Asociación Colombiana de Reumatología

Revista Colombiana de REUMATOLOGÍA

www.elsevier.es/rcreuma

Reflexion Article

Inadequate sleep as a limiting factor in achieving remission in patients with rheumatoid arthritis

Amarilis J. Pérez De Jesus[a,*], *Nahir S. Pérez Soto*[a], *Miguel A. Vázquez Padua*[b]

[a] *Rheumatology Service, Clinical and Research Department, Caguas Rheumatology Center Clinic, Caguas, Puerto Rico*
[b] *Rheumatology Service, Clinical Research Department, Total Outcomes Partners, LLC, Caguas, Puerto Rico*

ARTICLE INFO

Article history:
Received 16 February 2023
Accepted 18 May 2023

Keywords:
Rheumatoid arthritis
Sleep quality
Inflammatory cytokines
Cognitive therapy
Sleep disturbances

ABSTRACT

Introduction: Good sleep has a restorative effect at the cellular level and helps maintain the body's homeostasis.
Objectives: Given our clinical experiences, we propose that sleep quality should be evaluated in patients with rheumatoid arthritis. Poor sleep quality should be considered as a factor that may impact clinical outcomes in patients with rheumatoid arthritis.
Materials and methods: We researched medical literature on clinical and physiological pathways associated with sleep quality.
Results: There is evidence that interleukin-6 and tumor necrosis factor have a role in inflammatory and immune imbalance as well as in sleep disturbance in patients with rheumatoid arthritis, which leads to the chronic inflammatory process seen in these patients. Most patients with rheumatoid arthritis report sleep problems, be it insomnia or other complaints of non-refreshing sleep. Lack of sleep or poor sleep patterns in these patients further compromise their quality of life. In patients with RA, aetiologies such as restless leg syndrome (RLS), sleep apnoea syndrome, and Temporomandibular Joint Dysfunction (TMJ) syndromes might contribute to sleep disturbances. This lack of restful sleep might limit our goal, as treating physicians, to achieve remission states in these patients.
Conclusions: It is our opinion that sleep quality evaluation must be addressed, monitored, and treated as part of the management of patients with RA. Bad sleep adds an additional burden to disease activity in patients with RA, besides, it limits patients' possibility of achieving disease remission.

* Corresponding author.
E-mail address: ajperez@crcsalud.com (A.J. Pérez De Jesus).

El sueño inadecuado como factor limitante para alcanzar la remisión en pacientes con artritis reumatoide

Palabras clave:
Artritis reumatoide
Calidad del sueño
Citocinas inflamatorias
Terapia cognitiva
Trastornos del sueño

RESUMEN

Introducción: El buen sueño tiene un efecto restaurador a nivel celular y ayuda a mantener la homeostasis del cuerpo.
Objetivos: Dadas nuestras experiencias clínicas, proponemos que la calidad del sueño debe evaluarse en pacientes con artritis reumatoide. La mala calidad del sueño debe considerarse un factor que puede afectar los resultados clínicos en estos pacientes.
Materiales y métodos: Investigamos la literatura médica sobre vías clínicas y fisiológicas asociadas con la calidad del sueño.
Resultados: Existe evidencia de que la interleucina-6 y el factor de necrosis tumoral tienen un papel en el desequilibrio inflamatorio e inmunológico, así como en la alteración del sueño en pacientes con artritis reumatoide, lo que conduce al proceso inflamatorio crónico observado en estos. La mayoría de estos pacientes reportan problemas para dormir. La falta de sueño o los malos patrones de sueño comprometen aún más su calidad de vida. En pacientes con artritis reumatoide, etiologías como el síndrome de piernas inquietas, el síndrome de apnea del sueño y los síndromes de disfunción de la articulación temporomandibular pueden contribuir a los trastornos del sueño.
Conclusiones: Es nuestra opinión que la evaluación de la calidad del sueño debe abordarse, monitorearse y tratarse como parte del tratamiento de los pacientes con artritis reumatoide. El mal sueño agrega una carga adicional a la actividad de la enfermedad en estos, además, limita la posibilidad de los pacientes de lograr la remisión de la enfermedad.

Introduction

What is rheumatoid arthritis?

Rheumatoid arthritis (RA) is defined as a chronic, autoimmune, systemic, and inflammatory process that causes pain and inflammation of joints.[1] This type of arthritis affects the joints of the hands and feet symmetrically. RA affects about 1% of the population and is more commonly seen in females.[2] It has systemic involvement, affecting other organs, among them lungs, skin, eyes, and heart.[2] Patients with RA will present with pain, swelling on joints, fatigue, stiffness, and in some cases, fever. The cause is still unknown, although we do know that there are environmental and genetic factors involved in the disease process. Sleep disturbances, depression, and disease activity contribute to the fatigue associated with RA.[2]

Environmental factors involved in the disease process such as genetics, and exposure to cigarette smoke (cause a modification in proteins (conversion of arginine to citrulline) which are presented to T-cells, creating in turn, antibodies against these citrullinated proteins will start accumulating and produce immune complexes), sex, and geographic factors.[3]

Immune complexes lead to the activation of synovial cells that will produce autoantibodies and the activation of T-cells that stimulate cytokine production (IFN-γ, IL-2, IL-6, IL-12, IL-23, etc.). Tumor necrosis factor-alpha (TNF-α), and growth factors that will eventually perpetuate the inflammatory process in RA.

To manage the disease, we use medications such as disease-modifying antirheumatic drugs (DMARDS) or other disease-modifying agents like bDMARDS or biologic disease-modifying agents, which are specific and work by blocking the release of pro-inflammatory substances.

RA presents a wide range of symptoms including fatigue, which is one of the chief complaints. Fatigue is the personal perception of extreme tiredness or exhaustion not associated with a specific degree of activity nor is it relieved by rest and that interferes with activities.[2,4] Fatigue is a complaint manifested by 40% or more of RA patients.[2] Fatigue could be linked to the inflammatory process, depression, or alterations in sleep patterns.[2] Over 50% of patients with RA present with sleeping disorders, 2–3 times higher than the prevalence of sleep disorders in the general population.[1] These alterations in sleep patterns contribute to persistent symptoms like fatigue, worsening inflammatory processes, and an increase in joint pain.

Sleep disorders in rheumatoid arthritis

Sleep is a complex biological process that is necessary for the body to restore normal function, perform memory consolidation and immune system maintenance. Sleep is divided into stages called rapid eye movement (REM) and non-rapid eye movement (non-REM) where REM is the phase where most of the dreaming takes place and non-REM is when deep sleep happens. These phases occur in a repetitive manner through which the brain cycles 2–5 times a night.[5,6]

When we talk about sleep disorders (or sleep–wake disorders) we must keep in mind that there exist ten groups of sleep disorders according to the diagnostic and statistical manual of mental disorders (DSM-V). Some of the more common ones include insomnia, sleep apnea, parasomnia, narcolepsy, circadian rhythm sleep–wake disorders, and restless leg syndrome. Usually, patients with sleep disorders complain about time, quantity, or quality of sleep which leads to physical and emotional problems that affect their normal function and quality of life.[6] There is an inverse relationship between sleep and the immune system where changes in sleep affect the proper functioning of the immune system and immune dysfunction can in turn alter sleep patterns.[7] It stands to reason then that there would be an increased prevalence of these disorders in patients with RA, especially when taking into consideration the role that cytokines such as TNF-α have on the regulation of sleep.[8,9]

In the United States, between 30 and 40% of adults will report symptoms related to insomnia at least once in any given calendar year. With a prevalence of 10%, insomnia is characterized by dissatisfaction with the quantity or quality of sleep, with problems initiating or maintaining sleep, which lead to problems in normal functioning in work and social settings among other areas in the patient's life.[6] One study estimates that up to 70% of RA patients report poor sleep quality caused by insomnia.[5]

Sleep apneas are found within the classifications of sleep–wake disorders related to breathing. This classification is further divided into obstructive sleep apnea, central sleep apnea, and sleep-related hypoventilation. Obstructive sleep apnea (OSA) is the most prevalent one in this group and is characterized by interruptions in breathing due to upper airway occlusion while the patient is asleep.[6,8] Studies have suggested that OSA has an increased risk in patients with RA compared to the general population, with one study estimating OSA prevalence of 58.1% in patients with RA, in comparison the disease prevalence for OSA is estimated to be between 6 and 17% worldwide.[8] Patients with sleep apnea have been shown to have increased levels of pro-inflammatory cytokines TNF and IL-6 which would in turn contribute to increased pain perception in patients with RA who already show an increase in these pro-inflammatory cytokines as part of the disease mechanism.[1,10]

Restless leg syndrome (RLS) is characterized by a need to move one's legs. To fulfill the diagnostic criteria, it needs to be accompanied or caused in response to an unpleasant or uncomfortable sensation that the patient describes as creeping, crawling, itching, tingling, or burning. RLS is considered both a neurological and sensorimotor disorder where symptoms worsen at night or during rest and are only relieved by movement.[6] In RA, this disorder has a higher prevalence, with up to 30% of patients experiencing this disorder in comparison with a prevalence of 2–7.2% in the general population.[5,6,11] While another study showed that 63% of its participants experienced RLS.[12] RLS results in wake-up reactions and sleep interruption that can result in increased daytime sleepiness and fatigue in RA patients.[9,11]

Influence of altered sleep patterns on disease activity

Good and restful sleep is important for learning, memory, and mood as well as for psychological stability. In the case of rheumatic diseases adequate sleep is important to promote the process of tissue healing, regulation of the immune system, and cell repair. Sleep is a complex regulation of hormonal and neuromodulatory influences that help with the regenerative process.[5]

Patients with RA report poor sleep, multiple awakenings during the night, difficulty falling asleep, restless legs syndrome, fatigue, and daytime sleepiness. When evaluated with polysomnography most of these patients show normal sleep architecture, longer waking hours and reduced sleep.[5] Restless leg syndrome has been reported in about 20–30% of patients with RA, this leads to wake-up reactions and sleep interruption.[11] Sleep apnea syndrome is also more common in this group of patients as compared to the general population (which is 7%).[8] In these patients sleep apnea might be related to obesity, skeletal changes such as TMJ, or cervical spine damage by the arthritis, leading to upper respiratory tract obstruction.[8,9]

Using the Pittsburgh sleep quality index (PSQI) questionnaire that evaluates sleep quality. Rheumatoid arthritis patients have shown poor sleep quality compared to the general population.[2] This poor sleep quality translates into increased pain and fatigue.

About 72% of patients with rheumatic diseases report poor unrestful sleep patterns.[12] Some of them report sleep disturbances such as restless leg syndrome and or symptoms of sleep apnea (dry mouth, snoring, etc.).

Sleep enhances immune defenses

Sleep impairment may derange immune function which plays a role in inflammatory disorders. Sleep disturbances may impair T cell regulation and upregulate inflammatory cytokines, such as TNF-α, IL-6, and IL-1 (see Fig. 1). Chronic intermittent hypoxia as seen in sleep apnea syndrome also activates systemic inflammation by increasing inflammatory cytokines (TNF-α, IL-6).[7,9] Inhibition of T-cell co-stimulation using abatacept also leads to subjective reports of better sleep quality in patients with RA treated with this medication.

The use of other bDMARDS such as anti-TNF, IL-6 blockers, JAK inhibitors, and other biologics also contributes to better sleep quality and improvement in fatigue. In the same manner, the use of cDMARDS also contributes to less fatigue and better sleep quality since they decrease inflammation and pain in these patients.

In patients with RA the hypothalamic–pituitary axis (HPA) is also affected by alterations in the production of corticotropin-releasing hormones (CRH) and cortisol, which also contributes to altered sleep patterns and insomnia. In these patients with RA, the HPA axis is affected by oral steroids, which also contribute to insomnia.[5] This creates a vicious cycle that keeps the patient in a chronic state of sleep alterations and sometimes sleep deprivation. There is no

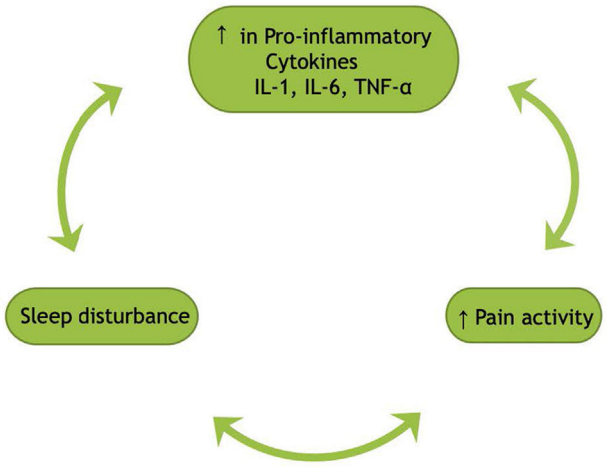

Fig. 1 – Bidirectional effect of sleep disturbance in RA, where an increase in pro-inflammatory cytokines like IL-1 (interleukin-1), IL-6 (interleukin-6), and TNF-α (tumor necrosis factor-alpha) can be either caused by the normal disease process or by an abnormal sleep process would interact with each other increasing the number of circulating cytokines and increased in sleep disturbances. Both factors would result in an increase in pain activity which would in turn affect both the levels of pro-inflammatory cytokines and adversely affect sleep in patients with RA.

doubt that disturbed sleep patterns contribute to worsening of the clinical manifestations of this disease.

Treatment

Managing clinical symptoms with NSAIDs, oral steroids, DMARDS and the use of biologics remains the gold standard of treatment for patients with RA. And the goal is to achieve remission of the disease. When we talk about sleep disturbances in these patients, things get more complex. Management of insomnia includes decreased use of caffeine, avoidance of prolonged naps during the daytime, and pain management. Other modalities of treatment for sleep disturbances include the use of medications (benzodiazepines), sleep hygiene, natural products, and antidepressants, among others.

Cognitive behavioral therapy

This includes sleep education, sleep hygiene, and relaxation techniques. Avoid blue-light exposure (TV, cellphones, etc.) close to bedtime. Go to bed at the same time each night.[5]

Benzodiazepine agonists

Have a strong sleep-promoting effect, but in the case of patients with RA might increase the risk of somnolence in the morning hours and the risk of falls.[5] Additionally, they pose a risk to habit forming and have negative effects on memory.

Antidepressants

Have limited effects in patients with RA and increase IL-6, which leads to further fatigue, worsening the patient's quality of life.[5]

Melatonin

Possesses sleep-enhancing effects. In patients with RA, findings have shown increased nocturnal melatonin levels.[5] There are increased levels of synovial fluid in patients with RA. There are increased levels of synovial fluid in patients with RA. So, in this population of patients, a deficiency in melatonin does not seem to be the cause for insomnia, arousing doubts about its benefits in the management of these patients. More studies are needed to establish if it is beneficial in RA patients.

Physical activity and exercise

Exercises are recommended for all patients with RA. A minimum addition of a walking program and stretching exercises into the patient's daily routine will result in a major benefit and well-being sensation. Patients need to avoid periods of full inactivity especially if they are experiencing a flare of the disease.

Fig. 2 is presented as a tool for the diagnosis and management of sleep disorders in patients with RA.

Implications

Sleep as it relates to RA has a bidirectional interaction, where sleep affects the severity of symptoms in RA and this increase in severity, in turn, affects sleep quality which in the end has a detrimental effect on patient's health outcomes and psychosocial well-being. Sleep disturbances increase the risk of RA causing immune dysregulation and increasing levels of inflammatory markers.[12] This is why it is important for clinicians to learn to recognize these sleep disorders and how to address them to achieve a better quality of life for their patients. Inadequacies in sleep patterns cause the patient to have more fatigue and myalgias, giving them the false sensation that their arthritis has worsened. Functional capacity, which is the ability of a person to perform activities needed for daily living, is also adversely affected by poor sleep quality thus altering the Disease Activity Score.[13]

When patients are asked about their global health as part of the elements to calculate the Disease Activity Score (DAS score), poor sleep quality may increase the value of this evaluation.[9] This might elevate the DAS score when in reality this perception of malaise is not directly associated with active RA disease but with fatigue and malaise associated with lack of sleep or poor sleep quality. We should be committed to assessing the patient's quality of sleep, and evaluating for pathologies such as restless leg syndrome, anxiety, depressive pathologies, sleep apneas syndromes, etc. because these are treatable conditions, and once these etiologies are corrected our patients will have better outcomes and better quality of life.

Sleep as well as pain assessments should be included during clinical assessment, but appropriate treatment should also be instituted to manage the sleep problem.[13]

History taking must address questions about quantity of sleep and quality of sleep: Do you awaken feeling rested?

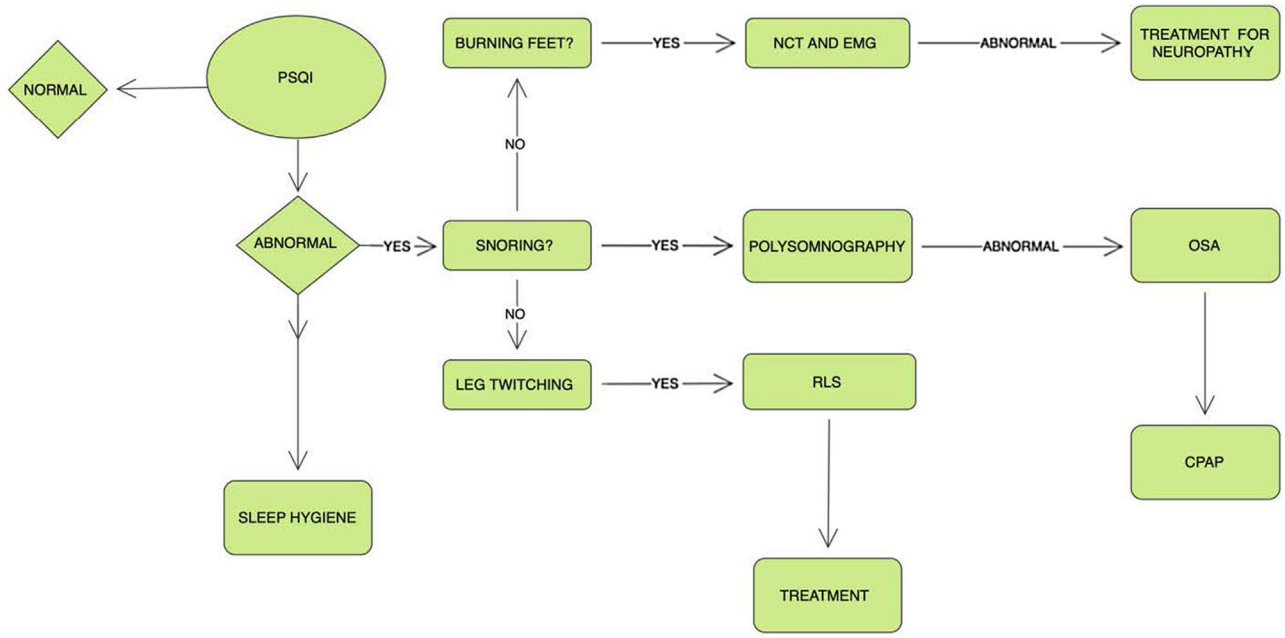

Fig. 2 – This flow chart indicates how to approach diagnosis and treatment for some of the most common sleep disorders found in RA patients. Using the Pittsburgh sleep quality index (PSQI) as a starting point to have a quantitative and measurable indicator of sleep disturbance. After administration of the PSQI a physician should identify symptomatic indicators of sleep disorders, such as leg twitching in RLS (restless leg syndrome). PSQI (Pittsburgh sleep quality index), NCT/EMG (nerve conduction test and electromyogram), CPAP (continuous positive airway pressure), and OSA (obstructive sleep apnea).

Do you snore? etc. In addition, sleep evaluation tools to identify etiologies associated with sleep disturbances, such as polysomnography, lower extremities NCT, and EMG (to exclude neuropathies as causes of sleep alterations) need to be used. The Pittsburgh sleep quality index (PSQI) should also be administered.[12] This test is a standardized and valid scale developed to differentiate poor from good sleepers and evaluate sleep quality in the previous month.[12]

Referral to psychiatric and cognitive behavior therapy for adequate management of insomnia, anxiety, and depression should also be considered and included as part of our standard of care. Evaluation and questions directed to establish sleep alterations should be as important as evaluating for morning stiffness and fatigue in RA patients.

Conclusion

It is well established that remission must be our goal for this population, but what if remission can't be achieved because of the role of disturbed sleep patterns in these patients? Measurements of disease activity take into consideration the patient's perception of the disease. What if the patient's perception is altered by the fact that they feel fatigued or lack adequate sleep? Patients should undergo a full exploration of sleeping patterns, utilizing standardized questionnaires, diagnostic criteria for each disorder, and clinical studies such as polysomnography studies.

Management of sleep disturbances must be an integral part of the treatment of patients with Rheumatoid Arthritis. Poor sleep leads to worsening fatigue and depression so this problem must be addressed in every patient with RA to ensure them a better quality of life. Sleep disturbances must be managed according to their respective pathology to decrease the negative impact this might have on RA disease activity.[13] More research studies should be done to establish what are the precipitating factors for sleep disturbance in RA patients. What happens in patients with lower joint counts and lower inflammatory markers, who are on biologic agents but objective disease activity measures such as DAS (Disease Activity Score) cannot achieve remission levels? Most patients have an improvement in clinical signs and symptoms of joint pains and inflammation but constantly complain of fatigue. Fatigue is one of the manifestations of lack or insufficient sleep. Persistent fatigue in RA patients without other signs or symptoms to suggest RA flare might be secondary to poor sleep quality. We emphasize the importance of sleep pattern exploration in every patient with Rheumatoid Arthritis.

Conflict of interests

The authors declare they have no conflict of interest.

Contribution of the authors to the manuscript

The authors worked as a research team from developing the concept, bibliographical research, and interpretation, to the various stages of manuscript drafting and critical review. As

the primary author, Dr. Amarilis J. Perez De Jesús was responsible for the initial research idea, contributing patients' clinical data and experiences to the research team, concept development, and the final review and approval of the manuscript. The second author, Nahir S. Pérez Soto contributed to the execution, evaluation, and interpretation of the bibliographical research, supporting the concepts presented, manuscript development, and final approval. In addition, Dr. Miguel A. Vázquez Padua contributed to the critical review of the content and the concepts presented, the literature review, manuscript revision, and final approval.

Funding

There was no funding to support this work and publication.

REFERENCES

1. Irwin MR, Olmstead R, Carrillo C, Sadeghi N, FitzGerald JD, Ranganath VK, et al. Sleep loss exacerbates fatigue, depression, and pain in rheumatoid arthritis. Sleep. 2012;35:537–43, http://dx.doi.org/10.5665/sleep.1742.
2. Hammam N, Gamal RM, Rashed AM, Elfetoh NA, Mosad E, Khedr EM. Fatigue in rheumatoid arthritis patients: association with sleep quality, mood status, and disease activity. Reumatol Clin. 2020;16:339–44, http://dx.doi.org/10.1016/j.reuma.2018.07.010.
3. Liao KP, Alfredsson L, Karlson EW. Environmental influences on risk for rheumatoid arthritis. Curr Opin Rheumatol. 2009;21:279–83, http://dx.doi.org/10.1097/BOR.0b013e32832a2e16.
4. Zielinski MR, Systrom DM, Rose NR. Fatigue, sleep, and autoimmune and related disorders. Front Immunol. 2019;10:1827, http://dx.doi.org/10.3389/fimmu.2019.01827.
5. Boeselt T, Koczulla R, Nell C, Beutel B, Guenter K, Cassel W, et al. Sleep and rheumatic diseases. Best Pract Res Clin Rheumatol. 2019;33:101434, http://dx.doi.org/10.1016/j.berh.2019.101434.
6. American Psychiatric Association. Sleep–wake disorders. In: Diagnostic and statistical manual of mental disorders. Arlington, Virginia: American Psychiatric Association; 2013. p. 361–422, http://dx.doi.org/10.1176/appi.books.9780890425596.
7. Chung WS, Lin CL. Sleep disorders associated with risk of rheumatoid arthritis. Sleep Breath. 2018;22:1083–91, http://dx.doi.org/10.1007/s11325-018-1639-1.
8. Wali S, Mustafa M, Manzar D, Bawazir Y, Attar S, Fathaldin O, et al. Prevalence of obstructive sleep apnea in patients with rheumatoid arthritis. J Clin Sleep Med. 2020;16:259–65, http://dx.doi.org/10.5664/jcsm.8178.
9. Coskun Benlidayi I. Sleep impairment: an obstacle to achieve optimal quality of life in rheumatoid arthritis. Rheumatol Int. 2018;38:2183–92, http://dx.doi.org/10.1007/s00296-018-4155-5.
10. Fragiadaki K, Tektonidou MG, Konsta M, Chrousos GP, Sfikakis PP. Sleep disturbances and interleukin 6 receptor inhibition in rheumatoid arthritis. J Rheumatol. 2012;39:60–2, http://dx.doi.org/10.3899/jrheum.110617.
11. Demir S, Kucuk A, Altas M, Cure E. Restless leg syndrome and sleep disorders in patients with rheumatoid arthritis and its relation with anemia parameters. Acta Med (Hradec Kralove). 2021;64:137–44, http://dx.doi.org/10.14712/18059694.2021.24.
12. Mustafa M, Bawazir Y, Merdad L, Wali S, Attar S, Fathaldin O, et al. Frequency of sleep disorders in patients with rheumatoid arthritis. Open Access Rheumatol. 2019;11:163–71, http://dx.doi.org/10.2147/OARRR.S201556.
13. Grabovac I, Haider S, Berner C, Lamprecht T, Fenzl KH, Erlacher L, et al. Sleep quality in patients with rheumatoid arthritis and associations with pain, disability, disease duration, and activity. J Clin Med. 2018;7:336, http://dx.doi.org/10.3390/jcm7100336.