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Fatigue, Physical Function and Quality of Life in Relation to Disease Activity in Established Rheumatoid Arthritis

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Abstract

Objectives: This study was intended to find out the relationship of fatigue, functional disability and Health-Related Quality Of Life (HRQOL) with disease activity in adult patients with active rheumatoid arthritis (RA) and to observe the effect of rehabilitation programme on these parameters.

Material and Methods: 106 patients participated and 96 completed the study. Disease Activity Score-28 (DAS-28), visual analogue scale for pain and fatigue, Multidimensional Assessment of Fatigue Scale (MAF), Health Assessment Questionnaire (HAQ), American College of Rheumatology revised criteria for functional status classification, World Health Organization Quality Of Life instrument (WHOQOL-BREF) were administered. A comprehensive rehabilitation programme comprising pharmacologic and non-pharmacologic therapy was continued for 6 months.

Results: Mean VAS fatigue, DAS28 & HAQ scores were 45.68, 5.14 and 1.16 respectively. Significant correlation (Pearson's r =0.82, $p<0.05$; r=0.75, $p<0.05$; r=0.85, $p=<0.05$) between the disease activity and the value of the VAS Fatigue, Global Fatigue (MAF) and HAQ score respectively and inverse co-relation between quality of life (QOL) domain scores and disease activity were observed. Similar results were also found in the final visit. Comprehensive rehabilitation reduced the disease activity, fatigue, functional disability and improved QOL.

Conclusion: High fatigue level, disability, pain and decreased QOL characterized RA disease activity. Reduction of DAS, Fatigue, HAQ scores with treatment improved QOL.

Key words: Quality of life, Disease activity, Rheumatoid Arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic disabling condition with unpredictable course and wide variation in severity[1]. Management requires regular assessment of disease activity. The current gold standard for assessment is the 28 joint disease activity score (DAS28)[2].

Although the joints are the major loci of disease activity, fatigue is a common extra-articular symptom that exists in all gradations of RA[3, 4]. Fatigue is typically defined as extreme and persistent tiredness, weakness or exhaustion mental, physical or both. Subjective fatigue has been defined as a sense of extreme tiredness or exhaustion[4, 5]. In fact an estimated 80-93% of individuals with RA experience fatigue[3, 6] and in one sample of RA patients 57% reported that fatigue was the most problematic aspect of their disease[4, 7]. Despite this, fatigue has typically been ignored in the assessment of symptom severity or outcome in many of the diseases in which it is found including RA.

In recent years there has been a broadening of focus in the measurement of health, beyond traditional health indicators such as mortality and morbidity to include measures of the impact of disease and impairment on

multiple aspects of the patients' life including Quality of Life (QOL). The World Health Organization defined QOL as "the individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"[8].

RA is a chronic inflammatory and disabling disease, causing disruption to the daily lives of patients. Self reported measures of functional ability are important indicators of health status in patients with rheumatoid arthritis (RA). Published in 1980, Health Assessment Questionnaire (HAQ) was among the first instruments based on patient centered dimensions and has established itself as a valuable, effective and sensitive tool for measurement of health status in RA[9]. Its component Health Assessment Questionnaire- Disability Index (HAQ-DI) specifically measures disability and physical function. Validated Indian version of HAQ was published in 2002. This can be self-administered in English or Hindi[10].

Aim of our study was to find out the correlations of fatigue, physical function (disability) and QOL with disease activity score-28 (DAS28) and to see changes of these parameters with disease activity after 6 months of treatment.

Patients and Methods

Following written informed consent, patients with RA were enrolled during the period of April, 2007-July, 2008 at the outpatient department of Physical Medicine and Rehabilitation and Rheumatology, IPGMER and SSKM Hospital, Kolkata. The study was approved by the Institutional Ethics Committee.

RA patients were selected on the basis of fulfilling the "Revised American Rheumatology Association Criteria" (1988)[11] met two eligibility criteria: age range 16-70 years and being able to read.

Of the 135 RA patients approached, complete data was available for 106 patients (78.52%) who were included in the study. Fifteen patients with missing data like radiographs, ESR, etc were not included in the final analysis of the study, since in the absence of this clinical data, calculation of Disease activity Scores (DAS) was not feasible. Eleven patients were deliberately excluded as they took more time to fill up the questionnaires and sought help almost in every question and three refused to take part in the study.

First 20 consecutive patients (fulfilling the criteria), attending the Rheumatology OPD (weekly) were included in the study. Follow up was done as per schedule. DAS score were calculated on every visit and treatment (Rx) was given according to that.

After 6 months a total of 96 patients (10 patients missing) attended our OPD with reports of prescribed investigation. During the 6 months' period patients were given pharmacological and non-pharmacological management. Monthly monitoring of drugs, exercise classes, physical modalities and counseling was done for each patient. Phone numbers were taken from each patient so that we could contact them when needed. Missing 10 patients could not be contacted because of incorrect addresses and phone numbers.

Out of 106 patients (at baseline), 80 patients were referred from other centers. Out of these, 60 patients did not take any disease modifying anti-rheumatic drugs (DMARDs). 20 patients took DMARDs and/or steroid according to their physician's advise. Other 26 patients were old follow up patients. All of them were on DMARDs with 15 patients taking more than one DMARD.

After assessment, every patient was prescribed at least two DMARDs and /or steroid as needed. All patients were advised not to take any NSAIDs before coming to the next visit for at least 24 hours.

Therapeutic exercises in the form of range of motion exercises, strengthening exercises (Isometric/ Isotonic), aerobic exercise like swimming, relaxation techniques were told to all patients. Splints, gait aids and assistive devices were given as needed by the patient. Patient education on the disease course, joint protection techniques and energy conservation techniques was also given.

DAS28 was calculated for the current disease activity according to 28 swollen (SJC28) and tender (TJC28) joint counts from the formula DAS28 = 0.56*sqrt (TJC28) + 0.28*sqrt (SJC28) + 0.70*Ln (ESR) + 0.014*patient global 0 to 100[12]. DAS score can range from 0 to 9.4. A DAS28 above 5.1 means high disease activity, 3.2- 5.1 moderate disease activity whereas a DAS28 below 3.2 indicates low disease activity[2].

Information on pain (100mm VAS), fatigue (100mm VAS and Multidimensional Assessment of Fatigue Scale[13]), functional disability (Health Assessment Questionnaire-Disability Index / HAQ-DI; Indian version)[10], functional classification (ACR1991 revised Global Functional status scale)[14] were recorded in all cases. The QOL was assessed using WHOQOL- BREF questionnaire to all patients. Raw scores were calculated and converted to a 0-100 scale.

In the treatment response studies, the clinical assessments were done before and after 6 months of treatment. During the 6 months period pharmacological and non-

pharmacological interventions were done according to the need of the patients. Necessary adjustments in the dosage were done monthly.

Statistically, the data was entered into Microsoft Excel and analyzed by Statistica Version 6 (Stat Soft Inc, Tulsa, Oklahoma, 2001). The data was been summarized by visual descriptive measures mainly mean and standard deviation of various groups and subgroups. Numerical variables were compared between groups by unpaired- t test while categorical variables have been compared by Fisher's exact test. Changes of numerical variables from baseline were assessed by Paired t test. The Pearson's correlation coefficient r was used to associate various numerical parameters with WHOQOL- BREF domains. All analysis was 2 tailed and $p < 0.005$ was considered statistically significant.

Results

Demographic Characteristics: The study group comprised 106 RA patients (Table 1).

Disease Activity: (Fig 1). Most of the patients were in the moderate to higher disease activity group. 48 patients (45.28%) had moderate disease activity, 49 patients (46.23%) had higher disease activity and only 9 patients (8.49%) had low disease activity. The mean DAS28 scores were 5.14 ± 01.34. Pearson's correlation coefficient r showed that DAS28 scores were significantly correlated with VAS pain ($r = 0.88$, $p < 0.05$). Seropositive RA had higher mean DAS score than that of seronegative RA. We did not find any association with disease duration and gender.

	RA Patients (n=106)	Control (n=49)
Sex (F/M)	71/35	34/15
Mean Age (years)	44.32+10.27	45.55+9.81
Education <Junior High High School >College	 14 68 24	 5 28 16
Mean Duration (years)	4.95+3.33	
Rural background	61	27
DAS 28 Low (<3.2) Mod (3.2-5.1) High (>5.1)	 9 (8.49%) 48 (45.28%) 49 (46.23%)	NA
HAQ - D1 Scores 0-1 Scores 1-2 Scores 2-3	 48 (45.28%) 53 (50%) 5 (4.72%)	49 (100%)

Table 1. Profile of cases and controls at initial visit

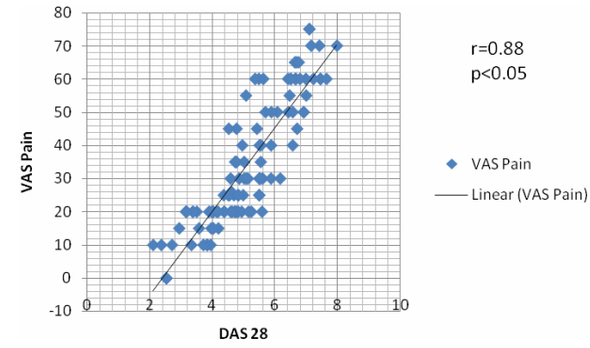

Fig 1. VAS Pain with DAS28 at baseline visit.

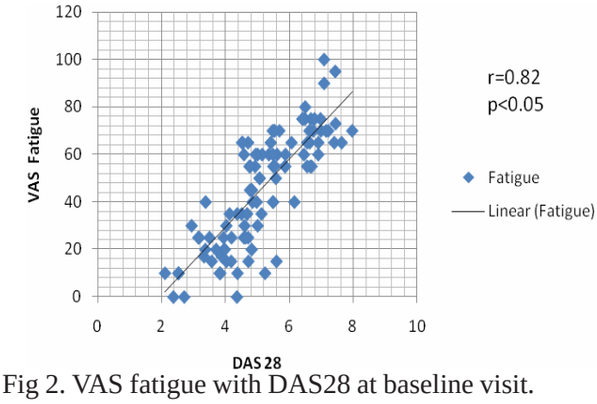

Fig 2. VAS fatigue with DAS28 at baseline visit.

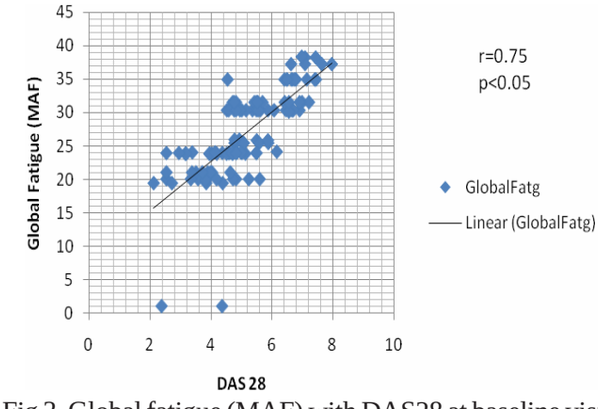

Fig 3. Global fatigue (MAF) with DAS28 at baseline visit

Fatigue: (Fig 2-3) The study revealed that 83 patients (78.30%) had clinically relevant fatigue (VAS score > 20mm) and 52 patients (49.06%) had high fatigue scores (VAS score > 50mm). Fatigue was also assessed using Multidimensional Assessment of Fatigue (MAF) scale (range 1 to 50). Higher the score the more severe was the fatigue. The mean global fatigue score (MAF) was 26.95 ± 6.56. The mean score (MAF scale) was slightly higher in female patients. Mean fatigue score (VAS scale) was also reported to be higher in female patients (46.49) than that of male patients (VAS 44.06) but no statistical significant difference was found in either parameters. Gender and rheumatoid factor did not show any significant role in fatigue scores. DAS28 and VAS fatigue showed

significant association, using Pearson's correlation coefficient r (r = 0.82, p < 0.05**).** Similar result was obtained when disease activity DAS28 was correlated with global fatigue scores (MAF) (r = 0.75, p < 0.05).

Fatigue was inversely correlated with the QOL domain scores, especially in physical health and psychological health. In these two domains, VAS fatigue was inversely correlated (physical health, r = "0.72, p < 0.05; psychological health, r = "0.74, p < 0.05). In MAF scale, similar results were obtained.

Functional Status: Patients' functional status estimation was done using ACR 1991 revised Global functional status scale. Maximum number of patients were in ACR functional class II (52 pts, 49.06%), followed by 26 patients (24.53%) in class I. The study revealed that maximum patients had HAQ-DI scores in between > 1-1.5 (36 patients = 33.96%) followed by scores > 0.5-1 (25 patients = 23.58%). Higher the score, more severe was the physical disability. The mean HAQ-DI score was 1.16 ± 0.60.

Significant co-relation was found between between DAS28 and functional disability (HAQ-DI, r = 0.85, p < 0.05). Moderate to strong inverse co-relations were found between the QOL domain scores and functional disability (HAQ).

Quality of Life: The mean WHOQOL domain scores of RA patients were as follows: in physical health (43.70 ± 16.75), psychological health (44.82 ± 19.48), social relationship (61.02 ± 11.99) and environmental domains (50.51 ± 10.21) at the initial visit. Among the domain scores, mean physical health (43.70 ± 16.75) and psychological health (44.82 ± 19.48) were comparatively lower than the other two domains.

Association study revealed that there was significant inverse co-relation between disease activity and Quality of Life domain scores (Physical r = "0.74, p < 0.05; psychological r = "0.74, p < 0.05; social r = "0.54, p < 0.05; environmental r = "0.58, p < 0.05). VAS pain was inversely correlated with QOL domain scores. In follow up visit similar results were obtained.

Treatment Response: Over 6 months, mean DAS-28 score had dropped from 5.10 ± 1.31 to 4.58 ± 1.25 (p value < 0.001) when the patient population completed the study was taken into account (n = 96). Documentation of the DAS scores is important to estimate the intensity & duration of therapeutic exercise to be prescribed as part of rehabilitation.

Over 6 months, fatigue scores decreased from a mean of 45.00 ± 23.46 to 37.46 ± 22.14 in case of VAS and 26.7 ± 6.54 to 23.27 ± 7.90 in case of MAF. At baseline,

Score	Initial Visit	Final Visit	p- value
DAS28	5.10 ± 1.31	4.58 ± 1.25	< 0.001

Table 2. Treatment response- disease activity

Grade	Initial Visit	Final Visit	*p*- Value
DAS Low (≤3.2) [n = 9]			
VAS Pain	9.44 ± 8.08	8.89 ± 8.21	= 0.73
VAS Fatigue	13.33 ± 10.90	10.67 ± 11.74	= 0.54
Global Fatigue	19.58 ± 7.25	12.02 ± 10.53	= 0.14
HAQ	0.29 ± 0.12	0.32 ± 0.14	= 0.35
ACR	1.22 ± 0.44	1.11 ± 0.33	= 0.59
DAS Medium (3.2-5.1) [n = 44]			
VAS Pain	24.23 ± 9.21	19.75 ± 9.21	**< 0.001**
VAS Fatigue	34.70 ± 17.35	28.86 ± 17.85	**< 0.001**
Global Fatigue	24.08 ± 5.28	21.51 ± 6.26	**< 0.001**
HAQ	0.92 ± 0.33	0.85 ± 0.35	= 0.10
ACR	1.68 ± 0.60	1.27 ± 0.54	**< 0.001**
DAS High (> 5.1) [n = 43]			
VAS Pain	49.07 ± 15.82	39.30 ± 15.91	**< 0.001**
VAS Fatigue	62.16 ± 16.92	51.86 ± 17.68	**< 0.001**
Global Fatigue	30.88 ± 4.72	27.43 ± 5.63	**< 0.001**
HAQ	1.58 ± 0.52	1.42 ± 0.52	**< 0.001**
ACR	2.53 ± 0.59	1.93 ± 0.80	**< 0.001**

Table 3. Improvement in pain, fatigue and functional status in Patients with different grades of disease activity

49.06% of the patients had high fatigue level (VAS scores > 50 mm), which came down to 40.63% after treatment. This fall in VAS fatigue and global fatigue scores was correlated with improvements in DAS 28 (p < 0.001).

Mean changes from baseline in the HAQ-DI score was "0.10 and that was "0.47 in ACR functional scale. Improvements in physical function were statistically significant (p <0.001) in both scales.

VAS pain scales, ACR functional class scores showed a consistent pattern of decrease in their mean scores in three groups. Statistically significant improvement was found in DAS medium and high group (especially in HAQ, pain score and ACR functional class). In low DAS group clinical improvement was found but it was not statistically significant. In HAQ-DI scores no statistically significant improvement found in DAS low and medium group though in high DAS group, both clinically and statistically significant improvement was found.

Following 6 months rehabilitation, WHOQOL Domain scores increased significantly except in social relationship domain. These results are consistent in all three groups

WHOQOL Domain	*p*- value
Physical health	= **0.001**
Psychological health	= **0.001**
Social relationship	= 0.25
Environmental	< **0.01**

Table 4. Treatment response: quality of life

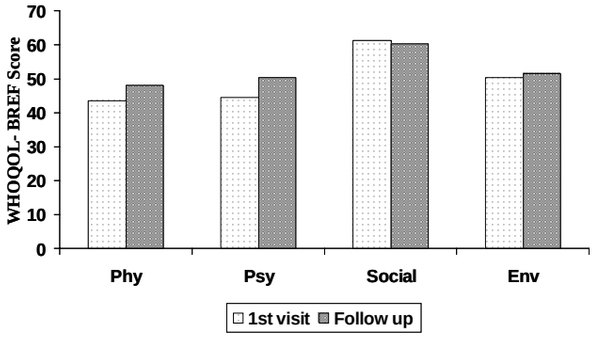

Fig 4. Effect of rehabilitative management on different domains of WHOQOL. Phy: Physical health; Psy: Psycological health; Social: Social relationship; Env: Environmental.

Discussion

The characteristics of the patient population in terms of mean age, gender and duration of symptoms were similar to those previously reported in Indian studies[15-17].

Fatigue is a dominant symptom in RA. Reduction in fatigue accompanied decrease in disease activity and pain. The fall mirrors decreased in DAS score and pain[18]. Similar to the previous reports[13], our study also showed that patients with active RA reported more fatigue. Fatigue score reduced from higher to lower value when active RA patients were treated with DMARDs and non-pharmacological management. VAS fatigue scores are simple and reproducible; however, multidimensional assessments may provide a more complete picture and improve our understanding of the clinical relationships of fatigue[18]. We found similar results using VAS scores and MAF scores. According to National Rheumatoid Arthritis Society the disease process (chronic inflammation of joints and other tissues) is the main cause of fatigue. They also found close relationship between fatigue, disease activity and the level of markers of inflammation such as the ESR (erythrocyte sedimentation rate) or the CRP (C reactive protein).

Although Huyser et al[4] found that subjective fatigue was not strongly related to greater RA disease activity, the strong association between disease activity and fatigue found in our study can be explained by the fact that when disease activity is high, other symptoms such as pain, depression, decreased endurance and psychological stability, physical disability etc. become more pronounced. These factors may be the reason for increased fatigue. Disease activity has been shown to adversely affect physical and psychological QOL in earlier studies[15, 16]. Our study established strong association not only between disease activity and physical health and psychological health domains of QOL but also between disease activity and factors like pain and functional disability (HAQ).

It has been reported that the fatigue level falls in RA patients after 12 weeks of therapeutic exercise programme[19]. Our study showed that this fall in fatigue accompanied decrease in disease activity when non-pharmacological therapy including exercise programme and energy conservation technique was coupled with pharmacologic therapy based on DMARDs.

The self reported total HAQ assesses fine movements of the upper extremities, locomotor activities of the lower extremities, and activities involving both the upper and lower extremities and trunk. HAQ is an important outcome measure in clinical trials and in the documentation of patient status in clinical care. RA significantly compromises functional capacity and increases functional disability. Our study revealed that mean scores of functional disability as measured by HAQ-DI was significantly associated with disease activity. This kind of information was quite predictable in view of the recent work involving both HAQ and other related instruments[20, 21]. Pain is a major symptom in rheumatoid arthritis and is the leading reason for patients seeking medical care[21-24]. In this study, high degree of disability as expressed by increased HAQ score can be attributed to pain along with synovitis and decreased mobility due to higher disease activity.

QOL instruments, such as the Health Assessment Questionnaire (HAQ) Disability Index and the SF-36, have proven validity and sensitivity for assessment of changes in QOL in clinical trials of disease-modifying anti-rheumatic drugs (DMARDs). However, these instruments are rarely utilized in clinical practice, and patients have reported that the actual clinical assessment alone does not address important parameters, such as fatigue and disturbed sleep, which significantly affect QOL[25]. A few studies assessing either non-pharmacologic therapies or DMARDs have incorporated these parameters[26-28]. In our treatment response study we assessed the combined effect of both pharmacologic and non-pharmacologic agents on these parameters. It was found that after 6 months of comprehensive management, mean HAQ-DI scores and ACR Global functional status score reduced significantly. These are consistent with the findings of previous studies using either of the two different kinds of modalities[26-28].

The WHOQOL-BREF has been validated against the original WHOQOL-100 and was found to have good test-retest reliability[29]. Our study revealed that RA had significant compromise in their QOL (measured by WHOQOL-BREF) when compared to -age-gender matched normal healthy population. Our results corroborate with other studies which employed the WHOQOL-BREF as well as other validated instruments to compare QOL in patients with RA and healthy controls[20, 21, 29- 31]. RA causes pain and physical and psychological impairments, and in many patients these impairments result in moderate to severe disabilities. Of all QOL domains, physical health was affected most. Despite physical disability, there was relative high score of social relationship and the environmental domains of QOL. The strong family support and joint family system in India could be a contributor to the relatively high scores in social domain. This is in keeping with other studies in the literature[15,16]. Pain and fatigue were inversely correlated with QOL domains. Co-relation studies also showed a significant effect of functional disability (HAQ-DI) and disease activity on QOL, with functional disability having the greatest strength of association.

Over 6 months of treatment, all QOL domain scores except social relationship domain increased significantly with improvement of disease activity. This can be explained by the fact that the social relationship domain in WHOQOL-BREF contains only three questions and has been considered less responsive to change than other domains and also because the initial value in this domain was already reasonably high possibly due to the strong family support system of India.

Depression, anxiety, other co-morbidities like fibromyalgia, diabetes mellitus, and cardiovascular, pulmonary and renal diseases can affect fatigue, QOL and HAQ irrespective of DAS28. Further studies incorporating these factors, collecting data on educational and socioeconomic status could throw light on this matter in a better and more comprehensive way.

Conclusion

Demographic parameters of our study population are similar to that of rheumatoid arthritis patients of this country as evidenced by the information gathered from the previous Indian studies. Six months treatment resulted into statistically significant reduction in disease activity. High fatigue level is related with the disease activity. Reduction in fatigue is accompanied by decrease in disease activity and pain. Treatment with combination of DMARDs and non-pharmacological management leads to reduction of fatigue score. The health related quality of life scores were significantly lower while HAQ scores were significantly higher with high disease activity, clearly indicating compromised quality of life and increased functional disability with increased disease activity status in these patients. Apart from pain and fatigue, HAQ score was also significantly associated with disease activity. Pain, fatigue, HAQ score were inversely co-related with QOL domain scores. Comprehensive rehabilitation comprising of pharmacotherapy and non-pharmacotherapy reduces functional disability and improves quality of life.

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