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FATIGUE IN RHEUMATOID ARTHRITIS REFLECTS PAIN, NOT DISEASE ACTIVITY

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Abstract

Objective: *To observe the relationship between pain and fatigue in Rheumatoid Arthritis patients.*

Study Design: *A Cross sectional observational study*

Study Duration: *06 months*

Study Place: *Tertiary Care Hospital, Lahore*

Methods: *A cross-sectional observational study was conducted over six months in the Rheumatology Department of a tertiary care hospital in Lahore. 200 patients were enrolled in the study after taking informed consent. Data were analyzed using SPSS 25, with significance set at p<0.05. Ethical approval was obtained beforehand.*

Results: *200 patients were enrolled in the study, and among them were 90 males and were 110 females. Fatigue was present in 191 patients and pain alongside in 127 patients. Fatigue and pain have strong corealtion. ESR and CRP did not correspond with the symptoms of pain. Among 200 patients, fatigue was more prevalent in females and pain was more present in males.*

Conclusion: *Rheumatoid arthritis (RA) Fatigue is a multifactorial symptom complicated by chronic pain and fatigue. Thus, the effective measures towards fatigue management must be multidimensional and patient-focused to integrate anti-inflammatory treatment with pain, and mental and psychosocial support. Such a comprehensive approach presents the greatest chance to improve the fatigue level and the overall life quality of people with RA..*

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease of inflammatory character of the synovial joint that has the potential to lead to both pain, swelling, stiffness of the joint, and the risk of joint dysfunction. RA happens when the immune system responds by attacking body tissues in the body unlike osteoarthritis which results when the body wears out through mechanical wear and tear. RA may impact the body

several joints such as wrist, knees and finger among other joints besides systemic effects that are beyond joints. The exact inducing agent of RA is not yet clear; still, several factors are believed to have an impact on the condition, and these are various components that relate to the development of the RA. These genes regulate the immune system activity (the immune response) and can render people vulnerable to autoimmune reactions. Smoking is a valuable environmental factor in RA development, particularly when there is the presence of genetic factor. Coming to other environmental triggers, we have silica dust exposure to some infectious agents. It can be partly explained by hormonal factors as they are much more prevalent in women. [1,2]

RA usually manifests itself in the form of symmetrical involvement of joints and in most cases, joints on both sides of the body are affected like the wrists, knees and fingers. It is also linked with morning stiffness which is the stiffness that exceeds 30 minutes, in the period after one has awakened. Fatigue, low grade fever, malaise are some other systemic symptoms. In some cases Extra-Articular Manifestations may be involved in the lung, heart, and the eyes. [3]

It is diagnosed both on history and on clinical examination and with the help of laboratory Tests, of which Blood tests may indicate a high amount of inflammatory markers (including, ESR, CRP) or the presence of either rheumatoid factor (RF) or anti-cyclic citrullinated peptide (anti-CCP) antibodies. Imaging Studies are least employed in diagnosis and comprise X- rays or MRI studies that can detect the existence of a joint damage or inflammation and giving the baseline details. [4]

RA is an incurable chronic illness, and treatment ought to aim at minimizing swelling, alleviating signs and the resulting harm to joints. DMARDs (Disease-Modifying Antirheumatic Drugs): Methotrexate This agent is a first-line agent used to slow the development of the disease. The new modality comprises biologic agents, which have promising future such as rituximab. The other interventions are NSAIDs, physical therapy and CBT. RA is a disease that is estimated to be afflicted by up to 18 million individuals all over the world and is further seen to be dominant in women and those aged above 55 years . The occurrence and the morbidity of RA have demonstrated fluctuating patterns and trends over the years, where the upward trends in specific characters were found. [5]

Fatigue is a complex symptom which instead of disappearing becomes long-lasting and significantly affects the quality of life. In contrast to tiredness, fatigue does not subside, even when the person rests, and is one of the most common grievances, both in autoinflammatory diseases and in chronic conditions. Fatigue may constitute the cognitive, physical, and emotional components and is an unrecognized problem of functionality in clinical practice. The pathophysiology of fatigue is complicated and multi-dimensional as it involves numerous biological and psychological factors. Neuro-information is one of such biological mechanisms. The pro-inflammatory types of cytokines, i.e. such as IL-1, IL-6 and TNF-a, directly affect CNS to modulate neurotransmission, behavior and neuroendocrine functions . These cytokines can be also acting distantly by passing the blood-brain barrier, or via neural pathways, eliciting a fatigued sickness behavior. [6]

There is also the mechanism of HPA axis dysfunction. Chronic fatigue states such as chronic fatigue syndrome (CFS) normally cause deregulations of cortisol release and feedback control, resulting in failure of the body to respond physiologically to stress or the inability to balance the energy terms. Fatigue pathogenesis has also been attributed to Mitochondrial dysfunction. Due to a cellular energy crisis that may occur in cells where the synthesis of ATP by oxidative stress or mitochondrial DNA malfunction is compromised, there will be greater fatigue. [7]. Also, ANS dysbalance, in particular, a decrease in the parasympathetic output and an increase in the sympathetic activity, may cause fatigue-related complaints, including orthostatic intolerance and cognitive dysfunction. [8]Fatigue is an adjunctive feature of most autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and multiple sclerosis (MS). Fatigue in RA and SLE is usually linked to disease and systemic inflammatory disease activity, and during the stage of remission may prevail based on other factors, including pain, depression, and lost sleep. [6,9]. Fatigue is a frequent manifestation in MS, and in a majority (>75 %) of patients it is cited as the most debilitating symptom of their disorder. It is also

postulated that immunologically-mediated demyelination within the CNS and axonal injury is the cause of fatigue in MS. This damage results in poor impulse passage in CNS which results in excessive energy needed in the process of functioning of neurons. [7]Fatigue is also common in chronic diseases like long-term kidney disease (CKD), heart failure and chronic obstructive pulmonary disease (COPD). In CKD, we are familiar with fatigue being associated with a number of factors, uremia, anemia and chronic inflammation, whereas in a heart failure, fatigue is at least partly related to reduced cardiac output, skeletal muscle dysfunction and poor perfusion. The COPD organ-system fatigue includes systemic inflammation, hypoxia and/or certain behavioral component of deconditioning. [10]Fatigue in chronic and autoimmune diseases entails the biopathological, psychological and social aspect mining. The biopsychosocial multi-disciplinary strategy will be needed to manage fatigue easily.

Fatigue is a common and incapacitating symptom in patients with rheumatoid arthritis (RA), which occurs in up to 80 percent of patients. It has important consequences on the ability of living freely, performing activities, and improving the mind at large- possibly more than joint-swelling or joint-pain. Fatigue in RA has a multifactorial relationship comprising illness specific cult and wispy factors. Fatigue in RA is a key issue of inflammation. The high production of pro-inflammatory cytokines very often leads to joint destruction, but also to the provision of fatigue as a systemic symptom, which includes tumor necrosis factor-alpha (TNF-), interleukin-1 (IL-1), and interleukin-6 (IL-6). These cytokines affect the work of the central nervous system, causing neuroinflammation and changed activity of neurotransmitters, which may be expressed as the feeling of fatigue. [11]

In our study, we aim to study effect of fatigue in RA, as a manifestation of pain and not a symptom.

Methodology

An observational study with a cross section was undertaken, and the informed consent was taken following ethical review board of the hospital. It was a six months research which took place between June and December 2022. The research was carried out in Rheumatology outpatient department of tertiary care hospital in Lahore. Eligible adult patients were recruited (aged 18 years and above) and must fulfill the 2010 ACR/EULAR classification criteria of RA. To reduce potential variations of disease activity caused by recent therapeutic prior to enrollment, all patients were on stable dosages of disease modifying anti- rheumatic drugs (DMARDs) with/ without biologics of at least 3 months.

Inclusion Criteria

- ACR/EULAR RA diagnosis
- Age 18 years and above
- Length of disease 6 months and above
- The possibility of making informed consent and filling answer questionnaires in the local language

Exclusion Criteria

- Overlapping autoimmune diseases (e.g. SLE, Sjogren syndrome)
- Chronic fatigue diagnosed
- Major psychiatric disorders (e.g. schizophrenia, bipolar disorder)
- Active infection, cancer or other systemic inflammatory diseases
- Pregnancy or lactation

The sample size of 200 participants was estimated with WHO sample size calculator relying on CI 90 percent and the margin of error being 5 percent. Sample size is computed using a medium effect size (r = 0.30) 2, alpha (alpha) = 0. 05 and power (1-beta) = 0. 80 to find out significant relationships between fatigue and independent variables.

Fatigue was evaluated with Fatigue Severity Scale (FSS) which is a validated self-report questionnaire that measures the effect of fatigue and its severity in the previous week rated on a 7-point scale, 1 = no fatigue, to 7 = severe fatigue, and Pain was assessed with Pain evoked score which is further classified as mild, moderate and severe pain. The Disease Activity Score in 28 joints (DAS28) was used to measure the activity of the disease as it takes into account 4 parameters:

1. Total number of tender joints (28 joints)
2. Number of swollen joints (28 joints)
3. C-reactive protein (CRP) or Erythrocyte Sedimentation Rate (ESR)
4. Global Patient Assessment (VAS)

Demographic information such as the age, gender, occupation, disease history, other co-morbids and

medication history were also captured in the questionnaire. SPSS V 25 was used to analyse data. Demographic and clinical variables were summarised using descriptive statistics. Pearson or Spearman correlation coefficients was employed in assistant of connections amid fatigue (FSS scores) and pain (VAS) and disease activity (DAS28). To understand independent factors of fatigue, a multiple linear regression was done with fatigue and dependent variable and pain, DAS28 scores, HADS scores, age, disease duration as independent variables. The cut-off point of statistical significance was $p < 0.05$.

Results:

This cross-sectional study conducted in 200 patients with rheumatoid arthritis (RA) proved that fatigue was highly related to the self-reported measures of pain rather than objective measures of disease activity. Each participant fulfilled the 2010 ACR/EULAR criteria of RA and possessed different levels of the severity and treatment history. The main goal was to determine the correlations among the fatigue, pain, and disease activity based on validated clinical and patient-reported outcomes measures. In our study, 90 (45.7%) were males and 110 (55.3%) were females. The mean age of participants was 52±5 years.

The measurement of fatigue was done through Fatigue Severity Scale (FSS), measuring pain, through Visual Analog Scale (VAS for pain) and disease activity was evaluated by the Disease Activity Score in 28 joints (DAS28) which comprises tender joint count (TJC), swollen joint count (SJC), Erythrocyte sedimentation rate (ESR), and patient global assessment.

Mild fatigue was found in 39 (26%) patients, moderate was found in 66 (44%) patients and 86 (57.3%) reported severe fatigue. The FSS Score was more than 4 in patients with severe fatigue. ($p=0.04$). Figure 1.1

Patients also complain of pain along with fatigue symptoms, and among 200 patients with RA, 127 (84.6%) complained of symptoms of pain, which occurred throughout their disease activity. Pain was persistent and trouble some feature in patients with severe fatigue, as compared to those having mild or moderate fatigue. Severe pain was reported in 79 (63.7%) patients, moderate was reported in 51 (40.7%) patients and 20 (15.7%) reported mild pain. Figure 1.2

On the other hand, the interrelation between fatigue and DAS28 was poor and barely significant ($r = 0.19$, $p = 0.048$). No remarkable pattern was envisaged in the connection between DAS28 scores and fatigue severity as patients by levels of disease activity (remission, low, moderate, high). ESR and CRP levels were also checked to correlate disease activity, fatigue and pain. ESR and CRP levels gave insight into the disease activity but does not correlate with pain and fatigue. Higher the ESR and CRP, lower were the fatigue and pain symptoms.

To find out the best predictors of fatigue, multiple linear regression was applied. Pain was found to be the strongest and independent predictor (beta = 0.61, $p < 0.001$) whilst DAS28 activity was not significant as a predictor when other variables are considered like pain, age, sex, disease duration, and depression scores. The model associated with about 48% of the variance in the fatigue score ($p<0.001$)

Our study also showed that symptoms of fatigue were more in women and that of pain, were more in males. Mild fatigue was present in 15 (7.1%) females, moderate was in 23 (13.5%) and 49 (25.6%) reported severe fatigue. Similarly, 7 (3%) males reported mild pain, 36(28.3%) reported moderate pain and severe pain in 53 (41.7%) male patients. Figure 1.3

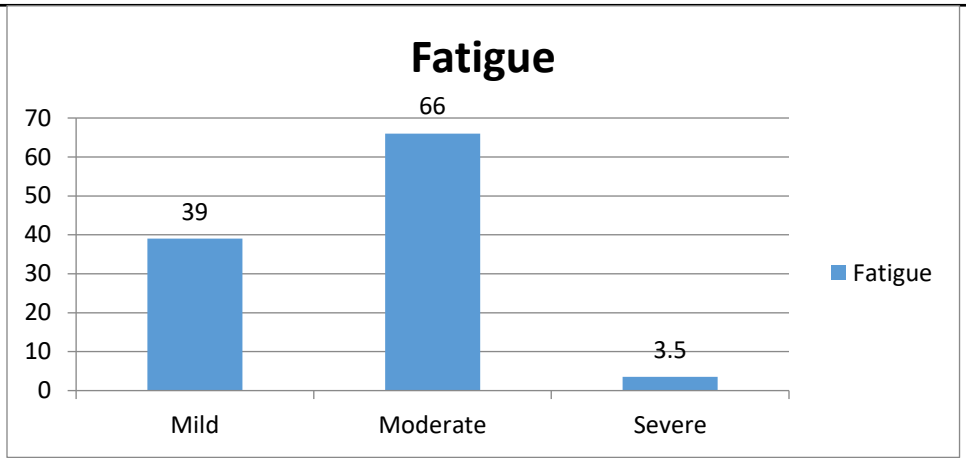


Figure 1.1 (fatigue in RA patients)

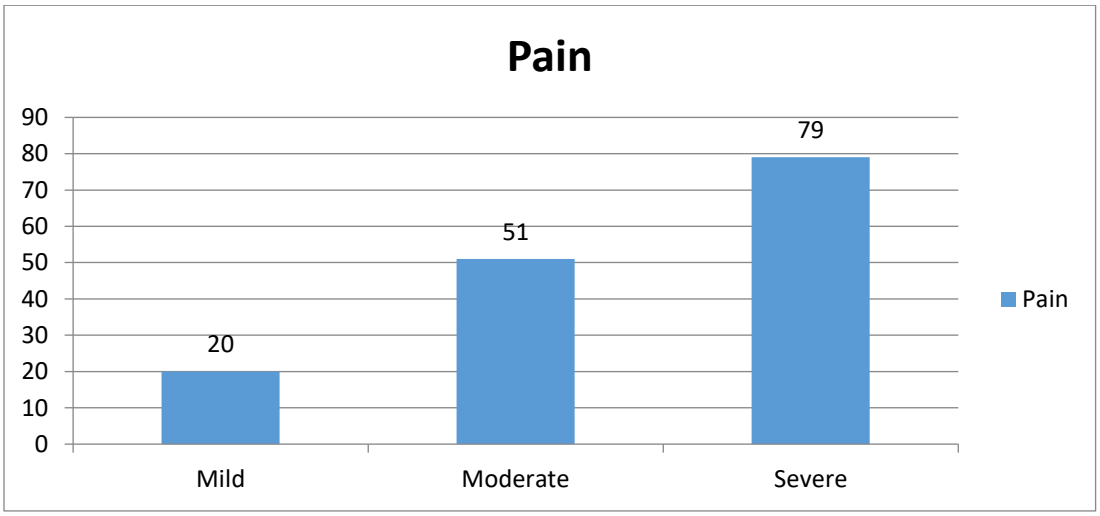
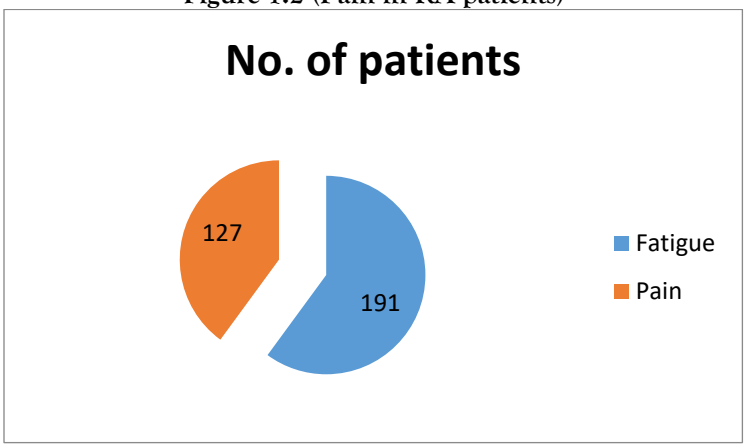


Figure 1.2 (Pain in RA patients)



Pie chart 1.1 (relationship between fatigue and pain)

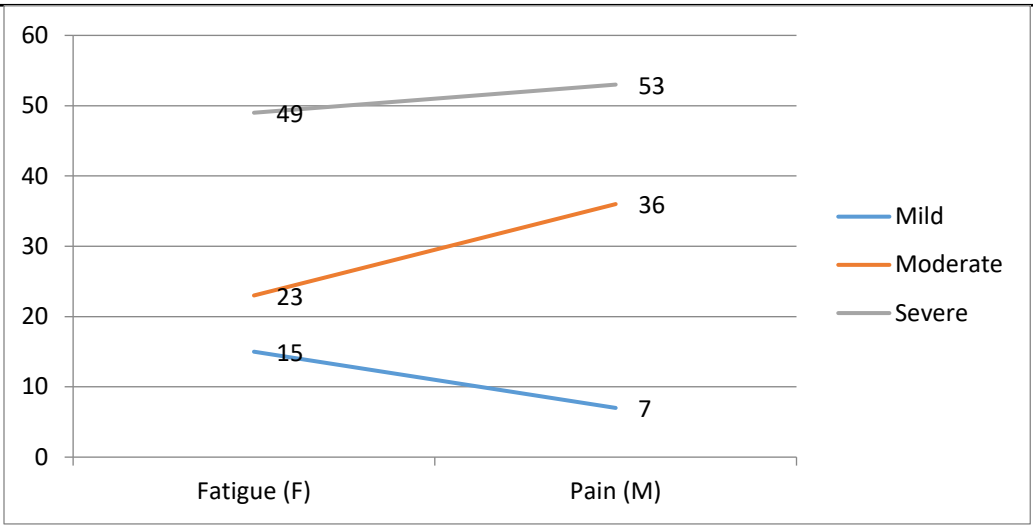


Figure 1.3 (Fatigue and Pain in female and male patients respectively)

Discussion

The present study provides additional support to the emerging body of evidence asserting that fatigue in rheumatoid arthritis (RA) is a core symptom, with pain perception playing a major role, and markers of objective disease activity (e.g., DAS28, ESR, CRP) having limited contributions. Our results align with the landmark reviews and clinical cohorts showing that the central role of subjective symptoms on fatigue. Notably, although inflammation has a relation to fatigue, its role becomes of minimal significance after having incorporated pain. A strong systematic review and meta-analysis on a total of greater than 121 studies and greater than 100,000 RA patients showed fatigue strongly correlated with pain and in the multivariate analysis, pain was the dominating factor over the disease activity and inflammatory markers. In a cross-sectional study of the 160 RA patients with Fatigue Symptom Inventory, Correlations were almost perfect of fatigue with VAS-pain (r = 0.96) which was compared to being moderately correlated with DAS28 (r = 0.77) and HAQ (r = 0.70) . In chronic RA, the number of tender joints and not the number of swollen joints or elevated ESR were identified as the main correlates of fatigue. In a study of 557 patients incorporating FACIT-F, pain VAS (r =-0.62), patient global (-0.64), and HAQ (-0.68) were highly correlated, whereas DAS28 was significant only because of tender joints and subjective measures. [12,13]

Although DAS28 is often associated with fatigue in unadjusted analyses, such a relationship is mainly due to the subjective items of DAS28, namely tender joint count and patient global assessment. Mediation analyses provided in clinical trials (e.g., baricitinib vs. adalimumab) demonstrated that improvement in fatigue was more closely associated with a decrease in pain than with a decrease in DAS28 itself. Fatigue improvement was mostly attributed to changes in composite disease activity scores at 30 percent, but over 50 percent was attributed to changes in pain. Residual associations between inflammation and fatigue have been proposed in some studies, e.g., normalization of CRP has been partly linked with fatigue improvement, perhaps, through effect on pain. [14] There are directly weak connections in case subjective symptoms are taken into consideration.

The psychological factors also contribute to fatigue in RA, and these factors include especially mood, self-efficacy, coping, and social support. A review of 29 studies showed low mood (depression/anxiety) correlation was the most consistent psychological correlate. The cognitions related to RA (e.g. beliefs about fatigue control) and self-efficacy were also significantly associated. Hewlett and group are the pioneers of fatigue research in RA, although they have indicated that fatigue is multifactorial, and have also designed cognitive-behavioral interventions that improve fatigue severity and its effect in randomized trials. [15]

Both fatigue and pain perception are increased by secondary mechanisms of pain, i.e. fibromyalgia or central sensitization. RA patients according to a study published on BMC Rheumatology met the criteria of fibromyalgia considering that these patients had an enhanced pain sensitivity and poorer mental health, which once again establishes the necessity to influence non-inflammatory mechanisms of pain. [16] Hyperalgesia with stress further highlights pain processing changes in a chronic pain state, which probably contributes to the fatigue through the enhancement of the nociceptive messages.

Prospective studies that follow-up their designs longitudinally also endorse the priority of pain as a predictor. CareRA is a five year follow-up trial of early RA patients that found that higher baseline pain, patient global assessment, disability and poor mental health were associated with more long term fatigue. Surprisingly, the number of swollen joints was predictive of poorer fatigue that means that subjective (disease) effect goes beyond objective evidence (inflammatory markers). Also, the biologic therapy users (n=106) indicated that the level of fatigue during 12 months was more described by emotional well-being and sex than by disease activity: the key contributors were pain and mood. These observations support the evidence of pain being a longitudinal predictor of fatigue. [17]

RA pain and fatigue is modulated by M-like mechanisms and by central sensitization. The literature review has enforced that there are indicators of generalized hyperalgesia among patients with RA, and the pathway of the disruption of nociceptive processing in the central nervous system has been supported. Co-morbid fibromyalgia (secondary FM) is known to occur in 1530% of RA patients, extending fatigue and pain through central sensitization pathways. Abner, central processes such as wind-up, decreased conditioned pain modulation and cognitive emotional sensitization increase pain and fatigue levels- even during the absence of controlled inflammation. [18]

Nociplastic pain or CNS-amplification of pain explains further the presence of persistent fatigue, with low disease activity. Similar to the cases of some RA subgroups, the center sensitization phenomenon contributes to increased pain levels, fatigue, cognition, and sleep disturbances in fibromyalgia. [19]

Psychosocial studies point at depression, anxiety, self-efficacy, coping styles, and social support, which are known to play a significant role in chronic fatigue but through the route of pain. Fatigue measures such as the BRAF-MDQ are associated with small-to-moderate correlation with psychological variables regardless of disease activity Cognitive-Behavioral therapy (CBT), exercise, and mindfulness are finely effective in reducing fatigue in RA trials, which are consistent with both pain and psychological distress interventions. [20]

The rat models of RA to a large extent demonstrate the complexity of the pain pathways that involves peripheral inflammatory mediators, peripheral sensitization, and CNS modulation. It is shown that these models highlight the part related to the persistence of pain over the inflammation and can blur the idea of treatment glued to neural plasticity as a source of treatment of pain associated with fatigue. [21]

Our study evaluated the correlation between fatigue, pain, and illness activity in 200 patients with rheumatoid arthritis (RA) with validated instruments, such as Fatigue Severity Scale (FSS), Visual Analog Scale of pain (VAS), and Disease Activity Score in 28 joints (DAS28). Most of the participants were women (55.3%) having an average age of 52+/-5 years.

Fatigue was quite high and 57.3 % of the patients reported severe fatigue. The fatigue and level of pain yielded a significant relation ($p = 0.04$), and 84.6 % of the patients complained of the pain. The most notable is that the people with severe pains (63.7%) were more prone to report they had severe fatigue and this aspect shows great correlation between the two symptoms clinically. On the other end, the fatigue-DAS28 associative ended up being modest ($r = 0.19$, $p = 0.048$), with no coherent design noted across groupings of disease activity. On the same line, the inflammatory markers (ESR and CRP) lacked positive correlation with fatigue or pain, as in many cases, in patients with high ESR or CRP, fatigue and pain tend to be diminished. Furthermore our study showed that fatigue was more prevalent in females and pain more prevalent in males.

Conflict of Study: Nil
Funding: Nil

Limitation:
It is single center study and sample size is small, hence results cannot be generalized. To get more adequate results, a large sample size and multicenter approach is necessary.

Conclusion
Fatigue in RA does not just indicate inflammation; it is a complex multifactorial combination of enduring pain, distorted central processing of pain, impaired functioning, emotional disturbance and individual coping abilities. Objective inflammation has a possible role in the early or active disease but little involvement in chronic fatigue when pain has been factored in. Hence, to accomplish fatigue management, strict principles of a holistic, patient-centered approach are required: a complex of anti-inflammation therapy and pain-oriented assistance and psychosocial support. This multidimensional solution has the highest potential of alleviating tiredness and improving the life of people that experience RA.

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