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The effect of vitamin D on restless legs syndrome: prospective self-controlled case study

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Abstract

Purpose To evaluate the effect of vitamin D on severity of restless legs syndrome in patients with idiopathic restless legs syndrome (RLS).

Methods Patients with idiopathic RLS completed questionnaires including the International Restless Legs Severity Scale (IRLSS) and were evaluated for vitamin D deficiency. Patients with deficiency of vitamin D were treated with 50,000 units per week for 2 months. At the end of the 2 months, vitamin D levels were re-measured and disease severity was re-evaluated in patients who reached adequate vitamin D level. Subgroups of IRLSS questionnaire were also analyzed.

Results Of 35 patients enrolled, 21 (60%) had vitamin D deficiency and received vitamin D therapy. In 2 patients, vitamin D levels did not rise to sufficient levels with supplementation and these 2 patients were excluded from analysis. The remaining 19 patients showed vitamin D levels increased from 13.2 ± 4.0 to 42.8 ± 9.6 ng/mL while IRLSS improved from 24.9 ± 5.1 to 21.1 ± 2.9 points ($p < 0.001$). Selected subscores of the IRLSS were also improved including symptom severity ($p < 0.001$), impact on sleep ($p < 0.001$), symptom measures ($p = 0.002$), and disease impact measures ($p < 0.001$). There were trends toward improvement in subscores of frequency ($p = 0.11$) and mood ($p = 0.051$).

Conclusions The findings suggest that vitamin D levels should be evaluated in patients with RLS and if vitamin D deficiency is revealed, consideration should be given to replacement therapy.u

Keywords Restless legs syndrome · Vitamin D · Sleep disorder

Introduction

Restless legs syndrome (RLS) is a neurological disorder characterized by an urge to move the affected body part, especially the legs, to relieve the uncomfortable sensations [1]. RLS may have an idiopathic origin or it may be related to other diseases including iron deficiency, diabetes mellitus, renal disease, polyneuropathy, spinal cord disease, or rheumotological disease [2]. There is no specific test to diagnose RLS. The diagnosis is based on the presence of five criteria determined by International Restless Legs Syndrome Study Group (IRLSSG) including the following: (1) the urge to move the legs, often accompanied by leg discomfort, (2) rest worsens the urge to move, (3) getting up and moving improves the urge, (4) evening or night worsens symptoms, (5) disorders that mimic RLS have been excluded [3].

The pathogenesis of the disease is not known exactly but dopamine, iron, and genetic profile are thought to play a vital role in the pathogenesis [4]. Because of unknown pathogenesis, there is no cure treatment in RLS, but dopamine agonist drugs such as ropinirole, pramipexole, and rotigotine are thought to be the first-line treatment options [5]. Before initiating dopamine agonist drugs, it should be determined whether RLS is primary or secondary. The most common cause of secondary RLS is iron deficiency. RLS is present in 25 to 35% of patients with iron deficiency anemia and it may resolve after effective iron replacement therapy [6]. Antidepressants can cause or worsen the symptoms of the disease in 9% of the patients [7]. RLS can also be expressed in several neurological disorders including stroke, multiple sclerosis, and migraine [8, 9].

Vitamin D is a fat-soluble, secostreoid prohormone, which is produced in skin by sunlight exposure. The pro-vitamin is

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transformed into a hormone known as calcitriol and plays a pivotal role in the calcium-phosphorus metabolism [10]. Recently, there has been growing interest in the effects of vitamin D on the inflammatory and immunomodulatory processes as well as the iron and dopamine metabolism [11–17]. After the discovery of vitamin D receptors in the thalamus, hypothalamus, sustantia nigra, and cortex, the possible role of vitamin D in different neurological conditions was recently investigated [18, 19]. The relationship between vitamin D and Parkinson disease is one of the most studied relationship among these conditions. This relationship is thought to be genomic and also non-genomic. Vitamin D is suggested to have an active controller role on the genetic regulation of the synthesis of acetylcholine, dopamine, serotonin, and gamma-aminobutryric acid [20, 21]. Moreover, vitamin D has a significant role in the active regulation of calcium in neurons and in the reduction of oxidative stress by interfering with the NO production through a non-genomic mechanism [16, 22]. As an example of the non-genomic role, vitamin D was reported to improve rigidity and akinesia and reduce levodopa dosage in a patient with PD. [23] Vitamin D is also effective on sleep cycle and mood, which are included in the RLS severity scoring [24–27]. So far, however, very little attention was paid to the association between RLS and vitamin D. Cakır et al. and Oran et al. showed that the incidence of RLS was higher in patients with vitamin D deficiency [28, 29]. However, Wali et al. found conflicting results on the effect of vitamin D on RLS symptoms [30, 31]. The extent to which vitamin D plays a role in RLS still remains unclear.

Our hypothesis is that replacement of vitamin D deficiency will reduce the severity of RLS. This effect may be observed through the symptoms we questioned on the RLS Severity Scale. In our opinion, clarifying the relationship between RLS and vitamin D is important in two ways. First, in the case of an effect, a treatment option will be determined to reduce the severity of the disease. Secondly, since vitamin D deficiency is a common condition and shows seasonal changes, this effect needs to be taken into account in further studies. This paper primarily aims to provide clinical evidence to show that vitamin D replacement therapy is effective in people with RLS and vitamin D deficiency.

Study design and methods

A self-controlled study approach was adopted to evaluate the effectiveness of vitamin D on the RLS. Patients who were diagnosed with idiopathic RLS according to IRLSSG criteria and who were able to report the required information concerning the severity of disease were included in this study. This study was performed in Bakirkoy Education and Research Hospital for Psychiatric and Neurological Diseases between October 2018 and February 2019.

Prior to the inclusion of the participants, the ethical approval was obtained from the local Ethics Board and every participant signed an informed consent. Patients who accepted to participate in the study underwent extensive neurological examinations by a neurologist. Ferritin, alkaline phosphate (ALP), magnesium, hemoglobin (HGB), urea, creatinine, calcium, vitamin B_{12}, hemoglobin A1c, fT3, fT4, and thyroid stimulating hormone were evaluated to rule out the secondary RLS diagnosis. The laboratory tests were performed in the same laboratory. The patients with iron deficiency, polyneuropathy, B_{12} deficiency, hypothyroidism, renal diseases, pregnancy, folate deficiency, and Parkinson diseases were not included in the study. To meet the inclusion criteria, patients had to be using the same dose of pramipexole for at least 6 months and also had not be using drugs including antidepressants, neuroleptic, neuropathic pain treatments, and lithium.

Vitamin D levels of the patients who met all inclusion criteria were evaluated. Venous blood samples were collected in plain glass tubes. Serum 25(OH) D levels were evaluated using an electrochemiluminescence method. A normal level of vitamin D was defined as a 25(OH)D level greater than 30 ng/mL (75 nmol/L). Vitamin D insufficiency was defined as a 25(OH)D level of 20 to 30 ng/mL (50 to 75 nmol/L) and vitamin D deficiency was defined as a 25(OH)D level less than 20 ng/mL (50 nmol/L) similar to the previous studies [32]. Participants were divided into two groups according to the vitamin D level: the control group with normal vitamin D levels and the study group with vitamin D deficiency. Patients with vitamin D insufficiency were not included in the analyses, since having 3 groups in small sample size would decrease the statistical power.

All patients were asked to fill the International Restless Legs Severity Scale developed by International Restless Legs Syndrome Study Group (IRLSSG). The scale consisted of 10 items. Each item was graded on a scale of 0 to 4. The disease severity was classified by following the scale: 0–10 points mild, 11–20 moderate, 21–30 severe, and 31–40 very severe. Questions 1, 2, and 6 were related to symptom severity, questions 7 and 8 were related to frequency, questions 4 and 5 were related to impact on sleep, and questions 9 and 10 were related to impact on mood. The test also evaluated the symptom measures (questions 1, 2, 4, 6, 7, and 8) and disease impact measures (questions 5, 9, and 10) [33, 34].

Idiopathic RLS patients with vitamin D deficiency who agreed to participate in the study used 50,000 units of vitamin D per week for 2 months [35]. At the end of the second month, vitamin D level was re-evaluated. Patients with 25(OH)D concentration greater than 30 ng/mL (75 nmol/L) and the control group were asked to fill the International Restless Legs Severity Scale again. The disease severity scores obtained at the beginning and at the end of the study were compared.

All analyses were carried out using SPSS (version 20). Descriptive statistics (mean, standard deviation, and frequency) were used for the demographic and clinical characteristics. Statistical analysis was performed using the chi-square test or Fisher's exact test for categorical parameters and the Student *t* test for continuous variables. Paired *t* test was used in order to compare disease severity scores at the beginning and at the end of the study. A p value < 0.05 was considered to be statistically significant.

Results

A total of 35 patients met all inclusion criteria and screened for vitamin D deficiency. Twenty-one patients had vitamin D deficiency (study group), 3 patients had vitamin D insufficiency, and 11 patients had normal vitamin D level (control group). Patients with insufficiency were excluded from the study for the reasons stated in the methods section.

Twelve participants in the study group and 6 participants in the control group were male. The mean age of the study group was 44.78 ± 8.56 and the mean age of the control group was 45.6 ± 5.86. All the participants were using pramipexole. The vitamin D deficiency group had higher dosages of pramipexole compared with the control group, but this difference did not reach statistical significance (Table 1). Due to hypertension, 2 patients in the study group were using amlodipine, while 1 patient in the control group was using perindopril arginine. Participants did not have any other comorbidities except hypertension. The initial mean vitamin D level was 13.15 ± 3.96 ng/mL and the initial Restless Legs Severity Scale score was 24.89 ± 5.09 in the study group, while the initial vitamin D level was 34.21 ± 8.76 ng/mL and the initial Restless Leg Severity Scale score was 21.29 ± 3.46 in the control group. Interestingly, for the participants with vitamin D deficiency, the initial Restless Legs Severity Scale scores were higher ($p = 0.04$). The demographics and characteristics of the study population are displayed in Table 1.

Twenty-one patients in the study group used vitamin D replacement therapy for 2 months. At the end of the 2-month period, 19 patients reached the targeted vitamin D level (greater than 30 ng/mL), and 2 patients who did not reach the adequate vitamin D level were excluded from the analyses. The study flow chart is given below (Fig. 1). At the end of the study, the mean vitamin D level of the study population was 42.78 ± 9.6 ng/mL and the total IRSLG severity score was 21.05 ± 2.89. The Restless Legs Severity Scale score significantly decreased (Table 2) ($p \leq 0.001$). At the end of the treatment, IRSLG severity score of the study group was similar to the initial severity score of the control group ($p = 0.84$).

To assess whether and how vitamin D affects RLS, we performed subgroup analyses including symptom severity, frequency, impact on sleep, impact on mood, symptom measures, and disease impact measures. Except symptom frequency and impact on mood, all the other parameters (symptom severity, impact on sleep, symptom measures and disease impact measures) were improved. The results obtained from the paired *t* test analyses are presented in Table 3.

Discussion

RLS is a neurological disease that can significantly reduce quality of life. It disrupts sleep and may result in psychiatric symptoms such as depression. There is no cure treatment. We have designed our study with the idea that vitamin D deficiency may also be related to RLS. We evaluated the effect of vitamin D replacement on the disease severity in patients with idiopathic RLS and vitamin D deficiency. We included only patients with idiopathic RLS in order to evaluate this effect more clearly. Vitamin D levels were evaluated at the

Table 1 The demographic and clinical aspects of the study population

	RLS with vitamin D Deficiency 21	RLS with normal vitamin D level 11	*p*
Age	44.78 ± 8.56	45.6 ± 5.86	9.78
Male	12	6	0.34
Vitamin D level	13.15 ± 3.96 ng/mL	34.21 ± 8.76 ng/mL	0.001
Treatment			
Pramipexole 0.25 mg	2	3	0.21
Pramipexole 0.50 mg	5	4	
Pramipexole 0.75 mg	14	4	
Restless Legs Severity Score (onset)	24.89 ± 5.09	21.29 ± 3.46	0.047
Co-medication			
Amlodipine	2	-	
Perindopril arginine	-	1	

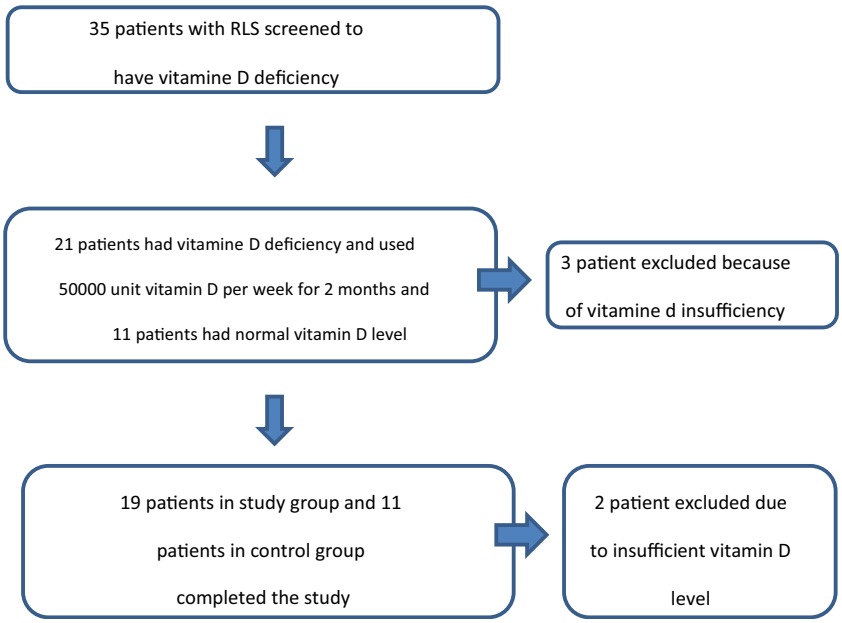

Fig. 1 The study flow chart

beginning of the study and interestingly the participants with vitamin D deficiency had higher initial IRSLG scores. Our finding was in agreement with the findings of Balaban et al. who suggested that the severity of the vitamin D deficiency is related to the severity of the disease [36].

Disease severity was decreased significantly after administration of vitamin D. Our results differ from Wali's 2019 estimate of vitamin D but are broadly consistent with his earlier study [30, 31]. Wali et al. published two studies (one class III and one class IV) investigating the effect of vitamin D on RLS symptoms, but found conflicting results. In the first study (2014), the effect of vitamin D was evaluated on the disease severity in 12 patients with RLS in a prospective self-controlled study. As the vitamin D level was increased from 21.7 to 61.8 ng/mL, the RLS severity was decreased from 26 to 10 [30]. This effect was statistically significant. However, the use of dopamine agonists or any other medication used for RLS was not mentioned. In 2019, Wali evaluated the efficacy of vitamin D in a randomized controlled study in 22 patients (with or without vitamin D deficiency), considering vitamin D as primary treatment acting on dopamine. It was shown the vitamin D did not improve any symptoms. However, the mean value of the vitamin D level was above normal limits in both placebo and control groups. Only 11 patients in both groups had vitamin D deficiency, and the vitamin D–deficient patients had a risk of developing RLS 4.24 fold more than the normal group. Moreover, it was concluded to further study on vitamin D–deficient patients. In our study, both study and control group patients were under pramipexole treatment at a sufficient dosage for at least 6 months, and vitamin D replacement therapy was only given to the vitamin D–deficient patients.

Very little is known about the relationship between vitamin D and RLS in the literature. However, the most prominent finding from the analyses is that vitamin D affects RLS. Cakır et al., Oran et al., and Wali et al. showed that the incidence of RLS was higher in patients with vitamin D deficiency [37]. This effect can be via dopamine, as vitamin D can affect the dopamine pathway through genomic or non-genomic mechanisms. The effect of vitamin D on RLS may be via this pathway. On the other hand, vitamin D is known to affect many systems including pain, sleep-awake cycle, and immune system. It has been reported that adequate vitamin D is necessary for reducing the number of nocturnal awakenings, altering sleep quality and also avoiding depression. Vitamin D may affect RLS; it may correct the symptoms questioned

Table 2 The IRLSSG severity scores of the patients with vitamin D deficiency

	Before the vitamin D replacement therapy	After the vitamin D replacement therapy	*p*
Vitamin D level	13.15 ± 3.96 ng/mL	42.78 ± 9.6 ng/mL	
IRLSSG severity scores	24.89 ± 5.09	21.05 ± 2.89	≤ 0.001

Table 3 IRLSS total score and subgroups of the test

	Onset	Last visit	*p*
Symptom severity	7.21 ± 1.65	6.42 ± 1.26	≤ 0.001
Frequency	5.31 ± 1.24	4.84 ± 0.83	0.11
Impact on sleep	5.05 ± 1.58	4.26 ± 0.99	≤ 0.001
Impact on mood	4.94 ± 1.07	4.36 ± 1.06	0.051
Symptom measures	7.47 ± 1.67	6.68 ± 1.37	0.002
Disease impact measures	15.05 ± 3.19	13.26 ± 1.96	≤ 0.001

when measuring the severity of RLS. Subgroup analyses were performed to find out which symptom pivotally resolved after vitamin D replacement. There was a marked improvement in the symptom severity, impact on sleep, and disease impact measures, but this improvement was not seen on mood and frequency. Therefore, it would be insufficient to consider the effect of vitamin D on RLS only through dopamine. In our study, sleep was significantly improved after vitamin D supplements.

In our study, vitamin D deficiency was detected in 60% of patients; this high prevalence seems to be related to the cultural characteristics of the geographical region. In a previous study conducted in the same city, vitamin D levels of patients admitted to the outpatient clinic were found as follows; 43.1% < 10 ng/mL, 31.9% between 10 and 20 ng/mL, 16.1% between 20 and 30 ng/mL, and only 8.9% > 30 ng/mL [38]. In a study conducted in a healthy population in Iran, in a similar geography, vitamin D deficiency was found in 26% and vitamin D insufficiency was found in 45.2% of the population [39]. The higher prevalence observed in these countries was associated with lifestyle patterns developed related to the social and religious beliefs like clothing. Alogal et al. investigated the effect of dressing on vitamin D and found vitamin D deficiency in 60% of those dressed in Islamic style. (whole body closed or only hand and face open) [40]. As the percentages of the male patients in both the study and control groups are more than half of the patients, the effect of the dressing seems to be less in our study.

Finally, a number of important limitations to this pilot study need to be considered. First, in treatment studies, there is a potential bias due to the placebo effect. However, it is emphasized that a placebo effect is higher in long-term studies. In our study, the duration was considerably shorter.

Taken together, although the current study is based on a small sample of participants, these findings suggest a role of vitamin D in RLS. The findings of this investigation broadly complement those of earlier studies and contribute additional evidence that this effect can be via symptoms such as sleep quality. Further investigation is required to develop a deeper understanding of the relationship between RLS and vitamin D and also to shed light on the mechanism underlying this effect.

Conclusion

Returning to the question posed at the beginning of this study, it is now possible to state that vitamin D effects RLS severity. In conclusion, we recommend that vitamin D levels should be evaluated in patients with RLS and the replacement therapy should be performed if vitamin D is deficient. These findings also will help other researchers design their work by taking into account the relationship of vitamin and RLS.

Compliance with ethical standards

The authors declare that they have no conflict of interest.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

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Comments

An increasing interest in many mechanisms of vitamin D potentially improves symptoms of a relatively rare sleep disorder but most importantly sleep itself. The awareness of treatment options without major side effects, besides conventional dopaminergic drugs, is definitely encouraging.

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