Restless Leg Syndrome and Sleep Disorders in Patients with Rheumatoid Arthritis and Its Relation with Anemia Parameters

Salih Demir[1], Adem Kucuk[2,*], Mustafa Altas[3], Erkan Cure[4]

ABSTRACT

Objectives: We aimed to investigate the prevalence of restless legs syndrome (RLS) and sleep disorders in patients with rheumatoid arthritis (RA), and the association of iron deficiency with them.

Materials and methods: The study included 72 patients with RA (59 females, 13 males), and 50 healthy control subjects (57 females, 15 males). Assessments were made using the International RLS Rating Scale, Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale, Fatigue Severity Scale (FSS), Beck anxiety and depression index and the SF-36 quality of life scores.

Results: We found that the frequency of RLS in RA patients was 29.1% and 13.8% in healthy control ($p = 0.021$). RA patients had 44.4% iron deficiency and 5.5% anemia of chronic disease. We found that 52.3% of patients with iron deficiency had RLS. There was an independent relationship between present of RLS and FSS (Beta [β] = 0.317, $p = 0.005$) and total iron binding capacity (TIBC) (β = 0.244, $p = 0.031$). There was an independent relationship between RLS severity score and PSQI (β = 0.264, $p = 0.025$) and social functionality (β = 0.302, $p = 0.009$).

Conclusion: The prevalence of iron deficiency is high in RA in the developing countries. Analysis obtained in patients with RA is suggestive of an association between iron deficiency and increased frequency of RLS. The presence of RLS in patients with RA negatively affects sleep quality, psychiatric status, and quality of life of patients with RA. TIBC value may be a predictive marker for early detection of RLS in patients with RA.

KEYWORDS

rheumatoid arthritis; restless legs syndrome; sleep disorders; iron deficiency; total iron binding capacity

AUTHOR AFFILIATIONS

[1] Department of Internal Medicine, Necmettin Erbakan University, Konya, Turkey
[2] Division of Rheumatology, Department of Internal Medicine, Necmettin Erbakan University, Konya, Turkey
[3] Department of Neurology, Necmettin Erbakan University, Konya, Turkey
[4] Department of Internal Medicine, Ota & Jinemed Hospital, Istanbul, Turkey
* Corresponding author: Division of Rheumatology, Department of Internal Medicine, Necmettin Erbakan University, Konya, Turkey; e-mail: drademk@yahoo.com

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INTRODUCTION

Rheumatoid arthritis (RA) affects approximately 0.5% to 1% of the population worldwide (1). RA is a systemic, chronic autoimmune disease that symmetrically leads to arthritis in the joints. Environmental and genetic factors play a role in the pathogenesis of RA, and its etiology is unclear (1, 2). It is three to four times more common in women than in men. In RA, patients may develop joint deformities, loss of function, and workforce loss due to bone erosions (1, 2). RA can affect the central and peripheral nervous system and many organs. Anemia is common in patients with RA and has multifactorial pathogenesis (3). Although most types of anemia can be seen in RA patients, iron deficiency anemia (IDA) and anemia of chronic disease (ACD) are common (3). In patients with RA, IDA is mostly caused by chronic blood loss from the gastrointestinal tract due to gastritis (due to the use of non-steroidal anti-inflammatory drugs), peptic ulcer, or diaphragmatic hernia. Most patients with IDA are asymptomatic (4).

The psychological effects of RA can be seen in many areas of life such as family life and social relationships, therefore, it can lead to mood disorders (5). These mood disorders can cause pain, increased disease activity, cytokine release, immune-modulatory responses, and sleep disorders in patients. The sleep structure is usually normal, but sleep is interrupted with increased arousals and movements during sleep (6). Studies have reported that sleep disturbance and difficulty maintaining sleeping are seen in 50–75% (7).

Restless leg syndrome (RLS) is a common disease associated with chronic, sensorimotor motion disorder, especially holding the lower limb (8). In this syndrome, especially in the period when the patient is inactive, such as evening and night, paresthesia and restlessness occur. The patient is partially or completely relaxed with movement (8). Although RLS pathophysiology is not fully understood, dopamine dysfunction and a decrease of cerebral iron and ferritin levels play a critical role in the central nervous system (9). RLS is a common disease accompanying RA. The patient's quality of life can be improved by rapid diagnosis and treatment of RLS (10).

Several studies in the literature have proven the presence of RLS in patients with RA (10–14). In this study, we aimed to show the frequency of IDA and the relationship of iron deficiency with RLS in RA patients. Second, we aimed to investigate the effects of RLS on sleep disorder, psychological conditions, and quality of life in RA.

MATERIAL AND METHOD

Seventy-two patients diagnosed as RA according to ACR/EULAR 2010 Rheumatoid Arthritis Classification Criteria (15) and followed up in our hospital's Rheumatology Outpatient Clinic were included in the study. Seventy-two healthy people with sociodemographic characteristics similar to the group of patients without known systemic disease were included in the study as a control group. Patients with known liver, kidney, thyroid disease, hypertension, diabetes mellitus, other systemic connective tissue diseases, malignancy, chronic neurological disease, pregnancy, alcohol dependence were excluded in the study. The patient and the control group were interviewed face-to-face and evaluated for RLS symptoms. Patients who ensure four of the following criteria recommended by the International Working Group were diagnosed with RLS: (i) the urge to move limbs with senses of paresthesia/dysesthesia; (ii) the need to move and feel relaxed when moving; (iii) exacerbation of symptoms while resting and relief of symptoms when moving; (iv) exacerbation of symptoms in the evening/night. The severity of RLS was determined using the IRLSSG-RS scale in both groups (16, 17).

BECK DEPRESSION INVENTORY (BDI)

Depression levels were evaluated with the BDI comprising 21 items ranging from 0 to 3. The highest score is 63. One of the most commonly used self-rated depression scales, BDI is adaptable to any age group and considered highly reliable (18).

BECK ANXIETY INVENTORY (BAI)

BAI is a Likert-type self-report inventory applied to determine the prevalence and intensity of anxiety symptoms experienced by the individual. The BAI scale tests subjective anxiety and somatic symptoms such as dizziness, difficulty breathing, dizziness, flushing, and heartbeat. The highest score that can be obtained from this test is 63 and covers 21 symptoms (19).

FATIGUE SEVERITY SCALE

FSS is a questionnaire comprising 9 questions in total. Fatigue severity is assessed in different situations during the past week. Items are scored on a 7-point scale. 1 = strongly disagree and 7 = strongly agree. The average FSS score is found by dividing the total score by 9. The score is interpreted as ≥4 fatigue. Higher scores show a higher level of fatigue (20).

PITTSBURGH SLEEP QUALITY INDEX (PSQI)

PSQI is used to assess sleep quality for 1 month. Includes nineteen separate items and seven component points; by collecting these points, a general score between 0 and 21 is obtained. Higher scores represent subjective sleep quality disorder. PSQI score> 5 is considered sleep disturbance (21).

EPWORTH SLEEPINESS SCALE (ESS)

The ESS which includes eight items related to falling asleep or sleepiness in eight different daily living activities is used to assess daytime sleepiness. The ESS score ranges from 0 to 24, and higher scores show more be sleep state during the day (22).

36-ITEM SHORT-FORM HEALTH SURVEY (SF-36) QUESTIONNAIRE

SF-36 is a general health-related quality-of-life questionnaire used to score for eight subscales, including physical

function, role-physical, role-emotional, social functionality, general health, mental health, vitality, and physical pain. These subscales are combined to create two high-level summaries called physical and mental health component summaries (23).

ETHICAL ISSUE

Before the study, the voluntary patient consent form was obtained from the patient and control groups. We obtained approval for the study from the local ethics committee (2019/1823).

BIOCHEMICAL PARAMETERS

Venous blood samples from both patients and the control group were collected after 10 to 12 hours of fasting. Glucose blood urea nitrogen, creatinine, lipid panel, and ALT were studied with the photometric method of the Abbott Architect C16000 analyzer. C-reactive protein (CRP) was studied with the nephelometric method of Coulter Immage 800 device. HDL was analyzed using a direct enzymatic method without precipitation. Hematological tests were analyzed by the Abbott Cell Dyn Ruby analyzer. Erythrocyte sedimentation rate (ESR) was analyzed with the automated device Westerr (Eventus vacuplus ES 100).

The diagnosis of IDA and ACD was made according to the current guideline. According to the hemoglobin, ferritin, and transferrin saturation values, the patients and the control group were divided into three groups as IDA, ACD, and normal (24).

STATISTICAL ANALYSIS

All statistical analyzes were done with SPSS 20 program. Results are given as mean ± standard deviation, median (minimum-maximum), and n (percent). Whether the groups showed homogeneous distribution was evaluated with the Kolmogorov-Smirnov Test. Data showing homogenous distribution were evaluated by Student T-Test and non-homogeneous data were evaluated by Mann Whitney U Test. Categorical data were analyzed with Chi-square test. Pearson correlation test and Spearman Rank test were used for correlation analysis. Independent variables affecting the RLS severity score were analyzed by linear regression analysis. A p-value <0.05 was considered significant.

RESULTS

Age (51.9 ± 11.4 vs 49.5 ± 11.2 years, p = 0.215), gender (F/M: 59/13 vs 57/15, p = 0.417), and body mass index (29.0 ± 5.5 vs

Tab. 1 Sociodemographic data of the patient and control groups.

Parameters	RA (n = 72)	Control (n = 72)	P value
Age (years) (mean ± SD)	51.9 ± 11.4	49.5 ± 11.2	0.215
Gender (F/M) (n)	59/13	57/15	0.417
BMI (kg/m²) (mean ± SD)	29.0 ± 5.5	29.0 ± 4.9	0.941
DASH-28	2.8 ± 1.0		
Anti-CCP + (n, %)	40 (55.6)	0	
RF + (n, %)	37 (51.4)	0	
Disease duration (years)	3 (1–18)		
Smoking (n)	8	16	0.016
Drinking (n)	0	2	0.248
Hypertension (n)	23	16	0.130
Osteoporosis (n)	2	1	0.500
Hydroxychloroquine (n)	39		
Steroid (n)	31		
Methotrexate (n)	37		
NSAIDs (n)	12	3	0.012
Leflunomide (n)	25		
Salazopyrin (n)	27		
Infliximab (n)	1		
Etanercept (n)	0		
Golimumab (n)	4		
Certolizumab (n)	2		
Tocilizumab (n)	7		
Rituximab (n)	1		

Abbreviations: Ra, rheumatoid arthritis; F, female; M, male; BMI, body mass index; DASH-28, The Disease Activity Score-28 for Rheumatoid Arthritis; Anti-CCP, anti-cyclic citrullinated peptide; RF, rheumatoid factor; NSAIDs, non-selective non-steroidal anti-inflammatory agents.

29.0 ± 4.9 kg/m^2, p = 0.941) values of patients with RA were similar to the control group. Anti-CCP was positive in 55.6% of patients and RF was positive in 51.4% of patients. While 15 (20.8%) of the patients were using biological agents, the remaining patients were receiving DMARD therapy. All sociodemographic characteristics of the patients are given in Table 1.

The hemoglobin level of the patients (p = 0.011) was significantly lower than the control group. The patients' iron level (68.9 ± 36.1 vs 78.6 ± 34.3) was lower than the control group, but not significant. The ferritin (53.3 [4.0–655.0] vs 45.7 [2.0–432.0]) and total iron-binding capacity (TIBC) (266.4 ± 73.5 vs 261.2 ± 71.3) values of the patients were similar to the ferritin and TIBC values of the control group. The Vitamin D level (18.0 ± 8.8 vs 14.3 ± 8.2, p = 0.009) of the RA group was higher than the control group. ESR, and CRP values of RA patients were higher than the control group. The albumin value of RA patients was lower than the control group. All laboratory results of the patients are seen in Table 2.

Thirty-two patients had IDA, and 11 of them had RLS. Four patients had ACD, and 1 of them had RLS. In the control group, seventeen individuals had IDA, and 4 of them had RLS. Four of 10 RLS individuals had IDA (Figure 1).

The numbers of RLS positive patients were 2-fold more than the control group (29.1% vs 13.8%, p = 0.021). The RLS severity scale of both groups was similar. ESS was slightly higher in the RA group than control but were not significant. The PSQI value of the RA group was significantly higher than the control group. BAI and BDI values of RA patients were significantly higher than the control group. Physician visual analogue scales (VAS) and patient VAS values of the patient group were significantly lower than the control group. In the patient group, SF-36's physical function, physical role, vitality, social function, pain, general health perception scores were significantly lower than the control group. The emotional role, mental health, and health status change values of SF-36 in the patient group were also lower than the control group. But it was not statistically significant. All results and p values are seen in Table 3.

Tab. 2 Biochemical results of the patient and control groups.

Parameters	RA (n = 72)	Control (n = 72)	P value
WBC (×109/L)	7.7 ± 3.6	7.8 ± 2.1	0.852
Neutrophils	4.8 ± 3.0	4.6 ± 1.7	0.757
Lymphocytes	2.1 ± 0.8	2.3 ± 0.7	0.042
Hemoglobin (g/dL)	12.7 ± 1.7	13.5 ± 1.7	0.011
RDW	14.6 ± 2.1	13.6 ± 1.6	0.001
Platelets (×109/L)	294.1 ± 78.9	280.9 ± 75.5	0.272
CRP (mg/dL)	4.1 (0.5–96.0)	3.1 (0.5–37.0)	0.021
ESR (mm/h)	16.5 (2.0–72.0)	11.0 (2.0–48.0)	0.007
FPG (mg/dL)	97.4 ± 13.9	99.6 ± 16.6	0.380
Creatinine (mg/dL)	0.70 ± 0.1	0.74 ± 0.1	0.152
Sodium (mEq/L)	140.4 ± 2.3	140.0 ± 1.7	0.318
Potassium (mEq/L)	4.4 ± 0.5	4.4 ± 0.4	0.709
Calcium (mg/dL)	9.3 ± 0.4	9.4 ± 0.4	0.135
Total cholesterol (mg/dL)	183.4 ± 40.2	185.6 ± 41.0	0.742
Triglyceride (mg/dL)	144.6 ± 84.9	144.6 ± 72.0	0.999
HDL (mg/dL)	52.1 ± 16.1	48.4 ± 12.3	0.122
LDL (mg/dL)	101.5 ± 32.2	106.2 ± 36.4	0.413
Albumin (g/dL)	4.2 ± 0.3	4.4 ± 0.3	0.001
AST (IU/L)	17.3 ± 7.6	16.4 ± 6.1	0.447
ALT (IU/L)	18.8 ± 9.4	18.7 ± 8.8	0.934
Iron ((µg/dl)	68.9 ± 36.1	78.6 ± 34.3	0.099
TIBC (ug/dL)	266.4 ± 73.5	261.2 ± 71.3	0.663
Ferritin (ng/ml)	53.3 (4.0–655.0)	45.7 (2.0–432.0)	0.876
Transferrin saturation (%)	29.8 ± 22.4	34.0 ± 20.3	0.249
TSH (mU/L)	1.9 ± 1.2	1.9 ± 1.0	0.978
Vitamin B_{12} (pg/mL)	378.4 ± 207.5	341.3 ± 169.5	0.242
Folic acid (ng/ml)	9.0 ± 4.3	8.4 ± 3.6	0.395
Vitamin D (ng/mL)	18.0 ± 8.8	14.3 ± 8.2	0.009

Abbreviations: RA, rheumatoid arthritis; WBC, white blood cell count; RDW, red blood cell distribution width; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FPG, fasting plasma glucose; HDL, high density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TIBC, total iron binding capacity; TSH, thyroid stimulating hormone.

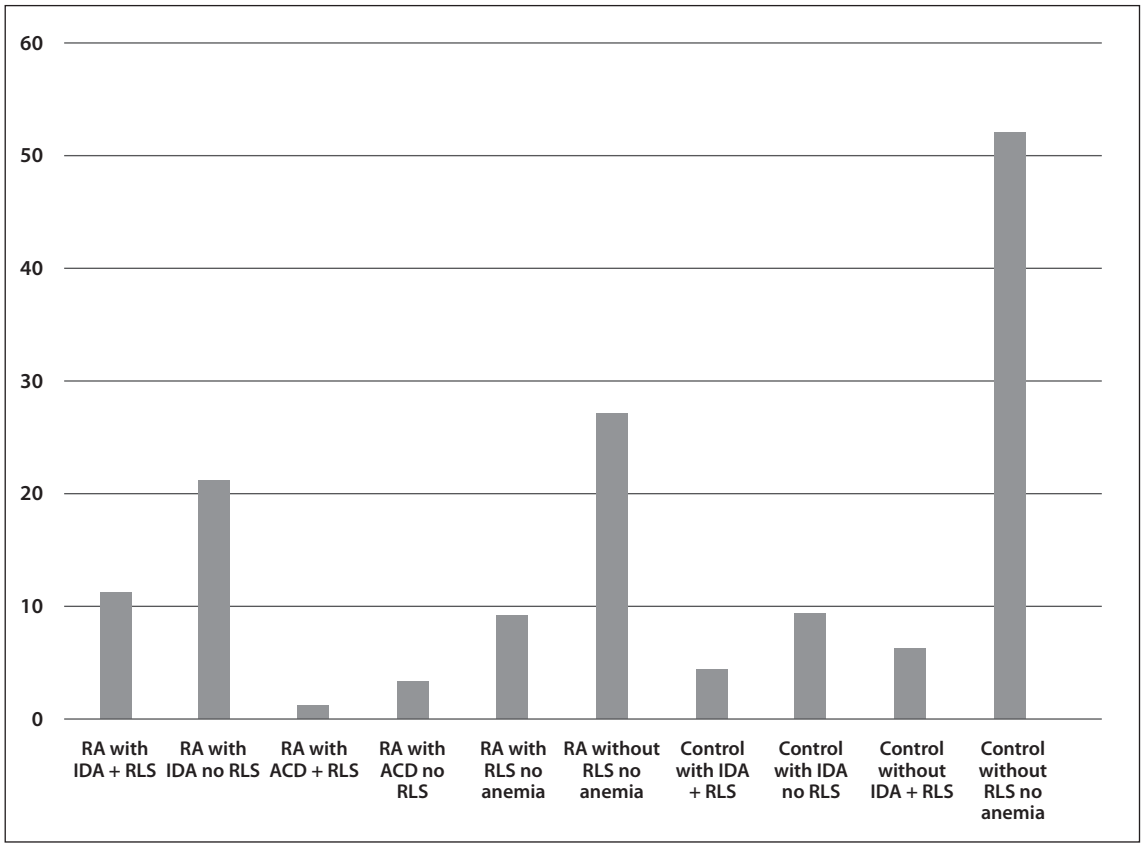

Fig. 1 Prevalence of RLS in RA patients with and without anemia.

Tab. 3 Evaluation of sleep and life quality of patient and control groups.

Parameters	RA (n = 72)	Control (n = 72)	P value
RLS (n, %)	21 (29.1)	10 (13.8)	0.021
RLS (F/M)	17/4	8/0	0.188
RLS severity score	12.5 ± 5.2	13.1 ± 6.4	0.830
ESS	5.3 ± 3.2	4.4 ± 3.4	0.141
PSQI	6.5 ± 3.5	4.3 ± 3.0	<0.001
PSQI ≥ 5, n (%)	43 (59.7)	23 (31.9)	0.001
ISI	9.0 (2.0–20.0)	2.0 (0.0–16.0)	0.001
FSS	3.3 ± 1.5	2.8 ± 1.6	0.094
BAI	8.5 ± 5.7	6.1 ± 4.8	0.008
BDI	9.7 ± 6.0	7.0 ± 5.6	0.007
Physical functioning	61.6 ± 21.2	75.9 ± 22.8	<0.001
Role physical	43.4 ± 41.5	63.1 ± 44.7	0.007
Role emotional	74.7 ± 32.1	83.4 ± 32.2	0.108
Vitality	45.6 ± 13.7	50.2 ± 14.3	0.049
Mental health	58.8 ± 10.0	61.7 ± 9.9	0.086
Social functioning	80.6 ± 19.7	89.5 ± 15.4	0.003
Bodily pain	68.8 ± 21.5	78.8 ± 24.2	0.010
General health	39.2 ± 16.1	47.1 ± 18.6	0.007
Change observed in health	45.2 ± 19.3	48.0 ± 25.1	0.458
Physician VAS	2.3 ± 1.4	1.2 ± 0.9	<0.001
Patients VAS	3.1 ± 1.5	1.8 ± 1.2	<0.001

Abbreviations: RA, rheumatoid arthritis; RLS, restless leg syndrome; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; FSS, Fatigue Severity Scale; BAI, beck anxiety inventory; BDI, Beck Depression Index; VAS, visual analogue scale.

When correlation analysis was performed in the patient group, we found that the RLS severity score was positively associated with PSQI, Insomnia Severity Index, Fatigue Severity Scale, BAI, BDI, pain, and TIBC values. We found a negative correlation between the RLS severity score and energy/vitality, mental health, and social functionality. Correlation analysis results are seen in Table 4.

Tab. 4 Correlation analysis results of patients.

Parameters	RLS severity score	
	r value	p value
PSQI	0.456	0.001
ISI	0.367	0.003
FSS	0.431	0.001
BAI	0.430	<0.001
BDI	0.339	0.006
Vitality	-0.389	0.001
Mental health	-0.266	0.033
Social functioning	-0.412	0.001
Bodily pain	0.291	0.018
TIBC	0.268	0.031

Abbreviations: RLS, restless leg syndrome; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; Fatigue Severity Scale; BAI, beck anxiety inventory; BDI, beck depression inventory; TIBC, total iron binding capacity.

In the multivariate regression analysis, there was an independent relationship between present of RLS and fatigue severity scale (Beta [β] = 0.317, p = 0.005) and TIBC (β = 0.244, p = 0.031). There was an independent relationship between RLS severity score and PSQI (β = 0.264, p = 0.025) and social functionality (β = 0.302, p = 0.009) (Table 5).

Tab. 5 Stepwise linear regression analysis.

Dependent variable	Independent Variables	Beta regression coefficient	P value
RLS	FSS	0.317	0.005
	TIBC	0.244	0.031
RLS severity score	PSQI	0.366	0.002
	Social functioning	0.302	0.009

Abbreviations: RLS, restless leg syndrome; FSS, Fatigue Severity Scale; TIBC, Total iron binding capacity; PSQI, Pittsburgh Sleep Quality Index.

DISCUSSION

In several studies, the frequency of RLS in RA patients was between 20–30%, and in healthy controls was found between 2–10% (10, 13, 14, 25). In our study, we found that the frequency of RLS in RA patients was 29.1% and 13.8% in healthy control. In the literature, only one study reported the frequency of RLS in RA as 63% (12). Since both diseases are more common in women, RLS is expected to be more common in female RA patients. Previous studies and our study reveal that RLS is more common in female RA patients (25).

RLS is also associated with other rheumatological diseases. The frequency of RLS was reported as 30.6% in systemic lupus erythematosus (SLE), 29.4% in Behçet's disease, 30.8% in ankylosing spondylitis, 40.7% in systemic sclerosis, and 64% in psoriatic arthritis (8,26). RLS is often associated with immune-based diseases such as Crohn, multiple sclerosis, psoriasis. In autoimmune diseases that damage the dopaminergic system such as Parkinson and SLE, the frequency of RLS has been reported to increase (27, 28). Previous studies suggest that symptoms in RLS patients occur because of damage to the dopaminergic pathway. In RLS patients, dopamine receptor agonists significantly relieve the patients' clinic (26–28). A better-known mechanism in RLS etiology is iron deficiency. The low iron level in the serum leads to an increase in the extracellular dopamine level, thereby reducing D2 dopaminergic receptors in the brain tissue (29). The formation of levodopa from tyrosine is catalyzed by the tyrosine hydroxylase enzyme, and this step is the rate-limiting step in dopamine synthesis. In iron deficiency, dopamine synthesis is reduced (30).

RA is a chronic inflammatory disease. Chronic inflammation causes iron to be trapped in macrophages and reduced iron supply to the bone marrow. A previous study reported the frequency of IDA in RA patients with RLS was 4.7% and the frequency of other anemia types was 3.1% (25). The frequency of IDA in patients with RA is between 30–60% in developing countries (4). Our RA patients had 44.4% IDA and 5.5% ACD. We found that 52.3% of patients with IDA had RLS and 25% of patients with ACD had RLS. When patients with both IDA and ACD were examined together, 57.1% of RA patients with RLS had anemia. In the current study, the control group had 23.6% IDA and individuals with IDA had 23.5% RLS. In the control group, 25% of individuals with RLS had DEA. While the TIBC level of our patients was like the control group, the iron level was lower than the control group. Although the ferritin values of our patients were not statistically significant, they were slightly higher than the control group. Ferritin is an acute-phase reactant. The ferritin values of our patients may be higher due to chronic inflammation than healthy control. Ferritin may not always be a good marker in demonstrating iron deficiency (24). Transferrin saturation is a more specific marker than ferritin in demonstrating iron deficiency (24). It is obtained by dividing the serum iron value by the serum TIBC value. TIBC increase alone is a strong marker in diagnosing IDA (31). In the regression analysis, we found an independent relationship between TIBC and RLS scores. In RA patients, TIBC can be a strong marker for the RLS severity score.

Vitamin D is an immune-modulating vitamin. Vitamin D is known to protect dopaminergic neurons against toxic substances. Therefore, vitamin D deficiency has been associated with RLS (32). In our study, vitamin D levels of RA patients were lower than normal, but higher than the control group. The relationship between RA and vitamin

D deficiency is known (33). We did not have any patients using vitamin D supplements; however, most RA patients may receive vitamin D therapy intermittently. It has been reported that vitamin D treatment does not improve RLS symptoms (34). We did not find a significant relationship between RLS and vitamin D in regression analysis.

Since RA is a disease with inflammation, many pro-inflammatory cytokine levels such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-alpha an increase in RA patients (2). Some cytokines such as IL-4, IL-10, IL-13, and transforming growth factor (TGF)-beta have been reported to adversely affect the non-REM sleep phase and lead to sleep disturbance (35). Some cytokines, such as TNF-alpha, show the diurnal rhythm. In RA patients, improvement of sleep quality with TNF-alpha blockade suggests that TNF-alpha and other pro-inflammatory cytokines are responsible for sleep disturbance (36). Previous studies have reported between 62–63% sleep disturbance in RA patient's disturbance (12, 36). We found that 59.7% of our patients had sleep quality impairment. In the correlation analysis, we found a strong relationship between RLS score and PSQI, insomnia severity index, FSS, and vitality.

The presence of anxiety and depression in RA patients has been reported in the literature (37). RA is associated with psychological disorders due to pain, physical disabilities, and restricting one's work, family, and social life. This results in anxiety, depression, and a sense of helplessness. Depression and anxiety are psychiatric disorders frequently seen in RA (38). Quality of life disorder, anxiety, and depression are also associated with RLS (39). In the correlation analysis, we found a strong relationship between RLS score and BAI and BDI tests. We also found a negative relationship between the RLS severity score and mental health, social functionality, and pain. According to our results, RA and RLS coexistence significantly affect patients with RA psychologically and socially.

CONCLUSION

The prevalence of IDA is high in patients with RA in developing countries. Analysis obtained in patients with RA is suggestive of an association between iron deficiency and increased frequency of RLS. The presence of RLS in patients with RA negatively affects sleep quality, psychiatric status, and quality of life of patients with RA. TIBC value may be a predictive marker for early detection of RLS in patients with RA.

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