

A Study To Correlate Disease Activity With Anxiety And Depression Among The Patients With Rheumatoid Arthritis With A View To Develop An Educational Module In Selected Hospital Bangalore.

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ABSTRACT

Background and objectives: Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects a person's joints, causing pain and disability. Individuals with RA show psychological distress and causes progressive functional deterioration which can further affect their quality of life, leading to noncompliance, depressive symptoms and even self harm in extreme cases of anxiety & depression. The objectives of this study were: To assess the disease activity of patients with rheumatoid arthritis; To assess the anxiety level of patients with rheumatoid arthritis; To assess the depression of patients with rheumatoid arthritis; To determine the correlation between disease activity and anxiety & disease activity and depression; To determine the association of disease activity with selected baseline variables, anxiety with selected baseline variables & depression with selected baseline variables.

Methods: Descriptive co relational design was used for the study. The setting selected was the Rheumatology OPD of SJMCH, Bangalore. 115 subjects were selected by using Convenience sampling technique. Structured interview technique was used to collect the baseline information and joint assessment was done and self administered questionnaire were given to the participants.

Results: It reveals that 72.2% of the patients were in the age group of ≥ 40 yrs. 85.2% were female affected with the RA and 67% subjects were skilled worker. Considering the domains of disease activity, 53.9% of the subjects were having moderate disease activity. 73.9% were minimally anxious and 50.4% were minimal form of depression. This study revealed that there was significant association between the family history of the patient with RA and the disease activity ($p= 0.03$). There was also an association between the trait anxiety and disease activity ($p= 0.04$) and also there is statistically significant association of trait anxiety with the state anxiety. ($p= 0.052$).

Conclusion: RA impairs the physiological and psychological wellbeing of the person. Thus the investigator hopes that the educational module will be an effective tool for the improving the overall wellbeing of the person with RA.

Key words: rheumatoid arthritis, anxiety, depression, disease activity

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I. INTRODUCTION

Rheumatoid Arthritis is an autoimmune disease that causes joint damages & pain. Patients affected with RA live with chronic pain and constant fatigue with or without physical disabilities. RA is a universal disease with a prevalence of 0.75% in adult Indian population. The long term prognosis is poor, 80% of affected patients are disabled and life expectancy is reduced by an average 3 to 18 years¹.

Recently, different new models of organizing care for patients with chronic disease has been introduced to optimize the treatment of the growing number of chronically ill people in Western countries². In the care of patients with medically stable chronic disease, medical specialists can allocate activities to other health professionals, allowing the specialists to divert their attention towards managing patients with more "serious" problems^{3,4}. Stable in this context means constant low activity of the chronic disease—that is, without flares. These substitution based models are believed to be better approaches to planning and delivering health care to chronically ill patients⁵.

Disease stability is derived from measurements of disease activity, which have a central place in the management of RA because reducing disease activity is the paradigm of treatment of RA. Measures of rheumatic disease activity can be classified as both process and outcome measures. Kirwan defined process as "the abnormal physiological consequences that follow from the cause of the disease" and outcome as "the

suffering or loss of health (death, disability, discomfort, iatrogenic, economic) of the patient caused by the disease process⁶. Disease stability can be defined as the lack, within certain limits, of changes or fluctuations in parameters of a disease within a defined period of time. To assess disease stability a time component has to be included in the measure: based on subsequent measures of disease activity, the degree of disease stability can be assessed.

Studies using self report measures of depressive symptoms suggest considerably higher rates (i.e. 40%), although the levels of symptomatology may be subclinical. Longitudinal studies suggest cumulative risk for depression and intermittent recurrence over time [i.e. 40% over 9 years]. The prevalence rates of depression in RA are well above those reported in the general community or primary care but similar to other chronic conditions. Depression in RA is associated with higher levels of disease activity, pain, fatigue, work disability, health service use but lower treatment compliance and increased suicide risk and mortality⁷.

Given the importance of effective screening for depression and anxiety in RA, it is essential to ensure that they are being appropriately measured with available scales. Furthermore, it has been noted that the rates of depression and anxiety vary considerably across studies partly due to differences in assessment scales. Those differences create difficulties in comparing results across studies and, for clinicians, in interpreting with confidence to what degree various scales may identify those who are at risk for depression or anxiety and require referral for further assessment⁸.

NEED FOR THE STUDY:

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects a person's joints, causing pain and disability. RA is more common in older people, but there is also a high prevalence in young adults and adolescents. It affects women more frequently than men. High rates of depression and anxiety have been shown in patients with RA⁸.

Rheumatoid arthritis (RA) is a long-term, fluctuating, inflammatory and systemic disease of unknown etiology which causes chronic synovial inflammation leading to joint destruction. In Portugal, the estimated prevalence was about 0.8% in 2001 with the incidence varying between 2-4 cases per 10,000 people each year⁹.

RA causes progressive functional deterioration leading to disability and impaired quality of life (QOL). Individuals with RA show psychological distress. More than 80% of persons having RA have clinically important fatigue. Pain, the main symptom of RA, affects up to 84% of individuals and negatively affects multiple aspects of life. RA occurs owing to an immune response, in which the body's immune system attacks its own healthy cells. The diagnosis depends mainly on the symptoms and signs. Radiographs and laboratory investigations may confirm the diagnosis or exclude other diseases with similar symptoms, such as systemic psoriatic arthritis, lupus erythematosus, and fibromyalgia.

Several studies have identified depressive symptoms as an important aspect in RA. The prevalence of depressive symptoms in RA has been reported to vary between 6% and 65%, according to the screening methods used and to the samples studied¹⁰⁻¹¹. A recent review described a mean prevalence of 19% of depression among RA patients¹². Anxiety symptoms and disorders have been less studied separately, because they are a very frequent dimension of depression, making it difficult to separate anxiety symptoms from depressive ones¹³. Some studies have found a prevalence of almost 40% of anxiety symptoms in RA¹⁴.

Approximately 20% of RA patients are unable to work in the first 2~3 years of the disease, and the frequency of work disability increases over time so that one-third of all patients are unable to work within 10 years following diagnosis. Disease activity and severity, functional disability, and morning stiffness have been reported to increase the inability of patients with arthritis to work. Advanced age, female gender, co-morbid conditions, low education level, and jobs requiring physical work are all patient-related risk factors.

Rheumatoid arthritis causes a person's immune system to mistakenly attack healthy tissue. Along with the joint, RA can affect many of the body organs including heart, eye, brain as well as skeleton. Rheumatoid arthritis can also cause the bones to lose density and becoming thinner, thereby more prone to fractures.

Patients with RA also report reduced quality of life in several domains, such as physical health, level of independence, environment and personal beliefs, compared with the healthy population. Quality of life in RA is affected by fatigue, pain, stiffness and impaired physical functioning¹⁵⁻¹⁶. In addition, Quality of life is also influenced by socioeconomic factors such as age, employment, economic status and lifestyle habits¹⁷.

As limitation of activity increases, it can further affect their quality of life, leading to noncompliance, depressive symptoms and even self harm in extreme cases of anxiety & depression. Though there are research studies on anxiety & depression among patients with RA, there appears to be lack of research studies done in India to correlate disease activity with anxiety and depression among the patient with rheumatoid arthritis. Thus the investigator felt a strong need to correlate anxiety and depression with disease activity among patients with rheumatoid arthritis. Based on the findings, the investigator wishes to develop an educational module for rheumatoid arthritis patients.

OBJECTIVES OF THE STUDY:

Objectives are:

1. To assess the disease activity of patients with rheumatoid arthritis.
2. To assess the anxiety level of patients with rheumatoid arthritis.
3. To assess the depression of patients with rheumatoid arthritis.
4. To determine the correlation between
 - i. disease activity and anxiety.
 - ii. disease activity and depression.
5. To determine the association of
 - i. disease activity with selected baseline variables.
 - ii. anxiety with selected baseline variables.
 - iii. depression with selected baseline variables.

ASSUMPTION:

Patients with rheumatoid arthritis may experience anxiety and depression.

Disease activity may affect the psychological well being of the rheumatoid arthritis patients.

HYPOTHESIS:

H₁: there will be a significant correlation between disease activity and anxiety among patients with rheumatoid arthritis at 0.05 levels of significance.

H₂: there will be a significant correlation between disease activity and depression among the patient with rheumatoid arthritis at 0.05 levels of significance.

H₃: there will be a significant association of

- a) disease activity with selected baseline variables at 0.05 levels of significance.
- b) anxiety with selected baseline variables at 0.05 levels of significance.
- c) depression with selected baseline variables at 0.05 levels of significance

II. MATERIALS AND METHODS:

RESEARCH APPROACH:

In view of the nature of the problem and the objective to be achieve, Quantitative approach was found to be more appropriate for this study.

RESEARCH DESIGN:

In view of the study, the research design selected was non experimental descriptive correlational design.

SAMPLING PROCEDURE: convenience sampling technique used.

SAMPLE: The samples comprises of rheumatoid arthritis patients visiting outpatient department in St. John's medical college hospital.

SAMPLE SIZE: To estimate correlation between the anxiety and depression and DAS in RA patient considering the population level correlation at 0.5, power of the study at 80% and at 5% alpha error the required sample size is 95 patients. The sample size of the pilot study was 10 patients with rheumatoid arthritis³⁰

INCLUSION CRITERIA:

- Patients who are diagnosed with rheumatoid arthritis since minimum 1 year.
- Patients age between 18-60 years

EXCLUSION CRITERIA:

Patients with documented mental illness and those undergoing psychiatric treatment.

INSTRUMENT USED:

The following instruments are used in this present study to measure the variables in the research problem and it consist of 4 section

Section 1: Proforma to elicit baseline variable

Section 2: Proforma to elicit disease activity

Section 3: proforma to elicit level of depression

Section 4: Proforma to elicit level of anxiety

DESCRIPTION OF TOOLS:

Section 1: Proforma to elicit baseline variable:

In this study baseline variables were age, gender address, occupation , duration of illness, other co-morbidities. Family history of RA, current medication and trait anxiety inventory. These state trait anxiety inventory was developed by Spielberger et al in 1977 to measure the trait anxiety. This inventory consist of 20 statements and it has a rating scale of (1-4). 9 items are indirect scoring and rest of the 11 items are direct scoring method. The maximum and minimum scoring of these inventory are 80and 20 respectively.

Section 2: Proforma to elicit disease activity

The disease activity score-28 (DAS-28) was developed by the P.L.C.M. Riel to measure the disease activity of rheumatoid arthritis patient. It include 28 tender joint and swollen joint, erythrocyte sedimentation rate / C- Reactive Protein, and also a general health of a patient assessed by the researcher with the help of Visual Analogue Scale. The level of disease activity can be interpreted as follows:

DAS28 <2.6	Remission
DAS28 ≥2.6to≤3.2	Low
DAS28 >3to≤5.1	Moderate
DAS28>5.1	Severe

Section 3: proforma to elicit level of depression

The level of depression among RA patient was measured by the standardized tool named as Patient health questionnaire-9.The PHQ-9 was developed by Dr. Robert J. Spitzer, Dr. Janet B.W. Williams, Dr. Kurt Kroenke, and colleagues from Columbia University. These scale has 9 question with the rating scale of 0-3. The minimum score is 0 and the maximum score is 27. The depression severity as follows:

PHQ-9 SCORE	INTERPRETATION
0-4	None- minimal
5-9	Mild
10-14	Moderate
15-19	Moderately severe
20-27	Severe

Section 4: Proforma to elicit level of anxiety

The level of anxiety was measured by using GAD-7 scale.The Generalized Anxiety Disorder Scale-7 (GAD-7) is a 7-item, self-rated scale developed by Spitzer and colleagues (2006) as a screening tool and severity indicator for GAD. This scale has 7 items and each items rated 0-3.the maximum score obtained in this scale is 21 and the minimum score is 0. Anxiety disorder can be classified as per the level:

GAD-7	INTERPRETATION
0-4	Minimal
5-9	Mild
10-14	Moderate
15-21	Severe

RELIABILITY OF THE TOOL:

Franseen J and his colleague established the reliability of DAS 28 by test retest method and it was found to be reliable where the p value 0.80. Udehi M and his associates established the reliability of PHQ-9 by cronbachs alpha method and it was found to be reliable where the p value 0.92. Lowe B and his associates established the reliability of GAD-7 by cronbachs alpha method and it was found to be reliable where the p value 0.89.

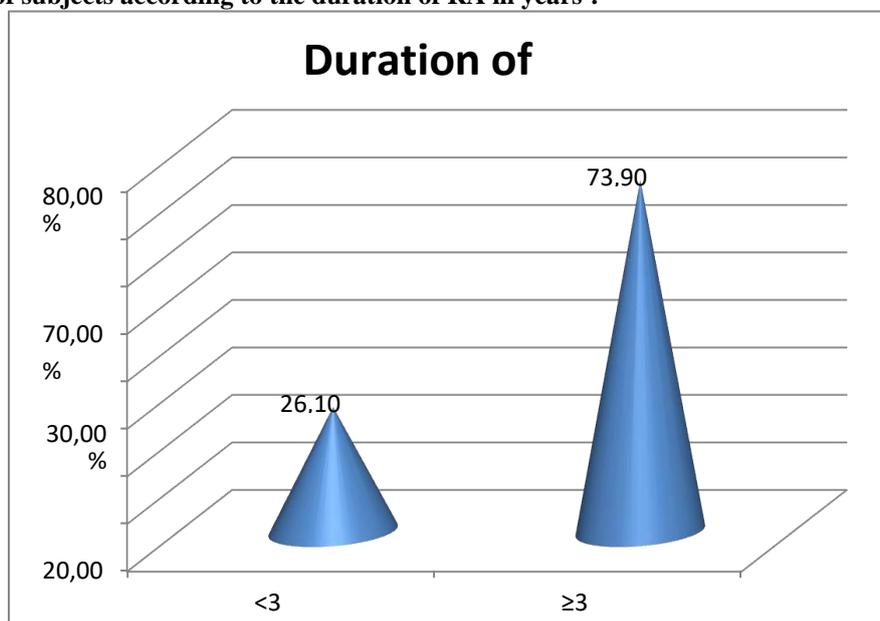
III. RESULTS:

Section 1: Description of demographic variables of the subjects:

SL NO	DEMOGRAPHIC VARIABLE	FREQUENCY	PERCENTAGE
1.	Age <40yrs	32	27.8
2.	Age ≥40yrs	83	72.2
3.	GenderFemale	17	14.8
	GenderMale	98	85.2
	Income ≤27351	7	6
	Income 26355 – 52733	18	13.9
	Income 19759 – 26354	11	9.6
	Income 13161 – 19758	27	23.5
	Income 7887 – 13160	30	26.2
	Income 2641 – 7886	17	14.8
4.	Occupation ≤2640	7	6
	Occupation Professional	5	4.3
	Occupation Semi-professional	6	5.2
	Occupation Clerical	20	17.4
	Occupation Skilled	77	67
	Occupation Unskilled	6	5.2
	Occupation Unemployed	1	0.9
5.	Trait anxietyLow	37	32.1
	Trait anxietyModerate	77	66.9
6.	Medication High	1	0.86
	Medication Immunosuppressants	27	23.5
	Medication Immunomodulators	5	4.3
	Medication Both	71	61.7
	Medication Noncompliant	12	10.4

In the present study 27.8% of the subjects were in the age group of < 40 yrs while 72.2% of the subjects were in the age group of ≥ 40yrs. Mean age of the subjects was 46.3 years. 85.2% of the subjects were female whereas only 14.8% were male. With regards to occupation, 67% subjects were skilled workers and 17.4% were clerical workers. In case of income, 26.2%, 23.5% and 14.8% of the subjects belonged to (7887-13160),(13160-19758) and (2641-7886) respectively. In view of medication used by the subjects, 61.7% of the subjects used combination therapy of immunosuppressants and immunomodulators

Distribution of subjects according to the duration of RA in years :



26.1% of the subjects had RA for the duration of < 3yrs and 73.9% of the subjects had RA for the duration of \geq 3yrs with mean duration of 6.5year

Distribution of the subjects according to the co- morbidities: 60% of the subjects with RA had no co – morbidities whereas 40% of the subjects with RA had comorbidities mainly diabetes and hypertension.

Distribution of the subjects according to Family history: 84.3% of the Subjects had no family history of RA but 15.70% of the subjects had a family history of RA

Section 2: Findings related to disease activity of the patients with RA

Distribution of the subjects based on the level of disease activity: 53.9% of the subjects had moderate disease activity. The median of the DAS-28 scores was 3.43.

Section 3: Findings related to anxiety of the patients with RA

Distribution of the subjects based on the level of anxiety:73.9% of the subjects had minimal anxiety. The median score of 4 on the GAD7 scale.

Section 4: Findings related to depression of the patients with RA

Distribution of the subjects based on the level of depression: 50.4% of the subjects had minimal form of depression. The median score of PHQ -9 was 3.

Section 5: Correlation between disease activity and anxiety

Study shows that there is a very weak positive correlation between disease activity and anxiety of the patient with RA which was statistically significant at 0.05 level of significance.

Section 6: correlation between disease activity and depression

Study shows that there is a weak positive correlation between disease activity and depression of the patient with RA which was statistically significant at 0.05 level of significance.

Section 7: association of disease activity and selected baseline variables

It that there was a statistically significant association of disease activity with family history ($p=0.003$) and trait anxiety ($p=0.04$) at 0.05 level of significance respectively.

Section 8: association of anxiety and selected baseline variables

This study reveals that there was statistically significant association between the anxiety caused by the disease progression and trait anxiety of the subjects ($p=0.052$) at 0.05 level of significance.

Section 9: association of depression and selected baseline variables

Study depicts that there was no statistically significant association of depression with baseline variables like age, gender, income, occupation, duration of illness, comorbidities, family history and trait anxiety of a patient with RA

IV. DISCUSSION

Discussions related to the demographic variables

In the present study which was conducted among 115 RA patients, majority (72.2%) of the subjects belonged to the age group of 40-60 years with the mean age of 46.3years. With regard to the gender, females constituted 85.2% of the subjects while only 14.8% were males. Ratio of female: male was 6:1. In a similar study done in Brazil, it was found that the ratio of female: male was 8:1 which was much higher than that reported in western population but closer to some studies in developing countries. In the same study 98 patients were followed up to the outpatient department of rheumatology clinic, the mean age of the patient was 47.5 years ranging from 22 to 83 yrs¹⁸.

Present study showed that 15.7% of the subjects had a family history of RA where as majority of the subjects (84.3%) had no family history of RA¹⁹

In this study it was found that 40% of the subjects had a comorbid condition like hypertension and diabetes whereas the rest of subjects (60%) had no comorbidities. In a similar study 11.2% of the subjects had hypertension, and 8.3% of the subjects had hyperlipidemia²⁰.

Discussions related to the disease activity

Disease activity can be defined as a reversible clinical or laboratory manifestation reflecting the immunologic and inflammatory manifestation of organ. In this study disease activity referred to the extent to

which patients with rheumatoid arthritis experienced inflammation of joints manifested in the form of tenderness, swelling and pain which was measured by the scores obtained on the disease activity score-28(DAS28) scale. The scores of DAS28 <2.6 indicates remission phase; DAS 28 ≥ 2.6 to ≤ 3.2 indicates low disease activity, DAS28 >3 to ≤ 5.1 indicates moderate disease activity and DAS28 >5.1 indicates severe disease activity.

The disease activity explored in this study showed that 53.9% of the subjects had moderate disease activity. The median of the DAS-28 scores was 3.43 whereas only 8.7% had high disease activity. This could be because of the fact that 18.3% were in the remission phase of their disease as well as majority of the subjects were on disease modifying anti rheumatoid drugs. Similar findings related to disease activity were seen in another study done in Portugal wherein 47.5% of the subjects had moderate disease activity²¹.

Discussions related to the anxiety and depression

Rheumatoid arthritis is a crippling disease which affects the mental health of an individual, particularly in the form of anxiety and depression. The score obtained on GAD-7 scale, score of 0-4 represents minimal anxiety; 5-9 represents mild anxiety; 10-14 represents moderate anxiety and 15-21 represents severe anxiety level. The depression level of the subjects were measured by using the PHQ-9 and the depression severity was as follows: 0-4 indicates None- minimal; 5-9 indicate mild; 10-14 indicate moderate, 15-19 indicate moderately severe and 20-27 indicate severe depression. In the present study anxiety level of patients was measured by using GAD-7 which showed that 73.9% of them had a minimal anxiety and 7% had moderate level of anxiety. Depression level of subjects were also measured by using the PHQ-9 scale and it showed that the majority of the subjects (50.4%) had minimal depressive symptoms and 40.9% had mild depression. This may be because of the fact that majority of the subjects in this present study were experiencing moderate disease activity as they were compliant with the treatment. Similar findings were found in another study done in Greece in which 30.8% had anxiety and 21.8% were depressed²².

Discussions related to the correlation between disease activity with anxiety and depression of patients with rheumatoid arthritis.

There is a relationship between the disease activity and mental health of individual particularly in the form of anxiety and depression. Rheumatoid arthritis patients would have high inflammatory cytokines like TNF and IL-6 which also is a contributing factor for depression. Keeping this in mind a correlation was done between the disease activity and anxiety which showed a weak positive correlation ($r=0.02$). The investigator also correlated disease activity and depression, which showed a weak positive correlation ($r=0.286$) which was statistically significant at 0.05 level. This shows that as disease activity increases, the anxiety and depression level also increased. Since the disease activity was not very high in the present study, there was a weak correlation found. Similar to these findings, weak positive correlation was found in another study done in Turkey between the disease activity with anxiety and disease activity with depression ($r=0.341$; $r=-0.642$)²³ respectively, whereas a study done in Pakistan to correlate disease activity with depression, showed a weak positive correlation ($r=0.48$)²⁴.

Discussions related to the association of disease activity with the baseline variables

The symptoms experienced and the disease activity will vary from individual to individual based on their baseline characteristics. Therefore the investigator made an attempt to associate the disease activity with the baseline variables of the subjects such as age, gender, income, occupation, duration of RA, family history, trait anxiety score and medication. People with high trait anxiety showed higher disease activity (median score =3.43) which was statistically significant at 0.05 level. The trait anxiety is an inherent personality trait which makes a person more prone to experience higher symptoms. Person with higher trait anxiety score may tend to refrain from adopting the preventive and positive measures to control disease activity. Although there was no statistically significant association, there were variations in disease activity found with regards to certain baseline variables. With regards to age, median score of disease activity was high (3.51) among the older age group (≥ 40 years) compared to the younger age group (<40 years) whose median score was 3. This may be because of the fact that the younger age group has a better tolerance and strength for coping with the functional limitations.

The median score of disease activity among females were high (3.47) compared to the males. In the present study 85% of the subjects were females and also the fact that there is a difference in the genetic makeup and hormonal factors of the female compared to male could be a reason for such a finding. It is well known fact that female populations in India are housewives who tend to avoid seeking the access to health care. Literature has also shown an increased ratio for females with regard to prevalence.

The association of duration of diagnosis with disease activity showed that the median disease activity scores were more among the patients with shorter duration of illness. This may be because of the fact that the

duration has an impact on the efficacy of treatment and the time taken by the body to adapt to the disease and treatment.

Disease activity scores were found to be higher among those subjects with co morbidities. This may be because of the fact that presence of a co morbidity could worsen and add to the functional disability of a person.

Findings related to the association of anxiety with baseline variables

Anxiety can be categorized in two subsets: state anxiety which is situational and depends on the experience of the individual at the moment while trait anxiety refers to the constitutional anxiety expressed by a person. The two tend to be largely independent, and while state anxiety is a momentary condition, trait anxiety refers to the personality and is fairly stable⁴³. It was thought that the totality of anxiety exhibited by an individual is a reflection of both anxiety types and these may be influenced by the perceived social support. In the present study state anxiety was a study variable which was measured by GAD-7 scale whereas trait anxiety was considered as a baseline variable.

Though numerous symptoms associated with RA such as pain, decreased functional status, reduced income may be contributors to elevation in anxiety however there was a statistically significant association of state anxiety with trait anxiety. The p value was found to be 0.052 which was statistically significant at 0.05 levels. Those with moderate trait anxiety showed higher state anxiety. This confirms the fact that when a person has higher trait anxiety in their personality, it is likely to propagate higher anxiety scores as a result of the disease condition.

This study showed that younger age (<40yrs) group and those who were experiencing the symptoms of RA (<3yrs) were found to be more anxious (median score of 5) which may be due to uncertainty of impact of disease in their future. However there was no statistical significance found between the age and duration of RA with anxiety.

Patients with a family history of RA showed more anxiety. This may be because of the familial predisposition and concerns for other members of the family and also their experience of witnessing the disabilities of the other family member with RA. The negative cognitions often experienced in anxiety may contribute to how RA patients perceived their symptoms. The association was not statistically significant.

A study conducted in London, showed that there was significant association between anxiety and the subjective component of DAS-28: TJC which is similar to this present study.²⁶

Discussions related to the association of depression with baseline variables

In this present study it was found that there was no statistically significant association of depression with the baseline variables. But both the genders had a median score of 3 on PHQ-9. The depression scores did not differ among different age groups, it may be due to the nature of this disease and it is always accompanied by anxiety in early stage and depression in later stage.

In the present study, the subjects with shorter duration of ≤ 3 years had a median PHQ Score of 2.5 while those with longer duration of ≥ 3 years had a median PHQ-9 score of 3. It indicates that patients who have disease for prolonged period may experience depressive symptoms. Though subjects with co morbidities exhibit higher score of depression, the present study did not give such a findings.

In this study, depression score was same among those with or without co morbidity median score of 3). This may be due to the fact that the most common reason for depression that is experienced by the RA patients is the pain and swelling in the joints leading to disability which is not directly related to a co morbid condition. The negative cognitions often experienced in depression may contribute to how RA patients perceived their symptoms These findings were contradictory to another study done in Austria which showed an association of hypertension and chronic heart failure with depressive symptoms²⁷. Another study done in London also showed that there was a strong association between depression and the baseline variables like age, gender, follow up components of DAS-28.²⁸

Thus the investigator in this present study found that RA patients do experience anxiety and depression which differ according to the level of disease activity and all of these are influenced by certain demographic variables such as duration of rheumatoid arthritis, family history of rheumatoid arthritis, co morbidity and the trait anxiety.

V. CONCLUSION

The process of the study was an educative experience for the investigator. This experience helped the researcher to apply her theoretical knowledge of research during all the steps of research activity. The interview with the subjects and the findings of the study helped the researcher to develop an educational module which will be helpful for all the patients with RA.

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