Sleep Breath (2015) 19:579–583
DOI 10.1007/s11325-014-1049-y

ORIGINAL ARTICLE

The effect of vitamin D supplements on the severity of restless legs syndrome

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Received: 18 March 2014 / Revised: 29 June 2014 / Accepted: 5 August 2014 / Published online: 23 August 2014

Abstract
Purpose Clinical observation hinted improved symptoms of restless legs syndrome (RLS) after vitamin D supplements. Hence, the aim of this study is to evaluate the effect of vitamin D supplementation on the severity of RLS symptoms.
Methods Twelve adult subjects diagnosed with primary RLS and vitamin D deficiency were recruited. Patients with secondary RLS were excluded from this study. The complete cell count; serum levels of ferritin, iron, glycated hemoglobin, and vitamin D3 (25 (OH) vitamin D); and renal and bone profiles of the patients were assayed. Patients with vitamin D deficiency (<50 nmol/l) were treated with vitamin D3 supplements (high oral dose or intramuscular injection). The severity scores of RLS were reassessed after the vitamin D3 level was corrected to >50 nmol/l and compared with those before the administration of the supplements.
Results The median pretreatment vitamin D level was 21.7 nmol/l (13.45–57.4), which improved to 61.8 nmol/l (42.58–95.9) (P=0.002) with the treatment. The median RLS severity score improved significantly from 26 (15–35) at baseline to 10 (0–27) after correction of the vitamin D levels (P=0.002).
Conclusion This study indicates that vitamin D supplementation improves the severity of RLS symptoms and advocates that vitamin D deficiency is conceivably associated with RLS.

Keywords Restless legs syndrome · Vitamin D deficiency · Rating score · Diagnosis

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Introduction

Restless legs syndrome (RLS) is a distressing sensorimotor sleep-related disorder experienced by 5–10 % of the people in Europe and North America; however, RLS is less common in Asian populations (1–4 %) [1]. The prevalence of RLS is found to increase with age, with the incidence being 3 % for the age group of 18 to 29 years, 10 % for the age group of 30 to 79 years, and 19 % for the age group of 80 years and above [2]. Women are more prone to RLS than the men, and parity in women may be associated with an increased risk [3]. In most cases, RLS is a primary idiopathic disorder, but it also can be associated with a variety of underlying medical disorders. Secondary RLS is associated with iron deficiency, end-stage renal disease, diabetes mellitus, neuropathy, multiple sclerosis, and pregnancy among others.

Vitamin D may play an important role in dopamine system function, which may be the key player in the pathophysiology of RLS. It has been reported that vitamin D affects the nigrostriatal dopaminergic pathway, increases the levels of dopamine or its metabolites, and protects dopaminergic neurons against toxins [4]. However, the potential role of vitamin D in RLS has not been well studied. A 16-year-old girl with RLS secondary to vitamin D deficiency caused by chronic administration of carbamazepine was reported by Prakash et al.; they speculated an association between vitamin D deficiency and the development of RLS [5]. This study was carried out to evaluate the effect of vitamin D supplementation

on the severity of RLS symptoms and to provide more insights on the pathogenesis and potential new treatment options for RLS.

Methods

Subjects with vitamin D deficiency and idiopathic RLS, diagnosed according to the criteria defined by the International Restless Legs Study Group (IRLSG), were recruited between October 2011 and September 2012. The diagnostic criteria for RLS include the following: an urge to move the legs that is usually associated with uncomfortable sensations in the legs, worsening of these symptoms during rest, at least temporary relief brought on by activity, and worsening of symptoms in the evening [6].

Approval was obtained from the ethical committee of King Abdulaziz University Hospital, Jeddah. The interviews were carried out by physicians who were trained in the IRLSG diagnostic criteria and rating scale. Patients attending the general respiratory clinic were recruited if they satisfied the inclusion criteria, regardless of the purpose of their referral. Consent was then obtained from the patients, and individual interviews were conducted. Interviews included demographic data, focused history, comorbidities, and focused physical examination, in addition to IRLSG criteria, and the initial RLS severity score, defined as per the IRLSG criteria [7, 8]. Subjects underwent blood tests to exclude secondary causes of RLS which included complete cell count and serum levels of ferritin, iron, glycated hemoglobin, and renal and bone profiles, in addition to vitamin D level. Subjects with secondary RLS were excluded from further study.

Patients with idiopathic RLS and vitamin D deficiency, defined as a vitamin-D3 level of <50 nmol/l, were treated with vitamin D supplements administered either as a high oral dose or intramuscular injection. This administration route was selected according to the patient's preference and availability of the injectable form. The oral dose was administered in drops using one bottle of 28,000 IU of vitamin D per week. The parenteral dose used was 200,000 IU of vitamin D per month. This was administered in addition to oral calcium carbonate, along with a maintenance dose of 400 IU daily of vitamin D. The vitamin D supplements were continued until the vitamin D level was corrected. However, the maintenance dose was retained. Patients were not informed that vitamin D treatment might potentially affect their RLS symptoms. Subjects were interviewed every 1 to 2 months, and their vitamin D levels were checked. The severity score of RLS symptoms was recorded again on follow-up once vitamin D level was corrected to >50 nmol/l. Our hypothesis would be confirmed if the RLS symptoms score showed significant improvement.

Statistical analysis

Data were presented in the form of median and range. The comparison of paired data was made using the Wilcoxon signed rank test.

Results

Twelve subjects newly diagnosed with idiopathic RLS and vitamin D deficiency were identified (Table 1). The mean pretreatment vitamin D level for all patients was 21.7 nmol/l (range, from 13.45 to 57.4 nmol/l), which improved with treatment to 61.8 nmol/l (range, from 42.58 to 95.9 nmol/l) (P=0.002) (Fig. 1). The duration of treatment with vitamin D ranged from 3 to 8 months. The mean RLS rating score improved significantly from 26 (range, from 15 to 35) at baseline to 10 (range, from 0 to 27) when the vitamin D levels were corrected (P=0.002) (Fig. 2). Blood tests obtained were unremarkable apart from serum vitamin D levels.

Discussion

This pilot study indicates that correction of vitamin D level greatly improves symptoms of RLS and suggests a possible association between vitamin D deficiency and RLS.

It is worth mentioning that vitamin D deficiency is highly prevalent in the Saudi population. Alsuwadia et al. reported that one third of the adults in the community suffer from vitamin D deficiency [9]. This is more pronounced in females and in younger age groups. Wearing traditional clothes, deliberate avoidance of the sun, and inadequate dietary intake are likely to be the principal causes of low vitamin D levels in the Saudi community [9]. Our results shed light on the possibility that the prevalence of RLS in the Saudi population may be greater than that recognized in clinical practice. Unfortunately, the local data regarding the prevalence of RLS among Saudi

Table 1 Demographic data

Gender	Number	Mean age±SD (years)	Mean weight±SD (kg)	Mean height±SD (m)
Female	8	43.1±18.2	81.8±19.1	1.57±0.06
Male	4	26.5±12.9	64±15.6	1.59±0.09
Total	12	37.6±18.0	73.7±18.7	1.57±0.06

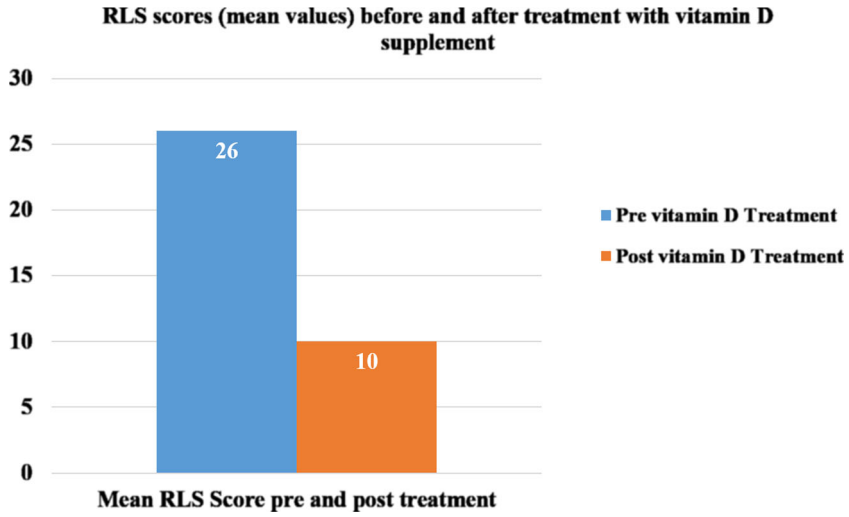

Fig. 1 RLS scores (mean value) before and after treatment with vitamin D supplement

people are limited. However, it has been reported that the prevalence of RLS among patients attending primary health care facilities is 5.2 % and that is highest among participants between 45 and 60 years of age [10].

Balaban et al. compared the serum vitamin D levels of RLS patients and matched controls to explore the correlation between the plasma vitamin D levels and the disease severity [11]. In their study, serum 25-hydroxyvitamin D levels in 36 female patients with RLS were measured and compared with those of 38 female healthy control subjects. The mean serum 25-hydroxyvitamin D levels were 7.31±4.63 ng/ml in female patients with RLS and 12.31±5.27 ng/mL in female control subjects (P=0.001). A significant inverse correlation between the vitamin D levels and disease severity of RLS was found in females (P=0.01, r=−0.47) [11]. Our study confirms the findings of Balaban et al. although the sample size in our study was not large enough to show any gender difference.

Diminished dopamine level is a key factor in RLS pathogenesis, which is possibly mediated by the impairment of the spinal circuits [12]. The dopaminergic diencephalospinal pathway modulates spinal dorsal horn cells and preganglionic sympathetic neurons. Decreased activity in this pathway increases the sympathetic neuron output, which alters the afferent input activity from muscle fibers and thereby may trigger RLS symptoms [11, 13–15].

Vitamin D may play an important role in the functioning of the dopamine system, but the potential role of vitamin D in RLS is not well studied. There is growing evidence that vitamin D is a neuron-activating steroid that is important for regulating both brain development and its function. Vitamin D has also been reported to play roles in neurodegenerative disorders, including multiple sclerosis and parkinsonism [16–18]. In particular, there is evidence from rodent models that prenatal vitamin D deficiency alters the development of

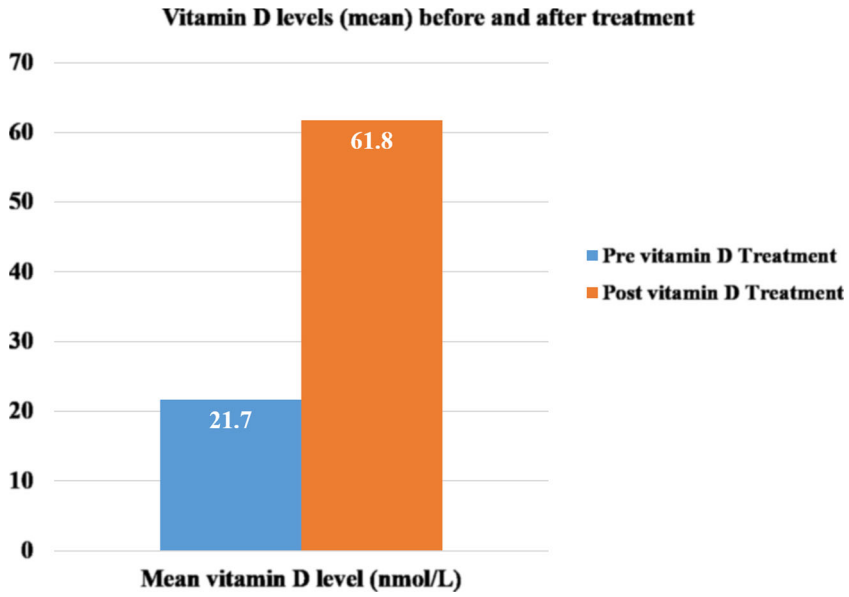

Fig. 2 Vitamin D level (mean) before and after treatment

dopaminergic pathways and that this disruption is associated with altered behavior and neurochemistry in the adult brain [19]. Cui et al. confirmed that vitamin D receptor is present in the nucleus of tyrosine hydroxylase (TH)-positive neurons in both the human and rat substantia nigra. In addition, they suggested that alterations in early-life vitamin D status might influence the orderly development of dopaminergic neurons [19]. On the same line, Newmark and Newmark hypothesized that chronically inadequate vitamin D intake in the USA is one of the significant factors in continued neuron cell death in the substantia nigra and hence plays an important role in the pathogenesis of Parkinson's disease [20]. However, Danielle et al. reported that reducing 25(OH)D serum levels in mice has no effect on the vulnerability of nigral dopaminergic neurons in vivo in a model system of parkinsonism [21]. Therefore, the available data regarding the role of vitamin D or its receptors in the dopaminergic system are still scanty and controversial.

In this study, we primarily investigated the serum vitamin D levels in idiopathic RLS cases. However, this study has some limitations including the small sample size, absence of a control group, and the use of rating scales as end-points for assessment of RLS severity.

These rating scales are exclusively based on subjective assessment and memory recall, does not require assessment of motor dysfunction, and are highly vulnerable to placebo effects.

Therefore, this report is actually an introduction for a future well-designed larger cohort or case-control studies on idiopathic RLS and their association with vitamin D status. Once a relationship is confirmed, the relationship between the vitamin D level and the severity of symptoms of RLS should be scrutinized. This should be done using the subjective validated rating scales together with the objective suggested immobilization tests (SIT). This is a symptom-provocation test measuring RLS severity multiple times a day while the patient is awake and resting under controlled conditions [22]. Further, the pathways involved in such vitamin D-modulated RLS can be explored.

In conclusion, this pilot study showed, for the first time, a remarkable improvement in severity of RLS with vitamin D supplementation and proposed a possible link between vitamin D deficiency and RLS. As a clinical implication, vitamin D supplementation may be a potential therapy or probably a preventive measure in the management of RLS. A larger study is indeed needed to confirm these findings.

Conflict of interest The authors have reported no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Funding support None

Author contributorship Siraj Wali and Ayman Krayem wrote the proposal, recruited the patients, interpreted the results, and wrote the manuscript. Afnan Shukr, Ayah Boudal, and Ahmad Alsaiari recruited the patients, conducted the statistical analysis, and wrote the manuscript.

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