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PREVALENCE AND CORRELATION OF DEPRESSIVE SYMPTOMS WITH FUNCTIONAL SCORES, THERAPY AND DISEASE ACTIVITY AMONG CROATIAN PATIENTS WITH RHEUMATOID ARTHRITIS: A PRELIMINARY STUDY

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SUMMARY

Background: *Rheumatoid arthritis (RA) is a chronic, autoimmune and disabling disease that significantly affects the quality of life. Additionally, significant number of patients with RA suffer from depressive disorders, which are commonly underrecognised and undertreated. We aimed to estimate the prevalence of depressive symptoms in Croatian RA patients and to assess the relationship between them and clinical correlates.*

Subjects and methods: *Fifty-four RA patients treated at the Clinic for Rheumatic Diseases and Rehabilitation at the University Hospital Centre Zagreb were prospectively enrolled in the study and evaluated for functional status using the Disease Activity Score 28 (DAS-28), Health Assessment Questionnaire (HAQ), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and Visual Analogue Scale (VAS) for pain and health related quality of life (HRQL) measurement. The depressive symptoms were assessed using the Beck Depression Inventory-II (BDI-II) questionnaire.*

Results: *Thirty RA patients (55.6%) had some sort of mood disorder, with 10 (18.5%) patients accounting as depressed. Positive correlation was found between depressive symptoms, higher disease activity and disablity during daily activities ($\tau b=0.385$, $p=0.001$ and $\tau b=0.282$, $p=0.024$ respectively). We found no significant association between depression and disease activity in the whole sample of RA patients, but for postmenopausal patients, the disease activity correlated with postmenopausal patients accounting as depressed (BDI-II score moderate or severe; $\tau b=0.363$, $p=0.021$). The use of biologic therapy correlated negatively with the disease acitivity, pain intensity and worse health related quality of life score ($\tau b=-0.360$, $p=0.06$; $\tau b=-0.310$, $p=0.07$; $\tau b=-0.380$, $p=0.01$ respectively).*

Conclusion: *Considering the high prevalence of depressive sympoms in RA patients and the effect on functional disability and quality of life, we wanted to emphasize the importance of recognizing and optimizing depression treatment through multidisciplinary approach in RA patients.*

Key words: *Rheumatoid Arthritis – depression - disease activity - functional disability - Beck Depression Inventory (BDI-II)*

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease with prevalence among the adult population of 0.2–1.2%. (Alamanos et al. 2006) It is the most common inflammatory arthritis for which there is currently no definitive cure. RA is characterized by pain and a progressive course leading to increased level of disability and developement of systemic complications. Due to the nature of the disease it is clear that patient's quality of life (QOL) is significantly affected, so the main treatment goals are reduction of inflammation and pain, in order to delay joint erosions and consequently functional disability (Matcham et al. 2014).

Among RA population, depression occurs as a common co-morbidity with prevalence approximately two to three times higher than the one in the general population, with calculated risk of depression developement of nearly 70% (Frank et al. 1988, Murphy et al. 1988, Dickens et al. 2002, Lu et al. 2016). Complications associated with depression in RA patients include an increased risk of work disability, mortality and myocardial infarction (Lowe et al. 2004, Ang et al. 2005, Giles et al. 2005, Scherrer et al. 2009). Beyond the increased risk for poor health and associated greater health care costs, depression also interferes with daily functioning and additionally worsens patient's QOL (Brown et al. 2012). Depression can impact physical behaviour and cause decrease in movement, a deconditioning of the body, loss of natural endorphins and increase pain (Covic et al. 2003, Neugebauer et al. 2003, Dodge et al. 2006, Fichna et al. 2007, Dinas et al. 2011, Milman et al. 2012, Rovner et al. 2012). It can also influence on the non-inflammatory components of the Disease Activity Score 28 (DAS-28), a well-established score for monitoring RA activity, through changing patients perception of their symptoms (Prevoo et al. 1995). It has also been shown that the loss of recreational and social activities in RA patients significantly increases risk of developing depressive

symptoms (Cordingley et al. 2014). Considering that there is an overlap of depressive symptoms and RA symptoms (e.g. fatigue, weight loss, insomnia and lack of appetite), depression often remains unrecognised (Dickens & Creed 2001, Sheehy et al. 2006, Nicassio 2008). The use of standardized psychiatric questionnaires like Beck Depression Inventory-II (BDI-II) questionnaire can be of great help in order to assess for depressive symptoms in these patients (Wang & Gorenstein 2013, Englbrecht et al. 2017).

The aim of this study was to show the prevalence of depressive symptoms in Croatian RA patients and to assess and evaluate the relationship between depressive symptoms, disease activity, pain, fatigue, quality of life and different drug therapy regimens.

SUBJECTS AND METHODS

Subjects

This cross sectional, single centre study started in 2011 at the Clinic for Rheumatic Diseases and Rehabilitation at the University Hospital Centre Zagreb, Zagreb, Croatia. Patients diagnosed with RA according to the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 criteria who were treated at the Clinic were prospectively enrolled in the study and assessed for disease activity, functional disability and the presence of symptoms applying to depression (Aletaha et al. 2010). Each patient signed informed consent and the study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Methods

All patients were examined by an experienced rheumatologist for current symptoms and completed specific scales and questionnaires under his/her's supervision. Visual analogue scale (VAS) was used for measurement of patient's pain level and health related quality of life (HRQL) (Ferraz et al. 1990, Hjermstad et al. 2011). VAS was presented as a straight, 100 mm horizontal line with ends being marked as the extreme limits of the measured parameter. For pain assessment, the left end of the line was marked as "no pain", and the higher score indicated greater pain intensity. For HRQL assessment, the end left of the line was marked as "good health", and the higher score indicated worse health. DAS-28 score was used to determine the disease activity, where score ≥5.1 was considered as high disease activity, score 3.2-5.1 as moderate, score 2.6-3.2 as low disease activity and score ≤2.6 as remission. (Prevoo et al. 1995) Health Assessment Questionnaire (HAQ) was used to assess the functional ability of patients, where HAQ score 0 was considered as mild, score 1 as moderate and score 2 as severe disability (Kirwan & Reeback 1986). Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire was used to assess patient's fatigue (Cella et al. 2005, Singh et al. 2014). The BDI-II was used to assess depressive symptoms, where BDI-II score 0 was considered as normal, score 1 as mild mood disturbance, score 2 as borderline depression, score 3 as moderate depression, score 4 as severe depression and score 5 as extreme depression. Patients with BDI-II score accounting as moderate, severe and extreme depression were considered as depressed for the purpose of statistical analyses (Krug et al. 1997, Wang & Gorenstein 2013).

Statistical Analyses

Statistical analyses were performed using the IBM SPSS Statistics 20 program. Descriptive statistics were used to describe continuous and categorical variables. Medians and ranges were determined for continuous variables and relative frequencies were computed for all variables. Cross tabulation was used to analyse the relationship between categorical data with Kendall's tau b correlation coefficients. The magnitude of the correlation coefficient was used to gauge the strength of the correlation as follows: $|\tau b|>0.70$ is strong correlation, $0.50<|\tau b|<0.70$ is moderately strong correlation, $0.30<|\tau b|<0.50$ is weak to moderately strong correlation, and $|\tau b|<0.30$ is weak correlation. Kruskal-Wallis test was used for comparison of three or more independent groups. A value of $p<0.05$ was deemed statistically significant.

RESULTS

Patient characteristics

A total of 54 RA patients were enrolled in the study, the age median was 59 years (range 26-82 years) and the median of the disease duration was 12.5 years (range 0-45 years). Patient characteristics are shown in Table 1. Additionally, none of the patients were taking antidepressants and only one postmenopausal patient was on hormone replacement therapy. Biologic therapy included adalimumab, etanercept, tocilizumab and rituximab. The mean VAS pain score was 60.37±22.77, VAS HRQL score was 58.11±23.99 and FACIT-F score was 28.67±10.77.

Depression prevalence, disease activity and functional scores in RA patients

Thirty patients (55.6%) had some sort of mood disorder, with 10 (18.5%) patients accounting as depressed. We found that both BDI-II score and DAS-28 score correlated positively with HAQ score ($\tau b=0.385$, $p=0.001$ and $\tau b=0.282$, $p=0.024$ respectively), indicating that patients with more depressive symptoms and higher disease activity experienced greater disablity during daily activities. The highest BDI-II scores were present among patients with severe to very sever HAQ scores ($p=0.005$) (Figure 1). BDI-II, DAS-28 and HAQ scores

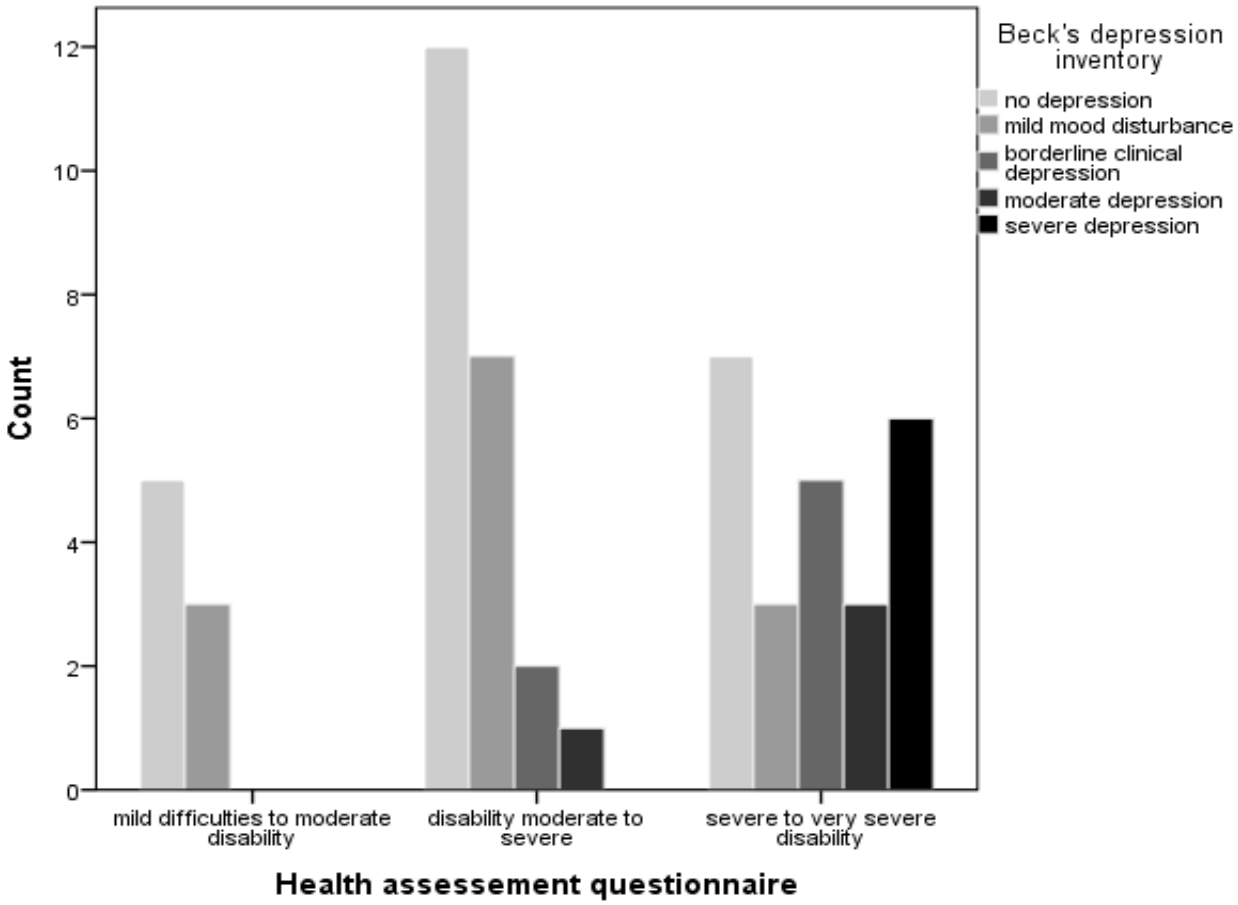

Figure 1. The BDI-II categories among RA patients according to HAQ disability score

positively correlated with VAS pain and VAS HRQL scores, while negative correlation was established with FACIT-F score (Table 2). This implies that patients with more depressive symptoms, higher disease activity and disability in daily activities experienced more pain, more fatigue and had lower HRQL. We found no significant association between BDI-II score and DAS-28 score in the whole sample of RA patients, but for postmenopausal patients there was significant positive correlation between DAS-28 score and patients accounting as depressed (BDI-II score moderate or severe; τb=0.363, p=0.021), which shows that in postmenopausal patients, the disease activity and depression severity depend on each other.

Influence of different drug regimens on functional scores and depressive symptoms

Negative correlation was found between the use of biologic therapy and DAS-28, VAS pain and VAS HRQL score (τb=-0.360, p=0.06; τb=-0.310, p=0.07; τb=-0.380, p=0.01 respectively), which showed that patients receiving biologic therapy had lower disease activity, less pain and better HRQL (Table 2). The use of opioid analgesic positively correlated with the use of benzodiazepines (τb=0.316, p=0.21), while the use of both opioid analgesics and benzodiazepines postively correlated with BDI-II score (τb=0.421, p=0.001 and τb=0.429, p=0.001 respectively). Opioid analgesic use also correlated positively with HAQ score (τb=0.407, p=0.002). These results indicate that patients with more depressive symptomes were prone to use greater amount of opioid analgesics and benzodiazepines, while more disabled patients were prone to use greater amounts of opioid analgesics, as well as vice versa (Table 2).

Interrelation of pain, HRQL, FACIT-F scores and inflammatory markers

As expected, positive correlation was found between VAS pain score and VAS HRQL score (τb=0.625, p=0.000), and both scores correlated negatively with FACIT-F score (τb=-0.248, p=0.010 and τb=-0.306, p=0.002 respectively). This showed that patients with worse pain and HRQL scores experienced more fatigue in daily living. VAS pain score correlated positively with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels (τb=0.197, p=0.041 and τb=0.216, p=0.025 respectively), which indicated that patients with elevated inflammatory markers experienced greater pain.

Table 1. RA patient characteristics

Patient characteristics	Number of patients
Sex	
male	7 (13%)
female	47 (87%)
Positive family history for rheumatic diseases	16 (29.6%)
Postmenopausal women	38 (70.4%)
Serology	
positive RF	51 (94.4%)
positive anti-CCP	49 (90.7%)
Drug treatment	
corticosteroids	45 (83.3%)
MTX	27 (50%)
SSZ	2 (3.7%)
LFL	6 (11.1%)
biologic therapy*	13 (24.1%)
NSAID	32 (59.3%)
opioid analgesic	18 (33.3%)
benzodiazepine	9 (16.7%)
DAS-28	
remission	5 (9.3%)
low disease activity	2 (3.7%)
moderate disease activity	22 (40.7%)
high disease activity	25 (46.3%)
HAQ	
mild difficulties to moderate disab.	8 (14.8%)
moderate to severe disability	22 (40.7%)
severe to very severe disability	24 (44.4%)
BDI-II	
no depression	24 (44.4%)
mild mood disturbance	13 (24.1%)
borderline clinical depression	7 (13%)
moderate depression	4 (7.4%)
severe depression	6 (11.1%)

RF - rheumatoid factor; anti-CCP - cyclic citrulinated peptide antibody; MTX – metothrexate; SSZ – sulfasalazine; LFL – leflunomide; NSAID - non-steroidal anti-inlfammatory drug; DAS-28 - Disease Activity Score 28; HAQ - Health Assessement Questionnaire; BDI-II - Beck Depression Inventory II; *adalimumab, etanercept, tocilizumab, rituximab

DISCUSSION

To the best of our knowledge, this is the first study in our country conducted to assess the prevalence of depressive symptoms in RA patients, as well as interrelation between them, the disease activity and patient's functional status. In our study 30 (50.6%) RA patients had some sort of mood disorder, with 6 (11.1%) patients diagnosed with severe depression, 4 (7.4%) patients with moderate depression but none with extreme depression. Our results are in accordance with some of the previously conducted studies, which showed similar prevalence of depression among RA population. (Matcham et al. 2013, Jamshidi et al. 2016, Masood et al. 2017) RA is a disease marked by chronic systemic inflammation of the joints and previous research has confirmed that systemic inflammation, measured by acute-phase reactants and proinflammatory cytokines is often associated with the development of depression (Capuron & Dantzer 2003, Howren et al. 2009). It has also been suggested that systemic inflammation in general may be associated with, cause, or contribute to the developement of depressive symptoms during different disorders of chronic inflammation, such as diabetes mellitus and chronic obstructive pulmonary disease (Evans et al. 2005, Dantzer et al. 2008, Miller et al. 2009). On the other side, depression alone may lead to increased production of pro-inflammatory cytokines, thereby contributing to interrelation between depression and higher RA disease activity (Fuller-Thomson & Shaked 2009, Howren et al. 2009). Our patients with more depressive symptoms and higher disease activity also experienced greater disablity during daily activities. The distribution of depression categories was significantly higher among patients with severe to very severy disability, as shown in Figure 1. Also, patients with more depressive symptoms, higher disease activity and disability in daily activities experienced more pain, more fatigue and had lower HRQL (Table 2).

Table 2. Relationship between drug therapy, pain level, health related quality of life and fatigue with disease activity, depression and functional disability in patients with rheumatoid arthritis

	Kendall's tau_b	DAS-28	BDI	HAQ
Biologic therapy	correlation coefficient	-0.360*	-0.153	-0.098
	p-value	0.006	0.223	0.453
Opioid analgesics	correlation coefficient	0.192	0.421*	0.407*
	p-value	0.142	0.001	0.002
Benzodiazepines	correlation coefficient	0.108	0.429*	0.219
	p-value	0.408	0.001	0.095
VAS pain	correlation coficient	0.377*	0.218*	0.404*
	p-value	0.001	0.040	0.000
VAS health related quality of life	correlation coficient	0.397*	0.235*	0.335*
	p-value	0.000	0.027	0.002
FACIT-F	correlation coficient	-0.260*	-0.402*	-0.372*
	p-value	0.017	0.000	0.001

DAS-28 - Disease activity scale-28; BDI - Beck Depression Inventory; HAQ - Health Assessement Questionnaire; VAS - visual analouge scale; FACIT-F - Functional Assessement Chronic Ilness Therapy-Fatigue; *statistically significant; **The magnitude of the correlation coefficient was used to gauge the strength of the correlation as follows: $|\tau b|>0.70$ strong, $0.50<|\tau b|<0.70$ moderately strong, $0.30<|\tau b|<0.50$ weak to moderately strong and $|\tau b|<0.30$ weak correlation

These findings from our sample of RA patients matched the findings from other studies (MacKinnon et al. 1994, Dickens et al. 2002, Cordingley et al. 2014). Patients with elevated inflammatory markers experienced greater pain, and patients with greater pain and lower HRQL also experienced more fatigue in daily living. The bidirectional relationship of functional disability, fatigue and inflammatory markers i.e. disease acitivity, was proposed throughout several studies, with the exatct cause-effect mechanism still prone to discussion (De Berardis et al. 2006, Davis et al. 2008, Howren et al. 2009). We found no significant association between RA disease activity and depressive symptoms in the whole sample of RA patients. A pattern which has been demonstrated in a number of studies too (Dickens et al. 2002, Sato et al. 2013, Jamshidi et al. 2016). Some of the previous research indicated that RA disease acitivity is not a reliable predictive factor for depression developement among RA patients, but on the other hand, a few of other studies have shown an association between disease activity and depression (McFarlane & Brooks 1988, Dickens & Creed 2001, Mella et al. 2010, Ho et al. 2011). We did found a significant correlation only among postmenopausal patients accounted as depressed (BDI-II score moderate or severe) and RA disease activity ($\tau b=0.363$, $p=0.021$). This indicates that in postmenopausal patients, the disease activity and depression severity are mutualy dependent. A finding which was also noted in several research of Zautra et al. (Zautra et al. 1994, Zautra & Smith 2001).

Patients treated with biologic therapy had significantly lower RA disease activity and better functional status (Table 2). This confirms better disease control with the use of biologic therapy and contributes to the theory of correlation of depression and rheumatic diseases caused by production of pro-inflammatory cytokines (Evans et al. 2005, Dantzer et al. 2008, Miller et al. 2009). Our results showed a positive connection between opioid and benzodiazepine use; patients who used more opioid analgesics also used more benzodiazepines. Additionally, patients with more depressive symptomes were prone to use greater amounts of opioid analgesics and benzodiazepines, while more disabled patients were prone to use greater amounts of opioid analgesics, as well as vice versa (Table 2). This results are prone to disscussion. The question is, do depressive patients use more of these drugs because of underlying, unrecognised depression? Or vice versa, are the drugs responsible for making them susceptible to the developement of mood disorders and depression. A recent study by Goesling et al. showed that patients who used opioids had worse phenotypic profile (higher pain severity, worse physical functioning) and reported more symptoms suggestive of depression that nonopioid users, while patietns with depressive symptoms were more likely to be taking opioids at higher levels of functioning. Their findings supported the hypothesis that patients may be self-medicating affective pain with opioids (Goesling et al. 2015).

Our study had several limitations. First, being a preliminary study the sample size is relatively small, which may limit it's applicability. Second, there was a gender bias, considering that 87% of patients were female. Third, this was a cross-sectional study which limited the opportunity to evaluate the relation of depressive symptoms throught the course of this chronic disease. Therefore a larger studies with long-term follow up are warranted, in order to comprehense this complex bidirectional relationship.

CONCLUSION

The results of our preliminary study clearly show the high prevalence of depressive symptoms in Croatian RA patients. Early recognition of the disease and adequate treatment can greatly affect the psychological status of patients. A multidisciplinary approach to RA patients is therefore essential for establishing their well being in mulptile domains. Considering that conserning proportion of depressed patients in general population do not receive adequate treatment, and the prevalence of depression in RA population being even higher, it is particularly important to recognize and timely treat depression in RA patients, due to potential physical and psychological benefits. Finally, it can be assumed that optimal treatment of RA patients should also involve adequate management of possible depressive disorders alongside regular RA treatment. Our intention is to continue this study to clarify the effectivness of psychiatric interventions, where applicable, for further improvement of QOL in RA patients.

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Conflict of interest: None to declare.

Contribution of individual authors:

Iva Žagar & Valentina Delimar: conceptualized and designed the study, collected the data and performed the statistical analysis, drafted the manuscript, approved the final version.

Mislav Pap: collected the data, contributed to the interpretation of analyzed data, drafted the manuscript, approved the final version.

Doroteja Perić: drafted the manuscript, approved the final version.

Nadica Laktašić Žerjavić & Porin Perić: conceptualized and designed the study, drafted the manuscript, approved the final version.

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