



## The Relationship Between the Frequency and Severity of Restless Legs Syndrome and Anemia in Patients With Ankylosing Spondylitis

Hasan GOGEBAKAN<sup>1</sup> , Aysegul AKYUZ<sup>2</sup> 

<sup>1</sup>Division of Rheumatology, Department of Internal Medicine, University Of Health Sciences, Bursa State Hospital, Bursa, Turkey

<sup>2</sup>Department of Neurology, Health Sciences University Erzurum Regional Education and Research Hospital, Erzurum, Turkey

### ABSTRACT

**Background** The study aims to determine the frequency of restless legs syndrome (RLS) in patients with ankylosing spondylitis (AS) and the relationship between the International Restless Legs Syndrome Study Group Rating Scale (IRLSSG-RS) score and anemia.

**Material and Methods** It was a case-control study that included 106 patients with AS and 106 age- and sex-matched healthy controls in the rheumatology clinic of a training and research hospital. The patients were divided into two groups according to their hemoglobin levels. A hemoglobin level lower than 12 g/dL in women and less than 13 g/dL in men was the criterion for anemia.

**Results** Although the frequency of RLS was higher in AS patients than in control groups, there was no significant difference in the IRLSSG-RS score between AS patients and control groups. 23 (57.5%) of the AS patients with anemia had RLS, and the IRLSSG-RS score was  $21.3 \pm 5.7$ . Of the AS patients without anemia, 11 (16.7%) had RLS, and the IRLSSG-RS score was  $15 \pm 6$ . Statistically significant differences between AS patients with and without anemia regarding RLS frequency and IRLSSG-RS score were found. The IRLSSG-RS scores of AS patients were negatively correlated with serum iron and hemoglobin level.

**Conclusions** Patients with AS had a higher RLS frequency than the control group; AS patients with anemia had a higher RLS and IRLSSG-RS score than AS patients without anemia. Also, a negative and significant correlation was found between the IRLSS-RS score and serum iron and hemoglobin levels in AS patients.

*Turk J Int Med* 2023;5(1):41-47

DOI: [10.46310/tjim.1177257](https://doi.org/10.46310/tjim.1177257)

**Keywords:** Ankylosing spondylitis, international RLS study group rating scale score, restless legs syndrome, anemia, prevalence.



Received: September 19, 2022; Accepted: November 23, 2022; Published Online: January 29, 2023

**Address for Correspondence:**

Hasan Gogebakan, MD

Division of Rheumatology, Department of Internal Medicine, University Of Health Sciences, Bursa State Hospital, Bursa, Turkey

E-mail: [drgogebakan@hotmail.com](mailto:drgogebakan@hotmail.com)



## Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease that primarily leads to structural damage and functional limitation involving the axial skeleton and is more common in young adult men (male: female ratio 3-4:1).<sup>1,2</sup>

Anemia of chronic disease (ACD) due to underlying systemic inflammatory reactions, which is related to abnormal iron use, a decline in erythropoietin answer, and reduced red blood cell survival, is normochromic normocytic anemia.<sup>3</sup> The key role of increased liver production of hepcidin which is stimulated by excessive production of inflammatory cytokines, particularly IL-6, has been shown in the pathogenesis of ACD. Hepcidin regulates systemic and cellular iron metabolism, and its increased production reduces the reuse of iron in ACD, typically in macrophages.<sup>4</sup> Although ACD is the second most common type of anemia after iron deficiency anemia, it is most common among patients with chronic disease.<sup>5</sup> In addition to subclinical intestinal inflammation, non-steroidal anti-inflammatory drugs, which can lead to peptic and duodenal ulcers, can cause iron deficiency anemia in AS patients.<sup>6</sup>

Restless legs syndrome (RLS) is a neurological condition characterized by abnormal sensations that occur mainly at rest and at night. RLS primarily affects the legs and rarely the arms.<sup>7</sup> Many studies have found RLS between 2-15% of the healthy population.<sup>8,9</sup> An increased prevalence of RLS has been detected in some rheumatic diseases compared to the general population. Iron deficiency is associated with higher frequency and more severe RLS in various rheumatic diseases.<sup>10,11</sup> In several studies, the frequency of RLS was higher in AS patients than in healthy controls. In another study, iron deficiency anemia was more common in AS patients accompanied by RLS than in healthy controls.<sup>12,13</sup> The study aimed to determine the frequency of RLS in patients with AS and the relationship between the International RLS Study Group Rating Scale (IRLSSG-RS) score and anemia.

## Material and Methods

One hundred and six patients who applied to the rheumatology outpatient clinic of Health Sciences University Erzurum Regional Training and Research Hospital and were previously diagnosed with AS according to the modified New York classification criteria<sup>14</sup> were included in the study. In the control group, 106 healthy volunteers who applied to our hospital for routine controls were recruited. Patients with diabetes mellitus, other rheumatological diseases, kidney, liver, thyroid diseases, amyloidosis, chronic heart failure, respiratory disease, malignancies, chronic alcoholism, neurological diseases, autoimmune hemolytic anemia, vitamin B12 and folic acid deficiency were excluded from the study. Patients who were pregnant and taking medications that could potentially affect RLS were also excluded from the study. Complete neurological and rheumatological examinations were performed for all participants. The study did not include patients with abnormal neurological examinations, including sensory or motor impairments.

Since RLS can also be seen in patients with polyneuropathy, nerve conduction studies were performed on all patients to exclude the presence of polyneuropathy.

The patients were divided into two groups in terms of hemoglobin levels. The anemia criterion was determined as a hemoglobin level below 12 g/dL in women and 13 g/dL in men.<sup>15</sup>

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the disease activity of AS, was selected as the standard tool used in both daily practice and clinical trials. Patients with a total BASDAI score  $\geq 4$  indicate high disease activity.<sup>16</sup> The Turkish version of the Bath Ankylosing Spondylitis Functional Index (BASFI) was used to evaluate functional insufficiency.<sup>17</sup>

According to the criteria of the IRLSSG, the diagnosis of RLS was revised by the IRLSSG in 2014; unpleasant sensation of discomfort in the legs that is usually but not always followed by sudden leg movement, unpleasant sense of discomfort in the legs followed by abrupt movement occurs or worsens during rest or inactivity, this condition improves with movement, e.g. walking or stretching, at least as long as the movement continues, this happens only at night or worse at night than

during the day, which another disease cannot explain.<sup>18</sup> The patient who met all criteria was accepted as RLS. A face-to-face interview with an experienced neurologist determined the presence of RLS.

The severity of RLS was investigated using the IRLSSG-RS.<sup>19</sup> The IRLSSG-RS consists of ten questions linked to symptom severity, impact on daily functions, mood, sleep and symptom intensity and frequency, with a maximum total score of 40 (maximum RLS severity), graded on a 4-point Likert scale. The Clinical Research Ethics Committee of Erzurum Region Training and Research Hospital (decision no:2020/07-85, dated: 06.04.2020), Erzurum, Turkey, approved the study. The patients and the control group provided written, informed consent and the work was carried out by the Declaration of Helsinki.

#### Statistical Analysis

SPSS Inc.'s for Windows 14.0 (Chicago, IL, USA) Statistical Package for Social Sciences was utilized for statistical analysis. Norm-compliant data were presented as mean, standard deviation, while non-compliant data were presented as

mean, standard deviation (median [range]). Categorical variables were presented as number (n) and percentage (%). In independent groups, variables matching the parametric assumptions were evaluated using the t-test and Mann-Whitney U-test, whilst categorical variables were examined using the chi-square test. A Pearson correlation analysis was performed to determine whether the variables were correlated. P-values of 0.05 or lower were considered significant.

## Results

The general clinical characteristics of patients with AS and the control group and the medical treatment of patients are shown in Table 1. There was no significant difference between the patient and control groups regarding age, gender, level of iron, folic acid, vitamin B12 and hemoglobin. 34 (32.1%) of 106 AS patients had RLS. However, the frequency of RLS was higher in AS patients than in control groups, with no significant difference in IRLSSG-RS score between AS patients and control groups (*Table 1*). There were no statis-

**Table 1.** Baseline demographic and characteristics of ankylosing spondylitis patients and control group.

	Patients with AS	Healthy controls	P value
Age (years)†	35.04±7.92	36.49±12.05	0.432
Sex (male/female) n (%)	76 (71.6)/30 (28.4)	74 (69.8)/32 (31.2)	0.945
Hemoglobin (g/dL)†	14.08±1.94	14.09±1.68	0.816
Ferritin (ng/mL)†	80±67.36	46.68±48.17	0.000
Iron (µg/dL)†	65 (19-241)	71 (13-164)	0.761
Folic acid (ng/mL)†	6.77±2.74	6.85±2.82	0.982
Vitamin B12 (pg/mL)†	287.21±63.87	288.28±66.46	0.938
Presence of RLS n (%)	34 (32.1)	11 (10.4)	<0.001
IRLSSG-RS score†	19.3±6.5	17.1±3.1	0.195
Uveitis n (%)	20 (18.9)	-	-
Peripheral joint involvement n (%)	24 (22.6)	-	-
Inflammatory bowel disease n (%)	9 (8.4)	-	-
NSAID n (%)	46 (43.4)	-	-
Biological therapy n (%)	52 (49.1)	-	-
Salazopyrin n (%)	8 (7.5)	-	-

† Mean±standard deviation.

AS: ankylosing spondylitis, RLS: restless legs syndrome, IRLSSG-RS: International Restless Legs Syndrome Study Group Rating, NSAID: non-steroidal anti-inflammatory drug.

**Table 2.** Clinical characteristics and laboratory values of ankylosing spondylitis patients with and without anemia.

	AS patients with anemia (n: 40)	AS patients without anemia (n: 66)	P value
Age (years)†	36.60±8.48	34.09±7.47	0.045
Sex (male/female) n (%)	25 (62.5)/15 (37.5)	53 (80.3)/13 (19.7)	0.034
Hemoglobin (g/dL)†	12.9±0.73	15,30±1.35	0.000
Ferritin (ng/mL)†	96.8±98.5	70.3±35	0.662
Iron (µg/dL)†	43.3±20.1	96.1±42.7	0.000
Folic acid (ng/mL)†	7.77±3.44	6.17±2.02	0.001
Vitamin B12 (pg/mL)†	292.03±67.74	284.29±61.76	0.865
BASDAI†	5.28±1.77	4.08±2.04	0.008
BASFI†	3.86±2.16	3.18±2.06	0.148
CRP (mg/dL)†	11.08±8.86	7.22±5.25	0.043
ESR (mm/h) †	20.30±13.77	14.59±8.00	0.000
Presence of RLS† n (%)	23 (57.5)	11 (16.7)	<0.001
IRLSSG-RS score†	21.3±5.7	15±6	0.005

† mean±standard deviation.

AS: ankylosing spondylitis, RLS: restless legs syndrome, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, IRLSSG-RS: International Restless Legs Syndrome Study Group Rating Scale.

tically significant differences in serum ferritin, vitamin B12 levels and BASFI between AS patients with and without anemia (Table 2). 23 (57.5%) of the AS patients with anemia had RLS, and the IRLSSG-RS score was 21.3±5.7. Of the AS patients without anemia, 11 (16.7%) had RLS, and the IRLSSG-RS score was 15± 6. Statistically significant differences between AS patients with and without anemia were found in terms of RLS frequency and IRLSSG-RS score (Table 2). Iron levels were lower in patients with AS with anemia than those without anemia. However, folic acid levels, age of patients, BASDAI, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values were found to be statistically higher (Table 2).

In the anemia group of patients with AS, 18 had iron deficiency anemia, and 22 had chronic disease anemia. Ten patients (55.5%) in the iron deficiency anemia group had RLS, 13 patients (59.0%) in the chronic disease anemia group had RLS, and there was no statistically significant difference between these two groups (p=0.376). The IRLSSG-RS score was 15.4 ±10 in the iron defi-

ciency anemia group and 15.7±8.9 in the chronic disease anemia group, with no statistically significant difference (p=0.185).

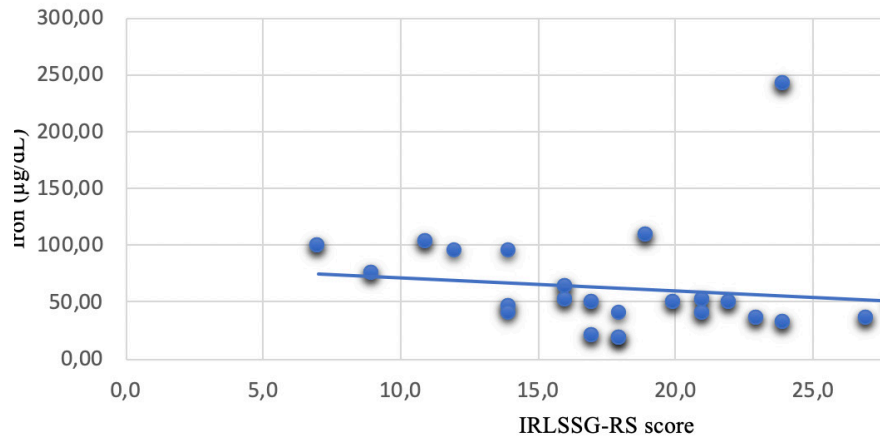
The IRLSSG-RS scores of AS patients were not correlated with age, CRP, ESR, folic acid level and BASDAI but were negatively correlated with serum iron (Figure 1) and hemoglobin level (Figure 2) (Table 3).

**Table 3.** Correlation between the IRLSSG-RS severity and age, CRP, ESH, hemoglobin, iron, folic acid, BASDAI in patient with ankylosing spondylitis.

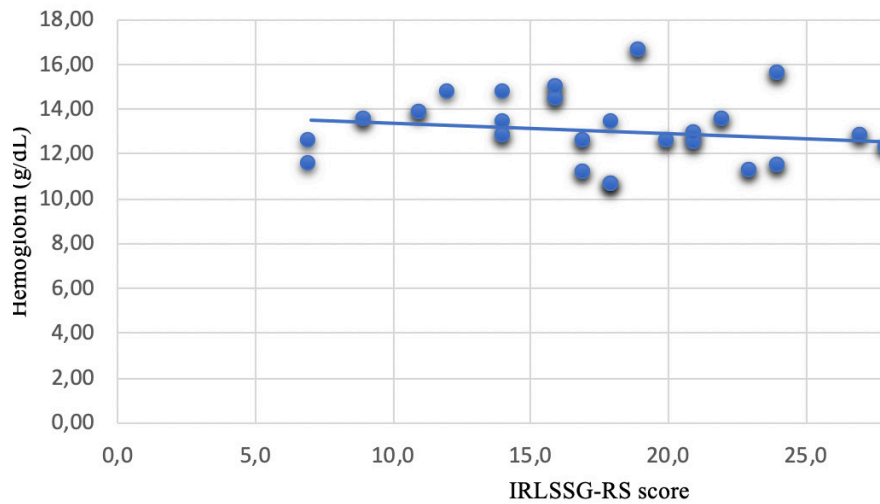
	IRLSSG-RS	
	r	p value
Age	-0.193	0.203
C-reactive protein	0.258	0.141
Erythrocyte sedimentation rate	-0.273	0.118
Hemoglobin	-0.329	0.044
Iron	-0.395	0.007
Folic acid	-0.063	0.680
BASDAI	0.091	0.610

r: Pearson and Spearman’s correlation coefficient.

IRLSSG-RS: International Restless Legs Syndrome Study Group Rating Scale, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.



**Figure 1.** Serum iron level was significantly and negatively correlated with IRLSSG-RS (International Restless Legs Syndrome Study Group Rating Scale) scores.



**Figure 2.** Hemoglobin level was significantly and negatively correlated with IRLSSG-RS (International Restless Legs Syndrome Study Group Rating Scale) scores.

## Discussion

Three main findings emerged from this study. Firstly, patients with AS have a higher RLS frequency than the control group. Secondly, AS patients with anemia had RLS more often, and IRLSSG-RS scores were higher than AS patients without anemia. Third, a negative and significant correlation was found between the IRLSS-RS score and serum iron and hemoglobin levels in patients with AS.

Dopaminergic dysfunction is thought to be the underlying cause of the pathophysiology of RLS.<sup>20</sup> Studies have shown that RLS occurs more frequently in patients with rheumatological disorders such as rheumatoid arthritis, scleroderma, Sjogren's syndrome, and fibromyalgia.<sup>21-24</sup> Tekatas and Pamuk<sup>13</sup> and Demirci et al.<sup>12</sup> reported that the frequency of RLS in patients with AS was 30.8% and 36.4%, respectively. We found the frequency of RLS in patients with AS to be 32.1%. The frequency of RLS in healthy people in our control group was 10.4%, and the rates were similar to the frequency in the range of 2-15% determined in the general population.<sup>9,13,25,26</sup>

Several reasons have been suggested for the relationship between AS and RLS. First, long-term use of nonsteroid antiinflammatory drugs for chronic pain conditions is common in patients with AS. It may lead to gastrointestinal blood loss, resulting in higher subclinical iron deficiency.<sup>27</sup> There is also an association between chronic pain and RLS, and it may also be associated with a neurochemical predisposition resulting from chronic pain conditions and an abnormality of the immune system.<sup>28</sup>

Küçük et al.<sup>29</sup> also showed that in patients with systemic lupus erythematosus (SLE), the prevalence of RLS is higher than in the normal population, and anemia appears to be an essential determinant of the presence and severity of RLS in SLE patients. Our study revealed the presence of RLS more frequently in patients with AS compared to the healthy population. There was a negative correlation between hemoglobin and serum iron levels and IRLSS-RS score in AS patients.

This study had several limitations. It had a relatively limited number of patients. The cross-sectional planning of the study is one of the other limitations.

## Conclusions

In this study, patients with AS had a higher RLS frequency compared to the control group, AS patients with anemia have a higher RLS and higher IRLSSG-RS score than AS patients without anemia, and also a negative and significant correlation was found between IRLSS-RS score and serum iron and hemoglobin levels in AS patients.

### Acknowledgement

We are grateful to our patients for their contributions to this study. Also, the authors are thankful to all laboratory workers for their vigorous efforts. Any financial assistance does not partially or fully sponsor this research.

### Conflict of interest

The authors have no conflicts of interest to declare.

### Funding Sources

No specific funding from the public, private, or non-profit sectors was received to carry out the work mentioned in this article.

### Ethical Approval

For this study, approval was obtained local ethics committee with decision number 2020/07-85.

### Authors' Contribution

All authors shared responsibility for the study's conception, literature review, critical review, data processing, statistical analysis, and manuscript preparation.

## References

1. Chen HA, Chen CH, Liao HT, Lin YJ, Chen PC, Chen WS, Chou CT. Factors associated with radiographic spinal involvement and hip involvement in ankylosing spondylitis. *Semin Arthritis Rheum*. 2011 Jun;40(6):552-8. doi: 10.1016/j.semarthrit.2010.07.008.
2. Dean LE, Jones GT, MacDonald AG, Downham C, Sturrock RD, Macfarlane GJ. Global prevalence of ankylosing spondylitis. *Rheumatology (Oxford)*. 2014 Apr;53(4):650-7. doi: 10.1093/rheumatology/ket387.
3. Adamson JW. The anemia of inflammation/malignancy: mechanisms and management. *Hematology Am Soc Hematol Educ Program*. 2008;2008(1):159-65. doi: 10.1182/asheducation-2008.1.159.
4. Fleming MD. The regulation of hepcidin and its effects on

- systemic and cellular iron metabolism. *Hematology Am Soc Hematol Educ Program*. 2008;2008(1):151-8. doi: 10.1182/asheducation-2008.1.151.
5. Dallman PR, Yip R, Johnson C. Prevalence and causes of anemia in the United States, 1976 to 1980. *Am J Clin Nutr*. 1984 Mar;39(3):437-45. doi: 10.1093/ajcn/39.3.437.
  6. Niccoli L, Nannini C, Cassarà E, Kaloudi O, Cantini F. Frequency of anemia of inflammation in patients with ankylosing spondylitis requiring anti-TNF $\alpha$  drugs and therapy-induced changes. *Int J Rheum Dis*. 2012 Feb;15(1):56-61. doi: 10.1111/j.1756-185X.2011.01662.x.
  7. Nagandla K, De S. Restless legs syndrome: pathophysiology and modern management. *Postgrad Med J*. 2013 Jul;89(1053):402-10. doi: 10.1136/postgradmedj-2012-131634.
  8. Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, Ferini-Strambi L. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med*. 2005 Jun 13;165(11):1286-92. doi: 10.1001/archinte.165.11.1286.
  9. Bjorvatn B, Leissner L, Ulfberg J, Gyiring J, Karlsborg M, Regeur L, Skeidsvoll H, Nordhus IH, Pallesen S. Prevalence, severity and risk factors of restless legs syndrome in the general adult population in two Scandinavian countries. *Sleep Med*. 2005 Jul;6(4):307-12. doi: 10.1016/j.sleep.2005.03.008.
  10. Ondo W, Tan EK, Mansoor J. Rheumatologic serologies in secondary restless legs syndrome. *Mov Disord*. 2000 Mar;15(2):321-3. doi: 10.1002/1531-8257(200003)15:2<321::AID-MDS1019>3.0.CO;2-I.
  11. Hening WA, Caivano CK. Restless legs syndrome: A common disorder in patients with rheumatologic conditions. *Semin Arthritis Rheum*. 2008 Aug;38(1):55-62. doi: 10.1016/j.semarthrit.2007.09.001.
  12. Demirci S, Demirci K, Dođru A, İnal EE, Koyuncuođlu HR, Şahin M. Restless legs syndrome is associated with poor sleep quality and quality of life in patients with ankylosing spondylitis: a questionnaire-based study. *Acta Neurol Belg*. 2016 Sep;116(3):329-36. doi: 10.1007/s13760-015-0564-3.
  13. Tekatas A, Pamuk ON. Increased frequency of restless leg syndrome in patients with ankylosing spondylitis. *Int J Rheum Dis*. 2015 Jan;18(1):58-62. doi: 10.1111/1756-185X.12323.
  14. Linden S Van Der, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. *Arthritis Rheum*. 1984 Apr;27(4):361-8. doi: 10.1002/art.1780270401.
  15. Nutritional anaemias. Report of a WHO scientific group. *World Health Organ Tech Rep Ser*. 1968;405:5-37.
  16. Akkoc Y, Karatepe AG, Akar S, Kirazli Y, Akkoc N. A Turkish version of the Bath Ankylosing Spondylitis Disease Activity Index: Reliability and validity. *Rheumatol Int*. 2005 May;25(4):280-4. doi: 10.1007/s00296-003-0432-y.
  17. Karatepe AG, Akkoc Y, Akar S, Kirazli Y, Akkoc N. The Turkish versions of the Bath Ankylosing Spondylitis and Dougados Functional Indices: Reliability and validity. *Rheumatol Int*. 2005 Oct;25(8):612-8. doi: 10.1007/s00296-004-0481-x.
  18. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, Zucconi M, Ferri R, Trenkwalder C, Lee HB; International Restless Legs Syndrome Study Group. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria--history, rationale, description, and significance. *Sleep Med*. 2014 Aug;15(8):860-73. doi: 10.1016/j.sleep.2014.03.025.
  19. Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, Trenkwalder C; International Restless Legs Syndrome Study Group. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med*. 2003 Mar;4(2):121-32. doi: 10.1016/s1389-9457(02)00258-7.
  20. Nagandla K, De S. Restless legs syndrome: Pathophysiology and modern management. *Postgrad Med J*. 2013 Jul;89(1053):402-10. doi: 10.1136/postgradmedj-2012-131634.
  21. Hening WA, Caivano CK. Restless legs syndrome: A common disorder in patients with rheumatologic conditions. *Semin Arthritis Rheum*. 2008 Aug;38(1):55-62. doi: 10.1016/j.semarthrit.2007.09.001.
  22. Taylor-Gjevrev RM, Gjevrev JA, Skomro R, Nair B. Restless legs syndrome in a rheumatoid arthritis patient cohort. *J Clin Rheumatol*. 2009 Feb;15(1):12-5. doi: 10.1097/RHU.0b013e318190f94c.
  23. Prado GF, Allen RP, Trevisani VMF, Toscano VG, Earley CJ. Sleep disruption in systemic sclerosis (scleroderma) patients: Clinical and polysomnographic findings. *Sleep Med*. 2002 Jul;3(4):341-5. doi: 10.1016/S1389-9457(02)00013-8.
  24. Stehlik R, Arvidsson L, Ulfberg J. Restless legs syndrome is common among female patients with fibromyalgia. *Eur Neurol*. 2009;61(2):107-111. doi: 10.1159/000180313.
  25. Bayard M, Avonda T, Wadzinski J. Restless legs syndrome. *Am Fam Physician*. 2008 Jul 15;78(2):235-40.
  26. Yilmaz NH, Akbostanci MC, Oto A, Aykac O. Prevalence of restless legs syndrome in Ankara, Turkey: An analysis of diagnostic criteria and awareness. *Acta Neurol Belg*. 2013 Sep;113(3):247-251. doi: 10.1007/s13760-012-0153-7.
  27. Smale S, Tibble J, Sigthorsson G, Bjarnason I. Epidemiology and differential diagnosis of NSAID-induced injury to the mucosa of the small intestine. *Best Pract Res Clin Gastroenterol*. 2001 Oct;15(5):723-38. doi: 10.1053/bega.2001.0231.
  28. Weinstock LB, Walters AS, Pauksakon P. Restless legs syndrome - Theoretical roles of inflammatory and immune mechanisms. *Sleep Med Rev*. 2012 Aug;16(4):341-54. doi: 10.1016/j.smrv.2011.09.003.
  29. Kucuk A, Uslu AU, Yilmaz R, Salbas E, Solak Y, Tunc R. Relationship between prevalence and severity of restless legs syndrome and anemia in patients with systemic lupus erythematosus. *Int J Rheum Dis*. 2017 Apr;20(4):469-73. doi: 10.1111/1756-185X.12793.

