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Impact of Fibromyalgia on Disease activity in Inflammatory Arthritis: A Cohort Study Conducted at Tertiary Care Hospital of Peshawar, Pakistan

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ABSTRACT

Objective: To determine the frequency of fibromyalgia in patients with inflammatory arthritis and to evaluate the impact of fibromyalgia treatment on disease activity in these patients.

Study Design: Prospective cohort study.

Place and Duration of Study: Rheumatology Division, Lady Reading Hospital, Peshawar Pakistan, from Apr to Dec 2021.

Methodology: A total of 400 patients were enrolled in the study of which 320 were diagnosed with rheumatoid arthritis, 55 with ankylosing spondylitis and 25 with psoriatic arthritis. The diagnosis of fibromyalgia was made with 2016 American College of Radiology Criteria and patients were classified according to the presence or absence of fibromyalgia. Disease Activity Score-28 for Rheumatoid Arthritis with Erythrocyte Sedimentation Rate (DAS28-ESR), Bath Ankylosing Spondylitis Disease Activity Index and Disease Activity in Psoriatic Arthritis Score-28 were recorded for rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis, respectively. Patients of fibromyalgia were treated by either pregabalin or duloxetine with 3-month follow-up. Patients with Widespread Pain Index <7 and Symptoms Severity Scale <5 after treatment for 3 months were labeled as responders.

Results: Fibromyalgia was present in 90(28.1%) patients with Rheumatoid Arthritis, 14(25.5%) with ankylosing spondylitis and 8(32%) with Psoriatic arthritis. Fibromyalgia was more common in Rheumatoid Arthritis patients whose disease duration exceeded 5 years (*p*-value <0.001). Similarly, obesity significantly contributed to Fibromyalgia development in Rheumatoid Arthritis (*p*-value <0.001) but not in Ankylosing spondylitis and Psoriatic arthritis patients. Disease duration >5 years, obesity, female gender and rising age increased the odds of developing Fibromyalgia in inflammatory arthritis with respective OR (95%CI) 28.2(9.24-76.8), 11.3(3.9-28.7), 1.76(0.94-3.3) and 1.81(1-3) with statistically significant differences in DAS-28 and Bath Ankylosing Spondylitis Disease Activity Index scores before and after treatment of Fibromyalgia with *p*-values <0.001. No significant association was observed in Erythrocyte Sedimentation Rate and C-reactive protein values before and after treatment in inflammatory arthritis.

Conclusion: Patients with concomitant Fibromyalgia presented higher disease scoring parameters than without Fibromyalgia. Proper diagnosis and treatment greatly reduces the disease activity scores in these patients.

Keywords: Ankylosing spondylitis, Fibromyalgia, Inflammatory arthritis, Psoriatic arthritis, Rheumatoid arthritis.

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INTRODUCTION

Fibromyalgia (FM) is a syndrome of persistent widespread pain, stiffness, fatigue, disturbed sleep, and cognitive difficulties, often accompanied by multiple unexplained symptoms like depression, anxiety and functional impairment of daily routine activities.[1] FM is a common condition encountered by rheumatologists, with a general prevalence of 2-4%,[2] increasing with age and more common in women, with women to men ratio ranging from 2:1 to 30:1.[3] FM can have similar clinical picture to inflammatory arthritis (IA) can be a diagnostic challenge to the rheumatologist.[4] IA is an umbrella term used to describe various arthritides, like rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS) and inflammatory bowel disease related arthritis, characterized by swelling, pain and inflammation of multiple joints.[5] Recent literature has reported that the prevalence of FM in RA, AS and PsA is considerably higher compared to general population with a pooled prevalence of 18-24%, 14-16% and 18% respectively.[4] Comorbid FM greatly impacts the severity of disease in patients with IA and may lead to unnecessary prescription of potentially toxic anti-rheumatic medications, or lead to treatment discontinuation by blunting patient reported outcomes, which leads to decrease quality of life and financial loss to the patient.[6] As there is no published data regarding the

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impact of fibromyalgia on disease activity in IA, this current study was designed to determine the frequency of FM complicating IA including RA, AS and PsA and its impact on disease activity with an aim to determine the improvement in disease activity of inflammatory arthritis by treating FM in such patients.

METHODOLOGY

The prospective cohort study was approved by the Institutional Research and Review Board of Lady Reading Hospital, Peshawar Pakistan, (IREB Ref No: 165/LRH/MTI). The study was conducted at Rheumatology Outpatient Department, LRH, Peshawar Pakistan, from April till December 2021. Sample size was calculated by Raosoft online sample size calculator with prevalence of FM as 25.8.[7]

Inclusion Criteria: Adult patients of either gender, with a diagnosis of Inflammatory Arthritis (RA, AS, PsA) and aged 18 to 75 years, were included.

Exclusion Criteria: Patients of inflammatory arthritis with comorbidities like Diabetes, Hypothyroidism and psychiatric disorders, were excluded.

We enrolled 407 patients, of which 7 were lost during follow-up, with remaining total 400 patients, 320 had RA, 55 patients had AS, and 25 patients had PsA. All patients were guided verbally in local language, with written, informed consent obtained from all enrolled participants All enrolled patients underwent detailed interviews regarding duration of disease, symptoms, and investigations (ESR and CRP), BMI calculation, history of past and present medications, disease activity score and musculoskeletal examination. All data was recorded on a predesigned proforma. Patients diagnosed with concurrent FM were treated for FM and followed for a period of 3 months to determine the effect of FM treatment on disease activity scores of IA. All patients were allowed to continue their current treatment and treatment for fibromyalgia was added for patients who were diagnosed with FM. Patients with established diagnoses of RA according to the ACR 2010 criteria, Ankylosing Spondylitis according to ASAS Criteria for axial and peripheral Spondyloarthropathy 2009, and Psoriatic Arthritis according to CASPER Criteria 2006. Diagnosis of FM was made using 2016 American College of Rheumatology (ACR) Criteria. Disease Activity scores were measured as DAS-28-ESR, BASDAI and DAPSA-28. Patients diagnosed with FM were treated with standard fibromyalgia therapy.[8] Patients were considered as treatment responders whose Widespread Pain Index (WPI) decreased to <7 and Symptoms Severity Scale (SSS) decreased to <5, after receiving treatment of FM for 3 months. SPSS version 22.0 was used to analyze the data. Numerical data was presented as Mean±SD while frequencies and percentages were used to describe categorical data. Student's t test was applied along with multiple regressions to find out the possible associations. All statistical tests were two tailed with *p*-value ≤0.05 considered significant.

RESULTS

Out of 400 patients, 320(80%) had RA, 55(13.8%) patients were suffering from AS and 25(3.2%) had PsA. All demographic details are summarized in Table-I. Among 320 RA patients, 73(22.8%) were males while 247(77.2%) were females. The mean age was 39.1±12.1 years with mean BMI being 27.1±2.8. The mean duration of disease in RA Group was 7.32±3.9 years. FM was present in 90(28.1%) patients in RA Group. The mean ESR and CRP in RA patients were 26±10.3 and 10.71±7.3, respectively.

Table-I: Demographic and Clinical Data of Study Participants (n=400)

Variables	Rheumatoid Arthritis (n=320, 80%)	Ankylosing Spondylitis (n=55, 13.8%)	Psoriatic Arthritis (n=25, 3.2%)
Gender (M/F) n(%)	73(22.8)/ 247(77.2)	33(60)/22(40)	18(72)/7(28)
Age (years) Mean±SD	39.1±12.1	31.5±8.5	36.2±8.1
18-39, n(%)	177(55.3)	46(83.6)	17(68)
40-59, n(%)	122(38.1)	9(16.4)	8(32)
>60, n(%)	21(6.6)	0	0
BMI (kg/m2) Mean±SD	27.1±2.8	26.2±2.0	27.36±2.0
Normal, n(%)	50(15.6)	9(16.4)	2(8)
Overweight, n(%)	204(63.8)	43(78.2)	18(72)
Obese, n(%)	66(20.6)	3(5.5)	5(20)
Disease Duration (years) Mean±SD	7.32±4.5	5.2±3.9	9.92±4.2
<5, n(%)	93(29.1)	27(49.1)	2(8)
5-10, n(%)	166(51.9)	22(40)	13(52)
>10, n(%)	61(19.1)	6(10.9)	10(40)
Fibromyalgia (No/Yes) n(%)	230(71.9)/ 90(28.1)	41(74.5)/ 14(25.5)	17(68)/8(32)
ESR (mm/h) Mean±SD	26±10.3	16.36±9.1	27.50±8.0
CRP (mg/l) Mean±SD	10.71±7.2	4.57±3.3	14±5.7

In RA patients, significant associations were found between FM and duration of disease, increasing BMI and increasing age. The duration of disease was directly associated with FM, where FM was more

common in patients whose disease duration were 5-10 years and >10 years with p-value and OR (95CI); <0.001, 9.3 (3.3-247) and <0.001, 28.2 (9.2-76.8) respectively. Similarly, increasing BMI majorly contributed to the occurrence of fibromyalgia in RA patients. Logistic regressions revealed that overweight and obese RA patients were at significant risk of developing FM as compared to those with normal BMI having *p*-value and OR (95%CI) of 0.01, 3.2 (1.27-7.8) and <0.001, 11.3 (3.9-28.7) respectively. There was no association between gender and fibromyalgia (*p*-value 0.09) but females were 1.76 times more likely to develop fibromyalgia as compared to males (OR (95%CI, 1.76 (0.94-3.30). Increasing age was also found to contribute to FM causation in RA. Regression analysis reveals that the middle age Group (40-59 years) are more prone to develop FM in RA with *p*-value, OR 95%CI is 0.02, 1.81(1-3). Same analysis were also performed for patients with AS and PsA to see whether any significant association was found between patients with FM to those without FM (Table-II). However, there is significant difference in DAPSA 28 in patients who had FM compared to those without FM (28.3±5.0 vs 18.71±6.4, *p*-value= 0.001).

The values of ESR and CRP were evaluated before and after 3 months follow-up in FM patients, given in Table-IV, showing no statistically significant association.

Table-III: Effect of FM Treatment on Disease Activity in Rheumatoid Arthritis and Ankylosing Spondylitis (n=400)

Rheumatoid Arthritis (DAS-28 ESR)			
Severity of disease	**Before treatment n(%)**	**After treatment n(%)**	***p*-value**
Remission	0(0)	4(4.4)	<0.001
Low disease activity	3(3.3)	24(26.6)	
Moderate disease activity	40(44.4)	60(66.6)	
High disease activity	47(52.2)	2(2.2)	
Ankylosing Spondylitis (BASDAI)			
Inactive	3(21.4%)	12(75%)	0.001
Active	11(78.6%)	2(25%)	

DISCUSSION

In our study the frequency of FM was 28.1% in RA (n=320), 25.5% in Ankylosing Spondylitis (n=55) and 32% in psoriatic arthritis (n=25). A recent cross-sectional study, reported the prevalence of FM in RA (n=62) and psoriatic arthritis (n=64) as 17.7% and 26.5% respectively[9] while a meta-analysis comprising of 40 studies reported the pooled prevalence as 21% in RA, 13% in AS and 18% in PsA.[10] One study reported FM in PsA of 73(17.8%) while another reported 38.3% prevalence of FM in patients with psoriatic arthritis.[11] Obesity can cause increased production of inflammatory biomarkers leading to systemic inflammation and contributes to pain development.[12] In RA, obesity

Table-II: Comparison of Demographic Factors in Inflammatory Arthritis With and Without Fibromyalgia (n=400)

Variables	**Rheumatoid Arthritis**			**Ankylosing Spondylitis**			**Psoriatic Arthritis (PsA)**		
	Fibromyalgia No/Yes	***p*-value**	**OR (95% CI)**	**Fibromyalgia No/Yes**	***p*-value**	**OR (95% CI)**	**Fibromyalgia No/Yes**	***p*-value**	**OR (95% CI)**
Disease duration (years)									
<5	89/4	Reference	Reference	22/5	Reference	Reference	1/1	Reference	Reference
5-10	117/49	<0.001	9.3(3.38-24.78)	16/6	0.5	1.6(0.47-6.11)	10/3	0.47	0.3(.01-7.4)
>10	27/34	<0.001	28.2(9.24-76.85)	4/2	0.58	2.2(0.33-14.55)	6/4	1.0	0.6(.03-15)
BMI (kg/m2)									
Normal BMI	45/5	Reference	Reference	8/1	Reference	Reference	1/1	Reference	Reference
Overweight	150/54	0.01	3.2(1.27-7.8)	31/12	0.42	3.0(0.45-36.9	13/5	0.52	2.6(0.11-52)
Obese	27/34	<0.001	11.3(3.9-28.7)	2/1	0.45	4.0(0.14-83.7)	3/2	1.0	1.5(0.05-37)
Gender									
Male	59/14	Reference	Reference	26/7	Reference	Reference	13/5	Reference	Reference
Female	174/73	0.09	1.76(0.94-3.30)	16/6	0.74	1.39(0.20-2.44)	4/3	0.63	1.9(0.37-11.3)
Age (years)									
18-39	135/42	Reference	Reference	35/11	Reference	Reference	13/4	Reference	Reference
40-59	78/44	0.02	1.81(1–3)	6/3	0.67	1.59(0.38–6.6)	4/4	0.35	3.2(0.6-2.7)
>60	17/4	0.78	0.7(0.26–2.2)	0	-	-	0	-	-

In RA Group, 47 patients had high disease activity followed by moderate in 40 and low disease activity in 3 patients. Significant differences were observed (*p*-value <0.001) after standard treatment for 3 months, only 2 patients were in the high disease activity Group. Similarly, significant reduction was found in BASDAI scores in AS Group (*p*-value =0.001). All these values are summarized in Table-III.

not only increases the susceptibility to the disease development but also leads to increase joint damage and pain.[13] In our study, FM was also found to be highly significant in both overweight and obese people with *p*-value <0.001 respectively and is similar to previous studies in which overweight and obese individuals have high incidence of FM as compared to non-obese people. Furthermore, weight reduction significantly improved FM symptoms.[14] According to the published literature, RA and FM is more common in women than in men (RA, 3:1, FM, 9:1) and women are more sensitive to pain.[15] Our study findings supported this, but the results were not statistically significant. The prevalence of FM increased with increasing age with middle age Group being highly affected,[16] consistent with our study findings. The mean difference between ESR and CRP values were not significant between RA Group with or without FM because these factors are not greatly affected by FM, similar to the findings of another study.[17] Comorbid FM indicate high disease activity scores (DAS28) in patient with RA (DAS28=5.19±0.73) than those without FM (DAS28=3.7±0.08), consistent with many studies published earlier where significant differences in DAS28 were reported.[17,18] In our study, post follow-up analysis revealed significant reduction in DAS28 (*p*-value <0.001) due to concomitant FM that worsened the baseline disease activity scores, as reported in recent literature.[19] Occurrence of FM in AS varies from 4% to 50%[20] but in our study, occurrence of FM in AS (n=55) was 25.5% (31.8% in women and 21.2% in men), in agreement with a study which reported 25% prevalence of FM in AS (n=36).[21] Two studies[22,23] reported the prevalence of FM in AS of 16.9% and 12.7% respectively, consistent with our findings, with high frequency of FM in women than men.[23] In agreement with our findings, studies have reported significant difference in DAPSA 28 scores in patient who had FM in PsA.[24,25]

Table-IV: Effect of FM Treatment on CRP and ESR in Inflammatory Arthritis, (n=400)

Variables	Rheumatoid Arthritis		*p*-value
ESR	Before Treatment	After Treatment	0.71
	26	24	
CRP	10.71	9.73	0.08
Ankylosing Spondylitis			
ESR	16.36	20.23	0.29
CRP	4.57	5.92	0.29
Psoriatic Arthritis (PsA)			
ESR	27.50	26.25	0.99
CRP	14	12.63	0.74

LIMITATION OF STUDY

Radiological investigations, like X-rays of the joints were not performed in patients to find preexisting damage. Similarly, musculoskeletal ultrasound was not performed which could differentiate between active diseases either due to inflammation versus FM.

CONCLUSION

Patients with FM had higher severity of pain and disease activity scoring (DAS28-ESR, BASDAI and DAPSA 28) than those without FM and proper diagnosis and treatment greatly improved disease activity scores.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

WH & SK: Conception, study design, drafting the manuscript, approval of the final version to be published.

SA & ZUD: Data acquisition, critical review, approval of the final version to be published.

SHM & IH: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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