INTRODUCTION
Rheumatoid arthritis (RA) is a chronic polyarticular inflammatory disorder affecting the musculoskeletal system. It is a disabling disease which directly affects the quality of life. Fibromyalgia (FM) is another common clinical syndrome which results from a defect in central pain processing. It is characterized by chronic, widespread musculoskeletal pain, fatigue, sleep disturbance, physical and psychological impairment. Prevalence of fibromyalgia has been reported as 12 – 17% among rheumatoid arthritis patients compared to 2 – 5% in the general population. The term “fibromyalgic RA” has been introduced for RA patients having co-existing fibromyalgia.

Co-existent fibromyalgia is known to adversely affect the various disease indices used to measure rheumatoid arthritis disease activity like DAS-28, HAQ and SF-36. DAS-28 has special importance in patients with RA while formulating their treatment decision regarding disease modifying drugs (DMARDs) and biologics, which are expensive therapies. DAS-28 is known to over-estimate the disease activity in fibromyalgic RA. If DAS scores are disproportionately high in relation to the actual level of synovitis as in fibromyalgic RA, DAS assessment becomes ambiguous.

In a developing country like Pakistan, various factors like socioeconomic and psychological may have an impact on perception and consequent disability of this disease. Associated fibromyalgia in RA patients may lead to over-assessment of disease activity which can lead to unnecessary changes in the therapy. Therefore, the present study was conducted to determine the correlation of disease activity score (DAS) with and without fibromyalgia in the patients with rheumatoid arthritis.

METHODOLOGY
It was a cross-sectional study, patients were enrolled using non-randomized convenient sampling. Study was carried out in the Department of Rheumatology, Pakistan Institute of Medical Sciences, Islamabad, for a period of 6 months (November 2011 to April, 2012). Patients above 16 years of age, of either gender, diagnosed to have rheumatoid arthritis according to ACR/EULAR criteria, 2010, included in the study. Patients with other autoimmune diseases or psychiatric illnesses were excluded. A written consent...
was taken from all patients who fulfilled the inclusion criteria. Study was approved by the Hospital Ethics Committee.

The DAS-28 score is the disease activity score which measures disease activity in patients with rheumatoid arthritis in 28 joints (Figure 1). It comprises of four measurements: swollen joints, tender joints, ESR, patient's self assessment of his/her general health (GH) on visual analogue scale ranging from 0 to 100 (0 means no effect and 100 means maximum affected life due to disease).

DAS-28 calculated from the following formula:

\[
0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.70 \times \log(ESR) + 0.014 \times GH
\]

Specific DAS-28 calculators are available on net and healthcare provider has to simply fill in the required values (www.4s-dawn.com/DAS-28/DAS-28.html).

DAS-28 measures RA disease activity as high (> 5.1), moderate (> 3.2 – 5.1), low (2.6 – 3.2) or disease in remission (< 2.6).

The sample size was calculated using 95% confidence level, alpha error of 5%, baseline incidence of rheumatoid arthritis 0.55%, precision of 0.27%, the estimated sample was 103 cases, however, keeping in mind a 25% lost to follow-up and non-response, we enrolled a total of 138 cases. Data was entered and analyzed in Statistical Package for Social Sciences (SPSS) version 11.0. The study variables were age, sex, marital status, RA disease duration, DAS-28 score and number of tender points for FM according to ACR 1990 criteria.

Descriptive statistics were used to calculate means and standard deviations from continuous numerical variables i.e. age, disease duration and DAS-28 score. Frequency and percentages were calculated from all categorical variables i.e. gender, marital status and disease activity score. The association of disease activity scores and presence or absence of RA factor with presence or absence of fibromyalgia using chi-square test was done. Mean DAS-28 score and disease duration were also compared among patients with and without fibromyalgia using student's t-test. A p-value of < 0.05 was considered significant.

RESULTS

A total of 138 patients of rheumatoid arthritis were enrolled. The mean age of patients was 42.9 ± 12.0 years, ranging from 21 to 77 years. Majority of the study subjects (77.0%) were below 50 years of age. Female gender was predominant with a proportion of 92%. Male to female ratio was 0.08: 1.

The distribution of demographic characteristics was compared among the fibromyalgic and non-fibromyalgic patients. Fibromyalgia was more frequent in individuals of more than 30 years of age (93.5%) compared to younger ones (6.5%), however, the difference was not statistically different (p = 0.12) from RA patients without fibromyalgia (75.7%) and (24.3%) respectively. Furthermore, the average DAS-28 score was significantly different between patients with fibromyalgia (5.4 ± 1.5) and without fibromyalgia (4.1 ± 1.2) in age group after 30 years (p = < 0.001). Gender distribution revealed 96.8% females with fibromyalgia compared to (90.7%) without fibromyalgia and the difference among gender was not statistically significant (p = 0.26, Table I).

Duration of RA was less in patients having fibromyalgia (5.6 years) compared to patients without fibromyalgia (7.6 years); however, this difference was not statistically significant (p = 0.14, Table II).

Thirty one out of 138 cases were found to have fibromyalgia (22.4%). DAS score was high (5.3 ± 1.5) in

| Table I: Demographic characteristics in patients with and without fibromyalgia. |
|--------------------------|--------------------------|--------------------------|--------------------------|
| Age categories (years)   | With fibromyalgia (n = 31) | Without fibromyalgia (n = 107) | Total (n = 138) |
| 21 to 30                 | 2 (6.5%)                  | 26 (24.3%)                | 28 (20.2%)               | 0.12               |
| 31 to 40                 | 11 (35.5%)                | 23 (21.5%)                | 34 (24.6%)               |                   |
| 41 to 50                 | 9 (29.0%)                 | 37 (34.6%)                | 46 (33.3%)               |                   |
| 51 to 60                 | 6 (19.4%)                 | 10 (9.3%)                 | 16 (11.6%)               |                   |
| 61 to 70                 | 3 (9.7%)                  | 9 (9.3%)                  | 12 (8.7%)                |                   |
| 71 or above              | 0 (0.0%)                  | 2 (1.9%)                  | 2 (1.4%)                 |                   |
| Age (years)              | Mean ± SD                | 45.4 ± 10.7               | 42.2 ± 12.3              | 42.9 ± 12.0       | 0.19               |
| Gender                   | With fibromyalgia (n = 31) | Without fibromyalgia (n = 107) | Total (n = 138) |
| Male                     | 1 (3.2%)                  | 10 (9.3%)                 | 11 (7.9%)                | 0.26               |
| Female                   | 30 (96.8%)                | 97 (90.7%)                | 127 (92.1%)              |                   |
| Marital status           | With fibromyalgia (n = 31) | Without fibromyalgia (n = 107) | Total (n = 138) |
| Married                  | 29 (93.5%)                | 93 (88.2%)                | 122 (88.4%)              | 0.29               |
| Unmarried                | 2 (6.5%)                  | 14 (11.8%)                | 16 (11.6%)               |                   |

*p-value has been calculated using chi-square and t-test at < 0.05 significance level. It is based on comparison of RA with and without fibromyalgia.
the patients with fibromyalgia, showing high disease activity compared to patients without fibromyalgia (3.9 ± 1.2) and this difference in mean was statistically significant (p = < 0.001, Table II).

High disease activity was significantly associated with presence of fibromyalgia (58.1%) compared to (21.7%) without fibromyalgia (p = 0.001). Low disease activity and remission was more prevalent in patients without fibromyalgia (15.0% and 14.0%) compared to those with fibromyalgia (3.2% and 3.2%) respectively (Table III).

The average values of all the DAS score parameters (number of swollen joints, number of tender joints, ESR and patient health assessment) were significantly high (2.8, 13.1, 38.9, 62.7) in the fibromyalgia group compared to non-fibromyalgia patients (1.7, 4.1, 30.7, 38.0 respectively, Figure 2).

**DISCUSSION**

RA is a chronic inflammatory disease and advent of biologic therapies has led to dramatic changes in its treatment. Monitoring and evaluation of disease activity in RA is done with DAS-28 which is a valid test of disease activity and therapeutic efficacy. Fibromyalgia is another chronic rheumatic disease, characterized by diffuse musculoskeletal pain along with additional somatic and psychological symptoms. Chronic nature of disease disturbs normal routine and quality of life. There are many other disease activity monitoring indices in RA; however, DAS-28 is commonly used worldwide because of its convenience in the outpatient setting.

In the current study, the DAS-28 was compared among RA patients with secondary fibromyalgia to look for any association. High number of patients was found to be suffering with fibromyalgia (22.4%). Previous data also suggests a high prevalence rate in patients with RA i.e. 12 – 20%. A study from North India showed 15% fibromyalgia in their RA patients. Recent studies, one from Turkey reported an even higher incidence (30.1%) of fibromyalgia in their RA population while other from UK showed 17% of RA patients having fibromyalgia. The reason of relatively high prevalence in our population could be due to the indigenous socio-economic, psychological, cultural and environmental circumstances. Secondly, nutritional deficiency like vitamin D and anorexia arising due to active RA disease could contribute to these fibromyalgic symptoms. This rationale is supported by a study conducted in the UK which showed that vitamin D deficiency is associated with anxiety and depression in fibromyalgia. Another recent study from Pakistan also showed low vitamin D levels in fibromyalgic patients.

The mean age of presentation in this study population was 42.9 years. A comparative age findings (42.3 years) has been reported by Sivas and colleagues. Naranjo et al. and Vilaseca have reported higher age means 53.0 years and 64.0 years respectively. This difference in age could be because of uncontrolled active RA since onset due to lack of early approach to expert health care provider in our population as compared to developed parts of world.

Female gender remained predominant in the current study which in fibromyalgia group was 97%. This was in concordance by earlier studies as well; Naranjo et al. reported that 88% cases were females with fibromyalgic RA. Both RA and fibromyalgia in isolation also has a known predominance for female gender.

The duration of disease was long in the RA group (7.6 years) compared to fibromyalgia (5.6 years) in the current study. Sivas et al. also found that duration of disease was shorter in fibromyalgia group (0.73 year).

**Table II:** Disease duration and DAS-28 score with and without fibromyalgia (n = 138).

<table>
<thead>
<tr>
<th>Rheumatoid arthritis</th>
<th>With fibromyalgia (n = 31)</th>
<th>Without fibromyalgia (n = 107)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration (years)</td>
<td>Mean ± SD</td>
<td>5.6 ± 6.2</td>
<td>7.6 ± 6.7</td>
</tr>
<tr>
<td>DAS score</td>
<td>Mean ± SD</td>
<td>5.3 ± 1.5</td>
<td>3.9 ± 1.2</td>
</tr>
</tbody>
</table>

* p-value has been calculated using t-test at < 0.05 significance level.

**Table III:** Association of DAS categories with and without fibromyalgia (n = 138).

<table>
<thead>
<tr>
<th>Rheumatoid arthritis</th>
<th>With fibromyalgia (n = 31)</th>
<th>Without fibromyalgia (n = 107)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease activity score (DAS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High disease activity</td>
<td>18 (58.1%)</td>
<td>23 (21.7%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Moderate disease activity</td>
<td>11 (35.5%)</td>
<td>53 (49.5%)</td>
<td></td>
</tr>
<tr>
<td>Low disease activity</td>
<td>1 (3.2%)</td>
<td>16 (15.0%)</td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>1 (3.2%)</td>
<td>15 (14.0%)</td>
<td></td>
</tr>
</tbody>
</table>

* p-value has been calculated using chi-square at < 0.05 significance level.

Figure 2: Comparison of average of parameters of DAS in the study (n = 138).
compared to (8.6 years) RA group. Naranjo also found shorter arthritis duration in fibromyalgic RA (8 years) compared to RA alone patients (9 years). The mean DAS score was significantly high in patients with fibromyalgia (5.3) compared to RA patients only (3.9). Vilaseca also witnessed a similar trend of higher DAS in fibromyalgia patients.

Coming to the primary objective, it was found out that high disease activity was significantly associated with presence of fibromyalgia compared to those having RA alone. These results showed that patients with high disease activity score in RA have more tendencies to develop fibromyalgia. Many others have also seen a similar trend. Wolfe et al. reported that fibromyalgic RA group had more abnormal measures of function, pain, disease activity and psychological status. Vilaseca and associates found that number of tender joints, global assessment by patient, functional and emotional aspects were worse in patients with fibromyalgic RA. They concluded that co-existence of fibromyalgia increases DAS in women with RA. The point of view of few investigators that DAS score overestimates the true status of patients with fibromyalgia becomes valid. Thus, putting patients to an unjustified increased treatment at the expense of adverse events and higher costs becomes an important issue.

This is first study of its kind in Pakistan. The limitations of this study are the absence of any intervention and long-term monitoring of the study cases. Also the severity of RA once fibromyalgia was controlled is not monitored. Long-term follow-up study is required for fibromyalgic RA patients to see the future behaviour of both associated conditions during the disease course i.e. if RA disease activity is controlled in fibromyalgic RA group whether their fibromyalgic symptoms persist or not.

CONCLUSION

DAS-28 constitutes a useful tool for assessing disease status in rheumatoid arthritis patients in outpatient setting but has certain limitations. Increased disease activity scores in RA must be assessed in detail for possible co-existence of fibromyalgia which can spuriously give high DAS values and affect treatment decisions.

REFERENCES


