

Evaluation of Serum Vitamin D Levels in Patients with Carpal Tunnel Syndrome

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ABSTRACT

BACKGROUND AND OBJECTIVE: Low levels of vitamin D are associated with clinical effects such as gastrointestinal disorders, cardiovascular disorders, autoimmune disorders, neuropathic diseases, cancer and metabolic syndrome. Carpal Tunnel Syndrome (CTS) is the most common cause of compression neuropathy, which has recently been linked to vitamin D deficiency in the onset or severity of symptoms. Therefore, this study was performed to evaluate the serum levels of vitamin D in patients with carpal tunnel syndrome.

METHODS: This case-control study was performed on 100 patients referred to the neurology clinic of Ayatollah Rouhani Hospital with clinical symptoms of CTS for at least 3 months and 100 patients as a control group who referred to the same clinic for nerve conduction velocity test and did not show symptoms of CTS in clinical examination and electrophysiology. Patients' function, disease severity and pain were measured based on the Boston Carpal Tunnel Questionnaire (BCTQ). Serum vitamin D levels were also measured and compared between the two groups.

FINDINGS: The mean age of patients was 43.53 ± 10.68 years and controls were 45.48 ± 7.12 years. The mean serum vitamin D levels in patients and controls were 19.18 ± 11.39 ng/dL and 21.39 ± 15.93 ng/dL, respectively. In controls, 57 women suffered from vitamin D deficiency ($p < 0.05$). There was no significant difference between the two groups in terms of disease severity, function status, pain severity, electrophysiological defect, involved hand, dominant hand and symptoms associated with vitamin D deficiency and there was a negative correlation in vitamin D levels with disease severity, function and pain of patients.

CONCLUSION: The results showed that there was a relationship between serum vitamin D levels and gender. In addition, a negative correlation was observed between serum vitamin D levels and patients' disease severity and function and electrophysiological defects.

KEY WORDS: Vitamin D, Carpal Tunnel Syndrome, Median Nerve Neuropathy.

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Introduction

Humans get their vitamin D needs from two major sources. One is cholecalciferol (Vit D3), which is synthesized from 7-dihydrocholesterol and absorbed by the skin as ultraviolet rays by 90-95%, and the other is ergocalciferol (Vit D2), which is supplied through diet. The main source of vitamin D in the human body is sunlight on the skin. Since the metabolism of vitamins D2 and D3 occurs in the same way, they are commonly known as vitamin D. 25-hydroxyvitamin D [25(OH)D] is the largest metabolite of vitamin D, and vitamin D deficiency is determined by measuring its serum level (1,2). Vitamin D is associated with the body's metabolism and serum levels of calcium and phosphorus. Low levels of vitamin D are associated with clinical effects such as gastrointestinal disorders, cardiovascular disorders, autoimmune disorders, neuropathic diseases, cancer and metabolic syndrome (3). In one study, the prevalence of Carpal Tunnel Syndrome (CTS) in the community was estimated to be 4–5%, which was more common in the age group of 40–60 years, and 60–80% of patients were women (4). CTS causes pain, numbness, tingling, and fear of losing strength in the hands, which is associated with decreased quality of life and socioeconomic outcomes. The most common risk factors for CTS are pregnancy, obesity, alcohol consumption, occupation, place of residence, rheumatoid arthritis, hypothyroidism, acromegaly and amyloidosis (5-7). Median nerve entrapment leads to carpal tunnel syndrome due to increased intra-carpal tunnel pressure for pathophysiological or mechanical reasons. Due to the role of the median nerve in the sensation and movement of the upper limb and its location in carpal tunnel syndrome, clinical symptoms appear in both primary and secondary forms (8). Early symptoms include pain in the neural pathway to the distal upper extremity, i.e. the first to third finger and outside the fourth finger, palm and paresthesia, which is an unpleasant feeling of numbness and tingling in the same pain path. The above symptoms often worsen at night and the patient wakes up (9). The results of some studies have shown that this disease is more prevalent in females and in the ages of 21 to 61 years (at least 3 to 4 times more). It is also more common in the population of workers than in the general population (10). In a case-control study on CTS patients, vitamin D levels were lower than controls, and pain in patients with vitamin D deficiency was significantly more severe than in patients with normal vitamin D levels (11). Similar results were observed in another study on 63 patients with CTS and 40 patients

without the disease. In this study, patients with moderate CTS had significantly lower vitamin D levels than healthy controls, but no association was found between pain and vitamin D (12). However, in the study of Lee et al., out of 135 patients with CTS, no significant difference was observed in the level of vitamin D of patients and controls (13).

Contradictory results in existing studies can be related to differences in the type of study, small sample size, low study power and inappropriate statistical analysis. Due to the importance and high prevalence of vitamin D deficiency in our society and the possible association of this disorder with carpal tunnel syndrome and studies that had contradictory results, this study was conducted to investigate the relationship between serum vitamin D levels in patients with CTS. It was performed at the clinic of Ayatollah Rouhani Hospital in Babol in 2017.

Methods

This case-control study was performed on patients with carpal tunnel syndrome and control group after approval by the ethics committee of Babol University of Medical Sciences with the code IR.MUBABOL.HRT.REC.1397.029. The patients of this study were among the patients referred to the neurology clinic of Ayatollah Rouhani Medical Center who had clinical symptoms of CTS for at least three months. The control group was selected from those who referred to the same clinic for nerve conduction velocity and did not have CTS in clinical examination and electrophysiology. Patients treated with vitamin D, drugs that affect nerve conduction velocity, history of hand surgery, compressive neuropathies not related to CTS, polyneuropathy, radiculopathy, inflammatory myopathy, patients with diabetes and hypothyroidism and wrist osteoarthritis were excluded. The sample size was calculated based on the formula according to the standard deviation of 0.1 and the effect size of 0.4 to find at least 4 ng/ml difference between the patient and control groups with 80% power and 95% confidence interval (14).

The demographic information questionnaire was used to collect information about age, gender and duration of pain caused by CTS. During the examination, Tinel test and Phalen test were used to assess CTS sensory manifestations. Electrophysiological tests were performed on all patients by electromyography (NR SIGN EEG 5000Q; Canada). The temperature of organs was maintained

above 32°C. Nerve conduction studies (NCSs) of the median nerve were performed by stimulating the median nerve in the second finger. Sensory nerve action potential (SNAP) was measured by placing a surface electrode on the wrist at a distance of 13 cm from the stimulatory electrode. The sensory nerve conduction velocity (SNCV) and sensory nerve action potential (SNAP) were measured. Motor NCSs were performed by stimulating the median nerve in the wrist and elbow. Ulnar SNAP and ulnar locomotor NCSs were also measured. Patients with ulnar nerve involvement were also excluded from the study. Based on the results of electrophysiological tests, patients were divided into two categories: CTS approved based on electrophysiology and patients with negative symptoms and electrophysiology. The variables studied in these patients are DSL (distal sensory latency of median nerve) in milliseconds, which is considered abnormal when it is longer than 3.5 milliseconds, and DML (distal motor latency of the median nerve) in milliseconds, which is considered abnormal when it is longer than 4.2 milliseconds. The severity of the electrophysiological defect was categorized by the modified neurophysiological grading system as follows: Slight CTS: standard negative result with abnormal comparative test; Mild CTS: long DSL and normal DML of median nerve; Medium CTS: long DSL and DML of median nerve; Severe CTS: Lack of median nerve DSL and abnormal DML; Extreme CTS: Lack of sensory response and thenar motor (15).

Simultaneously with electrophysiological evaluation, blood samples were collected to measure serum 25-hydroxyvitamin D levels. The samples were kept at -30 °C. Radioimmunoassay was used to determine the serum level of 25-hydroxyvitamin D. Based on the results of serum vitamin D level in ng/ml; Normal levels: more than 30; Insufficiency: 20 – 30; Deficiency: levels below 20 and above 100 were considered equivalent to toxicity levels and liver problems (16). In the present study, patients with serum levels less than 20 ng/dL were considered as patients with vitamin D deficiency. The Boston questionnaire was used to determine the severity and quality of CTS, the validity of which has been confirmed in previous studies (17). In this study, the standard Persian Boston BCTQ (Boston Carpal Tunnel Questionnaire) was used to assess the severity of pain, symptoms and functional status of carpal tunnel syndrome in patients.

The first part of the questionnaire includes 11 questions related to the severity of symptoms, and 5

questions of this part are about pain score and each question has 5 points. The second part is about patients' functional status, which includes 8 questions about the degree of disability; 5 points are assigned to each question. At the end, the scores of each section are summed and divided by the number of questions and a number based on 5 is obtained; higher score indicates more disability of the patient. In this study, patients' pain scores were calculated based on the first 5 questions of the section related to the severity of symptoms (18). The highest score is 5 (indicates more severe symptoms or more disability of the patient) and the lowest score is 1. Patients were explained about the study and written consent was obtained from the patients. Data were analyzed using SPSS version 23.0 and statistical tests of T-Test, Chi-Square and ANOVA, while $p < 0.05$ was considered significant.

Results

In the present study, there was no statistically significant difference between demographic parameters in both patient and control groups. Nine people out of 72 female patients, and two people out of 76 female controls had a history of underlying diseases, which showed a statistically significant difference ($p = 0.030$). Demographic parameters of patients with mean serum levels of vitamin D in ng/dL including ages less than 50 (17.35 ± 9.67) compared to ages 50-64 (23.48 ± 13.92), no underlying disease (18.18 ± 9.82) compared to the underlying disease (29.33 ± 19.83) and people with high school diploma and above (16.81 ± 7.88) compared to illiterate people (25.08 ± 15.23) showed statistically significant differences (Table 1). The mean serum vitamin D levels in patients and controls were 19.18 ± 11.39 ng/dL and 21.39 ± 15.93 ng/dL, respectively. Patients living in rural areas with 55%, female patients with 91% and married patients with 96% had the highest frequency among patients. Negative correlation of vitamin D level with left DSL, right DML, left DML and positive correlation of vitamin D level with right DSL were obtained using electromyographic test results (EMG/NCV), which were not significant. Furthermore, the negative correlation between serum vitamin D level in patients and disease severity, function and pain score were not statistically significant (Table 2). The highest prevalence in dominant right hand (80%) and both involved hands (78%) with symptoms of tingling, positive Phalen test, positive Tinel sign, negative

reverse Phalen test and mild electrophysiological defect was observed in patients with serum vitamin D levels

less than 20, and no statistically significant difference was observed in any of the variables (Table 3).

Table 1. The frequency of demographic information in patients and controls based on serum vitamin D levels

Variable		Frequency(%)		P	Frequency of vitamin D in the control group(%)		P	Frequency of vitamin D in the case group(%)		P	Mean±SD		P
		Patients	Controls		<20	≥20		<20	≥20		Patients	Controls	
Age (years)	<50	72(72)	76(76)	0.551	45(45)	31(31)	0.305	45(45)	27(27)	0.430	^a 17.35±9.67	20.65±14.02	0.099
	50–64	25(25)	23(23)		16(16)	7(7)		12(12)	13(13)		^b 23.48±13.92	21.87±19.39	0.741
	≥65	3(3)	1(1)		-	1(1)		2(2)	1(1)		27.33±18.01	67.00±0.00	0.197
Gender	male	9(9)	15(15)	0.192	4(4)	11(11)	0.003	4(4)	5(5)	0.352	21.33±8.83	^a 30.60±16.48	0.136
	female	91(91)	85(85)		57(57)	28(28)		55(55)	36(36)		18.97±11.63	^b 19.77±15.37	0.696
BMI (kg/m ²)	<25	13(13)	10(10)	0.182	6(6)	4(4)	0.989	7(7)	6(6)	0.913	22.00±14.46	27.40±18.50	0.440
	25–29.9	29(29)	29(29)		18(18)	11(11)		23(23)	16(16)		19.97±11.76	22.18±14.80	0.496
	≥30	48(48)	61(61)		37(37)	24(24)		29(29)	19(19)		17.77±10.16	20.03±16.03	0.396
Occupation	Employee	6(6)	10(10)	0.414	6(6)	4(4)	0.963	3(3)	3(3)	0.886	21.50±12.42	20.49±10.23	0.862
	Self-employed	19(19)	14(14)		5(5)	9(9)		11(11)	8(8)		18.42±9.36	19.09±12.67	0.862
	Housewife	75(75)	76(76)		46(46)	30(30)		45(45)	30(30)		19.19±11.88	21.93±17.13	0.255
Underlying disease	Yes	9(9)	2(2)	0.030	1(1)	1(1)	0.747	4(4)	5(5)	0.352	^a 29.33±19.83	19.00±4.24	0.499
	No	91(91)	98(98)		60(60)	38(38)		55(55)	36(36)		^b 18.18±9.82	21.44±16.09	0.097
Education	illiterate	13(13)	10(10)	0.931	6(6)	4(4)	0.876	13(13)	10(10)	0.931	^a 25.08±15.23	26.49±28.10	0.878
	without high school diploma	50(50)	52(52)		32(32)	20(20)		50(50)	52(52)		19.64±11.97	21.16±15.27	0.578
	Diploma and above	37(37)	38(38)		23(23)	15(15)		37(37)	38(38)		^b 16.81±7.88	20.65±12.61	0.124
Marital Status	Single	2(2)	3(3)	0.902	2(2)	1(1)	0.931	2(2)	3(3)	0.902	16.50±4.95	15.63±8.14	0.904
	Married	96(96)	95(95)		58(58)	37(37)		96(96)	95(95)		19.45±11.51	21.38±15.94	0.337
	widower/widow	2(2)	2(2)		1(1)	1(1)		2(2)	2(2)		9.00±1.41	30.50±28.99	0.405
Place of residence	city	45(45)	44(44)	0.887	29(29)	15(15)	0.372	45(45)	44(44)	0.887	18.62±12.39	18.58±12.63	0.987
	village	55(55)	56(56)		32(32)	24(24)		55(55)	56(56)		19.64±10.60	23.60±17.92	0.160

Table 2. Mean demographic variables and serum vitamin D levels in patients and controls

Variable	Mean±SD		P-value	Correlation coefficient
	Patients	Controls		
Age (years)	43.53±10.68	45.48±7.12	0.130	
BMI (Kg/M ²)	30.16±4.70	31.18±4.82	0.128	
Disease severity	3.55±0.76	-	0.864	- 0.017
Patients' function	3.68±0.77	-	0.596	- 0.054
Patients' pain score	3.48±1.01	-	0.645	- 0.047
Right DSL	4.08±0.77	-	0.879	0.011
Left DSL	4.17±0.87	-	0.919	- 0.007
Right DML	4.03±1.08	-	0.974	- 0.002
Left DML	4.03±1.03	-	0.637	- 0.034

Table 3. Frequency of total clinical information based on vitamin D deficiency in patients with carpal tunnel syndrome

Variable		Total	Vitamin D		P-value
		Number(%)	<20	≥20	
Involved hand	Both	78(78)	47(47)	31(31)	0.388
	Right	9(9)	5(5)	4(4)	
	Left	5(5)	2(2)	3(3)	
Dominant hand	Left	7(7)	3(3)	4(4)	0.152
	Right	80(80)	51(51)	29(29)	
	Both	13(13)	5(5)	8(8)	
Associated symptoms	numbness	74(74)	44(44)	30(30)	0.875
	tingling	83(83)	51(51)	32(32)	0.272
	irritation	20(20)	14(14)	6(6)	0.263
	pain	81(81)	48(48)	33(33)	0.913
Phalen test	Positive	66(66)	36(36)	30(30)	0.207
	Negative	34(34)	23(23)	11(11)	
Tinel test	Positive	72(72)	43(43)	29(29)	0.814
	Negative	28(28)	16(16)	12(12)	
Reverse Phalen test	Positive	47(47)	27(27)	20(20)	0.766
	Negative	53(53)	32(32)	21(21)	
Electrophysiological defects	Slight	28(28)	18(18)	10(10)	0.900
	Mild	34(34)	18(18)	16(16)	
	Medium	30(30)	18(18)	12(12)	
	Severe	6(6)	4(4)	2(2)	
	Extreme	2(2)	1(1)	1(1)	

Discussion

In this study, serum vitamin D levels in patients were lower than controls and decreased significantly. In addition, serum levels less and more than 20 ng/dL of vitamin D in the control and patient groups were not statistically significant in terms of demographic variables. A limited number of studies have examined the relationship between CTS and vitamin D. In a study on women in Turkey, 90 people with CTS with electrophysiological diagnosis had lower serum vitamin D levels, and the severity of CTS pain in patients with vitamin D deficiency was significantly higher than in patients with normal serum vitamin D levels. D was normal (11). In another study that assessed serum vitamin D levels in 135 women with CTS with electrophysiological diagnosis in South Korea, there was no significant relationship between patients and controls regarding serum vitamin D levels. However, lower levels of vitamin D were seen in women under 50 (13). As in both studies, serum vitamin D levels in patients with CTS were significantly lower than controls in the present study. In a controlled study with 108 patients, the pain and functional ability of

hospitalized patients was assessed using the Boston Questionnaire (BQ) and a significant relationship was observed between BQ and serum vitamin D levels (19). In another study among patients with vitamin D deficiency, CTS pain was significantly increased and serum vitamin D levels were reduced, and patients' BMI was higher than the control group with normal vitamin D levels. There was also a significant negative correlation between serum vitamin D levels and BMI as well as Boston pain score, positive nerve conduction velocity and distal motor latency (DML) (20). In the present study, almost all patients had serum vitamin D levels below 20, which was quite evident in women under 50 years of age. In addition to the basic physiological differences between men and women, the reason for this can be associated with high prevalence of vitamin D deficiency in Mazandaran region due to weather conditions and lack of sunlight. In addition, sick men and women had lower serum vitamin D levels than controls, which can increase the severity of pain due to CTS. In a study on people with CTS with symptoms of numbness, and tingling, serum vitamin D levels were not significantly different between the two

groups, and higher rates of distal motor latency were observed in patients with vitamin D deficiency (21). In another study, patients with vitamin D deficiency had significantly higher pain scores and vitamin D levels had a negative correlation with the range of motion of the median and ulnar nerve branches (22). In contrast to these studies, there was no statistically significant difference in negative correlation coefficient of vitamin D levels and left DSL, right DML, left DML and positive correlation of right DSL between controls and patients with CTS in the present study. Contradictory results in the existing studies can be related to differences in the type of study, small sample size, low study power and inappropriate statistical analysis. However, there are several reasons in favor of the association between CTS and vitamin D deficiency. First, these two conditions are common in society, especially in northern Iran, and the high prevalence of vitamin D deficiency has been shown in this region and in patients with musculoskeletal diseases such as CTS (23,24). Obesity and metabolic syndrome are also common in northern Iran (25) and a significant relationship has been observed between CTS and vitamin D deficiency and between CTS and BMI. CTS is more common in obese people and vitamin D levels are lower in these patients (20). Second, the results of a study showed that vitamin D receptors were observed in

the endothelial cells of the subsynovial connective tissue of CTS patients. In this study, there was a significant correlation between vitamin D receptor expression and the severity of electrophysiological symptoms (26).

Based on the findings of the present study, serum levels of vitamin D were lower in CTS patients compared to controls. In addition, the severity of the disease and patients' function and pain score of patients had a negative correlation with vitamin D levels. Patients younger than 50 years had significantly lower levels of vitamin D, and women were more likely to suffer from vitamin D deficiency. Due to the association between vitamin D deficiency and carpal tunnel syndrome and the greater severity of the disease, routine screening for vitamin D deficiency in CTS patients and treatment of vitamin D deficiency in these patients and all women is recommended.

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