatic disease received HAD scale and VAS. The participation was voluntary and the patients did not receive any rewards.

4.3 Evaluations according to HADS, Chron's Disease Activity Index and Simple Clinical Colitis Disease Activity Index

4.4 The Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) was used to evaluate the widespread of the depressive and anxiety symptoms among the subjects of the research. This 14 mental health concerning questions questionnaire was created by A.S. Zigmund and R.P. Snaith in 1983. Currently, it is validated and widely used in the whole world to evaluate the depressive and anxiety symptoms in patients. One of the major advantages of the HAD scale is that it is validated among the different ethnic

groups. What is more, it is convenient to use during the interview with the patient. HAD scale was translated in Lithuanian in 1991, however its' use has not been validated yet. However, it is widely used in the clinical practice of Lithuanian medical doctors. (10)

Seven HADS questions evaluate the depressive symptoms and the other seven questions evaluate the anxiety symptoms. In the each of the questions the patient must choose one of the four statements that correctly describes their mental wellness during the past two weeks (0 – no sign of symptom; 3 – strong adverse effect of the symptom). The depressive and anxiety subscales are evaluated independently, and the results may vary between 0 and 21. The total score is categorized into the different groups: 0-7 – no signs of the depressive or anxiety symptoms; 8-10 – borderline abnormal; > 11 – likely depression or anxiety. (11)

4.6 Harvey-Bradshaw questionnaire

This questionnaire is a simplified version of Chron's disease activity index (CDAI). It was designed in 1980 to evaluate the activity and severity of the disease, so it only measures clinical parameters. Harvey-Bradshaw questionnaire consists of five questions related to the general well-being, pain in the abdominal area, enlarged stomach volume or sensitivity, the frequency of the liquid stools per day and the presence of any other complications. For every statement, patients had to choose the best answer describing his/her well-being during the past several months. The final score of less than 5 indicated remission; 5-7 – mild disease; 8-16 moderate disease and more than 16 - severe disease. (12)

4.7 Simple Clinical Colitis Disease Activity Index

This index was created in 1988 to evaluate the activity of ulcerative colitis. This questionnaire is composed of six questions concerning the bowel frequency at day/night, the urgency of defecation, the blood in stool, the general health and the non-gastrointestinal manifestations. For every question, patient had to choose the best answer describing his/her well-being during the past several months. The final score varied from 0, meaning no sign of disease activity, to 21, indicating utmost activity of the disease. (10)

4.8 The evaluation of the activity of rheumatic diseases

To evaluate the activity of the various rheumatic diseases, such instruments as DAS28 (Disease activity score at 28 joints), BASLAI (Bath Ankylosing Spondylitis), HAQ-DI (Health Assessment Questionnaire Disability Index) and the Visual analog scale (VAS, angl. Visual analog scale) are used in the clinical practice. The activity of the rheumatoid arthritis is assessed using DAS28, VAS and HAQ-DI and the activity of the ankylosing spondylitis is assessed using BASLAI and VAS. The evaluation of the activity of psoriatic arthritis is conducted using VAS. In this study, the rheumatic disease activity of the rheumatic patients was assessed using VAS while VAS evaluates not only the disease activity of psoriatic arthritis, but also the disease activity of rheumatoid arthritis and ankylosing spondylitis. VAS is a validated and subjective measure for the acute or chronic pain. Currently there is a wide selection of VAS scales ranging from 10-centimeter line to faces, indicating certain emotion, latter often being used with children. During this research pain was recorded by

handwritten mark on a 10-centimeter line, 0 meaning no pain and 10 – the worst pain. (13)

4.9 Statistics

Statistical analysis was conducted using IBM SPSS Statistics 23.0. The distribution of variables was analyzed using Kolmogorov-Smirnov test as the take was more than 50 patients. A two-sample T test was used to analyze normally distributed means and Mann-Whitney U test was performed to evaluate the non-normally distributed means. The chosen p value of significance was less than 0,05. For the normally distributed means, the effect size was evaluated using Cohen d value. The effect size of the non-normally distributed means was assessed using the effect size calculator for non-parametric tests.

The subjects were divided into two groups according to their treatment and described using CHI test.

5. Results

5.1 Comparisons

This study compared the symptoms of depression both in the general study population, which consisted of inflammatory bowel disease and rheumatic diseases patients, and in the populations of different disease groups. In the general study population, the study group included the patients with inflammatory bowel disease and rheumatic diseases receiving biological therapy. The control group was formed of the patients with inflammatory bowel disease and rheumatic diseases who did not receive biological medication. There was no significant difference in the disease activity between the study and the control groups (Table 4). In the clinical practice, different scales are used to assess the activity of the inflammatory bowel disease and the rheumatic diseases. For this reason, to unify the disease activity estimate of the general study population, the inflammatory bowel disease activity scale was divided into quartiles (1 - very low activity disease, 2 - low activity disease, 3 - moderate activity disease, 4 - high activity disease) and the range of intestinal inflammatory bowel disease activity estimate was assigned to each quartile. The estimate of the rheumatic diseases' activity was converted to the estimate of the newly developed general disease activity scale. Comparing the means of the overall HADS score, the difference between both groups was statistically significant (Table 4). Differences between the HADS depression subscale and the anxiety subscale were also statistically significant (Table 4).

Table 4. *Estimates of the disease activity and HADS score in the study and control groups of the general study population.*

	Study group	Control group	p value
Disease activity	9,42 ± 3,93	11,45 ± 6,12	0,05
HAD scale	7,96 ± 5,68	13,68 ± 6,72	**< .001(n_2 = 0,17; d_{cohen} = 0,90)**
HADS depression subscale	2,44 ± 2,50	3,91 ± 2,62	**0,001 (n_2 = 0,08; d_{cohen} = 0,61)**
HADS anxiety subscale	5,46 ± 3,89	**9,39 ± 4,59**	**< .001 (n_2 =0,18, d_{cohen} = 0,93)**

Analyzing the population of the inflammatory bowel disease patients alone, we also compared the incidence of the depressive symptoms between patients treated with biologic therapy and those treated with non-biologic therapy drugs. Disease activity did not differ between the two groups (Table 5). Comparing the means of the overall HADS score and the means of the HADS depression subscale and anxiety subscale, the difference between both groups was also statistically significant (Table 5).

Table 5. *Estimates of the disease activity and HADS in the study and control group in the inflammatory bowel disease population.*

	Study group	Control group	p value
Disease activity	8,00 ± 2,70	10,46 ± 6,92	0,18
HAD scale	8,30 ± 6,08	12,91 ± 6,21	**0,001 (n_2 = 0,13; d_{cohen} = 0,78)**
HADS depression subscale	2,61 ± 2,72	3,93 ± 2,52	**0,01 (n_2 - 0,07; d_{cohen} d_{cohen} = 0,57)**
HADS anxiety subscale	5,66 ± 3,98	8,98 ± 4,25	**< .001 (n_2 = 0,15; d_{cohen} = 0,85)**

Analyzing the study population of the patients with rheumatic diseases alone, patients were also divided into the biological therapy group and the group of patients treated with non-biological therapy. There was no difference in the disease activity between the two groups (Table 6). Comparing the means of the total HADS score, the difference between both groups was statistically significant (Table 6). Comparing the means of the HADS anxiety subscale, the difference was not statistically significant, but comparing the means of the depression subscale, the difference between the two groups was statistically significant (Table 6).

Table 6. *Estimates of the disease activity and HADS in the study and control group in the rheumatic disease population.*

	Study group	Control group	p value
Disease activity	61,82 ± 22,33	67,86 ± 16,75	0,33
HAD scale	7,27 ± 4,83	15,23 ± 7,56	**0,04 (d_{cohen} = 0,13)**
HADS depression subscale	2,09 ± 2,00	3,86 ± 2,88	**0,03 (n_2 = 0,10 d d_{cohen} = 0,66)**
HADS anxiety subscale	5,05 ± 3,76	10,23 ± 5,23	0,31

A more detailed analysis of the scales is provided in Tables 7-12.

Table 7. *Estimates of the HADS depression subscale of the study and control groups of the general study population.*

	Study group	Control group	p value
1. "I feel cheerful"	0,49 ± 0,56	0,85 ± 0,59	**0,001 (n_2 = 0,061; d_{cohen} = 0,512)**
2. "I still enjoy the things I used to enjoy"	0,43 ± 0,64	0,68 ± 0,77	0,05
3. "I look forward with enjoyment to things"	0,28 ± 0,48	0,52 ± 0,71	0,06
4. "I feel as if I am slowed down"	0,69 ± 0,83	0,97 ± 0,80	**0,03** (n_2 = 0,03, d_{cohen} = 0,33)
5. "I can laugh and see the funny side of things"	0,03 ± 0,17	0,21 ± 0,48	**0,005** (n_2 = 0,01, d_{cohen} = 0,23)
6. "I can enjoy a good book or radio or TV program"	0,34 ± 0,54	0,42 ± 0,56	0,32
7. "I have lost interest in my appearance"	0,35 ± 0,69	0,70 ± 0,86	**0,01** (n_2 = 0,03; d_{cohen} = 0,339)

Table 8. *Estimates of the HADS anxiety subscale in the study and control groups of the general study population.*

	Study group	Control group	p value
1. "I feel tense or 'wound up' "	1,00 ± 0,73	1,49 ± 0,88	**0,01 (n_2 = 0,06; d_{cohen} = 0,5)**
2. "I feel restless as I have to be on the move"	0,75 ± 0,77	1,00 ± 0,74	**0,04 (n_2 = 0,02, d_{cohen} = 0,3)**
3. "I can sit at ease and feel relaxed"	0,72 ± 0,70	1,32 ± 0,73	**< .001 (n_2 = 0,18; d_{cohen} = 0,73)**
4. "I get sort of frightened feeling as if something awful is about to happen"	0,75 ± 0,79	1,38 ± 0,97	**< .001 (n_2 = 0,09, d_{cohen} = 0,61)**
5. "I get sudden feelings of panic"	0,65 ± 0,65	1,12 ± 0,85	**0,01 (n_2 = 0,06; d_{cohen} = 0,52)**
6. "I get a sort of frigthened feeling like 'butterflies' in the stomach"	0,55 ± 0,81	0,82 ± 0,84	**0,03 (n_2 = 0,02; d_{cohen} = 0,31)**

7. "Worrying thoughts go through my mind"	0,75 ± 0,79	1,20 ± 1,01	**0,01 (n_2 = 0,04, d_{cohen} = 0,39)**

Table 9. *Estimates of the HADS depression subscale of the study and control group in the inflammatory bowel disease population.*

	Study group	Control group	p value
1. "I feel cheerful"	0,48 ± 0,59	0,82 ± 0,54	**0,004 (n_2 = 0,07, d_{cohen} = 0,56)**
2. "I still enjoy the things I used to enjoy"	0,41 ± 0,62	0,59 ± 0,69	0,19
3. "I look forward with enjoyment to things"	0,30 ± 0,46	0,50 ± 0,70	0,23
4. "I feel as if I am slowed down"	0,73 ± 0,90	0,80 ± 0,77	0,44
5. "I can laugh and see the funny side of things"	0,00 ± 0,00	0,25 ± 0,53	**0,002 (n_2 = 0,03; d_{cohen} =0,36)**
6. "I can enjoy a good book or radio or TV program"	0,41 ± 0,58	0,41 ± 0,58	0,87
7. "I have lost interest in my appearance"	0,32 ± 0,71	0,57 ± 0,82	0,10

Table 10. *Estimates of the HADS anxiety subscale of the study and control group in the inflammatory bowel disease population.*

	Study group	Control group	p value
1. "I feel tense or 'wound up' "	0,96 ± 0,79	1,50 ± 0,90	**0,01 (n_2 = 0,07, d_{cohen} = 0,57)**
2. "I feel restless as I have to be on the move"	0,91 ± 0,80	1,05 ± 0,71	0,29
3. "I can sit at ease and feel relaxed"	0,70 ± 0,70	1,34 ± 0,75	**< .001 (n_2 = 0,14; d_{cohen} = 0,82)**
4. "I get sort of frightened feeling as if something awful is about to happen"	0,70 ± 0,77	1,30 ± 1,00	**0,004 (n_2 = 0,08; d_{cohen} = 0,60)**
5. "I get sudden feelings of panic"	0,68 ± 0,71	1,05 ± 0,86	**0,03 (n_2 = 0,04; d_{cohen} = 0,41)**
6. "I get a sort of frigthened feeling like	0,50 ± 0,73	0,68 ± 0,77	0,20

'butterflies' in the stomach"			
7. "Worrying thoughts go through my mind"	0,82 ± 0,84	1,11 ± 0,99	0,17

Table 11. *Estimates of the HADS depression subscale of the study and control group in the rheumatic disease population.*

	Study group	Control group	p value
1. "I feel cheerful"	0,52 ± 0,51	0,91 ± 0,68	0,06
2. "I still enjoy the things I used to enjoy"	0,48 ± 0,68	0,86 ± 0,88	0,13
3. "I look forward with enjoyment to things"	0,24 ± 0,54	0,55 ± 0,74	0,12
4. "I feel as if I am slowed down"	0,62 ± 0,67	1,32 ± 0, 78	**0,004 (n_2 = 0,12; d_{cohen} = 0,75)**
5. "I can laugh and see the funny side of things"	0,10 ± 0,30	0,14 ± 0,35	0,68
6. "I can enjoy a good book or radio or TV program"	0,19 ± 0,40	0,46 ± 0,51	0,068
7. "I have lost interest in my appearance"	0,43 ± 0,68	0,96 ± 0,90	**0,04 (n_2 = 0,05; d_{cohen} =0,46)**

Table 12. *Estimates of the HADS anxiety subscale of the study and control group in the rheumatic disease population.*

	Study group	Control group	p value
1. "I feel tense or 'wound up' "	1,05 ± 0,59	1,46 ± 0,86	0,11
2. "I feel restless as I have to be on the move"	0,43 ± 0,60	0,91 ± 0,81	**0,04 (n_2 = 0,06; d_{cohen} = 0,49)**
3. "I can sit at ease and feel relaxed"	0,76 ± 0,70	1,27 ± 0,70	**0,02 (n_2 = 0,07; d_{cohen} = 0,55)**
4. "I get sort of frightened feeling as if something awful is about to happen"	0,86 ± 0,85	1,55 ± 0,91	**0,02 (n_2 = 0,08; d_{cohen} = 0,59)**
5. "I get sudden feelings of panic"	0,57 ± 0,51	1,27 ± 0,83	**0,003 (n_2 = 0,12; d_{cohen} = 0,74)**

6. "I get a sort of frigthened feeling like 'butterflies' in the stomach"	0,67±0,97	1,09 ± 0,92	0,07
7. "Worrying thoughts go through my mind"	0,62 ± 0,67	1,36 ± 1,05	**0,02 (n_2 = 0,09; d_{cohen} = 0,61)**

Estimates of the HADS anxiety subscale of the study and control group in the rheumatic disease population.

5.2 Literature

The research of the literature was conducted using the strategy of the *Center of Evidence based medicine* in Pubmed.

5.3 Reliability

The results of the Simple clinical colitis activity index, Harvey-Bradshaw questionnaire and HADS and the results of the HADS depression subscale and anxiety subscale were not normally distributed according to the Kolmogorov-Smirnov test ($p<0,05$).

The internal compatibility of the scales was evaluated using Cronbach α. The total internal compatibility of the HADS was satisfactory (Cronbach α = 0,88). The internal compatibility of the HADS depression and anxiety subscales individually was also very high (Cronbach α = 0,75 and 0,85

5.4 Summary of the results

This study is one of the researches comparing the onset of the depressive symptoms among patients with chronic diseases treated with biologic therapy and those with the same disease but treated with other medication. The findings of this study demonstrate a statistically significant difference in the incidence of the depressive symptoms between the study and control group, both in the overall study population and in the populations of inflammatory bowel disease and rheumatic disease groups alone. The total score of the HAD scale and the total scores of the depression and anxiety subscales were statistically significantly higher among non-biologically treated patients in the overall study population and in the inflammatory bowel disease population. In the rheumatic patient population, a statistically significant differences of the overall HAD scale score and the overall depression subscale score were observed between the study and control groups. In the general study population and in the inflammatory bowel disease population, depressive symptoms were best described by such statements as "I feel cheerful" and "I can laugh and see the funny side of things". In the rheumatic disease population, the depressive symptoms were best described by the statements "I feel as if I am slowed down" and "I have lost interest in my appearance". In both general study population and inflammatory bowel and rheumatic disease population, anxiety symptoms were best described by such statements as "I can sit at ease and feel relaxed", "I get sort of frightened feeling as if something awful is about to happen" and "I get sudden feelings of panic".

6. Discussion

6.1 Neuroinflammation

Despite the advance in the treatment of depression, the traditional treatment of this disease is not effective for the third of all the patients. In this paper, the traditional treatment of the depression is

considered to consist of the antidepressants and cognitive behavioral therapy or the interpersonal therapy. As it is more known how this therapy affects the symptoms of the depression and not the particular elements of the etiopathogenesis, not all the patients benefit from it. Thus, the studies of the undiscovered etiopathogenetic ways of the depression is the basis for establishing the new and more individualized depression treatment methods. In the last decade one of the new ways of the development of the depression linked to the inflammation and the kynurenine pathway arose. (14) It is claimed that so called neuroinflammation might cause the treatment resistant major depression. Such autoimmune systemic inflammatory diseases as rheumatoid arthritis, Chron's disease or multiple sclerosis are thought to be the source of the inflammatory markers important in the pathogenesis of major depression. (15)

The results of this study correspond to latest research on the inflammatory origin of the depression. The depression in thought to be linked to the chronic low activity inflammation, the activation of the cellular immunity and the activation of the responsive anti-inflammatory reflective system. Such pro-inflammatory factors as the dysregulation of the intestinal microbiota, obesity and smoking are thought to induce the inflammation and the depression as well. (16) The attempts to treat depression with anti-inflammatory medication also contributes to the evidence of the relation between depression and inflammation. It is scientifically proven that that the anti-inflammatory medication and antidepressants have a better effect on depressive symptoms in patients with chronic inflammatory diseases than anti-depressive treatment alone. (17) The suppression of the cytokines and other inflammatory pathways might become the effective way to treat the resistant depression or improve the depressive and anxiety symptoms in the chronic inflammatory disease patients. Moreover, the highly pronounced depressive and anxiety symptoms in the chronic inflammatory disease patients might become the indication to get biological treatment with TNF-alpha inhibitors or IL-6 inhibitors.

There is an explanation why the chronic systemic inflammation could cause depression. The most important inflammatory factors cytokines are able to cross the blood-brain barrier and enter the central nervous system. There is evidence, that TNF-alpha amounts increase in the body of patients with major depressive disorder as well. The TNF-alpha and other pro-inflammatory factors upregulate the kynurenine (KYN) pathway in the human body and thus contributes to the development of the depression. Normally, KYN pathway regulates tryptophan (TRY) metabolism and the serotonergic system. TRY is metabolized to KYN by indoleamine-2,3-dioxygenase (IDO) 1, IDO-like enzyme, IDO 2, and tryptophan-2,3-dioxygenase (TDO). Then KYN is metabolized to kynurenic acid and an *N*-methyl-D-aspartate receptor antagonist. TRY also can be metabolized to serotonin or 5-hydroxytryptamine (5-HT). Nevertheless, the pro-inflammatory cytokines increase the expression of IDO and activates the different KYN metabolic pathway, in which KYN is converted to the neurotoxic quinolinic acid (QA) which contributes to the neuroinflammation and the reduced neuroplasticity. Furthermore, the increased expression of IDO shifts TRY metabolism from serotonin synthesis to KYN formation and thus the serotonergic system decompensates. So, the dysregulated KYN pathways contributes to the development of depressive and anxiety behavior in two ways – by dysregulating the serotonergic

systems and by neurotoxicity to NMDA receptors. (18)

7.2 The link between depression symptoms and inflammatory bowel disease

Chron's disease and ulcerative colitis are inflammatory gastrointestinal tract disorders that manifest with abdominal pain, diarrhea and the blood in the stool. About 30% of inflammatory bowel disease patients suffer from such mental disorders as anxiety and depression. This rate was calculated using patient self-assessment tools, therefore the concept of the anxiety and depression among inflammatory bowel disease patients should not be confused with the diagnosis of the generalized anxiety disorder or major depression. (19)

It is thought that the brain-gut axis disorder is responsible for the development of both the psychic abnormalities and the inflammatory bowel diseases. According to the studies that analyze the links between mental state and the inflammatory bowel disease, the mental disorders are related to the unfavorable outcomes of the inflammatory bowel disease and the activity of the inflammation is bound to *de novo* development of the psychological disorders. According to the 2018 study by Gracie et al., the link between mental disorder and inflammatory bowel disease might be bidirectional. In other words, they might affect and activate each other. (16) It is thought that the stress and the excessive brain-gut axis activity that occur in the states of the mental disorders could affect the well-being of the gastrointestinal tract. The inordinate activity of the brain-gut axis increases the secretion of the glucocorticoids and makes the walls of the gut more permeable. The stress induces the rise in the secretion of the catecholamines. Thus, the increased activity of the sympathetic nerves system activates the foamy cells and the macrophages that secrete the cytokines. All these mechanisms contribute to the development of the inflammation in the wall of the gut. (20) The increased permeability of the gut wall enhances the possibility of the gastrointestinal tract microbiota to interact with the central nervous system. According to the animal study of the ulcerative colitis, the composition of the microbiota has the impact on the variations of the behavior of the laboratory mice. (21) Such effects depend on the reflexes of the vagal nerve. As it is stimulated (for example, by the high amount of so called "good bacteria" in the gastrointestinal tract) the pro-inflammatory cytokines are blocked and the inflammation decreases. However, the high amounts of the TNF- α and cortisol inhibit the vagal nerve reflex and the inflammation in the gut increases.

7.3 The link between depression symptoms and rheumatic diseases

Depression and anxiety are highly comorbid with the rheumatic diseases. The prevalence of the depression is known to be higher in the population with psoriatic arthritis than in the general population. The 2017 study by Wu et al. compared the risk of depression between patients with psoriasis or psoriatic arthritis and healthy individuals. According to the study, the risk of the depression in the psoriasis and psoriatic arthritis groups was 14% and 22% respectively higher than in the group of healthy individuals (22). According to the systematic review conducted in 2019 by Jamshidi et al., as many as 47-83% of Iranian citizens with rheumatoid arthritis experience depressive symptoms. (23) It has been thought for a long time that depression and anxiety in rheumatic diseases patients could be caused by chronic pain, disability and drug side effects. However, the recent studies of the links between peripheral inflammation

and changes in the brain have revealed that rheumatic diseases as possible risk factors of the mental disorders. Both in the rheumatic diseases and depression the increased amounts of pro-inflammatory mediators, acute phase proteins and chemokines are identified. Some studies have shown the higher levels of IL-6, IL-17, TNF-alpha in the depressed patients without comorbidities. The concentrations of these mediators are also higher in such rheumatic diseases as psoriatic arthritis. In other words, the higher concentrations of the inflammatory mediators in rheumatic disease may provoke the onset of the depressive symptoms.

However, there are theories that the development of the rheumatic disease might be activated by the immune response to the psychiatric stress and the activation of the hypothalamic-pituitary-adrenal axis. Because of the hyperactivity of the hypothalamic-pituitary-adrenal axis, the higher concentrations of corticoliberin and cortisol are excreted in the patients with depression. The action of corticoliberin is associated with the pathological processes in the joints in arthritis. (24)

The recent studies show that the associations between rheumatic diseases and depressive symptoms have the tendency to be bidirectional. Not only pro-inflammatory mediators in rheumatic diseases possibly contribute to the onset of the depressive symptoms, but the dysfunction of the hypothalamic-pituitary-adrenal axis might also lead to the persistence of the chronic systemic inflammation.

8. Conclusions

The Subjects treated with a TNF-alpha inhibitor or an IL-6 inhibitor experienced fewer depressive symptoms than those treated with non-biologic therapy that has fewer specific effects on cytokines. A reduction in depressive symptoms was observed among the biologic-treated subjects in both the overall study population and in the inflammatory bowel disease and rheumatic disease populations alone. This supports the hypothesis that rise in the levels of inflammatory mediators such as TNF-alpha and IL-6 contribute to the onset of depressive symptoms, and inhibitors of these mediators reduce such symptoms. In the general study population and in the inflammatory bowel disease study population, biologic therapy had a positive effect on both depressive and anxiety symptoms (assessed on the HAD scale by depression and anxiety subscales, respectively). In the rheumatic disease study population, the anxiety symptoms were affected less than the depressive symptoms.

This study contributes to the literature on the links between systemic inflammation, chronic diseases and the depression, and to the evidence that biologic therapy reduces inflammatory mediators and may be important in identifying and treating the etiopathogenic factors of depression. This study also contributes to a broader understanding of the psychoemotional state of the patients with systemic chronic diseases.

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