J Surg Med. 2024;8(1):1-6.
https://doi.org/10.28982/josam.7511

JOSAM

Research article
https://jsurgmed.com/

Journal of Surgery and Medicine

e-ISSN: 2602-2079

A study of the correlation between magnesium and ferritin levels and the severity of the disease and sleep quality in restless legs syndrome

Sibel Üstün Özek

University of Health Sciences, Prof. Dr. Cemil Taşçıoğlu City Hospital, Department of Neurology, Istanbul, Turkey

ORCID of the author(s)

SÜÖ: https://orcid.org/0000-0003-1165-2648

Corresponding Author
Sibel Üstün Özek
University of Health Sciences, Prof. Dr. Cemil Taşçıoğlu City Hospital, Department of Neurology, Istanbul, Turkey
E-mail: sibelustun@hotmail.com

Ethics Committee Approval
The study was approved by the Ethics Board of the University of Health Sciences, Prof. Dr. Cemil Taşçıoğlu City Hospital (No: 1225, Date: April 2, 2019).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2024 January 6

Abstract

Background/Aim: Restless legs syndrome (RLS) is a chronic neurological disease that impairs sleep quality, causes emotional stress and affects daily activities. While the association between disease severity and low iron and ferritin levels is known, the magnesium (Mg) results are contradictory. This study aimed to investigate the influence of low Mg and ferritin levels on the severity of the disease and sleep quality.
Methods: A case-control study included 50 RLS patients aged 18–78 years and 50 healthy control patients. Mg and ferritin levels were measured, considering values below <1.8 mg/dL and 75 ng/mL as low. Both groups completed the International Restless Legs Syndrome Study Group score (IRLSSG score) to assess the severity of RLS, as well as the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS) to evaluate subjective sleep quality.
Results: The mean age of RLS patients and the control group was 47.06 (13.35) years and 43.30 (15.43) years, respectively (P=0.196). The RLS patients had an IRLSSG score of 25.16 (6.85). The PSQI total scores, subscale scores, and ESS scores of RLS patients were significantly higher than those of the control group. However, no significant difference was observed in the IRLSSG score, PSQI, and ESS scores based on Mg and ferritin levels. Sleep latency was found to be shorter in individuals with Mg deficiency.
Conclusion: Sleep disorders are prevalent among RLS patients. No correlation was found between Mg and ferritin levels and disease severity or sleep disorders. Furthermore, Mg deficiency did not appear to exacerbate the IRLSSG score or sleep disorder scores.

Keywords: restless legs syndrome, daytime somnolence, magnesium, ferritin, Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale

How to cite: Özek SÜ. A study of the correlation between magnesium and ferritin levels and the severity of the disease and sleep quality in restless legs syndrome. J Surg Med. 2024;8(1):1-6.

Introduction

Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is a chronic neurological condition characterized by an irresistible urge to move the legs, accompanied by sensations of pain, burning, and tingling. Although not intensely painful, these sensations can be highly disruptive [1,2]. The discomfort typically arises during periods of rest, worsens at night, and significantly impairs sleep, leading to chronic sleep disorders and emotional distress [3]. Accurate diagnosis enables effective symptom management, and in some secondary cases, a complete cure may be possible. RLS can be primary or secondary, with the latter resulting from underlying conditions that cause iron deficiency and local dopamine dysfunction in the brain. Approximately 25–30% of iron deficiency-related conditions, such as pregnancy, renal failure, and anemia, can lead to the development of RLS [4-6].

The recommended medications for treating RLS include dopamine agonists, alpha ligands, and opioid agonists [7]. Although not listed in the guidelines, treatments such as tramadol, magnesium sulfate, and baclofen have been attempted [8]. Marshall et al. conducted a comprehensive evaluation of cases involving magnesium and RLS, concluding that magnesium administration did not affect RLS symptoms [9]. However, contrasting findings have been reported in other studies [10,11].

We aimed to investigate the clinical impact of magnesium deficiency, given the lack of evidence-based research on magnesium use and the various approaches to magnesium replacement. We sought to examine and test our hypothesis that lower levels of ferritin and magnesium correspond to greater disease severity and compromised sleep quality, as well as increased daytime sleepiness. Our study aimed to determine whether magnesium and ferritin deficiencies contributed to elevated IRLSSG scores while also assessing concurrent daytime sleepiness and sleep quality using the Epworth Sleepiness Scale (ESS) and the Pittsburgh Sleep Quality Index (PSQI).

Materials and methods

Patients diagnosed with RLS according to the diagnostic criteria of the International Restless Legs Syndrome Study Group at a neurology clinic between 1 January 2017 and 1 April 2019 were included in the case-control study. A total of 100 patients with RLS (36 females and 14 males) and 50 controls (34 females and 16 males) were included. Only patients with idiopathic RLS were included, and those with secondary causes such as chronic renal failure, chronic liver failure, and pregnancy were excluded. The patients' sex, age, disease duration, medication usage, smoking habits, presence of RLS in the family, and laboratory test results (magnesium and ferritin) were recorded. For magnesium and ferritin measurements, 5 mL of blood was drawn from the patients after a 12-h fasting period using a yellow serum separation gel tube. The samples were immediately centrifuged at 4°C, 4000 rpm for 10 min. Magnesium levels were determined using a colorimetric method, and ferritin levels were determined using a chemiluminescent immunoassay with a Roche Cobas Integra 400 Plus analyzer. A magnesium value above 1.8 mg/dL was considered normal, while below 1.8 mg/dL was considered low. Recent literature suggests that the normal ferritin value should be above 75 ng/mL, so the cut-off value for ferritin was set at 75 ng/mL.

At the same time, the severity of the disease was assessed using the Restless Legs Evaluation Scale, and the concurrent sleep quality and daytime sleepiness were evaluated using the ESS and the PSQI. In our study, we assessed the IRLSSG score, as well as the magnesium and ferritin levels of patients diagnosed with RLS. The control group consisted of patients who visited our neurology outpatient clinic for a general medical examination and were assigned the code Z00.0. These patients had no psychiatric, metabolic, systemic, or sleep disorders. Their neurological examination, imaging, and neurophysiological examinations were normal. Only sleep questionnaires were administered to the control group. Ethical issues prevented the collection of magnesium and ferritin values in the control group.

The International Restless Legs Syndrome Study Group score (IRLSSG score) is a scale comprising 10 items to be completed by patients. These items assess the frequency and severity of RLS symptoms experienced during the previous week. The scale is particularly useful in evaluating the effectiveness of treatment.

The Turkish version of the PSQI was validated, and its reliability was assessed in 1996 by Ağargün et al. [12]. The PSQI is a self-report questionnaire comprising 19 items that evaluate sleep quality and disorders over the previous month. The items cover various aspects such as subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The total score on the PSQI ranges from 0 to 21, with a score above 5 indicating poor sleep quality. The PSQI is a valuable, valid, and reliable tool for assessing sleep quality.

The ESS was employed to evaluate the patients' daytime sleepiness and the likelihood of dozing off in various situations. The ESS is a questionnaire that assesses behavioral sleepiness using a four-point self-rating scale. It measures the perceived likelihood of dozing off in eight different situations during recent times. The ESS was developed by Johns [13] and has been demonstrated to be a valid and reliable tool for assessing overall sleepiness levels. It has also been validated and found to be reliable for use in studies on sleep and sleep disorders in Turkey. Individuals scoring 11 and above on the ESS are considered to have excessive daytime sleepiness.

The study received approval from the Ethics Board of the University of Health Sciences, Prof. Dr. Cemil Taşçıoğlu City Hospital (No: 1225, Date: April 2, 2019). Informed consent was obtained from all participants included in the study.

Statistical analysis

Statistical analyses were performed using the Number Cruncher Statistical System software. Descriptive statistics (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used to evaluate the study data. The normality of quantitative data was assessed using the Shapiro-Wilk test and graphical examinations. Student's t-test was utilized for two-group comparisons of normally distributed quantitative variables, while the Mann-Whitney U test was employed for two-group comparisons of non-normally

distributed quantitative variables. The Kruskal-Wallis and Dunn-Bonferroni tests compared non-normally distributed quantitative variables among more than two groups. For comparing qualitative data, Pearson's Chi-square, Fisher's exact, and Fisher-Freeman-Halton tests were applied. Correlations between quantitative variables were evaluated using Spearman's correlation analysis. Statistical significance was defined as $P<0.05$.

Results

The patient group consisted of 36 women (72%) and 14 men (28%), while the control group comprised 34 women (68%) and 16 men (32%). The average age of the patients with RLS and the control group was 47.06 (13.35) years and 43.30 (15.43) years, respectively ($P=0.196$). The IRLSSG scores of the RLS-positive group are shown in Table 1, indicating gender, age, family history, and treatment status (Table 1). There was no statistically significant difference between the two groups in terms of age, sex, and smoking ($P=0.363$, $P=0.663$, and $P=0.262$, respectively). The mean IRLSSG score was found to be 25.16 (6.85).

Table 1: Evaluation of the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale Scores by IRLSSG score of RLS-positive group.

		IRLSSG score		
		Min-Max (Med)	Mean (SD)	*P*-value
Gender	Female (n=36)	12-37 (26.5)	26.28 (6.43)	0.045 [a]
	Male (n=14)	7-38 (21)	22.29 (7.29)	
Age	Female Male	18-78 (47.5) 30-77 (47.5)	46.22 (13.07) 49.21 (14.32)	0.483 [b]
PSQI Total	Good (n=4)	18-26 (23)	22.5 (3.7)	0.316 [a]
	Bad (n=46)	7-38 (25.5)	25.39 (7.03)	
Epworth Level	0-5 (n=27)	7-35 (26)	25.37 (6.98)	0.648 [c]
	6-10 (n=13)	13-37 (21)	23.38 (7.01)	
	11-12 (n=1)	30	30	
	13-15 (n=4)	21-28 (26)	25.25 (3.10)	
	>15 (n=5)	15-38 (26)	27.60 (8.91)	
Treatment	None (n=32)	7-38 (26.5)	26.03 (6.95)	0.234 [b]
	Yes (n=18)	12-37 (25)	23.61 (6.56)	
Family History	None (n=36)	12-38 (26)	26.11 (6.26)	0.116 [a]
	Yes (n=14)	7-37 (21)	22.71 (7.88)	
Magnesium	Low (n=12)	13-34 (27.5)	26.67 (6.15)	0.333 [a]
	Normal (n=38)	7-38 (25)	24.68 (7.06)	
Ferritin	Low (n=45)	12-38 (25)	25.6 (6.03)	0.418 [a]
	Normal (n=5)	7-35 (18)	21.2 (12.34)	

IRLSSG: International Restless Legs Syndrome Study Group, RLS: Restless legs syndrome, [a] Mann-Whitney U Test, [b] Student t-test, [c] Kruskal-Wallis Test

When evaluating the PSQI subscales of the patient group, statistically significant differences were observed in the scores obtained for subjective sleep quality, sleep latency, sleep duration, habitual sleep effectiveness, sleep disorder, and daytime dysfunction subscales compared to the control group ($P<0.001$). Additionally, the use of sleeping aids was significantly higher in the patient group ($P=0.002$) (Table 2).

The patient group obtained significantly higher scores for total ESS than the control group ($P=0.007$). A statistically significant difference was found in the ESS levels between the two groups ($P=0.012$). Moreover, the proportion of participants in the patient group scoring above ESS 15 was significantly higher than that of the control group.

No differences were found between the PSQI subscores and ESS severity in relation to ferritin levels (Table 3).

The scores obtained by the patients for the PSQI subscales "Subjective Sleep Quality", "Sleep Duration", "Sleep Effectiveness", "Sleep Disorder", "Sleeping Aid", and "Daytime Dysfunction", as well as for the total scale, showed no statistically significant differences in relation to magnesium levels ($P=0.289$, $P=0.924$, $P=0.435$, $P=0.233$, $P=0.350$, and $P=0.648$, respectively). However, patients with low magnesium levels had significantly lower scores in the PSQI "Sleep Latency" subscale ($P=0.019$). There was no statistically significant difference in the scores obtained by patients for total ESS in relation to magnesium levels ($P=0.615$) (Figure 1). When Epworth sleepiness levels were evaluated, there was a statistically significant difference in magnesium levels ($P=0.042$). However, the proportion of patients with low magnesium levels and ESS levels between 13 and 15 (indicating increased daytime moderate sleepiness) was higher than those with normal magnesium levels (Figure 2).

Figure 1: Distribution of sleep quality subscales by magnesium status

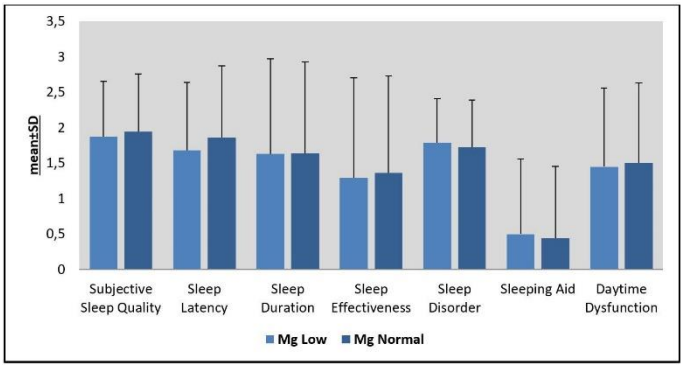
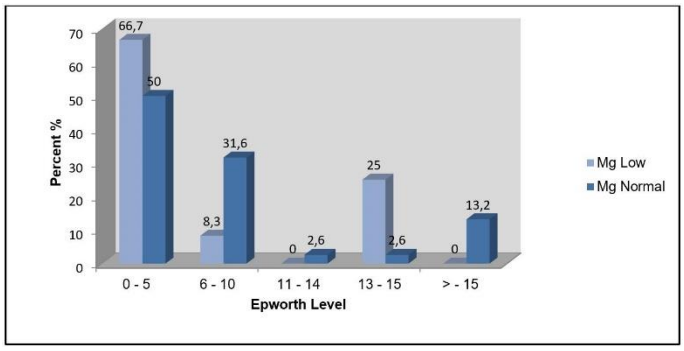


Figure 2: Distribution of Epworth level by Mg



No statistically significant differences were found between PSQI and ESS severity and the IRLSSG score ($P=0.316$ and $P=0.648$, respectively). However, the IRLSSG score of women was found to be significantly higher compared to that of men ($P=0.045$). Among the RLS cases, 64% remained untreated. Out of the RLS group, 15 out of 18 patients (36%) received pramipexole at doses ranging between 0.250 and 0.500 mg. One patient was taking gabapentin 600 mg, one patient was taking pregabalin 150 mg, and one patient was taking a combination of pramipexole and gabapentin. No significant difference in IRLSSG score was found between those who were receiving medication for RLS and those who were not ($P=0.234$). There was no difference in IRLSSG score between individuals with and without a family history of RLS ($P=0.116$). Similarly, no significant difference was found between smokers and non-smokers in terms of IRLSSG score ($P=0.312$). Additionally, there were no significant differences in RLS severities of the patients in relation to magnesium and ferritin levels ($P=0.333$, $P=0.418$, respectively). Furthermore, no significant correlation was found between age and IRLSSG score ($P=0.316$).

A statistically significant moderate-level positive correlation of 0.441 was found between the scores obtained by the patients under the PSQI "Subjective Sleep Quality" subscale and the IRLSSG score (r=0.441; $P<0.001$). Additionally, a

statistically significant weak positive correlation of 0.294 was observed between the scores obtained under the "Sleep Duration" subscale and the IRLSSG score (r=0.294; *P*=0.038). Furthermore, a statistically significant moderate positive correlation of 0.473 was identified between the scores obtained under the "Daytime Dysfunction" subscale and the IRLSSG score (r=0.473; *P*<0.001). Likewise, a statistically significant moderate positive correlation of 0.487 was found between the total scores obtained for the PSQI and the IRLSSG score (r=0.487; *P*<0.001). However, no statistically significant correlations were found between the scores obtained under the PSQI "Sleep Latency", "Sleep Effectiveness", "Sleep Disorder", and "Sleeping Aids" subscales and the IRLSSG score (*P*=0.104, *P*=0.058, *P*=0.427, and *P*=0.421) (Table 4).

No statistically significant correlation was found between the total scores obtained by the patients for the ESS and the IRLSSG score (*P*=0.809).

Table 4: Evaluation of the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale Scores by IRLSSG score

	IRLSSG score	
	r	*P*-value
Age	0.021	0.885
Subjective Sleep Quality	0.441	<0.001
Sleep Latency	0.233	0.104
Sleep Duration	0.294	0.038
Sleep Effectiveness	0.270	0.058
Sleep Disorder	0.115	0.427
Sleeping Aid	0.116	0.421
Daytime Dysfunction	0.473	<0.001
PSQI Total	0.487	<0.001
Epworth Total	-0.035	0.809

IRLSSG: International Restless Legs Syndrome Study Group, r: Spearman's Correlation Coefficient

Table 2: Evaluation of the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale Scores by group

			Groups		
		Total	**Control**	**Patient**	***P*-value**
Subjective Sleep Quality	Min-Max (Median)	0-3 (1)	0-2 (1)	0-3 (2)	<0.001 [a]
	Mean (SD)	1.39 (0.88)	0.84 (0.51)	1.94 (0.82)	
Sleep Latency	Min-Max (Median)	0-3 (1)	0-3 (1)	0-3 (2)	<0.001 [a]
	Mean (SD)	1.44 (1.04)	1.02 (0.89)	1.86 (1.01)	
Sleep Duration	Min-Max (Median)	0-3 (0)	0-2 (0)	0-3 (2)	<0.001 [a]
	Mean (SD)	1.00 (1.19)	0.36 (0.6)	1.64 (1.29)	
Sleep Effectiveness	Min-Max (Median)	0-3 (0)	0-2 (0)	0-3 (1)	<0.001 [a]
	Mean (SD)	0.71 (1.18)	0.06 (0.31)	1.36 (1.37)	
Sleep Disorder	Min-Max (Median)	0-3 (1)	0-2 (1)	0-3 (2)	<0.001 [a]
	Mean (SD)	1.42 (0.67)	1.12 (0.52)	1.72 (0.67)	
Sleeping Aid	Min-Max (Median)	0-3 (0)	0-0 (0)	0-3 (0)	0.002 [a]
	Mean (SD)	0.22 (0.75)	0 (0)	0.44 (1.01)	
Daytime Dysfunction	Min-Max (Median)	0-4 (1)	0-2 (0)	0-4 (1.5)	<0.001 [a]
	Mean (SD)	0.93 (1.06)	0.36 (0.56)	1.5 (1.13)	
PSQI Total	Min-Max (Median)	0-17 (5)	0-8 (4)	3-17 (11.5)	<0.001 [a]
	Mean (SD)	7.09 (4.60)	3.76 (1.68)	10.42 (4.16)	
Sleep Quality	Good	36 (36.0)	32 (64.0)	4 (8.0)	<0.001 [b]
	Bad	64 (64.0)	18 (36.0)	46 (92.0)	
Epworth Total	Min-Max (Median)	0-24 (4)	0-12 (4)	0-24 (5)	0.007 [a]
	Mean (SD)	5.66 (5.24)	4.06 (3.32)	7.26 (6.27)	
Epworth Level	0-5	63 (63.0)	36 (72.0)	27 (54.0)	0.012 [c]
	6-10	24 (24.0)	11 (22.0)	13 (26.0)	
	11-12	4 (4.0)	3 (6.0)	1 (2.0)	
	13-15	4 (4.0)	0 (0.0)	4 (8.0)	
	>15	5 (5.0)	0 (0.0)	5 (10.0)	

[a] Mann-Whitney U Test, [b] Pearson Chi-square Test, [c] Fisher-Freeman-Halton Test

Table 3: Evaluation of Pittsburgh Sleep Quality Scale and Epworth Sleepiness Scale Scores according to ferritin levels

		Ferritin		
		Low (n=45)	**Normal (n=5)**	***P*-value**
Subjective Sleep Quality	Min-Max (Median)	1-3 (3)	0-3 (2)	0.508 [a]
	Mean (SD)	2.2 (1.1)	1.94 (0.82)	
Sleep Latency	Min-Max (Median)	1-3 (2)	0-3 (2)	0.802 [a]
	Mean (SD)	2 (1)	1.86 (1.01)	
Sleep Duration	Min-Max (Median)	0-3 (2)	0-3 (2)	0.802 [a]
	Mean (SD)	1.8 (1.3)	1.64 (1.29)	
Sleep Effectiveness	Min-Max (Median)	0-3 (1)	0-3 (1)	0.900 [a]
	Mean (SD)	1.4 (1.52)	1.36 (1.37)	
Sleep Disorder	Min-Max (Median)	0-2 (2)	0-3 (2)	0.529 [a]
	Mean (SD)	1.4 (0.89)	1.72 (0.67)	
Sleeping Aid	Min-Max (Median)	0-0 (0)	0-3 (0)	0.488 [a]
	Mean (SD)	0 (0)	0.44 (1.01)	
Daytime Dysfunction	Min-Max (Median)	0-3 (2)	0-4 (1.5)	0.508 [a]
	Mean (SD)	1.8 (1.1)	1.5 (1.13)	
PSQI Total	Min-Max (Median)	5-15 (12)	3-17 (11,5)	0.925 [a]
	Mean (SD)	10.6 (4.39)	10.42 (4.16)	
Sleep Quality	Good	4 (8.9)	0 (0.0)	1.000 [b]
	Bad	41 (91.1)	5 (100.0)	
Epworth Total	Min-Max (Median)	2-9 (5)	0-24 (5)	0.571 [a]
	Mean (SD)	5 (3.08)	7.26 (6.27)	
Epworth Level	0-5	24 (53.3)	3 (60.0)	1.000 [c]
	6-10	11 (24.4)	2 (40.0)	
	11-12	1 (2.2)	0 (0.0)	
	13-15	4 (8.9)	0 (0.0)	
	>15	5 (11.1)	0 (0.0)	

[a] Mann-Whitney U Test, [b] Fisher's Exact Test, [c] Fisher-Freeman-Halton Test

Discussion

The total PSQI and all of its subscales were significantly higher in patients with RLS than the normal controls. However, no significant difference was found in the IRLSSG score, sleep quality, and daytime sleepiness based on ferritin values. Similarly, no difference was found in IRLSSG scores based on magnesium values. Apart from the sleep latency subscale, there was no difference in the total PSQI and other components. When comparing sleep latency based on magnesium values, it was observed that those with lower levels had shorter sleep latency, suggesting that magnesium deficiency does not have an aggravating effect. Although no difference was found between magnesium levels and ESS scores, there was a higher distribution of increased daytime moderate sleepiness scores among those with magnesium deficiency. However, this was unrelated to nighttime sleep quality.

The prevalence of RLS in adults in Europe and North America ranges from 2% to 3%. A prevalence study conducted by Sevim et al. [14] in Turkey, which involved 3234 individuals, reported an RLS ratio of 3.19%. RLS was found to be more common in women, smokers, and individuals living at high

altitudes. Our study also had a higher percentage of females, and the IRLSSG score was significantly higher among women.

Studies have shown that RLS can manifest as more severe in patients with familial characteristics, with higher IRLSSG scores observed in those who have a family history of the condition [15,16]. However, in our study, no significant difference was found in terms of the IRLSSG score between individuals with and without a family history of RLS.

While it has been reported in the literature that smoking and coffee can exacerbate RLS symptoms [17], there are also reports suggesting that smoking may alleviate the symptoms [18]. However, our study found no significant difference between smokers and non-smokers in relation to RLS symptoms.

The effectiveness of oral or intravenous (IV) iron treatment has been demonstrated in patients with serum ferritin levels below 50 ng/mL. Recent studies recommend maintaining ferritin levels above 75 ng/mL [19]. The treatment of RLS often involves magnesium (Mg) supplementation and ensuring adequate iron stores.

Ferritin deficiency reflects impaired iron metabolism, and studies have indicated that central nervous system iron deficiency contributes to the development of RLS in affected patients [20]. Iron deficiency is believed to potentially induce dopaminergic dysfunction, as iron serves as a cofactor in the dopamine generation process via tyrosine hydroxylase, potentially exacerbating RLS symptoms [21]. However, in our patient population, no significant correlation was found between ferritin levels and the IRLSSG score. The most commonly used medication among our patients was a dopamine agonist [7].

Magnesium is involved in more than 300 biochemical reactions in the body [22]. It acts as a natural antagonist of NMDA receptors and an agonist of GABA receptors, which have a relaxing effect on the body and contribute to improved sleep [23]. Magnesium supplementation is often recommended as a potential remedy for relieving symptoms of RLS or periodic limb movement disorder (PLMD), and it is commonly prescribed for leg cramps as well. A daily magnesium supplement of 500 mg has been associated with significant improvements in various aspects of sleep, including sleeplessness severity index, sleep duration, sleep effectiveness, sleep onset latency, as well as changes in serum cortisol concentration, renin levels, and melatonin [24].

All articles reporting the effects of magnesium supplementation on changes in RLS and/or PLMD were examined for a systematic review. No significant curative effect of magnesium was found. Following the quality assessment and synthesis of the evidence, it was reported that no conclusion was reached regarding the effectiveness of magnesium on RLS/PLMD. It is unclear whether magnesium helps to relieve RLS or PLMD or which patients benefit from it [9]. In one study, the magnesium-supplemented group showed considerable mitigation of periodic limb movements during sleep compared to the placebo group. Additionally, there was a significant increase in general sleep efficiency, rising from 75% to 85% [25].

According to a meta-analysis, magnesium was found to be ineffective in the general population when evaluated in the context of leg cramps. However, it showed a slight effectiveness in pregnant women [11].

Rondanelli et al. [26] conducted a study that found supplementation with magnesium resulted in an improvement in the total score of the PSQI. Furthermore, several studies demonstrate that magnesium deficiency affects the circadian cycle, depletes melatonin, and contributes to sleep disorders [27]. Hornyak et al. [25] demonstrated that magnesium treatment could be a beneficial alternative for patients experiencing insomnia related to RLS or periodic limb movement syndrome. Considering the existing literature on the administration and effectiveness of magnesium, our data suggest that magnesium deficiency does not exacerbate.

A study reported that magnesium deficiency could be a potential cause of increased RLS symptoms in patients undergoing dialysis [28]. Additionally, the potential therapeutic effects of magnesium and coenzyme Q replacement in patients with type 2 diabetes and RLS have been discussed [10].

While conclusive evidence is lacking, it is advisable to exercise caution regarding the extensive use of magnesium and remain vigilant for potential complications. One such complication is the increased risk of constipation, which can lead to toxic symptoms and harm prognosis, potentially even resulting in mortality. Therefore, patients should be cautioned about the risk of constipation [29].

A high percentage of patients with RLS, specifically 94%, report difficulties in both falling asleep and maintaining sleep. Additionally, 84.7% of patients experience difficulty falling asleep, while 86% face challenges exclusively in maintaining sleep [30]. Among our patients, the sleep disorder frequency encompasses various parameters, including sleep quality, difficulties in falling asleep and maintaining sleep, and a reduction in the total sleep duration.

In a study, a significant percentage of patients with mild or severe RLS reported spending over 30 min to fall asleep, as well as waking up three or more times during the night, which is a commonly mentioned symptom of sleeplessness [3]. RLS often leads to interrupted sleep and is frequently reported as a cause of insomnia. The loss and disruption of sleep adversely affect overall health and daily functioning. Among healthcare professionals, a notable proportion experiences some degree of impaired sleep quality, with RLS and depressive symptoms also being frequent in this population [31]. The primary recommendation for managing sleep disorders is practicing good sleep hygiene [32].

None of the patients we assessed were receiving sleeping medication despite experiencing sleep problems; however, this percentage was higher compared to that of the normal control group. Similar findings were observed in a study involving 133 patients with RLS, where 85% of the patients reported difficulties in falling asleep or maintaining sleep [30]. In patients with RLS, sleep disorders are associated with a lack of energy and concentration on the following day [3]. Our patients exhibited higher levels of next-day sleepiness compared to the normal controls.

Limitation

Our study had certain limitations. First, our patient cohort consisted mainly of resistant cases seeking treatment at a neurology polyclinic in a tertiary-care training and research hospital, which may limit the generalizability of our findings.

Second, being a single-center study, it may not fully represent the broader population. Additionally, our study group was relatively small in terms of sample size. Furthermore, the number of patients with low magnesium levels was also limited within this group.

Conclusion

Our study did not find any correlation between magnesium and ferritin levels, disease severity, and sleep disorders. However, there were correlations observed between disease severity and total PSQI score, as well as subjective sleep quality, sleep duration, and the severity of daytime dysfunction. Importantly, we did not observe any aggravating effects of magnesium deficiency. Therefore, it is crucial to exercise caution when prescribing supplementary treatments, such as magnesium, without conclusive evidence.

References

1. Ekbom KA. Restless legs syndrome. Neurology. 1960 Sep;10:868-73. doi: 10.1212/wnl.10.9.868. PMID: 13726241.
2. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, et al. 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. Epub 2014 17 May. PMID: 25023924.
3. 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. PMID: 14592342.
4. Winkelman JW, Chertow GM, Lazarus JM. Restless legs syndrome in end-stage renal disease. Am J Kidney Dis. 1996 Sep;28(3):372-8. doi: 10.1016/s0272-6386(96)90494-1. PMID: 8804235.
5. Salih AM, Gray RE, Mills KR, Webley M. A clinical, serological and neurophysiological study of restless legs syndrome in rheumatoid arthritis. Br J Rheumatol. 1994 Jan;33(1):60-3. doi: 10.1093/rheumatology/33.1.60. PMID: 8162461.
6. O'Hare JA, Abuaisha F, Geoghegan M. Prevalence and forms of neuropathic morbidity in 800 diabetics. Ir J Med Sci. 1994 Mar;163(3):132-5. doi: 10.1007/BF02965972. PMID: 8200777.
7. Hening W, Walters AS, Allen RP, Montplaisir J, Myers A, Ferini-Strambi L. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. Sleep Med. 2004 May;5(3):237-46. doi: 10.1016/j.sleep.2004.03.006. PMID: 15165529.
8. Karadeniz Kaynak D. Sleep Disorders Behind the Complaint of Insomnia; Restless Legs Syndrome and Periodic Limb Movements Disorders of Sleep. Noro Psikiyatr Ars 2007;44:95-100.
9. Marshall NS, Serinel Y, Killick R, Child JM, Raisin I, Berry CM, et al. Magnesium supplementation for the treatment of restless legs syndrome and periodic limb movement disorder: A systematic review. Sleep Med Rev. 2019 Dec;48:101218. doi: 10.1016/j.smrv.2019.101218. Epub 2019 16 October. PMID: 31678660.
10. Metta V, Sampath N, Vm R, Iska A. Primary restless legs syndrome in patients with type 2 diabetes mellitus: Efficacy of magnesium & coenzyme q10 therapy. J Neurol Sci. 2015;357(S1):e271. doi: 10.1016/j.jns.2015.08.952.
11. Sebo P, Cerutti B, Haller DM. Effect of magnesium therapy on nocturnal leg cramps: a systematic review of randomized controlled trials with meta-analysis using simulations. Fam Pract. 2014 Feb;31(1):7-19. doi: 10.1093/fampra/cmt065. Epub 2013 26 November. PMID: 24280947.
12. Ağargün MY, Kara H, Anlar O. Pittsburgh Uyku Kalitesi İndeksi'nin Geçerliği ve Güvenirliği. Turk Psikiyatri Derg. 1996;7(2):107-11.
13. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991 Dec;14(6):540-5. doi: 10.1093/sleep/14.6.540. PMID: 1798888.
14. Sevim S, Dogu O, Camdeviren H, Bugdayci R, Sasmaz T, Kaleagasi H, et al. Unexpectedly low prevalence and unusual characteristics of RLS in Mersin, Turkey. Neurology. 2003 Dec 9;61(11):1562-9. doi: 10.1212/01.wnl.0000096173.91554.b7. PMID: 14663043.
15. Allen RP, La Buda MC, Becker P, Earley CJ. Family history study of the restless legs syndrome. Sleep Med. 2002 Nov;3 Suppl: S3-7. doi: 10.1016/s1389-9457(02)00140-5. PMID: 14592159.
16. Desai AV, Cherkas LF, Spector TD, Williams AJ. Genetic influences in self-reported symptoms of obstructive sleep apnea and restless legs: a twin study. Twin Res. 2004 Dec;7(6):589-95. doi: 10.1375/1369052042663841. PMID: 15607009.
17. Bayard M, Avonda T, Wadzinski J. Restless legs syndrome. Am Fam Physician. 2008 Jul 15;78(2):235-40. PMID: 18697508.
18. Oksenberg A. Alleviation of severe restless legs syndrome (RLS) symptoms by cigarette smoking. J Clin Sleep Med. 2010 15 October;6(5):489-90. PMID: 20957852; PMCID: PMC2952755.
19. Trenkwalder C, Winkelmann J, Oertel W, Virgin G, Roubert B, Mezzacasa A; FCM-RLS Study Investigators. Ferric carboxymaltose in patients with restless legs syndrome and nonanemic iron deficiency: A randomized trial. Mov Disord. 2017 Oct;32(10):1478-82. doi: 10.1002/mds.27040. Epub 2017 23 June. PMID: 28643901; PMCID: PMC5655783.
20. Trotti LM. Restless Legs Syndrome and Sleep-Related Movement Disorders. Continuum (Minneap Minn). 2017 Aug;23(4, Sleep Neurology):1005-16. doi: 10.1212/CON.0000000000000488. PMID: 28777173.
21. Earley CJ, Connor J, Garcia-Borreguero D, Jenner P, Winkelman J, Zee PC, et al. Altered brain iron homeostasis and dopaminergic function in Restless Legs Syndrome (Willis-Ekbom Disease). Sleep Med. 2014 Nov;15(11):1288-301. doi: 10.1016/j.sleep.2014.05.009. Epub 2014 16 June. PMID: 25201131.
22. Altura BM. Basic biochemistry and physiology of magnesium: a brief review. Magnes Trace Elem. 1991-1992;10(2-4):167-71. PMID: 1844549.
23. Kapur N, Friedman R. Oral ketamine: a promising treatment for restless legs syndrome. Anesth Analg. 2002 Jun;94(6):1558-9. doi: 10.1097/00000539-200206000-00034. PMID: 12032026.
24. Abbasi B, Kimiagar M, Sadeghniiat K, Shirazi MM, Hedayati M, Rashidkhani B. The effect of magnesium supplementation on primary insomnia in elderly: A double-blind placebo-controlled clinical trial. J Res Med Sci. 2012 Dec;17(12):1161-9. PMID: 23853635; PMCID: PMC3703169.
25. Hornyak M, Voderholzer U, Hohagen F, Berger M, Riemann D. Magnesium therapy for periodic leg movements-related insomnia and restless legs syndrome: an open pilot study. Sleep. 1998 Aug 1;21(5):501-5. doi: 10.1093/sleep/21.5.501. PMID: 9703590.
26. Rondanelli M, Opizzi A, Monteferrario F, Antoniello N, Manni R, Klersy C. The effect of melatonin, magnesium, and zinc on primary insomnia in long-term care facility residents in Italy: a double-blind, placebo-controlled clinical trial. J Am Geriatr Soc. 2011 Jan;59(1):82-90. doi: 10.1111/j.1532-5415.2010.03232.x. PMID: 21226679.
27. Durlach J, Pagès N, Bac P, Bara M, Guiet-Bara A. Biorhythms and possible central regulation of magnesium status, phototherapy, darkness therapy and chronopathological forms of magnesium depletion. Magnes Res. 2002 Mar;15(1-2):49-66. PMID: 12030424.
28. Sinniah D. Magnesium deficiency: a possible cause of restless leg syndrome in haemodialysis patients. Intern Med J. 2015 Apr;45(4):467-8. doi: 10.1111/imj.12715. PMID: 25827521.
29. Thanikonda V, Levine A. Hypermagnesemia in a Patient Taking Magnesium Oxide for Restless Leg Syndrome: Presenting as Shock. Am J Respir Crit Care Med. 2020;201:A5161 doi: 10.1164/ajrccm-conference.2020.201.1 MeetingAbstracts.A5161.
30. Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lespérance P. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. Mov Disord. 1997 Jan;12(1):61-5. doi: 10.1002/mds.870120111. PMID: 8990055.
31. Demir Ülkü F. Sleep quality & prevalence of restless legs syndrome among healthcare professionals. J Surg Med. 2020;4(2):144-7.
32. Burman D. Sleep Disorders: Restless Legs Syndrome. FP Essent. 2017 Sep;460:29-32. PMID: 28845959.