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Original Article

Serum 25-hydroxyvitamin D levels in restless legs syndrome patients

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ABSTRACT

Objective: Restless legs syndrome is characterised by discomfort during rest and an urge to move the limbs that is accompanied by abnormal sensations. Studies on disease pathophysiology have focused on dopaminergic dysfunction. Vitamin D may play an important role in dopamine function, but the role of vitamin D in restless legs syndrome has not been examined. We compared the serum vitamin D levels of RLS patients and matched controls and explored the correlation of plasma vitamin D levels with disease severity.

Patients/methods: We measured serum 25-hydroxyvitamin D levels in 36 patients with restless legs syndrome and compared them to 38 healthy control subjects.

Results: The mean serum 25-hydroxyvitamin D levels were 7.31 ± 4.63 ng/mL in female patients with restless legs syndrome and 12.31 ± 5.27 ng/mL in female control subjects ($p = 0.001$). We found a significant inverse correlation between vitamin D levels and disease severity in females ($p = 0.01$, $r = -0.47$).

Conclusion: The mean serum vitamin D levels were lower in female patients with restless legs syndrome. Low vitamin D levels may cause dopaminergic dysfunction in restless legs syndrome patients. Further studies are required to confirm these results.

1. Introduction

Restless legs syndrome (RLS) is a common sensorimotor neurological disorder that is characterised by an irresistible urge to move the limbs and abnormal sensations primarily in the ankles and calves at night, which leads to sleep disturbances [1]. The symptom severity varies widely. Some patients experience symptoms occasionally in stressful situations, and other patients encounter severe nightly symptoms that disrupt sleep [2]. The prevalence of RLS is 6–12% in Western populations, but distinctions between the mere presence of RLS and clinically significant RLS (symptoms frequent or severe enough to require treatment) reveals a prevalence of approximately 3% in the latter [3–5].

RLS may have an idiopathic or hereditary origin (primary RLS), or it may be related to several other medical conditions, such as iron deficiency, end-stage renal diseases, pregnancy, rheumatological disorders, and diabetes mellitus (secondary RLS). In addition, secondary RLS may be connected to neurological conditions such as Parkinson's disease (PD), spinal cord lesions, multiple sclerosis (MS), and polyneuropathy [6]. The majority of cases involve primary RLS [7].

The exact pathophysiology of RLS is not fully understood, but genetic factors, iron deficiency, and the dopaminergic system may play a role in RLS [8]. Dopaminergic dysfunction may play a central role in RLS. The strongest evidence for a dopaminergic role in RLS is the good pharmacological response to low-dose dopaminergic agents even on the first night of administration [6,8]. Dopaminergic dysfunction has been attributed to iron deficiency in RLS [9,10]. However, the mechanism underlying decreased iron concentrations in the brains of RLS patients is not understood [11]. Dopamine is an important neurotransmitter that controls motor and emotional behaviours [12,13].

Vitamin D plays an essential role in the pathogenesis of skeletal disorders and calcium homeostasis. Several researchers have suggested that an association exists between lower serum vitamin D levels and neuropsychiatric disorders such as dementia, depression, bipolar disorders, schizophrenia, PD, and MS [14,15]. Vitamin D administration affects the nigrostriatal dopaminergic pathway. Vitamin D administration increases the levels of dopamine or its metabolites and protects dopaminergic neurons against toxins [16]. Studies suggest an important role for vitamin D in dopamine function, but its role in RLS has not been investigated.

Our study compared the serum vitamin D levels of RLS patients and matched controls to examine the relationship between disease

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characteristics and vitamin D levels. We measured the serum levels of a vitamin metabolite, 25-hydroxyvitamin D (25[OH]D), in RLS patients and correlated this metabolite with the severity of RLS symptoms.

2. Methods

2.1. Patients and clinical evaluation

This study was conducted between September 2010 and March 2011 at the medical university hospital. This prospective case-control study was performed in consecutive idiopathic RLS patients with no comorbidities and with normal neurological examination results. RLS was diagnosed according to the International Restless Legs Syndrome Study Group (IRLSSG) essential criteria [17]. The following inclusion criteria were added: age between 18 and 49 years and free of RLS medications at the time of enrolment. The ratio of individuals with osteoporosis who receive vitamin D, calcium, and mineral treatment over the age of 50 years is high in the general population. Therefore, patients 50 years and older were not included in the study. The presence of secondary RLS was determined by clinical interview, physical examination, neurological examination, and laboratory investigation. Patients with abnormal results following a neurological examination, polyneuropathy, diabetes, renal failure, chronic hepatic failure, alcohol abuse, pathology in routine complete blood biochemistry, sedimentation, abnormal thyroid hormones, vitamin B12, and ferritin levels were excluded. Patients with known causes of secondary RLS, a familial history of RLS, or any medical conditions that would affect the assessment of RLS were excluded. This study included primarily non-familial idiopathic RLS cases because the pathogenic mechanisms of hereditary RLS are not known. Patients were also excluded if they had known causes of osteoporosis, systemic inflammatory or connective tissue disease, or a history of corticosteroid, oestrogen, bisphosphonates, calcitonin, calcium, or vitamin D therapy. Ferritin levels, body mass index (BMI), and cigarette smoking history of patients and control subjects were noted. Healthy age- and gender-matched control volunteer subjects were recruited from the general population. Control subjects were also screened for participation eligibility using exclusion criteria similar to those for the RLS patients.

The local ethics committee of the university approved the study. Informed consent was obtained from all subjects, and the study was conducted in accordance with the ethical standards for research involving human subjects in the Helsinki Declaration.

Patients completed the 10-item International Restless Legs Syndrome (IRLS) Rating Scale to assess RLS severity [18].

2.2. Biochemical measurements

Blood samples for vitamin D were taken and investigated during the same session in patient and control groups (January–March). A fasting blood sample was obtained, divided into aliquots, centrifuged, and transported on ice. Serum samples were assessed immediately. Serum 25(OH)D was assayed using an electrochemiluminescence immunoassay analyzer system (Elecsys Vitamin D, Cobas 6000 with e601 module, Roche Diagnostics, Germany) with a range of 3–70 ng/mL (7.5–175 nmol/L). The intermediate precision was 7.5% using a coefficient of variation. Calcium, phosphate, and alkaline phosphatase (ALP) were assessed using routine laboratory methods (Beckman Coulter analyser).

2.3. Statistical analysis

Statistical analyses were performed using SPSS for Windows 14.0 software (SPSS, Chicago, IL). The data of categorical variables are presented as counts and percentages; the data of continuous variables are presented as means and SD. The normality of the distribution was tested using the Kolmogorov–Smirnov test. Comparisons of variables between groups were performed using Student's *t*-test and Mann–Whitney *U*-test for numeric variables and the χ^2 test for categorical data. Pearson's correlation and multivariate regression analysis were used for correlations. In all analyses, *p* values below .05 were considered statistically significant.

3. Results

3.1. Clinical features

A total of 78 patients with idiopathic RLS were screened for this study. Twenty-six patients were excluded because they had a positive family history for RLS. Seven patients were excluded because their ferritin values were lower than 30 ng/mL. Five patients were excluded because they had a vitamin B12 deficiency and four patients were excluded because they were taking RLS medications at the time of enrolment. A total of 36 patients were eligible and agreed to participate in the study.

The 36 RLS patients (eight males and 28 females) had a mean age of 40 ± 7.32 years. The control group included 38 subjects (11 males and 27 females) with a mean age of 37.23 ± 9.87. The age ($p = 0.16$) and sex ($p = 0.51$) distribution were not significantly different between the two groups. The mean BMI and cigarette smoking history of the patients and control subjects were not different between the groups.

The mean ± SD duration of RLS was 6.20 ± 4.88 years. The mean ± SD IRLS score was 21.41 ± 8.23. All RLS patients suffered symptoms in the lower extremities. Three patients also experienced RLS symptoms in the upper extremities. Ten cases reported RLS symptoms 4–7 times per week. Eighteen cases reported RLS symptoms 1–3 times per week. Four patients experienced RLS symptoms once or twice every 15 days, and the remaining patients reported RLS symptoms less than once per month. Participant demographics and clinical characteristics are presented in Table 1.

Table 1
Demographic and clinical characteristics of RLS patients and control subjects.

	Patients with RLS	Control subjects	*p* Value
Number	36	38	
Sex (M/F)	8/28	11/27	0.51
Age (years) total	40.05 ± 7.32	37.23 ± 9.87	0.16
Age males	41.5 ± 6.27	36.45 ± 8.43	0.1
Age females	39.64 ± 7.65	37.96 ± 8.33	0.43
BMI total	25.49 ± 5.08	26.13 ± 3.24	0.52
BMI males	26.57 ± 4.11	25.64 ± 2.60	0.71
BMI females	25.18 ± 5.34	26.34 ± 3.51	0.1
Cigarette smoking (yes/no) males	3/5	2/9	0.34
Cigarette smoking (yes/no) females	9/19	7/20	0.67
Duration of illness (year) total	6.20 ± 4.85		
Duration of illness (year) males	5.87 ± 3.18		
Duration of illness (year) females	6.30 ± 5.31		
IRLS score total	21.45 ± 8.25		
IRLS score males	18.25 ± 9.91		
IRLS score females	22.32 ± 7.65		
Upper extremity involvement	3/36		

RLS: restless legs syndrome, M/F: male/female, BMI: body mass index, IRLS: International Restless Legs Syndrome Rating Scale. Values are expressed as mean ± SD. A *p*-value <0.05 was considered statistically significant.

3.2. Biochemical results

The mean serum 25(OH)D levels were 11.40 ± 6.23 ng/mL in males and 7.31 ± 4.63 ng/mL in females in the RLS patient group ($p = 0.07$). The mean serum 25(OH)D levels were 12.99 ± 5.43 ng/mL in males and 12.31 ± 5.27 ng/mL in females in the control group ($p = 0.75$). The mean ferritin levels were 84.50 ± 5.25 ng/mL in males and 70.46 ± 6.39 ng/mL in females in the RLS patient group ($p = 0.001$). The mean ferritin levels were 77.64 ± 8.87 ng/mL in males and 76.57 ± 8.20 ng/mL in females in the control group ($p = 0.70$).

Female RLS patients exhibited significantly lower serum 25(OH)D levels than female controls. The mean serum 25(OH)D levels were 7.31 ± 4.63 ng/mL in female RLS patients and 12.31 ± 5.27 ng/mL in female controls ($p = 0.001$). Similarly, the mean serum ferritin, calcium, and phosphate levels were lower and the ALP level was higher in female RLS patients compared to control subjects matched for gender. The mean 25(OH)D, ferritin, calcium, phosphate, and ALP levels were not different between the male RLS patients and the male control subjects (Table 2). A significant negative correlation was found between IRLS scores and 25(OH)D levels by Pearson's correlation analysis in the females ($p = 0.01$, $r = -0.47$) (Fig. 1). The results of the Pearson's correlation analysis did not show a correlation between IRLS rating scale scores and ferritin levels ($p = 0.28$). Finally, a multivariate linear regression model was designed between the IRLS scores, 25(OH)D levels, and ferritin levels. IRLS scores correlated with 25(OH)D levels ($p = 0.004$); a multivariate regression analysis did not show a correlation between IRLS rating scale scores and ferritin levels ($p = 0.1$).

Table 2
Comparison of biochemical variables between RLS patients and healthy controls.

	Patients with RLS	Control subjects	*p* Value
25(OH)D (ng/mL)			
Males	11.40 ± 6.23	12.99 ± 5.43	0.54
Females	7.31 ± 4.63	12.31 ± 5.27	0.001
Ferritin (ng/mL)			
Males	84.50 ± 5.25	77.64 ± 8.87	0.07
Females	70.46 ± 6.39	76.57 ± 8.20	0.03
Calcium (mg/dL)			
Males	9.12 ± 0.36	9.55 ± 0.44	0.07
Females	8.63 ± 0.45	9.67 ± 0.37	0.001
Phosphate (mg/dL)			
Males	3.26 ± 0.39	3.59 ± 0.53	0.06
Females	2.74 ± 0.21	3.78 ± 0.81	0.03
ALP (IU/L)			
Males	61.66 ± 18.06	60.88 ± 18.57	0.86
Females	107.40 ± 61.63	54.61 ± 14.19	0.001

RLS = restless legs syndrome. Values are expressed as mean ± SD. A *p*-value <0.05 was considered statistically significant.

4. Discussion

This study is the first investigation of serum vitamin D levels in RLS patients. We found significantly lower serum 25(OH)D levels in the female RLS patients compared with the female controls. Our study revealed an inverse association between 25(OH)D plasma concentrations and IRLS scores. We found higher IRLS scores in the female RLS patients with lower 25(OH)D concentrations. We did not find significant difference in serum 25(OH)D levels between male RLS patients and male control subjects. This result may be due to the small number of male patients in the study. Serum ferritin levels were lower in the female RLS patients than in the female control subjects. Beside this, correlation analyses did not show a correlation between disease severity and ferritin levels.

The aetiology and pathophysiology of RLS is not clear. Most RLS cases are idiopathic, but RLS also occur secondary to other conditions such as iron deficiency, uraemia, and pregnancy [11,19–21]. Approximately 50% of RLS patients report a positive family history

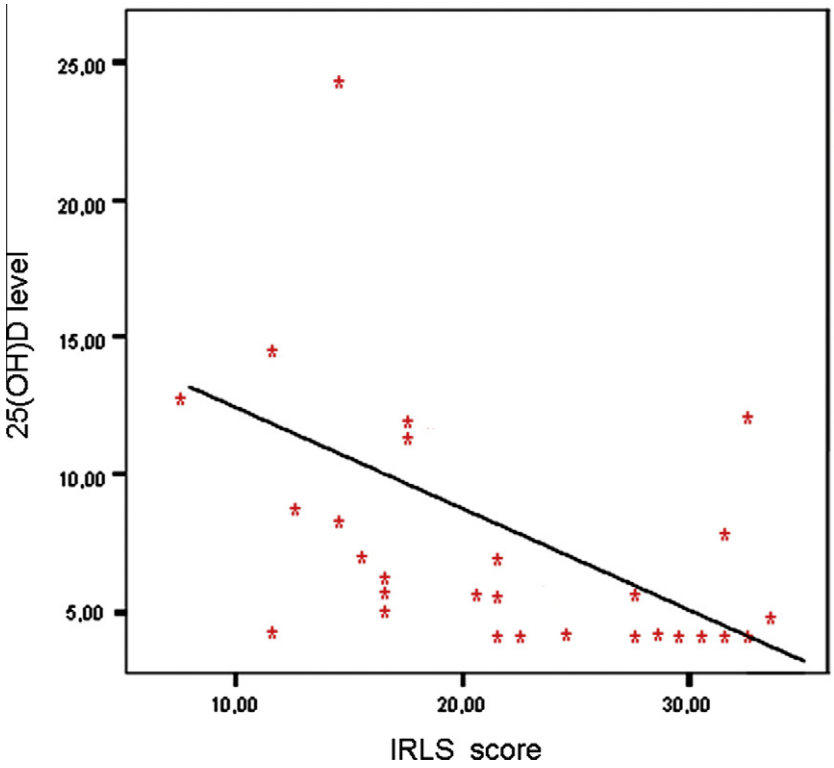

Fig. 1. Correlation between concentration of vitamin D and IRLS score in female RLS patients ($n = 28$, $r = -0.47$, $p = 0.01$).

[22,23]. Clinical and pharmacological studies suggest a central pathophysiological role for the dopamine system in RLS. Dopaminergic dysfunction is an important issue in RLS pathogenesis when lower dopamine levels accompany a primary condition or a secondary RLS [15,24].

Two recent PET studies reported a reduced utilisation of fluorodopa in the striatum [25,26]. Cervenka et al. [24] demonstrated significantly higher 11C-raclopride binding potential in RLS patients compared with controls. These authors proposed that the increased receptor levels were due to receptor upregulation in response to low levels of endogenous dopamine. RLS patients exhibit an altered dopaminergic profile in the putamen and substantia nigra compared with controls [10].

The efficacy of dopaminergic therapy supports dopaminergic dysfunction in RLS patients. Dopamine agonists successfully alleviate RLS symptoms. Dopaminergic transmission may be affected by genetic, metabolic, or nutritional factors, which may influence RLS at different neural levels and produce underlying changes in other motor or sensory structures that are implicated in RLS [27].

Diminished dopamine is a key factor in RLS pathogenesis, possibly via impairment in the descending modulation of spinal circuits [28]. The dopaminergic diencephalospinal pathway modulates spinal dorsal horn cells and preganglionic sympathetic neurons. Decreased activity in this pathway increases sympathetic neuron output, which alters the afferent input activity from muscle fibres. These events may trigger RLS symptoms [6,21,29,30].

Vitamin D is an important prohormone for serum calcium and phosphate homeostasis.

Vitamin D is obtained from the diet or synthesised in the skin after exposure to ultraviolet-B radiation from the sun. [31]. There are two common forms of vitamin D, vitamin D2, and vitamin D3, and each form originates from two distinct sources. Vitamin D2 is synthesised from yeast ergosterol and vitamin D3 is converted from lanolin 7-dehydrocholesterol in the skin during sunlight exposure. The liver converts vitamin D to its major circulating form, 25(OH)D, and the kidney synthesises the activated form, 1,25-dihydroxyvitamin D (1,25[OH]2D) [32].

A growing body of evidence supports a role for vitamin D in brain function and development, including vitamin D receptor numbers in the brain. Vitamin D also regulates dysfunctional processes in MS, PD, and other neurodegenerative disorders [13,33–35].

Vitamin D has important functions in the dopaminergic system. Vitamin D deficiency in weanling rats alters dopamine concentrations in the cortex [36]. Pretreatment with 1,25(OH)2D increases the levels of dopamine and its metabolites in the ipsilateral substantia nigra (SN) of rats with 6-hydroxydopamine (6-OHDA) lesions in the medial forebrain bundle [15]. Ibi et al. [16] reported that 1,25(OH)2D administration protects dopaminergic neurons against dopaminergic toxins.

Interestingly, low blood 25(OH)D levels are observed in infants with iron deficiency anaemia [37]. Elevations in blood and tissue iron concentrations are observed after the addition of vitamin D to the daily diet [38]. The blood concentrations of iron and vitamin D blood levels are interrelated. These interactions suggest that iron deficiency, which is an etiological factor of RLS, induces dopaminergic dysfunction via vitamin D deficiency. Concurrence of lower ferritin levels with lower vitamin D levels in female patients may be due to this interaction.

Prakash et al. [7] reported a young female epilepsy patient with severe RLS symptoms who, after an examination, was revealed to have a vitamin D deficiency and drug-induced osteomalacia. Vitamin D replacement alleviated RLS symptoms and induced a long-term remission. This case indicates the importance of vitamin D deficiency in RLS symptoms.

This study was conducted in a region with long-lasting winters, and people traditionally wear concealing clothing. These factors likely reduced sunlight exposure, which could have caused a vitamin D deficiency. However, causal mechanisms cannot be inferred from this case-control study. The neuroprotective mechanisms of vitamin D in RLS are important to consider. Vitamin D administration protects dopaminergic neurons against several toxins [15,16]. Vitamin D inhibits nitric oxide synthesis, upregulates enzymes in glutathione and neurotrophin synthesis, regulates neuronal calcium levels, and protects neuronal integrity [39–44].

This study has some limitations. The study primarily investigated serum vitamin D levels in idiopathic and non-familial RLS cases. Therefore, the results may be limited to this specific population. Real idiopathic cases, including familial RLS types, should be investigated. Numbers of male RLS patients are quite low in this study and may lead to insignificant results for men. Further studies should be done in large male populations with RLS to reach definitive results for vitamin D levels in males.

In summary, we found significantly lower serum 25(OH) D levels in female RLS patients compared to control subjects matched for gender. These results support an association between vitamin D deficiency and RLS, which may affect dopamine function. We recommend vitamin D deficiency screening in RLS patients even when other etiological factors are positive. Future studies are required to determine the efficacy of vitamin D in the prevention or treatment of RLS.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: doi:10.1016/j.sleep.2012.04.009.

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