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Efficacy of vitamin D replacement therapy in restless legs syndrome: a randomized control trial

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Abstract

Purpose Restless legs syndrome is a movement sleep disorder that may be linked to dopaminergic dysfunction and in which vitamin D may play a role. This 12-week randomized, placebo-controlled trial elucidated the efficacy of vitamin D supplements in decreasing restless legs syndrome symptom severity.

Methods Thirty-five subjects with restless legs syndrome, diagnosed using the International Restless Legs Syndrome Study Group criteria, were enrolled. The subjects were randomized to orally receive either vitamin D (50,000 IU caplets) or a placebo. All medications were administered weekly using a direct observation technique. Clinical assessments, including those for restless legs syndrome severity, were conducted at baseline and the end of the study using the International Restless Legs Syndrome Study Group rating scale. The serum vitamin D levels and bone profiles were measured at baseline and every 4 weeks. The primary endpoint was the change in the restless legs syndrome severity score from baseline to week 12. There were 17 and 18 patients in the vitamin D and placebo groups, respectively.

Results The groups did not differ with respect to age, sex, restless legs syndrome severity, or vitamin D levels. Participants in the vitamin D group showed no significant change in the mean restless legs syndrome severity score compared with the placebo group.

Conclusions The results suggest that vitamin D supplementation does not improve restless legs syndrome symptoms.

Clinical trial registration number ClinicalTrials.gov: NCT02256215 (available from: https://clinicaltrials.gov/ct2/show/NCT02256215).

Keywords RLS · Primary · Restless legs syndrome · Scale · Symptoms · Vitamin D

Introduction

Restless legs syndrome (RLS) is a movement disorder that affects normal sleep, causing impairments in productivity and quality of life [1]. RLS affects 6–12% of the western population and 8.4% in Saudi Arabia [2–5].

The pathogenesis of RLS is not fully understood; however, genetic predisposition, iron deficiency, and dysfunction of the dopaminergic system seem to play important roles in RLS [6]. Turjanski et al. [7] studied striatal dopaminergic dysfunction using positron emission tomography in patients with RLS. They reported reduced ^{18}F-dopa uptake by the caudate and putamen, which supported the hypothesis of central dopaminergic dysfunction in RLS. Furthermore, this hypothesis has been reinforced by several clinical trials in which various dopaminergic agents led to significant improvements in RLS symptoms [8–10].

Vitamin D might affect the nigrostriatal dopaminergic pathway. Several reports have revealed the potential role of vitamin D in dopamine function. In rats, it was reported that vitamin D deficiency was associated with altered dopamine concentrations in the cortex [11]. Experimentally, vitamin D raises dopamine levels and protects dopaminergic neurons against toxins [12]. Similarly, vitamin D was shown to increase the level of glutathione, which in turn seems to be responsible, at least in part, for the survival of dopaminergic neurons [13, 14]. In a rodent model, prenatal vitamin D deficiency was reported to disturb the development of the dopaminergic system, leading to alteration of the neurochemistry in the adult brain [15]. Cui et al. [15] reported that vitamin D receptors are found within the

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nuclei of tyrosine hydroxylase-positive neurons in the substantia nigra of both human and rat. Furthermore, Orme et al. [16] observed a dose-dependent increase in the number of rat dopaminergic neurons after the addition of 1,25-dihydroxyvitamin D3 to the culture media and concluded that vitamin D may increase the number of dopaminergic neurons.

Therefore, it is hypothesized that vitamin D deficiency could lead to dysfunction of the dopaminergic system, ultimately resulting in RLS. However, the role of vitamin D in the pathogenesis of RLS has not been adequately explored, as only a few observational studies have been reported. Balaban et al. reported considerably low vitamin D levels in females with RLS, indicating a link between low vitamin D levels and dopaminergic dysfunction in RLS [17]. Accordingly, vitamin D replacement may represent a safe treatment option for primary RLS. However, the paucity of evidence poses a limitation in providing patients with such therapy. Therefore, the aim of this trial was to study the effectiveness of vitamin D replacement in ameliorating RLS symptoms.

Materials and methods

This was a randomized double-blind placebo-controlled trial lasting 12 weeks. Subjects were recruited from a pool of RLS patients from the Sleep Medicine and Research Center, Jeddah, Saudi Arabia. In the pre-randomization phase, patients with primary RLS were identified based on the RLS diagnostic criteria of the International Restless Legs Syndrome Study Group (IRLSSG) [18]. Patients with primary RLS who met the inclusion criteria and agreed to participate were then randomized to take either vitamin D (50,000 IU) or placebo orally [19]. The serum vitamin D levels and bone profiles were determined at baseline and every 4 weeks during the 12-week period [19]. A clinical evaluation, which included the severity of RLS symptoms based on the IRLSSG rating scale, was performed at baseline and at the end of the study period [19, 20]. All medications were administered weekly using a direct observation technique. This technique involves assigning a trained physician to provide the medication directly to the participant and observing as the participant swallowed to ensure adequate compliance. During the study, the patients were monitored for treatment response and undesired effects through weekly clinical assessments, though they had open access to the research team by telephone (https://clinicaltrials.gov/ct2/show/NCT02256215).

Serum 25-hydroxyvitamin D

Vitamin D status is measured via assay of the major circulating form of the vitamin, serum 25-hydroxyvitamin D {25(OH) D}. The Institute of Medicine (IOM) has suggested that approximately 97.5% of the population meets the daily requirement for vitamin D by having a serum 25(OH) D value higher than 50 nmol/L [21, 22]. In our study, serum 25(OH) D levels were measured as a continuous variable and categorized for analysis into two categories: < 50 nmol/L (< 20 ng/mL) for deficiency and ≥ 50 nmol/L (≥ 20 ng/mL) for sufficiency. These values were based on the cut-off point of the IOM and the Standing Committee of Europe Doctors (www.cpme.eu).

Participant recruitment

The study participants were recruited through a survey conducted on school employees in Jeddah; 2600 subjects were randomly recruited and screened for RLS using the four IRLSSG criteria [1, 5]. The survey is a validated and reliable self-administered questionnaire on the diagnostic criteria for RLS, and consists of four "yes/no" questions [1]. Patients were considered to have RLS if they answered "yes" to all four questions. The potential participants (242 individuals with RLS) were contacted by telephone and were asked to participate in the study. Once initial approval was obtained, the individuals were asked to visit the Sleep Medicine and Research Center at King Abdulaziz University Hospital, which is a large academic medical center. Trained physicians interviewed the potential participants to confirm the eligibility of the participants and a diagnosis of RLS using the updated IRLSSG diagnostic criteria [18]. The detailed study steps and procedures were explained to the participants, and each participant signed a written consent form. The inclusion criteria included adult patients with primary RLS who were not on RLS treatment or receiving vitamin D therapy. The exclusion criteria are provided in Table 1 (https://clinicaltrials.gov/ct2/show/NCT02256215). The primary endpoint was a change in the total score of the IRLSSG rating scale from baseline to the end of week 12 [20] (https://clinicaltrials.gov/ct2/show/NCT02256215).

Study steps and procedures

Pre-randomization

(A) Screening: Trained physicians attempted to contact the RLS pool by telephone calls. Only 75 subjects responded positively and agreed to participate in the trial. Participants with an initial diagnosis of RLS who agreed to participate were then interviewed.

During the interview, the diagnosis of RLS was confirmed using the updated IRLSSG diagnostic criteria, which required clinical assessment (general physical and neurological examination) [18]. In addition, each participant underwent evaluation of the severity of symptoms using the IRLSSG rating scale [20]. The following blood tests were performed to exclude secondary RLS: complete blood count, serum vitamin D, serum ferritin, iron, glycosylated hemoglobin, renal profile, bone profile, and thyroid function.

Table 1 Detailed exclusion criteria for the study (https://clinicaltrials.gov/ct2/show/NCT02256215)

A. Presence of RLS-mimicking disorders:
   1. Arthritis
   2. Deep venous thrombosis
   3. Varicose veins or venous insufficiency
   4. Habitual foot tapping
B. Patients receiving medications that could trigger RLS:
   1. Antihypertensive medications, e.g., use of thiazide diuretics at a total dose > 37.5 mg/day
   2. Anticonvulsants, e.g., new use of anticonvulsant drugs within 6 months of screening. A stable regimen of anticonvulsants was allowed.
   3. Antiemetics (prochlorperazine or metoclopramide)
   4. Antipsychotics (haloperidol or phenothiazine derivatives)
   5. Antidepressants (selective serotonin reuptake inhibitors)
   6. Antihistamines, e.g., cold and allergy medications
C. Patients on medications or with conditions that may interfere with vitamin D absorption:
   1. Celiac disease
   2. Crohn's disease
   3. Chronic pancreatitis
   4. Cystic fibrosis
   5. Weight-reduction drugs
   6. Cholesterol-lowering drugs, e.g., cholestyramine
D. Patients with contraindications for vitamin D supplements:
   1. Hyperparathyroidism
   2. Kidney stones
   3. Liver diseases
   4. Granulomatous disorders
   5. Vitamin D level above the normal range (≥ 250 nmol/L)
E. Use of supplements containing vitamin D within 12 weeks of the recruitment visit
F. Use of supplements containing calcium within 1 week of the baseline visit or initiation of the protocol
G. History of intolerance to vitamin D supplements
H. For women only:
   1. Pregnancy (positive pregnancy test at screening)
   2. Currently breastfeeding
   3. Use of oral contraceptives or start of menopausal hormone therapy within 3 months of baseline

(B) Recruitment: Based on the screening results, individuals with a final diagnosis of primary RLS, as well as those who fulfilled the inclusion and exclusion criteria, were identified. Of these, only 35 subjects provided written informed consent to start the randomization phase.

Randomization

This was a double-blind trial in which the participants, investigators, and bio-statisticians were blinded to the group allocations and treatments (active control vs. placebo). Vitamin D supplements and placebo were available as caplets of the same color. Participants were allocated to one of two groups: A or B. Group A received vitamin D pills and group B received the placebo. The participants were allocated to the treatment groups by a computer-generated list. They were randomized using a stratified block randomization with blocks of varying sizes (2, 4, 6, and 8). A central web-based randomization system was used to create the randomization number lists.

A designated pharmacist prepared the medications at a central location. The pharmacist had access to the randomization number list with group allocations and prepared the medication packs such that they were labeled only with the dosing instructions and a randomization number. Medication packs were shipped to the study site at the beginning of the study. After a participant provided written informed consent and was enrolled in the study, the site study team accessed the web-based randomization system and obtained a randomization number for the participant. The study team then selected the medication pack with the matching randomization number and provided the pack to the participant. Only the designated pharmacist in charge of preparation of the medication packs had access to the randomization numbers with group allocation. The only other role of the designated pharmacist in the study was to prepare the medication packs prior to shipment to the study site. The group allocation of the participants was not revealed during the study unless requested by the principal investigator due to safety concerns. Un-blinding occurred after all patients completed the protocol and after the analysis code was written and finalized.

Post-randomization visits

Each participant was visited at work/home on a weekly basis for 12 weeks, and the vitamin D supplement/placebo was delivered using a direct observation technique. At each visit, the participants were assessed for treatment response and any adverse effects. Blood tests (total vitamin D levels and bone profiles) were repeated every 4 weeks. Participants with a vitamin D level above the normal range were dismissed from the study. Each participant was interviewed at the end of week 12 to determine the RLS rating score and the changes that occurred after the treatment period.

Sample size calculation

To calculate the required study sample size, we set the study power at 80% and the significance level at 0.05. We determined a difference of 10 points on the mean IRLSSG follow-up score between the intervention and placebo groups as being clinically significant, the standard deviation of the difference in the means to be 10, and an effect size of one. This was based on the validated IRLSSG rating scale for restless legs syndrome [23]. Furthermore, the sample size calculation was supported by post hoc analysis of data from two trials on patients with RLS that assessed the minimal clinically important change (MCIC) in the RLS severity score [24]. The required sample size was determined to be 34, with 17 participants in each arm.

Ethical and regulatory responsibilities and statement of compliance

This study was performed according to the Institutional Review Board (IRB)–approved protocol (HA-02-J-008) and related documents, as well as the Good Clinical Practice (GCP) guidelines and the applicable regulatory requirements of the King Abdulaziz University Hospital. All investigators agreed to adhere to the instructions and procedures described in the protocol, thereby adhering to the principles of GCP. All key persons and research staff had completed educational modules on the protection of human subjects and were certified by their local IRB.

Confidentiality

All information and data generated as part of the study concerning the participants were considered confidential. Access to the data was restricted to authorized staff of the local investigational team. Authorized personnel had the right to inspect and copy all files and reports relevant to this study. All data were entered into SPSS statistical software version 20.0 (SPSS Inc., Chicago, USA) and managed with multiple security feature levels, including data elements and the user. All information used in the data analyses and reporting of study results has identifiable references to the participants.

Statistical analysis

SPSS version 20.0 (SPSS Inc., Chicago, USA) was used to perform the statistical analysis. We used χ^2 tests and independent-samples *t* tests to compare the baseline characteristics between the groups. For outcome variables, a paired *t* test was used to separately compare the distributions of change in the RLS severity score in the two treatment groups. An independent-samples *t* test with the corresponding 95% confidence interval (CI) was used to compare the RLS severity score between the two groups. A two-sided probability with a *P* value of < 0.05 was considered statistically significant.

Results

Only 78 of the 242 suspected RLS patients were interviewed and confirmed to have RLS; of these, 50 (64.1%) had primary RLS. Thirty-five individuals with primary RLS were included in the study; 17 in the vitamin D group and 18 in the placebo group. The demographic characteristics were comparable between both groups and were not statistically different [19] (Table 2). However, there were 11 participants in each group with vitamin D deficiency.

Thirteen participants discontinued the study, seven at week 4 and six at week 8 (Fig. 1). At week 4, six participants withdrew consent (two in the vitamin D group and four in the placebo group). One individual was receiving vitamin D from another doctor, two left the country, two refused to continue, and one had abdominal pain (vitamin D group). At week 8, two participants withdrew consent (one in each group) and four reported experiencing side effects: three had fatigue/dizziness (placebo group) and one reported worsening of RLS symptoms (vitamin D group).

Although the vitamin D level remained unchanged during the study period in the placebo group ($P = 0.89$), it increased significantly in the vitamin D group ($P = 0.001$) [19] (Table 3). Nevertheless, during the 12-week period, patients in the vitamin D group did not show a significant change in the RLS severity score (mean difference = 4.2; 95% CI − 12.8 to + 4.4, $P = 0.32$) compared to those in the placebo group [19] (Table 4). This remained true even after limiting the data analysis to only participants with vitamin D deficiency (Table 5).

Discussion

Although 35 primary RLS cases were initially included in the study, only 22 participants completed the study; 12 in the vitamin D group and 10 in the placebo group. As anticipated, although the serum vitamin D level remained unchanged over the entire period of follow-up in the placebo group, it increased substantially in the vitamin D group. However, the mean RLS severity score did not change significantly in the vitamin D group, indicating that vitamin D supplementation does not reduce RLS severity [19].

It is hypothesized that vitamin D deficiency may lead to dysfunction of the dopaminergic system, ultimately resulting in the development of RLS, a condition in which accumulating data suggest that dopaminergic dysfunction plays a fundamental role [25]. To our knowledge, this trial is the first randomized controlled trial assessing the efficacy of vitamin D supplementation in

Table 2 Demographic profile of the study population ($n = 35$)

Variables	Vitamin D group	Placebo group	*P* value
Age (years), mean ± SD	42.7 ± 4.7	42.4 ± 5.5	0.91[a]
Initial restless legs syndrome severity score	14.60 ± 4.5	16.11 ± 6.2	0.41[a]
Male sex (%)	64.7%	72.2%	0.45[b]
Vitamin D level, mean ± SD (nmol/L)	42.6 ± 31.1	57.3 ± 42.4	0.25[a]

[a] Independent-samples *t* test

[b] χ^2 test

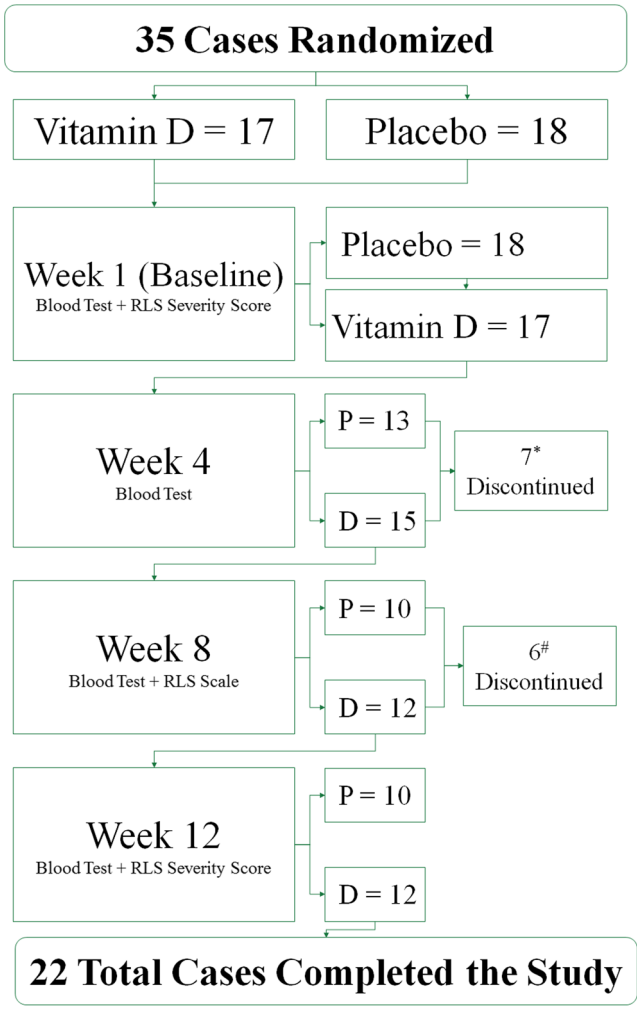

Fig. 1 Study flow chart

treating patients with RLS. Previous data in the literature are supportive of our study's hypothesis. Balaban et al. observed a significant inverse correlation between vitamin D serum levels and RLS symptom severity ($P = 0.01$, $r = -0.47$) [17]. Moreover, a pilot study [26] on 12 patients with primary RLS concurred with the findings of Balaban et al. [17], revealing that

Table 3 Vitamin D levels in both groups throughout the study period

Vitamin D level (mean ± SD)				
	Baseline	Week 4	Week 8	Week 12
Placebo group	57.3 ± 42.4	53.0 ± 23.4	54.1 ± 34.0	53.0 ± 34.3
Vitamin D group	42.6 ± 31.1	85.7 ± 25.0	98.7 ± 29.5	90.1 ± 38.4
P value[a]	0.25	0.001	0.004	0.028

[a] Independent-samples *t* test

Table 4 Restless legs syndrome severity score at baseline and week 12 among both groups

Restless legs syndrome severity score (mean ± SD)			
	Baseline	Last visit	*P* value[a]
Placebo group	16.11 ± 6.2	10.3 ± 11.1	0.040
Vitamin D group	14.60 ± 4.5	14.5 ± 08.2	0.540

[a] Two-tailed *P* value, paired-samples *t* test

correction of vitamin D levels positively affected the severity of RLS symptoms. Further, Oran et al. [25] reported that the prevalence of RLS was significantly higher among vitamin D-deficient individuals, suggesting a possible link between vitamin D deficiency and RLS. In addition, a population-based case–control study was recently performed to evaluate the link between RLS and vitamin D levels [27]. In this study, data from 201 participants were included in the analysis, including data from 78 with RLS and 123 healthy controls. Fifty-nine (75.6%) patients with RLS and 52 (42.3%) controls were diagnosed with vitamin D deficiency ($P < 0.001$). The odds ratio of developing RLS was 4.24 for patients with vitamin D levels < 50 nmol/L compared with healthy individuals, who had vitamin D levels ≥ 50 nmol/L ($P < 0.001$, 95% CI 2.3 to 7.9). Such studies propose a link between vitamin D deficiency and severity of RLS symptoms.

In the present study, the placebo group showed no significant change in their vitamin D levels throughout the study period, while those in the treatment group had a significant increase in their vitamin D levels. This indicates that the treatment group responded positively to therapy (Table 3). However, the fact that there was no effect on RLS symptoms despite a significant improvement in the vitamin D levels indicates that vitamin D supplements may not play a role in the treatment of RLS, though it may contribute to its pathophysiology (Table 4). Even after performing an analysis on only the participants with vitamin D deficiency, this finding remained true (Table 5). One possible explanation is that, in the pathophysiology of the disease, the level of vitamin D in the brain is more important than the serum level. Hence, the increment in vitamin D in our study may not have been adequate to sufficiently affect the brain level of

Table 5 Restless legs syndrome severity score in the vitamin D-deficient patients only[a]

Restless legs syndrome severity score (mean ± SD)			
	Baseline	Last visit	*P* value[b]
Placebo group	16.81 ± 6.3[a]	07.8 ± 13.9	0.038
Vitamin D group	14.82 ± 5.2[c]	13.8 ± 08.9	0.503

[a] Placebo group, baseline vitamin D level

[b] Two-tailed *P* value, paired-samples *t* test

[c] Vitamin D group, baseline vitamin D level

vitamin D. We propose that this is likely due to the relatively short duration of therapy (12 weeks) or the persistence of a suboptimal vitamin D level. The significant difference observed in the RLS severity score in the placebo group between baseline and week 12 could be due to a placebo effect ($P = 0.04$ and 0.038, respectively; Tables 4 and 5). However, the absence of this placebo effect in the vitamin D group raises concern that vitamin D may cause harm to patients.

This study has several limitations. Due to the discontinuation of 13 participants, the number of participants may not have been sufficient based on the estimated sample size. We suggest that focusing on vitamin D-deficient patients only, using an adequate sample size, is more appropriate for exploring the effectiveness of vitamin D supplements. Furthermore, the RLS severity score was mild to moderate; using more severe cases may help to better determine the role of vitamin D supplements. Finally, there is no objective measure of RLS symptoms, making it difficult to adequately monitor the effectiveness of any medication.

In conclusion, vitamin D supplements were not effective in improving RLS symptoms in our 12-week study. To investigate the role of vitamin D supplementation in treating patients with RLS, future studies should comprise a longer study period, adequate sample size that accounts for the loss of patients during follow-up, and recruitment of patients with RLS with severities spanning the full range that are vitamin D deficient.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics approval and consent for participation The study was approved by the Human Institutional Ethics Committee of King Abdulaziz University Hospital (Approval No. HA-02-J-008). Informed consent was obtained from all participants.

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