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The Relationship Between 25 (OH) Vitamin D Level and the Severity of Disease and Sleep Quality in Restless Legs Syndrome

Huzursuz Bacaklar Sendromunda 25 (OH) Vitamin D Düzeylerinin Hastalık Şiddeti ve Uyku Kalitesi ile Olan İlişkisi

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Abstract

Objective: Restless legs syndrome (RLS) is a common chronic sensory-motor neurologic disease with serious disabling effects on affected individuals' physical and emotional health and quality of life. The underlying pathophysiology of the disease is not clear but iron metabolism disorders and dopaminergic dysfunction along with a genetic predisposition are blamed, and recently vitamin D deficiency was considered to play an important role in RLS. In this study, we aimed to investigate the relationship of concentrations of a vitamin D metabolite, 25 (OH) vitamin D, with RLS severity and quality of sleep.

Materials and Methods: We enrolled 152 patients aged between 18 and 75 years who were referred to our general neurology outpatient clinic in Istanbul Training and Research Hospital, and diagnosed with RLS according to the International Restless Legs Syndrome Study Group diagnostic criteria, between September 2016 and September 2018. The patients were classified as the vitamin D deficiency group (<20 ng/mL, group 1) and normal vitamin D group (>20 ng/mL, group 2). Both groups were evaluated for their RLS severity index and Pittsburgh Sleep Quality Index (PQI). Both groups are compared statistically.

Results: Of the 152 patients, 89 patients had low vitamin D concentrations (<20 ng/mL) (group 1) and 63 had normal vitamin D concentrations (>20 ng/mL) (group 2). There was no significant difference in terms of age, sex, body mass index, and cigarette consumption ($p>0.05$). There were significant differences between the two groups in terms of upper extremity involvement, ferritin concentrations, PQI, and RLS severity scores ($p<0.05$).

Conclusion: The present study demonstrated that patients who are vitamin D deficient might have more severe RLS symptoms and an impaired quality of sleep compared with other patients with RLS.

Keywords: Restless legs syndrome, sleep quality, vitamin D

Öz

Amaç: Huzursuz bacaklar sendromu (HBS), bireyin fiziksel sağlığı, duygu durumu ve hayat kalitesi üzerinde olumsuz etkileri olan ve toplumda sık rastlanan sensorimotor özellikte kronik nörolojik bir hareket bozukluğudur. HBS patofizyolojisi tam olarak anlaşılamamakla birlikte, genetik alt yapının yanı sıra demir metabolizması bozuklukları ve dopaminerjik disfonksiyon sorumlu tutulmakta ve son zamanlarda vitamin D eksikliğinin de hastalığın ortaya çıkmasında rolü olduğu iddia edilmektedir. Bu çalışmada, idiyopatik HBS tanısı alan hastalarda, bir vitamin D metaboliti olan 25 (OH) vitamin D düzeylerinin HBS şiddeti ve bireylerdeki uyku kalitesi ile olan ilişkisi incelenmiştir.

Gereç ve Yöntem: İstanbul Eğitim ve Araştırma Hastanesi, Genel Nöroloji Polikliniği'ne Eylül 2016-Eylül 2018 tarihleri arasında başvurmuş, Uluslararası Huzursuz Bacaklar Sendromu çalışma grubu tanı kriterlerine göre HBS tanısı almış, 18-75 yaş arası 152 hasta çalışmaya dahil edildi. Hasta grubu vitamin D değeri düşük (<20 ng/mL) ve normal (>20 ng/mL) olarak 2 gruba ayrıldı. Her iki gruba HBS şiddetinin belirlenebilmesi amacıyla Uluslararası Huzursuz Bacaklar Sendromu Şiddeti Değerlendirme Skalası ve subjektif uyku kalitelerinin belirlenebilmesi amacıyla Pittsburgh Uyku Kalitesi Ölçeği (PQI) uygulandı. Gruplar kendi aralarında istatistiksel olarak karşılaştırıldı.

Bulgular: Toplam 152 hastanın 89'u 25 (OH) vitamin D değeri düşük grup (grup 1) ve 63'ü 25 (OH) vitamin D değeri normal (grup 2) olan gruba dahildi. Her iki grup arasında yaş, cinsiyet, vücut kitle indeksi ve sigara kullanımı bakımından istatistiksel olarak anlamlı bir farklılık yoktu ($p>0,05$). Grup 1 ve 2 arasında üst ekstremite tutulumu oranları, ferritin değerleri, PQI skorları ve HBS şiddetini gösteren IRLS skorları bakımından istatistiksel olarak anlamlı düzeyde farklılık saptandı ($p<0,05$).

Sonuç: Çalışmamız 25 (OH) vitamin D eksikliği olan hastalarda HBS şiddetinin daha fazla olduğunu ve uyku kalitesinin belirgin derecede bozulduğunu göstermektedir.

Anahtar Kelimeler: Huzursuz bacaklar sendromu, uyku kalitesi, vitamin D

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Introduction

Restless Legs syndrome (RLS) is a chronic sensorimotor neurologic movement disorder that has a significant negative impact on affected individuals' physical health, mood, and quality of life (1). Although it is common in women and older patients, it can be seen in all age groups (2). Despite its prevalence being relatively variable at 4-29%, in large-scale, community-based studies, diagnosis can often be missed or patients may be misdiagnosed (3). It presents with uncomfortable sensations in the form of an irresistible desire to move, classically involving the lower extremities, but also in the upper extremities and trunk (1,4). Symptoms tend to worsen later in the day and while at rest, and patients typically describe relief of symptoms with movement (5).

RLS can be classified as primary and secondary, etiologically. The primary form, also known as idiopathic RLS, is the form that has early onset in life, peaks in the second decade, and is thought to be a genetic predisposition. It constitutes approximately 70-80% of all patients with RLS (6). Although the role of genetic factors is well known, the responsible genes are still not fully determined and the syndrome is thought to have a multifactorial genetic background (7). Secondary RLS is secondary to several medical conditions such as pregnancy, end-stage renal failure, connective tissue diseases, rheumatic diseases, some drugs, diabetes mellitus, Parkinson's disease and other extrapyramidal system disorders, and multiple sclerosis (8). Although the pathophysiology of RLS is not fully understood, iron metabolism disorders and dopaminergic dysfunction are mainly responsible, as well as a genetic background, and it is claimed that the role of some neurotransmitters and the deficiency of vitamin D have a role in the emergence of the disease (7).

Vitamin D is a prohormone that plays an effective role in glucose metabolism; cardiovascular, immunologic, and dopaminergic system functions, in addition to muscle-skeletal system functions (9). It is thought to play a key role in the regulation of dopaminergic pathways and the rise of dopamine concentrations in the brain. There are many studies in the literature showing that low vitamin D concentrations may play a role in the pathophysiology of a number of neurologic and psychiatric disorders including Parkinson's disease, multiple sclerosis, dementia, and depression (10,11,12). Recent studies have reported that low vitamin D concentrations may cause dysfunction in dopaminergic pathways and may lead to the formation of RLS. Vitamin D supplementation causes a decrease in symptoms in these patients, which supports this hypothesis (13).

In this study, the relationship between 25 (OH) vitamin D concentrations, which is a vitamin D metabolite, severity of RLS, and sleep quality in individuals diagnosed as having idiopathic RLS was investigated.

Materials and Methods

Two hundred twenty-one patients aged 18-75 years who were admitted to the general neurology outpatient clinic of the Istanbul Training and Research Hospital between September 2016 and September 2018 and were diagnosed as having RLS according to the criteria of the International Restless Legs Syndrome Study Group (IRLSSG) were included in the study. All patients underwent detailed clinical and neurologic examinations. Patients with a possible etiologic cause of secondary RLS (chronic renal failure, osteoporosis, liver dysfunction, pregnancy) and patients with findings of polyneuropathy in nerve conduction and electromyographic studies were excluded from the study. After the exclusion criteria were applied, the remaining 152 patients were included in the study. Serum concentrations of alkaline phosphatase (ALP), calcium, phosphorus, ferritin, and 25 (OH) vitamin D were measured by taking venous blood samples. Patients were divided into two groups according to 25 (OH) vitamin D concentrations: group 1 with low 25 (OH) vitamin D concentrations (<20 ng/mL) and group 2 with normal 25 (OH) vitamin D concentrations (≥20 ng/mL). In order to determine the severity of RLS, the IRLSSG rating scale (14) and the Pittsburgh Sleep Quality Index (PSQI), the Turkish form of which has been validated (15,16), were applied to the patients in both groups.

Informed consent was given by all participants. The study was approved by the Istanbul Training and Research Hospital of Clinical Research Ethics Committee (Protocol number: 2011-KAEK-50).

Biochemical Investigations

Venous blood samples (10 mL) from the patients included in the study taken after fasting all night were transferred to transparent glass biochemistry tubes, centrifuged, and stored at -80 °C. Serum calcium, phosphorus, ALP, ferritin values and 25 (OH) vitamin D concentrations were analyzed using an enzyme-linked immunosorbent assay (ELISA) kit in the same laboratory and under appropriate conditions. Vitamin D deficiency was defined as <20 ng/mL.

The IRLSSG Rating Scale

All patients were evaluated using the IRLSSG rating scale, which consists of 10 questions and was developed by the IRLSSG in 2001 to determine the severity of the disease. This scale comprises questions containing the classic symptoms of the disease and answers to each question are rated between 0-4. Patients with 0-10 points are classified as having mild RLS, 11-20 points moderate, 21-30 points severe, and 31-40 points very severe RLS.

The Pittsburgh Sleep Quality Index

The validity and reliability study of the Turkish form of the PSQI, which is a widely used subjective measure of sleep quality, was made by Ağargün et al. (16) in 1996. Nineteen individual items generate seven 'component' scores: Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Answers to each item are rated between 0-3. The sum of scores for these seven components yields one global score. The global score ranges between 0-21 and scores >5 indicate impairment in quality of sleep.

Statistical Analysis

In the evaluation of the data obtained from the study, the SPSS 22.0.1 program (SPSS Inc., Chicago, IL, USA) was used. In comparisons between group 1 with low 25 (OH) vitamin D concentrations and group 2 with normal 25 (OH) vitamin D concentrations, Student's t-test or the Kruskal-Wallis test were

used for continuous variables and the chi-square test was used for categorical variables. The level of statistical significance was accepted as p<0.05.

Results

Eighty-nine of a total of 152 patients were included in group 1 with low 25 (OH) vitamin D values and 63 were included in the group 2 with normal 25 (OH) vitamin D values. There were 43 women (48.3%) and 46 men (51.6%) in group 1 and 28 women (44.4%) and 35 men (55.5%) in group 2. There was no statistically significant difference between the two groups in terms of age, sex, BMI, and smoking (p>0.05). The mean age of the patients was 46.13±13.30 years and the mean duration of disease was 27.02±14.99 months. The mean IRLSSG rating scale score was 20.40±9.86 and the mean PSQI was 8.16±5. Table 1 summarizes the data of parameters of the groups with low and normal 25 (OH) vitamin D values.

There were statistically significant differences between groups 1 and 2 in terms of upper extremity involvement rates, ferritin values, Pittsburgh scores, and IRLSSG scores indicating RLS severity (p<0.01).

Discussion

The most important result of our study was that the IRLSSG rating scale scores, indicating RLS severity, and the PSQI scores, which illustrate subjective quality of sleep, were higher in the group with low 25 (OH) vitamin D concentrations than in the group with normal 25 (OH) vitamin D concentrations, which indicated that the symptoms of RLS were more severe and quality of sleep was more impaired in patients with RLS with low 25 (OH) vitamin D concentrations (p<0.01). In addition, ferritin concentrations were lower (p<0.05), upper extremity involvement rates were higher (p=0.047), and disease duration was shorter (p=0.02) in these patients.

Mechanisms including dopamine dysfunction and iron deficiency are thought to play a role in the pathophysiology of RLS and they have exceled in studies (17,18). In recent studies of fluorine-18-L-dihydroxyphenylalanine positron emission tomography, it was claimed that dopamine receptors were elevated in response to low endogenous dopamine concentrations and that it caused hypoactive dopaminergic neurotransmission in patients with RLS (19). This hypothesis is supported by studies showing that dopamine concentrations in the putamen and substantia niagra were changed in patients with RLS (20). In addition, recent studies have shown that dopamine agonists used in the treatment of RLS provide relief from symptoms (21).

Vitamin D is a prohormone that plays an important role in the continuation of dopaminergic system functions, but its role in the pathophysiology of RLS has not yet been fully clarified (22). There are data suggesting that vitamin D-specific receptors are present in neuronal and glial tissue in the brain, and vitamin D is thought to have a detoxification effect in neurons by causing an increase in brain glutathione concentrations (23). In addition, vitamin D has been shown in studies to increase dopamine and dopamine metabolites by influencing nigrostriatal dopaminergic pathways and thus having neuroprotective effects (13). Therefore, deficiencies in vitamin D and its metabolites

Table 1. Comparison of demographic and laboratory parameters between group 1 and group 2

	Group 1 (n=89)	Group 2 (n=63)	p value
Age (years)	45.29±13.50**	47.33±13.03	0.314
Sex Female (n/%) Male (n/%)	 43 (48.3%) 46 (51.7%)	 28 (44.4%) 35 (55.6%)	 0.742
Duration of disease (months)	27.11±14.30	31.12±15.09	0.02*
Involvement of upper extremity Yes (n/%) No (n/%)	 29 (32.6%) 60 (67.4%)	 12 (19%) 51 (81%)	 0.047*
IRLSSG Rating Scale score	27.24±6.50	10.73±3.84	<0.01*
Pittsburgh score	11.64±3.36	3.25±1.25	<0.01*
25 (OH) vitamin D (ng/mL)	14.82±2.70	31.80±4.68	<0.01*
Ferritin (ng/mL)	24.19±8.88	54.57±9.75	<0.05*
ALP (IU/L)	73.65±10.29	78.82±10.58	0.180
Calcium (mg/dL)	8.77±0.44	8.46±0.82	0.260
BMI (kg/m^2)	27.45±4.24	27.82±4.49	0.604
Smoking Yes (n/%) No (n/%)	 30 (33.71%) 59 (66.29%)	 22 (24.71%) 41 (46.06%)	 0.877

*The level of statistical significance was accepted as p<0.05
**Data are given as mean ± standard deviation.
BMI: Body mass index, ALP: Alkaline phosphatase, IRLSSG: International Restless Legs Syndrome Study Group

may lead to dopaminergic dysfunction and consequently to the formation of RLS (5). In addition, increased concentration of vitamin D binding protein in cerebrospinal fluid in patients with RLS supports the role of vitamin D in the formation of disease (24). Wali et al. (13) gave vitamin D3 treatment to 12 patients with primary RLS with vitamin D deficiency for 3-8 months and compared the severity of RLS in the pre- and post-treatment periods in their study in 2014. The authors showed that the severity of RLS was significantly reduced in the post-treatment period (IRLSSG 10) than in the pre-treatment period (IRLSSG 26) (p=0.002). In another study conducted by Balaban et al. (8) in 36 patients, 25 (OH) vitamin D concentrations were reported to show a negative correlation with the severity of the disease (p=0.01). Similarly, in our study, the IRLSSG scores were significantly higher - suggesting more severe RLS - in patients with low 25 (OH) vitamin D concentrations than in patients with normal 25 (OH) vitamin D concentrations.

It was shown in many studies in patients with RLS that the symptoms of the disease can lead to severe sleep disturbances and deterioration in the quality of life (25). In a study of 317 patients in a hemodialysis center in 2017, 244 (77%) of the patients had RLS, and 15.6% had depression and impairment in quality of sleep, and there was a positive correlation between the severity of the disease and sleep disorders (26). In a recent study, the quality of sleep in 232 chronic dialysis patients was investigated and it was reported that the PSQI scores increased as the severity of disease increased, which mean quality of sleep worsened as the severity of disease increased. The authors suggested that this could also be explained by dopaminergic dysfunction, as well as disturbances and metabolic changes in iron homeostasis (27). In our study, we found that impairment in sleep quality in the group with 25 (OH) vitamin D deficiency was significant and that it was proportional to the severity of the disease; we consider that it might be a reflection of dopaminergic dysfunction in patients with vitamin D deficiency.

Another result of our study was that ferritin concentrations were lower in group 1. Since low ferritin level is a reflection of disturbance of iron metabolism, studies have shown that iron deficiency in the central nervous system has a role in the formation of the disease in patients with RLS (28). Iron deficiency is also thought to cause dopaminergic dysfunction, leading to worsening in the symptoms of RLS, because it acts as a cofactor in the production mechanism of dopamine via thyroxine hydroxylase (29). The low ferritin concentrations of both groups was a predictable condition because patients in both groups had RLS and none received any treatment. Ferritin concentrations were lower in patients with low vitamin D concentrations than in patients with normal vitamin D concentrations, which could contribute to higher concentrations of disease severity in patients with low vitamin D concentrations than in patients with normal vitamin D concentrations.

Higher rate of upper extremity involvement in patients with low vitamin D concentrations than in patients with normal vitamin D concentrations could be explained by the higher rate of severe and widespread disease in patients with low vitamin D concentrations. More severe disease could cause poor quality of sleep and impairment in quality of life, leading to consulting a physician earlier and to having shorter duration of disease.

Study Limitations

Our study has limitations. First, our study was a cross-sectional study, reflecting the data of a tertiary center, which might be insufficient to reflect the entire population. Second, the results of our study were limited. Vitamin D replacement therapy, which could lead to possible prospective changes in RLS severity and quality of sleep, was not administered and therefore these changes were not evaluated. Finally, the fact that our patient population was selected from moderate to severe cases with more prominent symptoms admitting to a tertiary center may have affected the results of the study.

Conclusion

In conclusion, our study shows that the severity of the disease is more pronounced in patients with 25 (OH) vitamin D deficiency and that it may lead to severe impairment in the quality of sleep. In patients with RLS, checking vitamin D concentrations in the etiologic search and giving vitamin D replacement treatment by physicians may provide relief in patients' symptoms and improve the quality of life. New prospective studies also evaluating the results of vitamin D treatment in a wider population of patients are needed.

Ethics

Ethics Committee Approval: The study were approved by the Istanbul Training and Research Hospital of Clinical Research Ethics Committee (Protocol number: 2011-KAEK-50).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Internally peer-reviewed.

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