Concomitant Diagnosis of Fibromyalgia and Ankylosing Spondylitis: Relation to Clinical Features and Plasma Pentraxin -3 Level

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Abstract: Background: Ankylosing spondylitis (AS) is a chronic systemic inflammatory rheumatic disease that specifically affects the spine and sacroiliac joint. AS diagnosis is often delayed in the clinical practice and this delay may cause the patients to miss the chance of early treatment. Fibromyalgia (FM) is a frequently encountered clinical syndrome, fibromyalgianess is a term used when patients who are diagnosed with inflammatory arthropathies meet the criteria for FM syndrome as shown in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjogren syndrome, and AS.

Objectives: We aimed primarily to assess the frequency of concomitant diagnosis of FM syndrome in AS patients and study its impact on clinical disease aspects. Secondary, our aim extended as a preliminary pilot study to assess the Plasma Pentraxin-3 (PTX-3) as a potential marker for the diagnosis of FM syndrome in AS patients.

Methods: Plasma PTX-3 in 61 AS patients was compared to 60 matched controls. FM was diagnosed by FM Rapid Screening Tool.

Bath AS disease activity index (BASDAI) and AS disease assessment score using C-reactive protein (ASDAS-CRP), Bath AS functional impairment index (BASFI), Bath AS metrology index (BASMI), AS quality of life (ASQoL) scale, Beck Depression Inventory, and Bath AS Radiology Index (BASRI) were assessed.

Results: The patients were categorized into two groups according to the concomitant diagnosis of FM syndrome. Group I included 14 (22.9%) AS patients who fulfilled the clinical diagnosis of FM syndrome. Group II included 47 (77.1%) AS patients without FM syndrome. AS patients with FM (Group I) had significantly (p<0.001) increased an average of ages, disease duration, diagnostic delay of AS, switching of bDMARDs, morning stiffness duration, ASDAS-CRP, BASFI, ASQoL score, BASDAI (p=0.008), and BDI score (p=0.005) compared to AS patients without FM (Group II). PTX-3 levels were significantly (p<0.001) higher in Group I (p<0.001) (median, 0.23; IQR, 0.15-0.41 ng/ml) than Group II (median, 0.13; IQR, 0.035-0.21 ng/ml) which showed no significant differences (p>0.05) compared to the controls. PTX-3 levels had significant positive correlations (p<0.05) with disease duration, BASFI, and ASQoL. Age, female sex, switch of biologic, ASDAS-CRP, and PTX-3 were significant predictors of FM in AS patients.

Conclusion: These results indicate that concomitant FM is a significant problem in patients with AS and its presence is associated with higher disease activity, impaired function as well as an overall negative impact on QoL. Easy scanning of suspicious cases of FM with FiRST questionnaire can be done in daily practice. PTX-3 is more or less accurate as the clinical features to improve the diagnostic certainty of FM in the presence of AS with a proven sensitivity of 62.3%, a specificity of 90%, a positive predictive value of 82.75%, and a negative predictive value of 73.9%.

Keywords: Fibromyalgia, Ankylosing Spondylitis, plasma Pentraxin-3.
1. INTRODUCTION

Ankylosing spondylitis (AS) is a chronic systemic inflammatory rheumatic disease, which belongs to the spondyloarthopathies (SpA) superfamily that specifically affects the spine and sacroiliac joint [1]. AS diagnosis is often delayed in the clinical practice, which may cause the patients to miss the chance of early treatment and leads to limited spinal and hip movement, increased disability, pain, poor quality of life (QoL), and functional status [2].

Fibromyalgia (FM) is a frequently encountered clinical syndrome, and it predominately affects females with a prevalence of about 2-7% of the general population [3]. It is presented by fatigue, sleep disturbances, stiffness in addition to widespread chronic pain, which is the hallmark of the disease. Collectively, these symptoms significantly impaired physical function and substantially impaired the QoL [4].

Fibromyalgianess is a term used when patients who are diagnosed with inflammatory arthropathies meet the criteria for FM syndrome as shown in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjogren syndrome, also sparse studies reported a prevalence of FM syndrome at 12.6-15% in patients with SpA [5-8].

Although there is much speculation about the aetiology of FM, one of the main theories is that cytokines may play a role in both; the aetiology of the disease and the intensity of the main symptoms [9, 10]. The researches on this issue are conflicting; however, recent studies indicate that in FM there is a generalized increase in pro-inflammatory cytokines secondary to the increased endogenous inducers and inflammation activators [11].

Pentraxin 3 (PTX-3), also called tumour necrosis factor-stimulated gene 14 (TSG14), is a member of the pentraxin (PTX) superfamily, which is differentiated to long PTX (PTX-3) and short PTX (including CRP, and serum amyloid A) [12]. In contrast to CRP, which is produced in the liver upon stimulation by interleukin-6 (IL-6), PTX-3 is produced directly in the inflamed tissue in response to pro-inflammatory cytokines such as interleukin-1beta (IL-1β) and tumour necrosis factor-alpha (TNFα) [13].

PTX-3 is produced in many cells such as dendritic cells, mononuclear and polymuclear phagocytes, fibroblasts, adipocytes, endothelial cells, synovioocytes, and alveolar epithelial cells. It plays a role in various biological processes such as female fertility, extracellular matrix deposition, inflammation, and immunity [14].

Recently, multiple studies have assessed PTX-3 levels in autoimmune disorders such as RA [13], SLE [15], systemic sclerosis (SSc) [16], AS, and FM [17] with conflicting results.

We aimed to assess the frequency of concomitant diagnosis of FM syndrome in AS patients and to study its impact on clinical disease aspects. Our aim extended as a preliminary pilot study to assess the PTX-3 as a potential marker for the diagnosis of FM syndrome in AS patients.

2. MATERIALS AND METHODS

2.1. Study Groups

Study design: This cross-sectional study was designed primarily to assess the frequency of concomitant diagnosis FM syndrome in AS patients and to study its impact on clinical disease aspects of the AS patients. Secondary, our study extended to assess the PTX-3 as a potential marker for the diagnosis of FM syndrome in AS patients as a preliminary pilot study.

Inclusion criteria: Sixty-one patients with AS diagnosed according to the modified New York criteria for the diagnosis of AS [18] and 60 healthy volunteers as a control group were included in our study. Patients were recruited from the outpatient clinic and inpatients’ unit of Rheumatology & Rehabilitation and Physical Medicine Department of National Care Hospital, Riyadh, Saudi Arabia (KSA). Exclusion criteria included patient age less than 18 years old, presence of acute infection, associated rheumatological diseases with AS, hepatic, renal, cardiac diseases, pregnancy, or malignancy. All patients with AS who were following in the hospital in the period between October 2019 and March 2020 and fulfilled the inclusion criteria were included in the study. After approval of the study scheme by the local ethical committee in the hospital according to the statement of the Helsinki Declaration of 1983, informed consent was taken from all participants.

2.2. Full Medical History and Examination

Medical files of the patients were reviewed and all the data regarding age, sex, disease duration, diagnostic delay until confirmed AS diagnosis, working, the practice of home-based training exercise program including classic breathing and posture exercises or aerobics, smoking, new pain or fatigue in the last few months were recorded. Detailed drug history was reported emphasizing on the type [non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) or biological DMARDs], the duration, number of switches between the bDMARD, and the cause if the drug was stopped.

Full medical examination with special attention to detailed spine examination, Schober’s test, and other measures (ear to wall, occiput to the wall, lateral flexion of the trunk) was done.

AS disease activity was assessed by Bath AS disease activity index (BASDAI) which consists of a 0 - 10 scale measuring discomfort, pain, and fatigue. Zero scores denote no problem and 10 being the worst problem in response to six questions about the five major symptoms of AS: fatigue, spinal pain, arthralgia (joint pain) or swelling, enthesitis, and the mean of morning stiffness duration and severity. The score ranged from 0 to 50 score and then it is divided by 5 to give a final 0 – 10 [19]. AS disease assessment score using C-reactive protein (ASDAS-CRP) showed back pain, patient global assessment, duration of morning stiffness and peripheral pain/swelling based on 0 -10 scale and calculated as ASDAS-CRP = 0.12 x Back Pain + 0.06 x Duration of Morn-
ing Stiffness + 0.11 x Patient Global + 0.07 x Peripheral Pain/Swelling + 0.58 x Ln (CRP+1) [20].

Bath AS functional impairment index (BASFI) was used to assess the AS functional impairment. It includes 10 questions assessing the limitations of function and the level of physical activity at home and work. The visual analogue scale was used to score each question from 0 (easy) to 10 (impossible), and the average value over the 10 questions was the BASFI score with a total range 0-10 [21].

The Bath Ankylosing Spondylitis Metrology Index (BASMI) with a range of 0-10 assessed the spinal mobility through five clinical tests: (a) lateral lumbar flexion, (b) tragus to the wall, (c) modified Schober’s test, (d) maximum bi-malleolar distance, and (e) cervical rotation [22].

AS quality of life (ASQoL) scale was used to assess the patients’ QoL as higher scores indicate poor QoL [23] and the presence of depression was evaluated by using Beck Depression Inventory as total scores were interpreted as follows: 0-4 points indicated none or minimal depression; 5-9 points indicated mild depression and ≥ 10 points indicated moderate depression [24].

All patients were screened for FM symptoms by Fibromyalgia Rapid Screening Tool (FiRST) which is self-questionnaire consists of six questions regarding the presence or absence of the following parameters of FM: widespread pain, fatigue, pain characteristics, non-painful abnormal sensations, functional somatic symptoms, sleep, and cognitive problems. Questions require only an answer of “yes” or “no”, with each “yes” answer worth 1 point, and patients were diagnosed to have concomitant FM syndrome if FiRST score ≥5 [25].

2.3. Radiographic Examination

Antero-posterior x-Rays for sacroiliac joint, cervical (anteroposterior), and lumbar spine (anteroposterior and lateral views) were obtained for the evaluation of radiological damage in the AS patients according to the Bath AS Radiology Index (BASRI) with a range of 0-12 [26].

2.4. Laboratory Assessment

Serum CRP was measured and plasma PTX-3 was assessed for the patients and healthy subjects on the same day of the clinical examination. Samples were stored at −20 ºC/-80 ºC until analysis. Plasma levels of PTX-3 were measured by a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) technique (Novatein Biosciences, USA), which had an analytic sensitivity of 0.02 ng/ml. Recombinant human PTX-3 at serial dilution and the plasma samples were added to the microtiter plate pre-coated with human PTX-3 antibody. After incubation and washing away the unbound PXT-3, a monoclonal antibody specific for human PTX-3 conjugated to horseradish peroxidase (HRP) was added to the wells. After a second incubation and washing procedures to remove unbound HRP conjugated antibody, the chromogenic substrate solution containing tetramethylbenzidine was added and colour developed in proportion to the amount of bound PTX-3. After the specified incubation period, the colour development was stopped by the addition of acid stop solution and the optical density (OD) was measured by the ELISA plate reader at 450 nm.

2.5. Statistical Analysis

The data were recorded on an “Investigation report form”. These data were tabulated, coded then analysed using the computer program SPSS (Statistical package for social science) version 22, quantitative data were expressed in the form of mean, standard deviation (±SD) or median and interquartile range (IQR). Qualitative data were expressed in the form of numbers and percent. The student's t-test was used to compare between the mean of two groups of numerical (parametric) data. For continuous non-parametric data, Mann-Whitney U-test was used for inter-group analysis, the Kruskal Wallis test was used to compare between more than two groups of non-parametric data, Pearson correlation coefficient (r) test was used for correlating different parameters. Inter-group comparison of categorical data was performed by using chi-square test (X2-value) and Fisher exact test, and some investigated parameters were entered into a logistic regression model to determine which of these factors was considered as a significant risk factor and identify its odds ratio. The sensitivity and specificity were examined at different cut off points using Receiver Operating Curve (ROC) analysis to determine the best cut off point as well as the diagnostic power of each test. P-value <0.05* was considered as a significant risk factor and identify its odds ratio. The sensitivity and specificity were examined at different cut off points using Receiver Operating Curve (ROC) analysis to determine the best cut off point as well as the diagnostic power of each test. P-value <0.05* was considered statistically significant and P-value <0.001** was considered highly significant in all analyses.

3. Results

This study was conducted on 61 adult patients with AS, and they were 50 (82%) males and 11 (18%) females with disease duration (median, IQR: 6, 4-7). Sixty adult healthy volunteers who were matched for age (P= 0.9) and sex (P= 0.4) served as a control group, Table (1).

Table 1. Comparison between Ankylosing Spondylitis patients and healthy controls, as regard age, sex, and the mean plasma Pentraxin -3 level.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AS Patients (No.=61)</th>
<th>Controls (No.=60)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) Mean (SD)</td>
<td>36.44 (5.14)</td>
<td>36.30 (5.58)</td>
<td>0.9</td>
</tr>
<tr>
<td>Sex NO. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>50 (82%)</td>
<td>45 (75%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Female</td>
<td>11 (18%)</td>
<td>15 (25%)</td>
<td></td>
</tr>
</tbody>
</table>

AS: ankylosing spondylitis, No.: number, SD: standard deviation, P> 0.05*: nonsignificant.

The AS patients were categorized into two groups according to the concomitant clinical diagnosis of FM syndrome. Group I included 14 (22.9%) AS patients who fulfilled the diagnosis of FM syndrome. Group II included 47 (77.1%) AS patients without FM syndrome.

Studying different demographic parameters between the two groups as regards; age, sex, disease duration, diagnostic delay of AS, working and smoking status, regular exercis-
ing, as well as the used medication and the number of patients switched bDMARDs during the disease course, are shown in Table (2).

Table 2. Comparison between ankylosing spondylitis patients with fibromyalgia syndrome (Group I) and ankylosing spondylitis patients without fibromyalgia syndrome (Group II) regarding demographic and clinical features.

<table>
<thead>
<tr>
<th>-</th>
<th>Group I (n=14)</th>
<th>Group II (n=47)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)Mean (SD)</td>
<td>41.9(4.3)</td>
<td>34.8(4.2)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Sex No (%)</td>
<td></td>
<td></td>
<td>0.049*</td>
</tr>
<tr>
<td>Male</td>
<td>9/50</td>
<td>41/50</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5/11</td>
<td>6/11</td>
<td></td>
</tr>
<tr>
<td>Disease duration (years) Median (IQR)</td>
<td>9 (6.75-11)</td>
<td>5 (3-6)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Diagnostic delay (months)</td>
<td>12 (12-19.5)</td>
<td>6 (6-12)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Working No. (%)</td>
<td>10 (71.4%)</td>
<td>45 (95.7%)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Smoker No. (%)</td>
<td>6 (42.9%)</td>
<td>9 (19.1%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Regularly exercise No. (%)</td>
<td>0 (0%)</td>
<td>33 (70.2%)</td>
<td>--------</td>
</tr>
<tr>
<td>NSAID use No. (%)</td>
<td>11 (78.6%)</td>
<td>21 (44.7%)</td>
<td>0.03*</td>
</tr>
<tr>
<td>csDMARD use No. (%)</td>
<td>3 (21.4%)</td>
<td>16 (34%)</td>
<td>0.4</td>
</tr>
<tr>
<td>bDMARD use No. (%)</td>
<td>8 (57.1%)</td>
<td>23 (48.9%)</td>
<td>0.4</td>
</tr>
<tr>
<td>History of bDMARD switch No. (%)</td>
<td>7(50%)</td>
<td>5(10.6%)</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

Group I patients were significantly older than group II patients (P< 0.001). Group I patients had significantly longer mean disease duration (p<0.001) and prolonged diagnostic delay of AS (P= 0.001) than Group II patients. In group I, FM syndrome was statistically significantly more frequent in the female patients (45.4%) than in the male patients (18%) (P= 0.04) as 5 females out of the total 11 female patients had concomitant FM syndrome in comparison to 9 males out of total 50 males were diagnosed to have concomitant FM syndrome. Significantly increased numbers of patients of group I were not working (P= 0.02) and were regularly using NSAIDs (P= 0.03) than group II. No patient in group I was regularly exercising compared to 70.2% of the patients of group II had regular exercise programs.

At the time of study, 19 AS patients were using csDMARD (methotrexate and / sulfasalazine) and 31 patients were using bDMARD (Etanercept / Adalimumab or Secukinumab). Sixteen of the included AS patients switched to another biologic during the course of the disease (One because of an insurance issue, 3 because of drug complication, and 12 because of persistent pain and disease activity). Although there was no statistically significant difference (P> 0.05) between both groups regarding the number of AS patients using either csDMARDS or bDMARDs, however, Group I had significantly increased switching in bDMARDs (P< 0.001) because of persistent pain than Group II (Table 2).

Table 3 shows that patients of Group I had statistically significantly increased median (IQR) of morning stiffness duration (P< 0.001), mean of BASDAI (P= 0.008), ASDAS-CRP (P< 0.001), BASFI (P< 0.001), ASQoL score (P< 0.001) and BDI score (P= 0.005) than patients of Group II but there was no statistically significant difference between both groups as regards the mean of BASMAI (P= 0.07), BASRI (P= 0.26) or serum CRP level (P= 0.07).

Table 3. Comparison between ankylosing spondylitis patients with fibromyalgia syndrome (Group I) and ankylosing spondylitis patients without fibromyalgia syndrome (Group II) regarding different clinical disease indices.

<table>
<thead>
<tr>
<th>-</th>
<th>Group I (NO.14)</th>
<th>Group II (NO.47)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning stiffness (minutes) Median (IQR)</td>
<td>50 (30-82.5)</td>
<td>30 (20-30)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>BASDAI, Mean (SD)</td>
<td>4.6±1.1</td>
<td>3.8±0.9</td>
<td>0.008 *</td>
</tr>
<tr>
<td>ASDAS-CRP, Mean (SD)</td>
<td>3.3±0.5</td>
<td>1.7±0.8</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>BASFI, Mean (SD)</td>
<td>7.5±1.01</td>
<td>4.3±1.7</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>BASMI, Mean (SD)</td>
<td>6.78±0.77</td>
<td>5.87±1.8</td>
<td>0.07</td>
</tr>
<tr>
<td>ASQoL, Mean (SD)</td>
<td>13.4±2.1</td>
<td>9.3±3.02</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>BDI, Mean (SD)</td>
<td>15.2±3.9</td>
<td>11.6±2.8</td>
<td>0.05 *</td>
</tr>
<tr>
<td>BASRI, Mean (SD)</td>
<td>5.64±1.91</td>
<td>5.17±1.2</td>
<td>0.26</td>
</tr>
<tr>
<td>CRP (mg/l) Mean (SD)</td>
<td>10.8±3.7</td>
<td>9.02±3.12</td>
<td>0.07</td>
</tr>
</tbody>
</table>

NO: number, IQR: interquartile range, SD: standard deviation, BASDAI: Bath ankylosing spondylitis disease activity index, ASDAS-CRP: ankylosing spondylitis disease activity score- C-reactive protein, BASFI: Bath ankylosing spondylitis functional index, BASMI: Bath ankylosing spondylitis metrology index, ASQoL: ankylosing spondylitis quality of life, BDI: Beck depression inventory, BASRI: Bath ankylosing spondylitis radiology index, P>0.05: nonsignificant, P< 0.05*: significant, P< 0.001**: highly significant.

Plasma PTX-3 levels were statistically significantly (p<0.001) higher in all AS patients (median, 0.26; IQR, 0.18-0.36 ng/ml) compared with the healthy controls (median, 0.11; IQR, 0.04-0.16 ng/ml) (Fig. 1). AS patients with concomitant FM syndrome (Group I) had statistically significantly elevated plasma PTX-3 (median, 0.23; IQR, 0.15-0.41 ng/ml) than AS patients without FM syndrome (Group II) (median, 0.13; IQR, 0.035-0.21ng/ml, P< 0.001) (Fig. 2), and the controls (median, 0.11; IQR, 0.04-0.16 ng/ml, P< 0.001). No significant difference (P=0.05) was found between patients of Group II compared to the healthy controls in regard to plasma PTX-3 levels.

Plasma PTX-3 levels were statistically significantly (P< 0.001**) higher in all AS patients (median, 0.26; IQR, 0.18-0.36 ng/ml) compared with the healthy controls (median, 0.11; IQR, 0.04-0.16 ng/ml). PTX-3: plasma pentraxin-3, AS: Ankylosing spondylitis, P<0.001**: highly significant.

AS patients with concomitant FM syndrome (Group I) had statistically significantly (P<0.001**) elevated plasma PTX-3 level (median, 0.23; IQR, 0.15-0.41 ng/ml) than AS patients without FM syndrome (Group II) (median, 0.13; IQR, 0.035-0.21ng/ml). PTX-3: plasma pentraxin-3, AS: Ankylosing spondylitis, P< 0.001**: highly significant.
Fig. (1). Comparison between Ankylosing Spondylitis patients and the healthy controls as regard the median plasma Pentraxin-3 level. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Fig. (2). Comparison between Ankylosing Spondylitis patients with Fibromyalgia (Group I) and those without Fibromyalgia (Group II) as regards the median plasma Pentraxin-3 level. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*
Plasma PTX-3 levels showed statistically significant positive correlations with disease duration (r=0.349, P=0.006), BASFI (r=0.28, P=0.02) and ASQoL (r=0.83, P=0.002) but there was no statistical significant correlation as regard to age (r=0.136, P=0.2), morning stiffness duration (r=0.249, P=0.06), BASDAI (r=0.14, P=0.11), ASDAS-CRP (r=0.2, P=0.27), BASMI (r=0.05, P=0.69), BDI (r=0.126, P=0.3), BASRI (r=0.21, P=0.11) or CRP levels (r=0.15, P=0.22) (Table 4).

Table 4. Correlation between plasma levels of PTX-3 levels and different clinical and laboratory disease parameters.

<table>
<thead>
<tr>
<th>Variables</th>
<th>r</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.136</td>
<td>0.2</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>0.349</td>
<td>0.006*</td>
</tr>
<tr>
<td>Morning stiffness (minutes)</td>
<td>0.249</td>
<td>0.06</td>
</tr>
<tr>
<td>BASDAI</td>
<td>0.14</td>
<td>0.11</td>
</tr>
<tr>
<td>ASDAS-CRP</td>
<td>0.20</td>
<td>0.27</td>
</tr>
<tr>
<td>BASFI</td>
<td>0.28</td>
<td>0.02*</td>
</tr>
<tr>
<td>BASMI</td>
<td>-0.05</td>
<td>0.69</td>
</tr>
<tr>
<td>ASQoL</td>
<td>0.83</td>
<td>0.002*</td>
</tr>
<tr>
<td>BASRI</td>
<td>-0.21</td>
<td>0.11</td>
</tr>
<tr>
<td>CRP mg/l</td>
<td>0.15</td>
<td>0.22</td>
</tr>
</tbody>
</table>

BASDAI: Bath ankylosing spondylitis disease activity index, ASDAS-CRP: ankylosing spondylitis disease activity score- C-reactive protein, BASFI: Bath ankylosing spondylitis functional index, BASMI: Bath ankylosing spondylitis metrology index, ASQoL: ankylosing spondylitis quality of life, BDI: Beck depression inventory, BASRI: Bath ankylosing spondylitis radiology index, P> 0.05: nonsignificant, P< 0.05*: significant.

The following variables were entered into a regression analysis: Age, sex, disease duration (months), time passed until diagnosis (months), working or not, smoking or not, switched bDMARD or not, morning stiffness (minutes), ASDAS-CRP and Plasma PTX-3 level.

The analysis showed that increased age (95% CI: 0.56–0.857, p < 0.001), female sex (95% CI: 0.066–1.056, P< 0.04), frequent switch of bDMARDS (95% CI: 0.02–0.33, P< 0.01), increased ASDAS-CRP (95% CI: 0.05–0.37, P< 0.001) and high PTX-3 levels (95% CI: 0.001–0.95, P< 0.04) were significantly predicting concomitant FM syndrome in AS patients.

ROC curve analysis showed that plasma PXT-3 level at a cut-off point of 0.23 ng/ml had a sensitivity of 62.3%, a specificity of 90%, a positive predictive value of 82.75%, a negative predictive value of 73.9% % as a diagnostic marker for concomitant FM syndrome in AS patients. The area under the curve was 0.858 (Fig. 3).

4. DISCUSSION

FM syndrome is a complex neurosensory disorder characterized by chronic diffuse musculoskeletal pain added to many symptoms like fatigue, sleep disturbances, and anxiety [5]. Inflammatory chronic back pain and fatigue are cardinal symptoms of AS; inflammatory back pain is the cornerstone clinical criterion for the diagnosis of AS. Fatigue is a major symptom affecting about 50-70% of AS patients and it markedly affects many disease aspects, including functional capacity, quality of life, mental health. It is a key point in BASDAI assessment for disease activity [1, 27].

The prevalence of FM syndrome among patients with definite rheumatic diseases was reported as 11-30% which was considerably higher than in the general population that has been estimated at 2-7%. It was reported to be 18-24% in RA, 14-16% in axial SpA, and 18% in psoriatic arthritis [6, 28].

This study was designed primarily to assess the frequency of concomitant diagnosis of FM syndrome in AS patients and to study its impact on different clinical disease aspects.

In our study, FM syndrome was diagnosed in 22.9% of AS patients and it was more frequent in females (45.4%) than in males (18%). This is in agreement with the reported prevalence which was in the range of 4.11 to 25.2% in different study’ designs [6, 7, 29-31]. FM syndrome is ten times more frequent in women and represents one of the most common causes of generalized musculoskeletal pain in women aged between 20 and 55 years [31]. It was clearly demonstrated that sex affects pain perception and women have greater pain sensitivity compared to males [32].

In our study, we noticed that all patients with FM syndrome were not exercising which concurred with other people who demonstrated just two out of the thirteen AS patients with FM in their study, were doing home-based exercise programs [33]. This is not surprising as pain and fatigue related to FM influence the capacity of these patients to do all kind of activities, even little movement in light of pain...
syndrome showed increased disease activity assessed by significantly magnifies disease activity values even when more disease activity. Studies that its presence significantly affects the degree of clinical characteristics of the AS patient, but it is agreed in all clinical aspects of AS patients varies according to the clinical, emotional, and social domains of QoL [37, 43]. Pain, discomfort, and fatigue [38, 44] including; the severity of the symptoms, the experienced pain and fatigue and considering the disease consequences are sufficient to incite depression. Furthermore, inflammatory/cytokine hypothesis of depression has been proposed [45], stating that inflammation itself had a role in depression. This explains the increased levels of CRP and TNFα in depressed individuals compared to non-depressed individuals [43, 44].

It makes sense that comorbid FM syndrome further increased the burden of AS disease [30] and negatively worsened patient’s QoL, this was evident in our result as, AS patients with concomitant FMS had significantly increased ASQoL scores denoting bad QoL than those patients without FM which was also found by others [8].

AS patient’s QoL can be affected for a variety of reasons including; the severity of the symptoms, the experienced pain, discomfort, and fatigue [45] which affects the physical, emotional, and social domains of QoL [46-49].

The effect of the comorbid FM syndrome on different clinical aspects of AS patients varies according to the clinical characteristics of the AS patient, but it is agreed in all studies that its presence significantly affects the degree of disease activity. Concomitant diagnosis of FMS in patients with AS significantly magnifies disease activity values even when more subjective elements are incorporated as in ASDAS-CRP score [30]. In our study, AS patients with concomitant FM syndrome showed increased disease activity assessed by both BASDAI and ASDAS-CRP scores than those patients without FM.

This was recorded obviously in a large meta-analysis study which was designed and systematically reviewed forty papers to investigate the prevalence of concomitant FM in adults with different inflammatory arthritis and quantify the impact of FM on disease activity scores. The authors revealed with great consistency statistically significant higher pooled DAS scores in patients with FM and AS than those without FMs (BASDAI mean difference 2.22; 95% CI: 1.86, 2.58) [5].

Similarly, this effect of concomitant FM syndrome on worsening the disease activity was reported in axial SpA [7, 38, 50-53], RA [54-56], and psoriatic arthropathies [52].

The presence of FM syndrome in AS patients gives a wrong impression of the increased degree of disease activity as it is difficult for the patients to discriminate between FM and AS symptoms during responding to self-assessment scores [33]. This renders the calculation of actual disease activity to be challenging even when more objective measures like swollen joint count or CRP levels are used [30, 57]. Second, as long as disease activity is the guide for planning and modification of the treatment this may lead to unnecessary initiation of a biologic drug, escalating the treatment, or switch to another drug [38]. In our results, although there were no significant differences between AS patients with concomitant FM and those without FM regarding the frequency of bDMARD use, however, patients with concomitant FM were more likely to switch to another bDMARD along the course of their disease.

Taking into account the complexity and overlap of AS and FM clinical pictures, it is not easy to differentiate and to ascertain the diagnosis of FM among AS patients. According to ACR 1990 criteria for FM diagnosis, the patient is first asked about the presence of chronic widespread pain in the 4 quadrants of the body and then screened for the presence of tender point which is the powerful discriminator between patients with FM syndrome and healthy controls. This may be difficult to be differentiated from soft tissue rheumatism and enthesopathy, commonly associates inflammatory SpA in general added to the fact that it is time-consuming and difficult to be implemented in daily practice [35, 58]. In the current study, FM syndrome was defined according to the FiRST which is a patient self-completed questionnaire for detecting FM in patients with chronic widespread pain. It was validated by the French Rheumatic Pain Study Group [25] and had a sensitivity of 90.5% and a specificity of 85.7% for the identification of FM patients. It has the advantage of being brief and easy to be used by the clinician in daily practice [38].

If the clinician is not aware of this overlap, AS patient may be first diagnosed as having FM, and AS diagnosis will be delayed with the subsequent delay in starting appropriate treatment. This negatively impacts their prognosis. The time lag between symptom onset and the diagnosis of the disease had been reported to be up to 13 years [59] and this was con-
firmed in our study as patients with concomitant FM syndrome showed significantly increased time lag between their first presenting symptoms until being diagnosed as AS [60].

Based on those speculations, our aim extended as a preliminary pilot study to assess the plasma PTX-3 as a potential marker for the diagnosis of FM syndrome in AS patients. Concerning the strength of the study, PTX-3 has been discussed before in FM and AS separately but to our knowledge, this is the first study to assess PTX-3 levels in AS patients with concomitant FM syndrome. PTX-3 might have an advantage over the clinical criteria for the diagnosis of concomitant FM in the AS patients, such as being measurable and could be repeated so it could be used potentially to monitor the improvement of the elevated disease activity scores caused by FM after its management in the AS patients.

Etiopathogenesis of FM syndrome is still obscure and lastly, many theories had been proposed. In 2001, Wallace et al. were the first to suggest the inflammatory aspect of FM [61]. Proinflammatory cytokines such as IL-8 and TNF-α have been detected in high levels in FM where IL-8 has been linked to modulation of sympathetic pain while TNF-α disrupts the blood-brain barrier causing adverse effects on brain cell function contributing to fatigue and anorexia that are seen in FM [62, 63].

PTX-3 is a long PTX produced by somatic and immune cells in response to proinflammatory stimuli turning on several ligands and exerting multifunctional properties. PTX-3 is not constitutively expressed in the central nervous system, but it can be found in neuronal cells and astrocytes after exposure to inflammatory signals (IL-1, TNF-α), toll-like receptor engagement, and autoimmune reactions [64].

Our study demonstrated that plasma PTX-3 levels were significantly increased in AS patients compared to the healthy controls and its levels were significantly elevated in patients with concomitant FMS than those without but there were no significant differences in plasma PTX-3 in AS patients without FMS compared to healthy controls.

It is not clear whether medical treatment of the AS has an effect on the plasma PTX-3 level, however, there is no disagreement between the two studied patient groups in terms of the type of treatment so this could not explain the increased levels of PTX-3 in the patients with concomitant FM syndrome.

Significantly elevated levels of plasma PTX-3 had been detected in FM patients in comparison to the healthy control by García et al. [65]. Another study demonstrated that isolated monocytes from FM patients produced more quantity of PTX-3 than monocytes of healthy individuals [66]. Moreover, studying PTX-3 levels in 94 women with FM syndrome confirmed higher PTX-3 plasma levels in FM patients than in healthy women [67].

Studies in the literature assessed PTX-3 in AS are conflicting. In agreement with our results, Nishihara et al. measured plasma PTX-3 in 11 patients with psoriatic arthritis, 70 patients with AS, and 90 matched controls and concluded that plasma PTX-3 levels were not increased even decreased in SpA compared to the controls, furthermore no differences in PTX-3 levels could be detected between psoriatic and AS patients [68]. On the contrary, Deniz [69] et al. demonstrated increased serum PTX-3 levels in AS patients. In another attempt to study the role of PTX-3 in AS pathogenesis, Zhang et al. investigated the association between PTX-3 single polymorphism (rs2305619) and AS susceptibility and showed that polymorphism does not have a direct association with the risk of AS development [70].

We could not explore any significant correlation between PXT-3 and disease activity scores or CRP in AS patients. This is in line with previous results that did not find any positive correlation between PTX-3 and traditional inflammatory markers including CRP and ESR in patients with AS [69, 71] as well as with other inflammatory diseases including psoriatic arthritis [72], small vessel vasculitis [73], Takayasu’s arteritis [74] and acute myocardial infarction patients [75].

Taken together our results, the increased plasma PTX-3 levels in the AS patients compared to the controls might be due to concomitant FM syndrome. Practically, it could be used to confirm the diagnosis of FM in patients with AS in addition to the clinical criteria and help to overcome the overlap of symptoms between both diseases. PTX-3 has the advantage of being measurable and can be repeated so it could be used as a potential marker to monitor disease activity scores after the management of FM.

Limitation of this study includes: First, the sex and age difference of FM on the level of PTX-3 level were not considered. Second, based on the current study, it cannot be stated whether the management of FM will affect the PTX-3 level or not. Although in the study, AS patients who had concomitant FM syndrome were not receiving any specific management for FM however, this is an important point of research. Third, the mean disease duration of AS patients was long that limited the generalizability of using the test in the AS patients in recent-onset disease. Fourth, testing PTX-3 is still used for research purposes and not yet commercially validated.

Conclusion

These results indicate that concomitant FM is a significant problem in patients with AS and its presence is associated with higher disease activity, impaired function as well as an overall negative impact on QoL. Easy scanning of suspicious cases of FM with FiRST questionnaire can be done in daily practice. PTX-3 is more or less accurate as the clinical features to improve the diagnostic certainty of FM in the presence of AS with a proven sensitivity of 62.3%, a specificity of 90%, a positive predictive value of 82.75%, and a negative predictive value of 73.9%. It is highly recommended to conduct a longitudinal study to assess the effect of the age and sex difference on PTX—3 level and the effect of management of FM on disease activity scores and PTX-3 levels in the AS patients with concomitant FM syndrome. Our
study opens a window for future multicentric studies to validate the use of PTX-3 as a potential marker for the diagnosis of FM syndrome in patients with AS before its application on a large scale.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
The study scheme was reviewed and approved by the ethical committee of scientific research of the Care National Hospital, Riyadh, Saudi Arabia.

HUMAN AND ANIMAL RIGHTS
KSA according to the statement of the Helsinki Declaration of 1983. Reference number: CNH_024. For more information, please contact Dr/M. Kattan (The committee chairman). Tel: 00966507908566

CONSENT FOR PUBLICATION
All patients gave informed consent before participating in this study.

AVAILABILITY OF DATA AND MATERIALS
The data and materials used in the study are available upon request.

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CONFLICT OF INTEREST
The authors declare any conflict of interest.

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