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Original Article / Özgün Araştırma

Is spinal cord injury a risk factor for vitamin D deficiency?

Omurilik yaralanması D vitamini eksikliği için bir risk faktörü müdür?

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ABSTRACT

Objectives: The aim of this study was to investigate whether spinal cord injury (SCI) is a risk factor for vitamin D deficiency.

Patients and methods: A total of 125 patients with SCI as the patient group and 142 patients with neurologically intact patients as the control group admitted to the inpatient or outpatient clinics of our Physical Medicine and Rehabilitation Hospital between January 2013 and December 2014 were included in the study. Data were retrospectively analyzed using the patient's electronic medical records. Serum 25-hydroxyvitamin D [25(OH)D] levels >30 ng/mL were accepted as normal, 20 to 30 ng/mL as insufficiency, and <20 ng/mL as deficiency.

Results: There was no statistically significant difference in terms of age, sex, and blood sample collection season between the study and control groups (p>0.005). The median serum 25(OH)D level of the SCI group was 12.6 ng/mL (3-59) and 14.4 (5.5-79) ng/mL of the control group. A total of 95.2% of SCI patients and 95% of the controls were vitamin D deficient or insufficient. Serum 25(OH)D levels in the study group were statistically significantly lower than the control group (p=0.006), although it did not reach clinical significance. In both groups, serum 25(OH)D levels were independent from sex and blood sample collection season (p>0.05). Only ambulation status of SCI patients was found to be a significant factor affecting serum 25(OH)D levels in SCI group.

Conclusion: Although it is difficult to conclude that SCI is a risk factor for vitamin D deficiency or insufficiency based on the results of our study, vitamin D insufficiency and deficiency are common among non-ambulated SCI patients, in particular. Therefore, serum 25(OH)D levels should be analyzed on a routine basis in SCI patients and adequate supplementation should be performed in case of deficiency or insufficiency.

Keywords: 25 hydroxyvitamin D; rehabilitation; spinal cord injury; vitamin D deficiency.

ÖZ

Amaç: Bu çalışmada omurilik yaralanmasının (OY) D vitamini eksikliği için risk faktörü olup olmadığı araştırıldı.

Hastalar ve yöntemler: Çalışmaya Ocak 2013 - Aralık 2014 tarihleri arasında Fizik Tedavi ve Rehabilitasyon Hastanemizin yatan hasta veya polikliniklerine başvuran 125 OY'li hasta hasta grubu olarak ve nörolojik olarak sağlam 142 hasta kontrol grubu olarak alındı. Hastaların elektronik tıbbi kayıtları kullanılarak veriler retrospektif olarak incelendi. Serum 25-hidroksivitamin D [25(OH)D] düzeyi >30 ng/mL normal, 20-30 arası yetersizlik ve <20 eksiklik olarak tanımlandı.

Bulgular: Çalışma ve kontrol grupları arasında yaş, cinsiyet ve kan örneği alınma mevsimleri açısından istatistiksel olarak anlamlı farklılık saptanmadı (p>0.005). Omurilik yaralanması olan grupta medyan serum 25(OH)D düzeyi 12.6 ng/mL (3-59) ve kontrol grubunda 14.4 (5.5-79) ng/mL olarak saptandı. Omurilik yaralanması olan hastaların toplam %95.2'sinde ve kontrollerin %95'inde D vitamini eksikliği veya yetersizliği vardı. Çalışma grubunda serum 25(OH)D düzeyleri, kontrol grubuna kıyasla, istatistiksel olarak anlamlı düzeyde daha düşük olmasına karşın (p=0.006), bu fark klinik olarak anlamlı değildi. Her iki grupta da, serum 25(OH)D düzeyleri cinsiyet ve kan örneği alınma mevsiminden bağımsızdı (p>0.05). Yalnızca OY hastalardaki ambulasyon durumu, serum 25(OH)D düzeylerini etkileyen anlamlı bir faktördü.

Sonuç: Çalışma bulgularımıza göre OY'nin D vitamini eksikliği veya yetersizliğinin bir risk faktörü olduğu sonucuna varılması güç olmakla birlikte, D vitamini yetersizliği veya eksikliği, özellikle ambule olmayan OY'li hastalarda yaygındır. Bu nedenle, OY'li hastalarda serum 25(OH)D düzeyleri rutin olarak incelenmeli ve eksiklik veya yetersizlik durumunda gerekli destek verilmelidir.

Anahtar sözcükler: 25-hidroksivitamin D; rehabilitasyon; omurilik yaralanması; D vitamini eksikliği.

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Vitamin D is a hormone which is important for serum calcium homeostasis.[1] It is well-known that low serum vitamin D (25 hydroxyvitamin-D [25(OH)D]) concentrations may lead to osteoporosis, osteomalacia, and rickets.[2,3] Moreover, in recent years, it has been proven that more than 30 different tissues express vitamin D receptors and extra-skeletal effects of vitamin D have been addressed.[4] Since then, muscle weakness, myalgia, diabetes mellitus, cardiovascular diseases, stroke, certain types of malignancies, depression, schizophrenia, autoimmune diseases, cognitive dysfunction, rheumatoid arthritis, chronic obstructive pulmonary disease, and even mortality have been associated with low serum concentrations of 25(OH)D.[2,5-14]

Although there is no consensus on serum 25(OH)D levels yet, values of <20 ng/mL are defined as deficiency, whereas between 20 and 30 ng/mL as insufficiency, and >30 as normal by Holick,[2] and also in our study. On the other hand, according to the Institute of Medicine, levels of <12 ng/mL refer to deficiency and >20 ng/mL to sufficiency.[15] In addition, the US Endocrine Society recommends levels of >20 ng/mL to prevent rickets and osteomalacia and >30 ng/mL to prevent cancer, autoimmune diseases, diabetes mellitus, cardiovascular, and infective diseases and also to strengthen its effects on the musculoskeletal and calcium metabolism.[16] Moreover Bischoff-Ferrari[17] have proposed levels between 36 to 48 ng/mL as optimal.

In patients with spinal cord injury (SCI), the risk for osteoporosis, falls, and fractures already increases independent from the vitamin D status, and may rise much more in case of vitamin D deficiency.[18,19] Moreover, pain, muscle weakness, and depression which are critical for rehabilitation practice are also associated with vitamin D deficiency, making diagnosis and treatment of vitamin D deficiency more important in SCI patients.[20]

In the rehabilitation era, several uncontrolled studies showed that SCI patients had low serum 25(OH)D levels.[21,22] However, due to the fact that serum 25(OH)D levels are already low even in healthy individuals,[23-25] clinical investigations with improved methodological quality are needed to be performed before describing SCI as a risk factor for vitamin D deficiency. Therefore, in this study, we aimed to investigate whether SCI is a risk factor for vitamin D deficiency.

PATIENTS AND METHODS

A total of 125 patients with SCI as the patient group and 142 patients with neurologically intact patients as the control group admitted to the inpatient or outpatient clinics of our physical medicine and rehabilitation center between January 2013 and December 2014 were included in the study. The patients in the control group were neurologically intact, ambulated patients with musculoskeletal symptoms. The study protocol was approved by the institutional ethics committee. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Exclusion criteria were as follows: <16 and >75 years of age, using drugs which can affect vitamin D metabolism or additional neurological diseases except from SCI, hepatic or renal failure, metabolic disorders such as osteoporosis, osteomalacia or rickets.

Data were retrospectively abstracted from the patient's electronic medical records. Age, sex, and serum 25(OH)D levels of the participants in both study and control groups were recorded. The date of the blood analysis was also documented for each patient and the patients were divided into two groups according to the blood sample collection date as summer (March-August) and winter (September-February), due to the known effects of season on serum 25(OH)D levels.

Serum 25(OH)D levels were analyzed by high-performance liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). This system was coupled to an Applied Biosystem® MDS Sciex API 3200 Triple Quadrupole LC-MS/MS. Serum 25(OH)D levels of >30 ng/mL were accepted as normal, 20 to 30 ng/mL as insufficiency, and <20 ng/mL as deficiency.

In addition, the etiology of SCI, time from SCI, functional level, and the American Spinal Cord Injury Association (ASIA) Impairment Scale (AIS) scores of the patients in the study group were noted.

All patients were divided into two groups according to the disease duration as 1 to 6 months and >6 months to investigate the effect of disease duration on serum 25(OH)D levels.

Statistical analysis

Statistical analysis was performed by using the SPSS version 15.0 software (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to analyze normally distributed continuous variables. Descriptive statistics were expressed in

Table 1. Demographic characteristics of the study and control groups

	Study group (n=125)			Control group (n=142)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			35.2±14			36±10	0.620*
Sex							
Female	49	39.2		66	46.5		0.231**
Male	76	60.8		76	53.5		
The blood sample collection period							
September-February	61	48.8		77	54.2		0.376**
March-August	64	51.2		65	45.8		

SD: Standard deviation; * Student's t-test; ** Chi-square test.

mean ± standard deviation (SD) or median (minimum-maximum) for continuous variables, while the number of cases and percentages were used for nominal variables. The Student's t-test was used to determine whether there was a statistically significant difference between the groups for the normally distributed continuous variables. The Mann-Whitney U test was used to investigate whether there was a statistically significant difference for abnormally distributed continuous or orderable variables. The chi-square test was used to compare categorical variables. For the intergroup comparison, the Kruskal-Wallis test was used for abnormally distributed numerical variables. A *p* value of <0.05 was considered statistically significant. Power analysis was performed using G*Power 3.1.9.2 software and power was calculated 0.64, when d (effect size) was 0.23 and α was 0.05.

RESULTS

Demographic and clinical characteristics of the patients in the study are shown in Tables 1 and 2. There was no statistically significant difference in the mean age, sex, and blood sample collection season between the study and control groups (p=0.620, p=0.231, and p=0.376, respectively) (Table 1).

Serum 25(OH)D levels in the study group were found to be lower than the levels of the control group, indicating a statistical significance (p=0.006). When the patients in the study and control groups were divided into three categories according to their serum 25(OH)D levels (as >30 ng/mL, 20 to 30 ng/mL and <20 ng/mL), there was no statistically significant difference between the number of patients in the study and control groups (p=0.149) (Table 3).

Table 2. Demographic and clinical characteristics of the study group (n=125)

	n	%	Mean±SD	Median	Min-Max
Disease duration (days)			511±755	282	30-4519
Disease duration					
1-6 months	45	36			
>6 months	80	64			
Level of lesion					
Cervical	31	24.8			
Thoracic	61	48.8			
Lumbar	33	26.4			
AIS class					
A+B	86	68.8			
C+D	39	31.2			
Ambulation status					
Ambulated	25	20			
Not ambulated	100	80			
Etiology					
Falling from a height	55	44			
Motor vehicle accident	34	27.2			
Non-traumatic	18	14.4			
Gunshot wound	11	8.8			
Crush injury	4	3.2			
Stab wound	2	1.6			
Diving into shallow water	1	0.8			

SD: Standard deviation; Min: Minimum; Max: Maximum; AIS: ASIA (American Spinal Cord Injury Association) Impairment Scale.

Table 3. Serum 25 hydroxyvitamin D levels of the groups

	Study group (n=125)				Control group (n=142)				
	n	%	Median	Min-Max	n	%	Median	Min-Max	*p*
25(OH)D (ng/mL)			12.6	3-59			14.4	5.5-79	0.006*
25(OH)D (ng/mL)									0.149**
0-20	103	82.4			104	73.2			
20-30	16	12.8			31	21.8			
>30	6	4.8			7	4.9			

Min: Minimum; Max: Maximum; 25(OH)D: 25 hydroxyvitamin D; * Mann-Whitney U test; ** Chi-square test.

In the study and control groups, serum 25(OH)D levels were found to be independent from sex and blood sample collection season (p>0.05) (Tables 4 and 5). Only ambulation status of SCI patients was found to be a significant factor affecting serum 25(OH)D levels in SCI group (p=0.046) (Table 4).

DISCUSSION

In our study, the median serum 25(OH)D levels were 12.6 ng/mL (3 to 59) and 14.4 ng/mL (5.5 to 79) in the study and control groups, respectively. A total of 95.2% of SCI patients and 95% of the controls were vitamin D deficient or insufficient. In consistent with our findings, in a study including 160 patients with chronic SCI, Javidan et al.[21] reported that the mean serum 25(OH)D level was 13.6 ng/mL regardless the age and sex. The authors also showed that 53% of the patients had serum 25(OH)D levels of <13 ng/mL. Similarly, Nemunaitis et al.,[22] in a survey of 100 SCI patients, reported a mean serum 25(OH)D level of 16.3 ng/mL and that 93% of patients were vitamin D deficient or insufficient. Age, sex, etiology, disease duration, injury level, or season were not associated with serum 25(OH)D levels.

In another study consisting of 96 patients with complete SCI, Oleson et al.[26] demonstrated that serum 25(OH)D levels were <32 ng/mL in 65% of acute and 81% of chronic SCI patients in the summer and in 84% of acute and 96% of chronic SCI patients in the winter. In this study, time from SCI was found to be associated with serum 25(OH)D levels, as expected. Based on these results, the authors recommended measuring serum 25(OH)D and parathyroid hormone levels *(i)* at the beginning of the rehabilitation period, *(ii)* at certain intervals within the first year after the injury in the adaptation period, and *(iii)* annually in chronic SCI.

Table 4. Serum 25 hydroxyvitamin D levels of the study group according to the clinical and demographic characteristics

		25(OH)D (ng/mL)		
	n	Median	Min-Max	*p*
Sex				
Female	49	12.4	3.3-59	0.576*
Male	76	13.7	3-38.7	
Blood sample collection date				
September-February	61	13.2	3-59	0.278*
March-August	64	12.5	3-50.1	
Level of lesion				
Cervical	31	11	5.2-28.3	0.524**
Thoracic	61	13.7	3-36.4	
Lumbar	33	13.5	5.7-59	
Disease duration				
1-6 months	45	13.5	3.3-38.7	0.809*
>6 months	80	12.5	3-59	
Extent of injury				
Motor complete (AIS A+B)	86	13.1	3-59	0.483*
Motor incomplete (AIS C+D)	39	12.4	3-38.7	
Ambulation status				
Ambulated	25	14.4	8.3-38.7	0.046*
Not ambulated	100	12.4	3-59	

Min: Minimum; Max: Maximum; 25(OH)D: 25 hydroxyvitamin D; * Mann-Whitney U test; ** Kruskal Wallis test; AIS: ASIA (American Spinal Cord Injury Association) Impairment Scale.

Table 5. Serum 25 hydroxyvitamin D levels of the control group according to sex and blood sample collection date characteristics

		25(OH)D (ng/mL)		
	n	Median	Min-Max	*p*
Sex				
Female	66	12.3	5.5-79	0.053*
Male	76	16.1	7.9-67.5	
Blood sample collection date				
September-February	77	13.9	6.3-79	0.654*
March-August	65	14.8	5.5-52	

Min: Minimum; Max: Maximum; 25(OH)D: 25 hydroxyvitamin D; *Mann-Whitney U test.

On the contrary of the study by Oleson et al.,[26] we showed that serum 25(OH)D levels were not associated with the disease duration. This finding was also consistent with the results reported by Nemunaitis et al.[22] In the Oleson's study,[26] however, the patients were divided into groups as the disease duration between 2 to 6 months and >1 year. On the other hand, Nemunaitis et al.[22] divided the patients into three groups as disease duration between 0 to 1 month, 1 to 3 months, and >3 months. Similarly, our patients were classified as the disease duration 1 to 6 months and >6 months, shorter than the periods defined by Oleson et al.[26] However, short disease duration might mask the expected effect of disease duration on serum 25(OH)D levels.

Fifty acute and chronic SCI patients of whom 36 were traumatic were studied in another study and the mean serum 25(OH)D levels were found to be 15.27 ng/mL.[27] In this study, all patients had serum 25(OH)D levels below 31 ng/mL, while incomplete SCI patients had lower serum 25(OH)D levels than complete SCI patients. This was probably due to the chronic debilitating etiology of the incomplete SCI cases who are in general non-traumatic in this study. These results were also similar to our findings.

On the other hand, Hummel et al.,[28] found that only 39% of the patients have serum 25(OH)D levels lower than 30 ng/mL in 62 chronic SCI patients. However, in this study, 86% of the patients were on vitamin D supplementation. Apart from these, in an outpatient rehabilitation clinic, out of 136 rehabilitation patients, 67% were vitamin D deficient or insufficient. The mean serum 25(OH)D levels were 18.7, 16.5, and 16.0 ng/mL in SCI, brain injury, and hereditary musculoskeletal diseases, respectively.[29]

Altogether, we may suggest that SCI patients are vitamin D deficient or insufficient. Our study also supports these results. The superiority of our study to the similar literature reports lies in the control group. There was a statistically significant difference in the mean serum 25(OH)D levels between the study and control groups; however, it did not reach clinical significance. In addition, when the patients in the study and control groups were divided into three categories according to their serum 25(OH)D levels (as >30 ng/mL, 20 to 30 ng/mL and <20 ng/mL), there was no statistically significant difference in the number of patients between the study and control groups. Therefore, despite the fact that 95.2% of our SCI patients had vitamin D levels below sufficiency level, it is still difficult to conclude that SCI is a risk factor for low vitamin D levels. Further large-scale studies including both patients and healthy controls are needed to establish a definite conclusion.

Furthermore, in our study, serum 25(OH)D levels of the SCI patients were not associated with season. Although season has a well-known effect on serum 25(OH)D levels due to the sunlight exposure, our results can be attributed to the fact that SCI patients have minimal social facilities to participate in outdoor activities and, thus, have minimal sunlight exposure in all seasons, as well as spring and summer.

Vitamin D deficiency is commonly seen in the overall population worldwide.[23-25,30,31] Nonetheless, it is a much more important health problem in the SCI population than in the healthy population due to its contribution to osteoporosis, falls, and fractures, for which SCI population is already at risk.

In addition, SCI is thought to be a precipitating factor for poor sunlight exposure, which is known to be the most important reason for vitamin D deficiency. Inadequate sunlight exposure due to prolonged hospitalization, immobilization, and poor social support make a contribution to this clinical condition. Ambulation, as demonstrated in our study, is an advantage for vitamin D synthesis among SCI patients.

On the other hand, there are some limitations to this study. Although the control group consisted

of neurologically intact and ambulated patients, the majority had chronic musculoskeletal pain. Of note, recent literature data have shown that low vitamin D levels are also common among patients with chronic musculoskeletal pain,[32-34] and, therefore 25(OH)D levels of the control group do not represent overall population. Further studies with healthy controls are needed to establish a definite conclusion.

In conclusion, although it is difficult to conclude that SCI is a risk factor for vitamin D deficiency or insufficiency based on the results of our study, vitamin D insufficiency and deficiency are common among non-ambulated SCI patients, in particular. Therefore, serum 25(OH)D levels should be analyzed on a routine basis in SCI patients and adequate supplementation should be performed in case of deficiency or insufficiency.

Declaration of conflicting interests

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