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Relationship between Sleep, Pain and Inflammatory Markers in Patients with Rheumatoid Arthritis

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ABSTRACT

Introduction: Rheumatoid Arthritis (RA) is known as a progressive chronic auto-immune disease. Measurement of inflammatory markers are applied for follow up the activity of disease. So determining factors that effects these markers such as sleep and pain can help to prevent the severity of disease. The aim of study was to determine the relationship between sleep disorders, pain and inflammatory markers in patients with RA.

Methods: Participants included 210 patients with RA referred to educational medical clinics of Imam Reza and Sina in Tabriz selected by convenience sampling. They were assessed by Sleep Disorders Questionnaire (SDQ) and Epworth Sleepiness Scale (ESS). Visual Analog Scale (VAS) also applied for pain measurement. Data were analyzed using SPSS ver.13 by descriptive and inferential statistics.

Results: Most of participants (74%) were female, the mean age of participants was 48.41 years. The mean (SD) of sleepiness was 13.14 (5.6) and pain 6.09 (2.14). Significant relationship obtained between sleep disorders and pain. As well as sleep problems had significant relation with CRP. Also pain had significant correlation with inflammatory markers.

Conclusion: Sleep pattern in RA appears to be disrupted by pain. Pain severity and sleep problems can predict increasing inflammatory markers that can be a clues of intensity of disease. So relieving pain and improved sleep can decrease the intensity of disease.

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Introduction

Rheumatoid Arthritis (RA) is a common systemic inflammatory diseases, which is known as a progressive chronic auto-immune illness with slow onset.[1] Global prevalence of the disease is 1% along the lifetime.[2] Sleep loss usually lead to disturbances in psychomotor and an increase in proinflammatory cytokine which affect health and well-being.[3] Also impairment in normal flow of sleep, lead to immune system disturbances and augmentation of symptoms of patients with RA.[3,4]

Inflammatory factors such as C-reactive protein (CRP) and erythrocytes sedimentation rate (ESR) usually increase in active RA, so measurement of CRP and ESR are applied for follow up the activity of disease and response to treatment.[1]

Determining the factors that lead to increase of these markers can help to prevent the severity of disease.

Accordingly, studies showed that sleep problems cause a decrease in pain threshold which worsen sleep problems and tend to increase inflammatory markers that augment pain sensitivity.[5]

Although studies have reported associations between disrupted sleep, pain and inflammatory responses[6], but their results are difficult to interpret owing to the complex effects of underlying clinical conditions such as RA.

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So, present study conducted to determine the relationship between sleep disorders and pain with inflammatory factors in patients with RA.

Materials and methods

In this descriptive-correlative study, 210 patients with RA referred to educational rheumatology clinics of Imam Reza and Sina, affiliated to Tabriz University of Medical Science of Iran were selected. From April to June 2014, the participants were chosen by convenience sampling. Research community included patients with RA diagnosed by a rheumatologist based on American College of Rheumatology (ACR) criteria. This criteria in 2010 included joints involvement, positive serology, disease period and positive of markers in acute stage of disease.[1]

Inclusion criteria were as follow: at least 18 years old, consent to participate in the study, at least six months after the definite diagnosis. Exclusion criteria consisted of other chronic physical and mental diseases or treated with psychotropic medications.

Sample size was determined based on a pilot study conducted in 20 patients with RA. The sample size was determined with respect to B=0.1 and 0.2 while the significance level was set at α=0.01, which obtained 186 patients with considering the possible loss, it increased to 210.

Participants were assessed by Sleep Disorders Questionnaire (SDQ), Epworth Sleepiness Scores (ESS) and Numeric Pain Rating Scale (NPRS). Sleep Disorders Questionnaire consists of 37 questions related to sleep disorders with yes (1) or no (0) choices. Scores of each questionnaire has been calculated and analyzed separately. The last part of SDQ, the Epworth Sleepiness Score consists of 8 items about probability of sleeping in situations, which ranges from 0 (never) to 3 (high chance of dozing). The total score of ESS considered in a scale of 0-24, so final grade class has been calculated as 3-9 (Normal), 10-13 (mild), 14-19 (moderate) and 20-24 (severe sleepiness).[7] The content validity of the Sleep Disorders Questionnaire was established by sending the questionnaires to 10 experts in this field in Tabriz University of Medical Sciences. Also the internal reliability of Cronbach Alpha obtained 0.86. Numeric Pain Rating Scale is a 10-centimeter scale in which 0 represents no pain and 10 severe pain.[8]

The inflammatory markers such as CRP and ESR obtained from recently blood tests of participants during one week. The CRP more than 1mg/L was considered as positive CRP.[9] Confidentiality of data, informed consent, and the right to resign anytime during the study were considered morally. This study was approved by ethics committee of Tabriz University of Medical Sciences (code 5.4.580). Data were analyzed using Statistical Package for Social Science (SPSS) version 13 (SPSS Inc., Chicago, IL). Quantitative variables were described as percent, frequency, mean (SD), as well as categorical variables were analyzed by chi-square test. Differences between subgroups of variables were analyzed using independent t test. Correlations between categorical or nominal variables were evaluated using Spearman test.

Results

This study performed by 210 patients with RA. Table 1 provides demographic data of patients. The distribution of self-reported sleep disorders showed the most sleep problems included napping day time (%83.80) and trouble falling sleep (%73.30) (Table 2). Most of participants (83.3%) had moderate to severe pain. Also they obtained 6.09 (2.14) in Visual Analogue Scale, and 13.14 (5.60) in sleepiness scale. Moreover 81% had positive CRP. Distribution of inflammatory factors are shown in table 3. Spearman test showed significant relationship (P<0.001) between pain and sleep problems such as apnea, twitch leg during sleep, napping daytime, and numbness in foot (Table 4).

Also Pearson correlations showed significant relationship between inflammatory markers (RF, r=0.23, P<0.001; CRP, r=0.32, P<0.001; ESR, r=0.59, P<0.001) with pain.

In addition, χ^2 test presented significant differences between apnea based on gender, snoring (P<0.001) and difficulty in falling sleep (P<0.001).

There was no significant difference in presence of apnea or overweight (P=0.139), while significant difference obtained between apnea and sleepiness (P<0.001).

The independent t test showed significant differences between CRP with presence of diabetes (P=0.001), hypertension (P=0.001), sleep problems (P<0.001), and pain (P=0.003) (Table 5).

Table 1. Distribution of participants according to demographic and clinical characteristics (n=210)

Characteristics	N (%)
Sex	53 (25.2)
Male	157 (74.8)
Female	
Marital	
Single	10 (4.8)
Married	191 (91.0)
Divorced	
Widow	4 (1.9)
Employment	5 (2.4)
employed	66 (31.0)
unemployed	144 (69.0)
Length of RA disease	
<5 years	54 (25.7)
5-10 years	73 (34.8)
>10 years	83 (39.5)
Hospitalization	
Yes	128 (61.0)
No	82 (39.0)
Hypertension	
Yes	63 (30)
No	147 (70)
Diabetes	
Yes	16 (7.6)
No	194 (92.4)
Age[€] (Yrs.)	48.41 (12.92)
Weight[€] (Kg)	72.60 (11.23)

[€] Mean (SD)

Table 2. Frequency of self-reported sleep disorders using SDQ* (n=210)

Sleep disorders	N (%)
Napping daytime	176(83.80)
Trouble falling sleep	154(73.30)
Numbness	148(70.50)
Snoring	140(66.70)
Sleep paralysis	132(62.90)
Kick or twitch feet	117(55.70)
palpitation	87(41.40)
Asphyxia	81(38.60)
Apnea	25(11.90)
Nightmare	48(22.90)
Sleep terrors	47(22.40)
Sleep walking	3(1.40)

*SDQ: Sleep Disorder Questionnaire

Table 3. Distribution of laboratory tests in participants (n=210)

Inflammatory factors	N (%)
CRP[a]	
Normal: < 0.8 mg/L	40 (19)
Low risk: <1.00 mg/L	56 (26.7)
Average risk: 1.00 - 3.00 mg/L	64 (30.5)
High risk: >3.00 mg/L	50 (23.8)
RF[b]	
16 IU/ml<Negative	108 (51.4)
+1 :16-30 IU/ml	71 (33.8)
+2 : 30-45 IU/ml	18 (8.6)
+3 : 45< IU/ml	13 (6.2)
ESR[c]	
Mean (SD) mm/hr.	30.99 (14.77)

[a]CRP: C Reactive Protein, [b]RF: Rheumatic Factor, [c]ESR: Erythrocytes Sedimentation Rate

Table 4. Correlations of sleep problems and pain (n=210)

Sleep Problems	r*	P
Apnea	0.55	<0.0001
Asphyxia	0.50	<0.0001
Delay in sleep	0.58	<0.0001
Twitch feet	0.45	<0.0001
Numbness	0.51	<0.0001
Nightmare	0.21	0.002
Sleep terrors	0.25	<0.0001
Snoring	0.50	<0.0001
Napping	0.29	<0.0001
Somnambulism	0.10	0.88

*Spearman test

Table 5. The relation between some physical characters with CRP (n=210)

Characters	β	t[a]	P[b]	CI 95%[c]
Sex	0.11	2.28	0.08	0.60, 8.40
Overweight	0.06	1.24	0.21	0.05, 0.23
Smoking	0.06	1.09	0.27	2034, 8.17
Heart disease	0.07	1.23	2.217	8.84, 2.02
Diabetes	0.18	3.33	0.001	4.25, 16.59
Hypertension	0.21	3.44	0.001	2.95, 10.87
Sleep Problems	0.34	3.87	0.001	0.66, 2.05
Pain	0.26	2.99	0.003	0.61, 2.99

[a] Independent t- test; [b] P<0.05 is significant; [c] Confidence interval

Discussion

The relationship between pain, sleep problems and inflammatory markers were investigated in patients with RA. In summary, this study indicated that sleep problems and pain were common in RA and there were significant relations between pain and sleep problems with inflammatory markers. Measuring inflammatory markers and effect of pain severity on sleep pattern can have an important role on recognizing changes due to RA changes on life conditions.

Results indicated that 78.6% of patients reported sleep disorders. This presents a high rate of sleep problems in patients with RA. These findings are in line with the

results of Gjevre et al. and Trehane et al. studies, in which, most patients with RA had sleep disorders.[11,12]

On the other hand, pain as one of the effective variables had meaningful relation with CRP. Studies showed sleep problems were associated with sedimentation level, joint stiffness, pain, weakness, anxiety, depression and disease duration.[12,13] In this regard, Lee Yoon showed that increase of inflammatory markers would increase pain.[14] Also Omoigui- based pain theory presented that the origin of all pains are inflammation, and tissue injury stimulates inflammatory indexes that leads to changes in indexes.[15]

On the other hand, pain is one of the factors influencing sleep pattern and rest. Findings indicated significant relation between pain with sleep problems such as apnea, twitch leg, napping, trouble falling sleep, and numbness of legs.[16] Daytime sleep can lead to problems in sleep patterns[17], so naps during the day was significantly correlated with pain in which pain severity would lead to sleep problems. However Lee et al., indicated no relations between CRP and pain threshold, while they found significant relation between pain, and number of painful joints.[4]

In this study, a direct relationship was obtained between CRP and twitch feet. Furthermore, significant differences obtained between apnea based on gender. Studies have suggested the possible involvement of inflammation in Obstructive Sleep Apnea (OSA). As this correlation is more apparent in females, it suggests that there may be a stronger relation between OSA and inflammation in females.[10]

Also results showed most of patients had short sleep, a delay in falling sleep of about 75 minutes, which analysis showed a negative correlation between sleep period and CRP. Prater and June in a study on sleep duration showed increased sleep duration was along with increased inflammatory indexes (CRP, IL-6).[18]

Krueger' findings focused on the relation between increased pre- inflammatory Cytokines with insomnia. Increase of cytokines and its effect on Hypothalamus Pituitary Adrenal axis causes increases in core body temperature and decrease of non REM stage that increase insomnia. This presents that sleep deprivation lead to activation of autonomous system and increase of Catecholamine's levels.[19]

Also results showed a significant relationship between sleepiness scores with CRP. Some studies presented meaningful correlation between sleep disorders and CRP level, while sleepiness scale had a negative correlation with CRP.[6] Moreover, pain, as one of the effective variables, had a positive meaningful relationships with C-reactive protein and ESR.

Also in this study, a significant relationship was observed between the incidence of hypertension and diabetes history that can be associated with changes in biological factors affecting inflammatory agents. Studies showed that an increase in glucose and lipids in blood following intake of high carbohydrate cause an increase in oxidative stress.[20] Also evidences show that glucose intake increases pro-inflammatory proteins.[21]

Conclusion

The present study confirms sleep problems and pain are common in patients with RA, which have significant relationship with inflammatory markers, and increased inflammatory markers can be affected by sleep problems and pain. As increase of markers without control would increase the intensity of disease. Sleep problems can also be a predicting factor of increasing CRP. So in this ways, by relieving pain and providing proper sleep we can decrease the intensity of disease and prevent of disease severity.

However, the bias in self-report of sleep problems and pain can be considered a limitation, because it is possible to

misremember. Further studies with more careful methods with other inflammatory markers would help support a broader generalization of results.

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Ethical issues

None to be declared.

Conflict of interest

The authors declare no conflict of interest in this study.

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