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ORIGINAL ARTICLE

The relationship between disease activity and depression in Egyptian patients with rheumatoid arthritis

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KEYWORDS

Depression;
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Abstract *Aim of the work:* To estimate the prevalence of depression and its relationship with disease activity parameters in Egyptian patients with RA.

Patients and methods: A cross sectional study was conducted on 170 patients with RA. The following values were assessed for each patient: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), swollen and tender joint counts (SJC and TJC), disease activity score 28 (DAS28), health assessment questionnaire score (HAQ), visual analogue scale (VAS) of pain and hospital anxiety and depression scale-depression subscale (HADS-D).

Results: The prevalence of depression was 15.29% (26 RA patients). In the depressed RA patients, positive significant correlations were found between HADS-D score and age, disease duration, HAQ score, VAS, DAS28 score and CRP. However, no significant correlation was found between HADS-D score and ESR, number of swollen and tender joints. No significant difference ($P > 0.05$) was found between depressed male and female patients with RA.

Conclusion: Patients with RA and co-morbid depression have worse health outcomes. RA cases should be monitored for accompanying depression during follow-up. The identification and treatment of depression in RA paramount to the overall management of RA.

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1. Introduction

Rheumatoid arthritis (RA) is a multifactorial, chronic, inflammatory disease affecting primarily the joints with prevalence of between 0.5% and 1% [1]. Pain, fatigue and disability, which may be considered as stress factors [2], are common challenges that may subsequently lead to psychological distress [3]. Depression commonly co-occurs with RA, in the range of 13–20% and above based on clinical assessments [4]. Studies

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using self report measures of depressive symptoms suggest considerably higher rates (i.e. 40%), although the levels of symptomatology may be subclinical [5]. The prevalence rates of depression in RA are well above those reported in the general community (2–4%) or primary care (5–10%) but similar to other chronic conditions [6]. Depression in RA is associated with higher levels of disease activity, pain, fatigue, work disability, health service use but lower treatment compliance [7] and increased suicide risk [8] and mortality [9].

Regular mood assessment by rheumatology clinical staff may serve to improve awareness and early identification of depression [7] and thus timely identification and treatment of depression in RA are critical to overall clinical management [10]. While not substituting for a psychiatric clinical assessment, the use of self-report scales may be a feasible option in rheumatology settings to identify patients at risk of depression. Regular screening, and early intervention or appropriate referral, where necessary, would provide a psychological 'window of opportunity' akin to that recommended in relation to clinical treatment of early RA [11].

While a number of screening instruments for depression are available, one of the most commonly used scales is the hospital anxiety and depression scale (HADS) [12]. The HADS was developed for use in hospital settings, with items chosen to reduce contamination with somatic or disease related symptoms. This scale has been used with RA populations and has been subjected to psychometric assessment of their reliability and validity including exploratory and confirmatory factor analyses [11,13–15].

This study was undertaken to estimate the prevalence of depression and its relationship with disease activity parameters in Egyptian patients with RA.

2. Patients and methods

This cross-sectional study was conducted on RA patients attending the outpatient clinic of Rheumatology and Rehabilitation department, Sohag University Hospital, in the period between October 2012 and March 2013. A total of 170 patients (female/male = 153/17) fulfilling the American College of Rheumatology (ACR) criteria for a diagnosis of RA [16] with a mean age of 43.75 ± 8.03 years were studied. The study included only RA patients with onset of depression following established diagnosis of RA. Excluded from our study were RA patients with history of previous psychiatric disorders, present chronic disorders other than RA (e.g. diabetes mellitus, chronic liver disease, chronic renal failure, etc.), and RA patients with secondary fibromyalgia. An informed consent was obtained from patients participating in the study. The study was approved by the local ethics committee of Sohag-University scientific review board. Age, sex, disease duration, swollen and tender joint counts of the RA patients were recorded. Visual analogue scale of pain (VAS), disease activity index 28 (DAS28) [17], health assessment questionnaire (HAQ) [18,19], erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were used to assess disease activity. Disease activity index 28 (DAS28) is a validated index of RA disease activity. It consists of four measures: 28 tender (TJC28) and swollen joint counts (SJC28), ESR, and the patient's general health (GH) measured on a 100 mm visual analogue scale. The disease modifying anti-rheumatic drugs (DMARDs) used in the study were methotrexate average dose 15 mg/week (either intravenous or subcutaneous), leflunomide 20 mg /day, and hydroxychloroquine 200–400 mg/day. Combination therapy with methotrexate and hydroxychloroquine was used in the majority of our patients followed by methotrexate and leflunomide combination while monotherapy with either methotrexate or leflunomide was used in some patients with RA. Prednisolone was used for short term intermittent control of disease activity in some RA patients.

2.1. Laboratory investigations

Serum RF and CRP concentrations were determined by immuno-nephelometry methods on Turbox nephelometer (Orion diagnostica, Finland). The concentrations were expressed as IU/ml for RF and mg/l for CRP. RF concentration $\geqslant$25 IU/ml and CRP concentration $\geqslant$6 mg/l were considered positive for RF and CRP respectively. The ESR was measured by the Westergren method.

2.2. Hospital anxiety and depression scale (HADS)

The hospital anxiety and depression Scale (HADS; [12]) is designed to measure both anxiety and depression in out-patient populations. Each subscale comprises seven items which are rated on a four-point scale and scored from 0 to 3 with total scores therefore ranging from 0 to 21 for each subscale. Scores between 0 and 7 represent 'no case'; 8–10 indicate 'possible case' and 11–21 suggest a 'probable case of anxiety/depression'. These cut points have been validated against clinical interviews with sensitivity and specificity around 0.80 [20]. In this study only the HADS-Depression subscale (HADS-D) was used.

Statistical analysis: The results were analysed by IBM-SPSS (version 19). Results were given as means and standard deviation. Student's *t*-test for continuous variables was used to examine the significance of differences between RA patients with and without depression. *P*-value less than 0.05 was regarded as significant. The correlation between HADS-D and age, disease duration, swollen and tender joint counts, VAS, DAS28, HAQ, ESR and CRP was analysed by Pearson correlation analyses. Linear regression analysis was used to evaluate the effect of clinical and demographic characteristics on HADS-D within the group of RA patients and depression. P value < 0.1 was considered significant.

3. Results

This study was carried on 170 RA patients (153 females and 17 males), their mean age was 43.75 ± 8.03, ranged from 34 to 68 years. The duration of RA was 3.74 ± 1.38, ranged from 2 to 9 years. The demographic and clinical characteristics of patients with RA are shown in Table 1.

Of the RA patients, the prevalence of depression was 15.29% (26 RA patients). Statistically high significant differences ($P < 0.001$) were found between depressed and non depressed RA patients as regards HADS-D, VAS, DAS28, number of tender joints, ESR and CRP. A statistically significant difference ($P < 0.05$) was found between both groups as regards the DMARDs and RA duration. No significant difference ($P > 0.05$) was found between depressed and non

Table 1 Demographic and clinical characteristics of RA patients (n = 170).

Characteristic (Mean ± SD)	RA patients (n = 170)
Age (years)	43.75 ± 8.03
Sex (F/M)	153/17
Disease duration in years	3.74 ± 1.38
Rheumatoid factor (%)	134 (78.8%)
VAS (0–100 mm)	39.41 ± 13.4
Number of swollen joints	1.21 ± 0.8
Number of tender joints	2.73 ± 0.99
DAS28 score	3.88 ± 0.35
HAQ score	1.45 ± 0.35
ESR (mm/1sthr)	24.14 ± 5.98
CRP (mg/l)	4.2 ± 3.67
HADS-D	5.85 ± 3.7
Medications	

VAS, visual analogue scale of pain; DAS28, disease activity for 28 joint indices score; HAQ, health assessment questionnaire; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; HADS-D, hospital anxiety and depression scale-depression subscale; MTX, methotrexate; LEF, leflunomide; HCQ, hydroxychloroquine.

depressed RA patients as regards gender, age, number of swollen joints and HAQ score (Table 2).

In the depressed RA patients, positive significant correlations were found between HADS-D score and age, disease duration, HAQ score, VAS, DAS28 score and CRP. However, no significant correlation was found between HADS-D score and ESR, number of swollen and tender joints (Table 3) (Fig. 1a and Fig. 1b).

On performing a linear regression analysis to assess the effect of clinical and demographic variables on HADS-D in RA patients with depression, it was found that age, RA duration and disease activity (DAS28) were significant predictors of depressive symptoms in RA patients (Table 4).

Table 3 Correlations between HADS-D and patients' characteristics in depressed RA patients (n = 26).

Characteristic (mean ± SD)	r test	P value
Age (years)	0.80	< 0.001 (HS)
Disease duration (years)	0.75	< 0.001 (HS)
VAS (0–100 mm)	0.53	0.005 (S)
Number of swollen joints	−0.15	0.48 (NS)
Number of tender joints	0.13	0.53 (NS)
DAS28 score	0.49	0.01 (S)
HAQ score	0.60	< 0.001 (HS)
ESR(mm/1st h)	0.08	0.69 (NS)
CRP(mg/l)	0.63	< 0.001 (HS)

VAS, visual analogue scale of pain; DAS28, disease activity for 28 joint indices score; HAQ, health assessment questionnaire; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

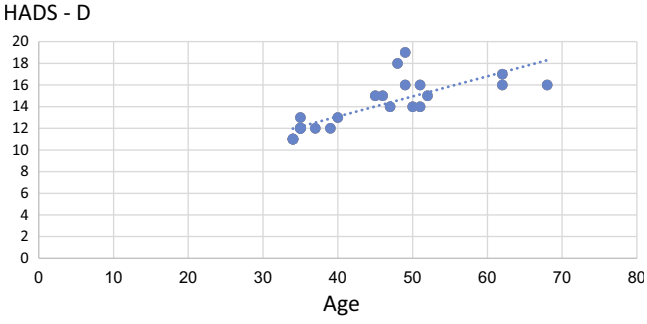

Figure 1a Correlation between HADS-D and age in RA patients with depression.

Table 2 Demographic and clinical characteristics of depressed and non depressed RA patients (26 versus 144 patients respectively).

Characteristic (mean ± SD)	Depressed RA patients (n = 26)	Non depressed RA patients (n = 144)	t test**/Chi square*	P value
Sex (M/F)	4/22	13/131	0.99*	0.32 (NS)
Age (years)	43.92 ± 9.96	43.72 ± 7.68	0.12**	0.91 (NS)
Disease duration (years)	4.35 ± 1.94	3.63 ± 1.23	2.49**	0.01 (S)
VAS (0–100 mm)	47.69 ± 21.41	37.92 ± 10.83	3.54**	0.001 (HS)
Number of swollen joints	1.42 ± 0.7	1.17 ± 0.81	1.48**	0.14 (NS)
Number of tender joints	1.92 ± 0.89	2.88 ± 0.95	4.77**	< 0.001 (HS)
DAS28	4.14 ± 0.45	3/83 ± 0.31	4.32**	0.001 (HS)
HAQ score	1.54 ± 0.21	1.43 ± 0.37	1.39**	0.16 (NS)
ESR (mm/1st h)	31.96 ± 3.84	22.73 ± 5.15	8.72**	< 0.001 (HS)
CRP (mg/l)	10.08 ± 3.42	3.14 ± 2.54	12.01**	< 0.001 (HS)
HADS-D	13.81 ± 2.32	4.41 ± 1.27	29.93**	< 0.001 (HS)
Medications:				
MTX + HCQ	13 (50.0%)	96 (66.7%)		
LEF + MTX	2 (7.7%)	24 (16.4%)	10.09*	0.02 (S)
MTX	7 (26.9%)	12 (8.3%)		
LEF	4 (15.4%)	12 (8.3%)		

VAS: visual analogue scale of pain; DAS28: disease activity for 28 joint indices score; HAQ: health assessment questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HADS-D: hospital anxiety and depression scale-depression subscale; MTX: methotrexate; LEF: leflunomide; HCQ: hydroxychloroquine.

* Chi square was used.

** Student's t test was used.

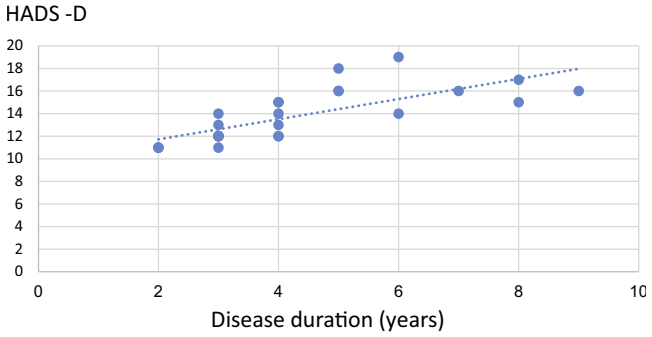

Figure 1b Correlation between HADS-D and disease duration in RA patients with depression.

Table 4 Linear regression analysis of clinical and demographic characteristics influencing HADS-D in RA patients with depression (n = 26).

Model	Beta	t	Sig.
Sex	−0.02–	−0.27–	0.79
Age (years)	−0.23–	−2.48–	0.01
Disease duration (years)	0.38	4.26	0.000
HAQ	0.09	1.25	0.21
DAS28	0.34	4.48	0.000

DAS28, disease activity for 28 joint indices score; HAQ, health assessment questionnaire.

No significant difference ($P > 0.05$) was found between male and female RA patients with depression except in the ESR where the difference was highly significant (Table 5).

As regards the DMARDs used for treatment of RA, no significant difference ($P > 0.05$) was found between different groups of RA patients and depression (Table 6).

4. Discussion

RA is a systemic inflammatory disease that affects people both physically and psychologically. Depression and anxiety frequently occur in RA [21]. Concomitant depressive or anxiety disorders in RA patients are associated with significantly poorer health-related quality of life [22]. Depression affects patients with RA beyond the burden of mental illness itself [23].

In the current study, prevalence of depression in patients with RA was 15.29%. In other studies conducted on patients with RA, major depressive disorder is common with a prevalence of 13–42% [15,24–27], at least double to four-times that in the general population. The wide range in the prevalence of depression in clinical studies of RA is likely due to the different methods used for measuring depressive symptoms [23]. Race/ethnicity is also a patient characteristic independently associated with depression in RA. Specifically, Asians with RA report less depression [28] while Hispanics with RA, particularly those who are not fully acculturated to mainstream Anglo society, report more depression [29].

In this study, a statistically high significant difference ($P < 0.001$) was found between depressed and non depressed RA patients as regards VAS, DAS28, number of tender joints, ESR and CRP. A statistically significant difference ($P < 0.05$) was found between both groups as regards RA duration. No significant difference ($P > 0.05$) was found between depressed and non depressed RA patients as regards gender, age, number of swollen joints and HAQ score. These results show that patients with RA and co-morbid depression have worse health outcomes [23]. In other words, poor clinical characteristics and function are associated with subsequent depressive symptoms [30]. In other studies, the duration of the rheumatic disease does not appear to differ between patients with and without depression [24,28].

In this study, no significant correlation was found between depression and gender while a positive significant correlation was found between depression and age. These results are contradictory with other studies [13,15,25,31]. In those studies, female gender and younger age have well-known associations with depression [23]. The reasons for this discrepancy between our study and those studies may be related to the racial differences or to the small number of patients used in our study. In our study, the disease duration was positively correlated with the degree of depression which was consistent with Isik et al. [27].

In the current study, a high positive significant correlation ($P < 0.001$) was found between depressed RA patients and VAS. Our results were similar to those reported in other studies [32,33]. Not surprisingly, pain has been indicated as a mechanism along the causal pathway for depression in those with RA [34–36]. Furthermore, depression may confound self-reports of pain [37]. Alternatively, pain in a patient with RA and co-morbid depression could be diagnostic

Table 5 Comparison between male and female RA patients (4 versus 22 patients, respectively) with depression.

Characteristic (mean ± SD)	Male (n = 4)	Female (n = 22)	t test	P value
Age (years)	45.50 ± 13.48	43.64 ± 9.57	0.34	0.74 (NS)
Disease duration in years	4.75 ± 2.99	4.27 ± 1.78	0.45	0.66 (NS)
VAS (0–100 mm)	45 ± 12.91	48.18 ± 22.81	0.27	0.79 (NS)
Number of swollen joints	1 ± 0	1.5 ± 0.74	1.33	0.20 (NS)
Number of tender joints	2 ± 0.82	1.91 ± 0.92	0.18	0.86 (NS)
DAS28 score	4.2 ± 0.36	4.13 ± 0.47	0.28	0.77 (NS)
HAQ score	1.5 ± 0.08	1.54 ± 0.22	0.37	0.72 (NS)
ESR(mm/1st h)	37.25 ± 4.11	31 ± 2.98	3.66	0.001 (HS)
CRP(mg/l)	11 ± 3.46	9.91 ± 3.48	0.58	0.57 (NS)
HAD-D	13.25 ± 2.22	13.91 ± 2.37	0.52	0.61 (NS)

VAS, visual analogue scale of pain; DAS28, disease activity for 28 joint indices score; HAQ, health assessment questionnaire; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; HADS-D, hospital anxiety and depression scale-depression subscale.

Table 6 The disease modifying anti-rheumatic drugs (DMARDs) used in RA patients with depression.

DMARDs	RA + depression ($n = 26$)	HADS-D (Mean ± SD)	Anova test	P value
MTX + HCQ	13 (50.0%)	(14.0 ± 2.55)	0.340	0.797 (NS)
LEF + MTX	2 (7.7%)	(13.5 ± 2.12)		
MTX	7 (26.9%)	(14.14 ± 2.27)		
LEF	4 (15.4%)	(12.75 ± 2.22)		
Total	26 (100.0%)	(13.81 ± 2.32)		

RA, rheumatoid arthritis; HADS-D, hospital anxiety and depression scale-depression subscale; DMARDs, disease modifying anti-rheumatic drugs; MTX, methotrexate; LEF, leflunomide; HCQ, hydroxychloroquine.

overshadowing – a process where the physical symptoms of RA are misattributed to depression [38].

In this study, a high positive correlation ($P < 0.001$) was found between HADS-D and HAQ scores, and a positive correlation was found between HADS-D and DAS28 scores. However, no significant correlation was found between HADS-D score and number of swollen and tender joints and ESR. In other studies, there is conflicting evidence as to whether or not RA disease activity measured by rheumatologist-documented swollen and tender joints affects depression. Some studies show a positive correlation between depression and RA disease activity scores [39–41] while others do not [28,42]. Regardless of acute disease activity measures, there is no doubt that limited function, as measured by the HAQ, is a strong predictor of depression in patients with RA [25,30,35,36,39,43–45]. Taking this one step further, loss of valued activities beyond functional decline has been shown to lead to depression [30,45]. This suggests that depression in RA may not be caused by the acute clinical manifestations of RA disease activity but instead caused by the long-term disability and joint damage associated with arthritis that results in the loss of valued activities [23]. On the other hand, Rathbun et al. suggest that depression may exacerbate pain and disease activity and decrease the efficacy of pharmacological (i.e. biologic and non-biologic DMARDs) and some non-pharmacological (e.g. cognitive behavioural therapy) RA treatments [46]. Further researches are needed to confirm these results.

Finally, in this study, a high positive significant correlation was found between depression and CRP. In patients with RA, there is conflicting evidence regarding the association of CRP with depression [35,47]. Compared with non-depressed individuals, depressed patients have activated inflammatory pathways, including increased expression of chemokines, adhesion molecules and cytokines [48]. Patients with major depression have increased serum and/or plasma concentrations of CRP [49,50], IL-6 [51,52] and proinflammatory TNF-α [53–56].

Indeed, disease activity has been associated with depression in RA both in cross-sectional [5,28,39] and in longitudinal research [39]. It is important that the finding of a correlation between disease activity variables and depression does not prove that depression is a direct consequence of disease activity. This relation may be mediated by psychological factors or another factor may be driving the relation. Depression may be an indirect consequence of psychological mechanisms such as the burden of symptoms and the uncontrollable nature of rheumatic diseases and their unpredictable course that may make patients more vulnerable to depression by mechanisms of learned helplessness [57].

Rheumatologists must consider depression as a consequence of both social context and biologic RA disease factors in order to assess which aspects contribute the most to depression in patients with RA. In the next 10 years, rheumatologists can substantially decrease depressive symptoms in their patients by addressing the root causes of depression: preventing pain and disability, decreasing systemic inflammation and designing and implementing evidence-based programs to mitigate the effects of depression in RA [7,58]. This entails moving beyond associations to establish causal relationships that in turn can lead to new and targeted therapies for depression in patients with RA [23].

In conclusion, depression appears to be common, and there is a need for greater recognition among rheumatologists of this relatively neglected condition. Also, there is a need for an acceptance of responsibility for identifying and managing it appropriately. As a treatable condition with a high prevalence that causes significant suffering, we feel that a greater emphasis on recognizing and treating depression in RA is warranted.

Conflicts of interest

The authors declare no conflicts of interest.

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