Research article

Disease activity and functional status and their relation to depression in patients with rheumatoid arthritis

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Abstract

Background: Rheumatoid arthritis (RA), one of the commonest forms of inflammatory arthritis, has significant societal impact with regards to cost, induction of disability and loss of productivity. This impact is magnified in the presence of comorbid mood disorders, as these constitute independent factors for unexplained flares and relapses.

Objective: The primary purpose of our study was to determine the correlation between disease activity and depression in RA patients.

Methods: Patients with RA attending rheumatology clinic at Aga Khan University Hospital, Nairobi were recruited into the study. The patients' disease activity and functional status were assessed using the Clinical Disease Activity Index and the Stanford Health Assessment Questionnaire respectively, whereas the level of depression was evaluated using the Patient Health Questionnaire-9. Pearson's correlation coefficient was calculated for the disease activity and functional status versus the depression scores, and relationship between the disease activity and depression scores was analyzed using Chi square tables.

Results: A total of 60 patients were enrolled into the study, whose mean age was 48.8 ± 13.6 years. There were 52 females (86.7%). The mean duration of RA symptoms was 71.6 ± 86.6 months, with the mean duration of RA treatment being 43.4 ± 64.5 months. Among the study participants, 28.3% had mild depression whereas 35% had moderate/ severe depression. There was a strong positive correlation between disease activity and depression ($p<0.001$), as well as between physical disability and depression.

Conclusion: This study found depressive symptoms in 63.3% of the patients, in spite of the study population being relatively young and having short duration of disease. The significant correlation observed between disease activity and depression illustrates the high likelihood of undiagnosed comorbid depression as a co-existing factor in persistently active disease, poor response to therapy and unexplained flare-ups in the Kenyan RA population.

Key words: Rheumatoid Arthritis, Depression, CDAI, PHQ-9, HAQ

Introduction

Rheumatoid Arthritis (RA) is one of the commonest forms of systemic inflammatory arthritis with substantial impact on the society with regards to mortality, cost implications, loss of productivity and induction of disability[1]. Comorbidities that aggravate the disease activity and severity further magnify these effects, resulting in worse functional outcome[2,3]. These include conditions that influence the ability of the patients to adhere to their treatment schedules such as cardiovascular diseases, depression and sleep disturbances[4,5]. Among these, depression is perhaps the most common, and its point prevalence among RA patients eclipsed that in the community with up to 15%[2,6] versus 2% as reported in a recent systematic review[7]. One study found that relapse in RA was influenced by the presence of psychological stress and mood status of the patients, prompting them to recommend that these factors should be examined in patients whose disease appear to be unresponsive to standard treatment schedules and for whom there were no explicit factors leading to disease flare ups[8]. Furthermore, response to interventions specific to RA disease was dwarfed by the presence of untreated depression[9], adding weight to the accumulating evidence that points to the fact that both quality of life and activity of disease in RA patients is greatly affected by the presence of comorbid depression. However, most of the RA patients with comorbid depression are not on treatment[10], despite international guidelines like the National Institute for Health and Care Excellence (NICE) guidelines recommendations for annual screening for depression in the RA patient population[11].

The noteworthy finding in the local RA studies is that the patients are younger compared with other populations, yet they also have greater disease activity, which could be the result of greater burden of depression[12,13]. This study being the first of its kind in this region was therefore undertaken in order to highlight the importance and necessity of guidelines regarding depression screening and management among patients on follow up for RA in this unique population, especially in light of the magnified risk of cardiovascular complications and mortality among those in whom this is left undiagnosed[14]. These guidelines have been noted to be largely unclear in Africa, and where present like in South Africa and in the recently launched Kenyan Consensus Expert Recommendations[15,16], they make no mention of the necessity for depression screening in RA patient population.

In this study, our primary aim was to demonstrate the relation between disease activity and functional status of RA patients to depression by using the Clinical Disease Activity Index (CDAI) score to evaluate the disease activity and Patient Health questionnaire 9 (PHQ-9) to assess depression scores.

Materials and methods

This was a prospective cross sectional, analytical study carried out from the adult rheumatology clinics at Aga Khan University Hospital, Nairobi between 1st September 2018 and 31st January 2019, during which a total of 60 RA patients meeting the ACR/EULAR 2010 criteria were recruited. Prior clearance was obtained from the Aga Khan University ethics committee, and patients who were found to have moderate to severe depression were referred for review by a psychiatrist. The PHQ-9 self-administered questionnaire was used to assess for depression; this tool is scored from 0-27; where no depression is represented by scores of 0-4, mild depression scored as 5-9, moderate depression scored as 10-14, moderately severe depression scored as 15-19 and severe depression indicated by scores of 20-27. The RA disease activity was calculated by the attending clinician using the CDAI tool. This is made up of four components – Tender Joint Count (TJC) score, Swollen Joint Count (SJC) score, provider global assessment of disease activity score and patient global assessment of disease activity score - which are summated to obtain the composite disease activity scores (i.e. 0.0-2.8: remission, 2.9-10.0: low disease activity, 10.1-22.0: moderate activity and 22.1-76.0: high activity). Correlation graphs were then plotted to evaluate the relationship between depression and disease activity.

CDAI is one of the validated tools for disease activity assessment in RA[17] and has recently been shown by Dhaon *et al*[18] to be better than DAS 28 (CRP) based criteria which has often been referenced as the gold standard measure, and is also the only validated tool whose use in daily clinical practice is not limited by the necessity of adjunctive laboratory tests for completion of patient scores[19], making it an invaluable option in resource constrained settings. We used PHQ-9, which is a succinct and freely available tool, to assess the levels of depression[20]. It is one of the three tools recommended by the NICE guidelines for screening for depression among rheumatology patients[21], and was demonstrated to be valid in a population of varied races and ethnicities[22]. The value, sensitivity and effectiveness of Stanford HAQ, which we used as the tool for disability assessment in RA, has been demonstrated over a period of over twenty years[23], and is accepted as the gold standard measure in these evaluations[24].

The following formula for calculating sample size for correlation studies was used[25]:

$$N = \left[\frac{Z_\alpha + Z_\beta}{C}\right]^2 + 3$$; Where, = the standard normal deviate for α, = the standard normal deviate for β,

$$N = \left[\frac{Z_\alpha + Z_\beta}{C}\right]^2 + 3$$

The assumptions are: a two tailed alpha (α) of 0.05 for 95% confidence, beta (β) of 0.20 for 80% power to detect a correlation coefficient (ρ) of 0.4 (R^2 Linear = 0.193, < 0.001) based on a 2015 study by Imran and others[26] which evaluated RA disease activity and its relationship to the level of depression among patients on clinic follow up at a tertiary care facility in Pakistan. Based on this, in order to detect the correlation coefficient of 0.4, the estimated minimum sample size required was determined to be 52 participants, after allowing for 10% loss due to failure to meet the inclusion criteria.

The data from the completed data collection tool was coded and entered into password secured SPSS database software for analysis. Categorical variables were expressed as frequencies and percentages whereas continuous variables were reported as means with standard deviations. Appropriate tests were used to assess for the normality of the continuous variables. Univariate analysis of the continuous variables was conducted using the Wilcoxon-Mann-Whitney U test or the Student's t-test whereas Fisher's exact test or Chi square (χ^2) was utilized for analysis of categorical variables. Correlation graphs were plotted using Pearson's method for the dependent vs independent variables.

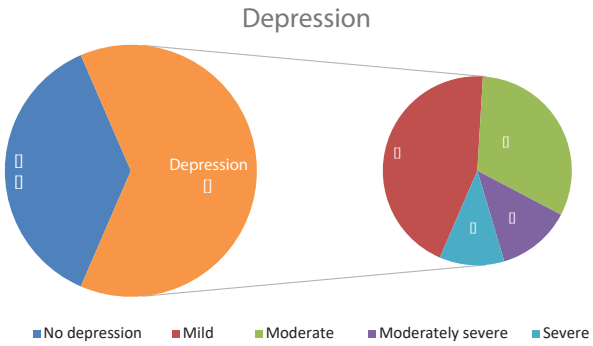
Results

Sixty patients on clinic follow up for RA were examined. Their mean age was 48.8 ± 13.6 years. There were 52 (86.7%) female patients and 8 (13.3%) male patients. Majority of the study participants (73.3%) had attained college level education. Hypertension was the commonest comorbidity (28.3%), followed by diabetes at 6.7%. Only 3.3% were known to have dyslipidemia, and none of the study subjects had a previously diagnosed cardiovascular disease. Smoking history (previous or current) was present in only one participant.

The mean duration since diagnosis of RA was 71.6 ± 86.6 months, and the mean duration on treatment for RA was 43.4 ± 64.5 months. RF status was known in 58 of the 60 patients studied, and the positivity rate was 79.3%, whereas Anti-CCP status was known in 57 patients, with positivity rate of 87.7%.

RA disease activity as scored by the CDAI revealed that 18.3% of the patients were in clinical remission while 81.7% had active disease (low activity - 30%, moderate activity - 31.7%, high activity - 20%). The depression scores were as follows: 36.7% had no depression whereas 63.3% had depression (28.3%: mild, 20%: moderate, 8.3%: moderately severe, 6.7%: severe depression) (Figure 1).

Figure 1: Depression scores



Comparative analysis was done for the demographic and clinical profiles of the studied population after stratification into remission/mild depression versus moderate/severe depression sub-groups. Age, gender, disease duration and RA treatment duration were all found to have no differences of statistical significance between the two sub-groups. This was the case as well when the analysis of the above variables was undertaken comparing those with controlled disease (remission and mild activity) to the group with uncontrolled disease (moderate and high activity). However, the TJC scores, the SJC scores, the provider global assessment of disease severity scores and the patient global assessment of disease severity scores were significantly different between those in the remission/mild depression category in comparison to those in the moderate/severe depression category (<0.05). These findings are summarized in Tables 1 and 2.

Table 1: Demographics and clinical profiles with respect to disease activity

Variables	RA disease activity		P
	Remission/Low disease activity (n = 29)	Moderate/Severe disease activity (n = 31)	
Demographics	Mean ± SD / N (%)	Mean ± SD / N (%)	
Age (years)	50.0 ± 10.9	47.7 ± 15.8	0.446
Gender (male, female)	5 (17.2%), 24 (82.8%)	3 (9.7%), 28 (90.3%)	0.465
Education (primary, secondary, tertiary)	3 (10.3%), 4 (13.8%), 22 (75.9%)	6 (19.4%), 3 (9.7%), 22 (71.0%)	0.696
Hypertension (No, Yes)	21 (72.4%), 8 (27.6%)	22 (71.0%), 9 (29.0%)	1.000
Clinical profiles			
RF (positive, negative)	7 (25%), 21 (75%)	5 (16.7%), 25 (83.3%)	0.525
Anti-CCP (negative, positive)	3 (11.1%), 24 (88.9%)	4 (13.3%), 26 (86.7%)	1.000
RA disease duration, months	70.0 ± 99.2	73.1 ± 74.7	0.743
RA treatment duration, months	37.2 ± 68.9	49.3 ± 60.6	0.664
TJC score	0.7 ± 1.1	7.7 ± 5.4	< 0.001
SJC score	0.4 ± 0.6	4.1 ± 3.6	< 0.001
Provider global assessment of disease activity	1.6 ± 1.3	5.3 ± 2.0	< 0.001
Patient global assessment of disease activity	1.6 ± 1.4	5.3 ± 2.3	< 0.001

RA = Rheumatoid Arthritis; RF = Rheumatoid Factor; Anti-CCP = Anti-Cyclic Citrullinated Peptide; TJC = Tender Joint Count; SJC = Swollen Joint Count; SD = Standard Deviation; N = Number

Table 2: Demographics and clinical profiles with respect to depression severity

Variables	Depression severity No/Mild Depression (n = 39)	Moderate/Severe depression (n = 21)	
Demographics	Mean ± SD / N (%)	Mean ± SD / N (%)	
Age (years)	50.4 ± 13.3	45.9 ± 14.0	0.235
Gender (male, female)	6 (15.4%), 33 (84.6%)	2 (9.5%), 19 (90.5%)	0.701
Education (primary, secondary, tertiary)	6 (15.4%), 5 (12.8%), 28 (71.8%)	3 (14.3%), 2 (9.5%), 16 (76.2%)	1.000
Hypertension (no, yes)	28 (71.8%), 11 (28.2%)	15 (71.4%), 6 (28.6%)	1.000
Clinical profiles			
RF (positive, negative)	8 (21.1%), 30 (78.9%)	4 (20%), 16 (80%)	1.000
Anti-CCP (negative, positive)	5 (13.5%), 32 (86.5%)	2 (10%), 18 (90%)	1.000
RA disease duration, months	72.6 ± 91.6	69.8 ± 78.6	0.749
RA treatment duration, months	38.2 ± 62.5	53.2 ± 68.5	0.802
TJC Score	2.1 ± 3.0	8.3 ± 6.3	< 0.001
SJC Score	1.5 ± 2.1	3.9 ± 4.2	0.029
Provider global assessment of disease activity	2.6 ± 2.2	5.0 ± 2.3	< 0.001
Patient global assessment of disease activity	2.5 ± 2.1	5.2 ± 2.7	< 0.001

RF = Rheumatoid Factor; RA = Rheumatoid Arthritis; Anti-CCP = Anti-Cyclic Citrullinated Peptide; TJC = Tender Joint Count; SJC = Swollen Joint Count; SD = Standard Deviation; N = Number

The CDAI score which is a gauge of disease activity in RA was found to have a strong positive correlation (Pearson Correlation) with the PHQ-9 score for depression severity ($r = 0.643$, $p = < 0.001$).

A strong positive correlation was noted between the functional status (measured by the HAQ) and depression severity ($r = 0.568$, $p < 0.001$). The strong correlation was similarly observed between the disease activity scores and the functional status evaluations ($r = 0.758$, $p = < 0.001$). The graphs demonstrating the correlations are outlined in the Figures 2 and 3.

Figure 2: Correlation graph between depression severity and disease activity in RA

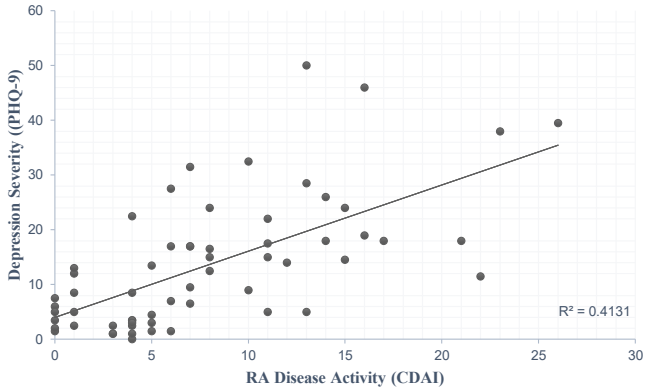
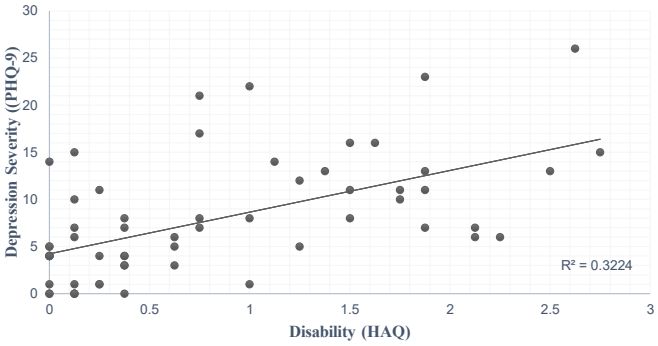


Figure 3: Correlation graph between severity of depression and functional status in RA



Our analysis of the depression scores for association with disease activity using the Fisher's exact test demonstrated significant association ($p<0.05$) as displayed in Table 3.

Table 3: Comparison between depression scores and disease activity scores

PHQ-9 depression score	CDAI score			
	Remission (n = 11)	Low activity (n = 18)	Moderate activity (n = 19)	High activity (n = 12)
No	9 (15%)	10 (16.7%)	2 (3.3%)	1 (1.7%)
Mild	2 (3.3%)	5 (8.3%)	7 (11.7%)	3 (5.0%)
Moderate	0	3 (5.0%)	5 (8.3%)	4 (6.7%)
Moderately severe	0	0	3 (5.0%)	2 (3.3%)
Severe	0	0	2 (3.3%)	2 (3.3%)

Analysis of the swollen joint count in comparison to depression scores indicated a strong correlation (r = 0.475, p = < 0.001). Association between the presence of swollen joints and the existence of depression was also demonstrated to be of statistical significance (p = 0.006).

Discussion

This study had striking similarities in terms of demographics and clinical characteristics with an earlier local study done in 2009 at the biggest public hospital in this country[12]. The similarities were seen on age, gender ratio, RF positivity rate and active disease percentage. Female predominance was conspicuous in this study just like in another RA study[4]. The participants' median age was 48 years while it was 36 months for duration of disease. These are comparable to the Sudanese RA population (in which median value for age was 49 years and for duration of disease was 48 months) in a study that compared them to Swedish counterparts (median age: 68 years; median duration of disease:107 months)[13]. This study also confirms the findings by Owino and colleagues[12] indicating that the RA patients in local set up have more active disease despite being relatively younger and having shorter duration of disease. More than 70% of the study population had up to tertiary level education, and given that most of these were young, female adults, potential economic loss to the society is high, as their productivity is cut down by the functional impairment and disability induced by their illness and aggravated by comorbid depression. Furthermore, within the household, these patients are likely to be unable to take part in chores and family activities which may result in strain and dysfunctional family units given that in the local communities, women are integral in the running of families' daily activities especially cooking, cleaning and upbringing of children.

Hypertension was the most common comorbid condition reported by the patients, followed by diabetes mellitus at 6.7%. Only 3.3% had dyslipidaemia and none of the patients reported a prior diagnosis of any cardiovascular disease, unlike other studies that suggest a great burden of comorbidities among RA patients[2]. Only one (1.7%) of the respondents reported a history of cigarette smoking. This mimics the finding of the study referenced above where no smokers were found among the Sudanese patients. More than 70% of the patients reported to have tertiary level education, likely because that this study was undertaken in a private tertiary level health facility.

Depressive symptoms were found in 63.3% of the RA patients we studied, which is much greater than the point prevalence of depression in RA which is approximated at about 15% in other studies[6]. However, these findings were much closer to the findings of a 2015 Pakistan study and a 2017 Chinese study that reported 71% and 62% depression among RA patients respectively[26,27]. Most of the study participants had active disease (30% = low activity, 31.7% = moderate activity, 20% = high disease activity) which is similar to the report from an earlier Kenyan study where 88% were found to have active disease[12].

Our study showed statistically significant linear correlation between the CDAI scores for disease activity and the PHQ-9 depression scores (r = 0.643, < 0.001). This represents further evidence that comorbid depression is a crucially linked factor in RA disease activity, and perhaps explains the notably high percentage of patients with active disease (>80%) given that depression was found to be present in 63.3% of the participants[3,10,28,29]. Indeed, the study also revealed significant association between activity of disease and the severity of depression.

Analysis of the CDAI scores further revealed that the difference between no/mild depression category and moderate/severe depression category was statistically significant for each of the components scored i.e. TJC (p<0.001), SJC (p = 0.029), provider global assessment of disease activity (p<0.001) and patient global assessment of disease activity (p<0.001) scores. There was no difference of statistical significance between the two categories with respect to age, gender, education level, disease duration since diagnosis or duration of treatment for RA. The correlation between physical disability and depression was also found to be strong (r=0.568, p<0.001). This reaffirms the predictive value of

functional status of RA patients on depression[3,30,31] which is in fact not unexpected given the strong correlation demonstrated in our study between disease activity and functional status ($r = 0.758$, $p<0.001$).

The utilization of CDAI score to assess disease activity in this study was informed in part by the distinct advantage it presents in clinical practice given that its use eliminates the need for laboratory investigation for acute phase proteins in contrast to the other validated tools including Simplified Disease Activity Index (SDAI) or the complex mathematical calculations required for DAS 28 scoring[17-19]. However, given that psychosomatic symptoms due to depression can arguably affect the subjective scoring of three of the components of the CDAI (i.e. TJC, provider global assessment and the patient global assessment of disease activity), we also assessed the more objective component – Swollen Joint Count (SJC) – in relation to depression in RA[32]. The analysis revealed that the positive correlation between SJC and depression was highly significant ($r = 0.475$, $p < 0.001$). Chi square was also used to confirm the meaningful association between the presence of tender joints and the presence of depression . Since SJC cannot be influenced by the presence of depressive symptoms, it is therefore deducible that this finding further corroborates the relation noted in the composite CDAI scores and the PHQ-9 scores.

Given that more than half of the participants had not achieved the recommended goal of RA therapy which is either remission (ideally) or low disease activity[11,15,16], it would be imperative that physicians recognise undiagnosed comorbid depression in RA patients and offer the necessary management, especially in those with persistently active disease, poor response to optimal therapy and unexplained flare ups[8,9,33].

Conclusion

This study found 63.3% of the RA patients to have depressive symptoms, in spite of this population being relatively young and having short duration of disease. A strong positive correlation was demonstrated between disease activity and physical disability in RA and the level of depression. Analysis of the swollen joint count, which eliminates the possible confounding effect of the physical symptoms of depression on disease activity, appears to confirm that this relation is maintained even when the subjective components of CDAI score are excluded. We recommend further studies to evaluate the impact of treating comorbid on disease activity and functional status in the local RA population.

Limitations: The study center being a tertiary level private referral hospital limits generalizability of the study findings. RA patients with more active disease, especially those exhibiting poor response to medications, may be the ones referred by other clinicians for follow up by consultant rheumatologists which may amplify the average disease activity scores above the scores in the general population. The symptoms of arthritis may mimic those of depression and this complicates the evaluation of disease activity versus depression scores, in spite of the tool used in this study having being noted in other studies to be reliable even in such a scenario. The depression score was evaluated by way of a self-administered questionnaire making the findings prone to reporting bias.

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