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ORIGINAL ARTICLE

The evaluation of vitamin D levels in patients with carpal tunnel syndrome

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Abstract The aim of this study was to evaluate the relationship between 25-hydroxyvitamin D (25(OH)D) levels and carpal tunnel syndrome (CTS). 25(OH)D levels were checked in 108 consecutive patients with CTS symptoms and 52 healthy controls. All patients underwent nerve conduction studies and completed Boston Carpal Tunnel Questionnaire (BQ) symptom severity and functional status scales to quantify symptom severity, pain status and functional status. There were 57 patients with electrophysiological confirmed CTS (EP+ group) and 51 electrophysiological negative symptomatic patients (EP− group). 25(OH) D deficiency (25(OH)D < 20 ng/ml) was found in 96.1 % of EP− group, in 94.7 % of EP+ group and in 73.8 % of control group. 25(0H) D level was found significantly lower both in EP+ and EP− groups compared to control group ($p = 0.006$, $p < 0.001$, respectively). Although mean vitamin D level in EP− group was lower than EP+ group, statistically difference was not significant between EP+ and EP− groups ($p = 0.182$). BQ symptom severity and functional status scores and BQ pain sum score were not significantly different between EP+ and EP− groups. We found no correlation with 25(OH) D level for BQ symptom severity, functional status and pain sum scores. 25(OH) D deficiency is a common problem in patients with CTS symptoms. As evidenced by the present study, assessment of serum 25(OH)D is recommended in CTS patients even with electrophysiological negative results.

Keywords Vitamin D · Carpal tunnel syndrome · Entrapment neuropathy · Boston Carpal Tunnel Questionnaire · Pain

Introduction

Vitamin D is a steroid molecule, mainly synthesized in the skin from 7-dehydrocholesterol by ultraviolet irradiation or obtained through the diet. The major circulating metabolite of vitamin D is 25(OH) Vitamin D (25(OH)D), with a half-life of 21–30 days. Serum concentration of 25(OH)D is the most reliable biochemical index of vitamin status [1]. For decades, the role of vitamin D was considered to be limited to the formation and maintenance of bone as well as homeostasis of calcium and phosphate. However, growing evidence suggests that vitamin D has a vast array of effects on the biological system together with an association with a number of conditions including cardiovascular diseases, metabolic syndrome, infections, autoimmune conditions, neurodegenerative diseases, and diabetic neuropathy [2]. Also, vitamin D deficiency has been reported to play a potential role in non-specific persistent painful conditions [3].

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy. Primary features of CTS include numbness, tingling, burning, and pain in the hand, and a reduction in grip strength and function of the affected hand [4].

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Based on a potential association between vitamin D deficiency and non-specific neuropathic symptoms, we aimed to compare 25(OH)D levels of patients with CTS symptoms with healthy controls and to examine the association between 25(OH)D levels and electrophysiological data, symptom severity, functional status, and pain severity in symptomatic patients.

Materials and methods

The patients in this study were consecutively selected from those referred to Bezmialem Vakıf University Hospital electrophysiology laboratory between April and June 2014 with suspected CTS because of symptoms such as numbness and/or tingling in the median nerve distribution with or without pain in the hand and arm. As control group, we enrolled healthy subjects from hospital staffs and healthy relatives of patients during the same study period consecutively, without complaints of numbness and tingling in the median nerve distribution. All controls were evaluated clinically by neurologists in terms of sensorial findings in median nerve distribution, Phalen's test and Tinel's sign. Subjects with normal examination findings were enrolled as control in this study. Patients and healthy controls were excluded if they had a known history of polyneuropathy, cervical radiculopathy, rheumatological disease, hereditary neuropathy with liability to pressure palsy, renal failure, and alcohol abuse or if there was a history of surgery or trauma involving the upper limb and/or neck. Subjects currently receiving vitamin D treatment were also excluded. All candidates provided written informed consent, and the study protocol was approved by the local medical ethics committee.

Electrophysiological examination was performed in all patients with a Keypoint electromyography device (Medtronic, Skovlunde, Denmark). Limb temperature was maintained above 32 °C. Median nerve sensory nerve conduction studies (NCSs) were performed with an orthodromic technique that stimulated the median nerve at digit II. Sensory nerve action potentials (SNAP) were recorded by surface electrodes placed over the wrist at a distance of 13 cm from the active stimulating electrode. The sensory conduction velocity (SCV) and peak-to-peak sensory nerve action potential amplitude (SNAP) were measured. Motor NCSs were performed by stimulating the median nerve at the wrist and elbow. The median nerve compound muscle action potentials (CMAP) were recorded by surface electrodes placed over the abductor pollicis brevis muscle with median nerve stimulation 6 cm proximal to the active recording electrode. The distal motor latency (DML) was measured at the onset of the CMAP. We calculated the motor conduction velocity (MCV) and baseline-to-negative peak amplitude of the CMAP. A median nerve sensory conduction velocity <48 m/s and a median nerve distal motor latency >4.2 ms were considered abnormal. When the standard tests yielded normal results, median to ulnar comparison for the fourth finger was performed and the fourth finger median and ulnar SNAP peak latency difference was calculated. A difference greater than 0.4 ms was considered abnormal. Ulnar nerve sensory and motor conduction studies were carried out to rule out ulnar nerve involvement and to evaluate electrophysiological findings of another nerve besides the median nerve. Ulnar SNAP were recorded by surface electrodes placed over the wrist at a distance of 10 cm from the active stimulating electrode at fifth digit. Motor NCSs were performed by stimulating the ulnar nerve at the wrist, below the elbow (4 cm below the medial epicondyle) and above the elbow (6 cm above the medial epicondyle) and recording CMAP by surface electrodes placed over the abductor digiti minimi muscle. Reduced (<8 μV) or absent ulnar SNAP amplitude and/or slowing of MCV across the elbow to less than 50 m/s or reduced MCV >10 m/s across the elbow compared with the distal segment and/or conduction block across the elbow, more than 20 % were considered as ulnar nerve involvement. Patients with ulnar nerve involvement were excluded from the study. According to the results of the electrophysiological examination, patients were categorized into subgroups of electrophysiologically confirmed CTS (EP+ group) and electrophysiologically negative symptomatic patients (EP− group).

The severity of electrophysiological impairment was scored with a modified neurophysiologic grading system as follows: Minimal CTS, standard negative hands with abnormal comparative tests; Mild CTS, slowing of median digit-wrist segment and normal DML; Moderate CTS, slowing of median digit-wrist segment and abnormal DML; Severe CTS, absence of median SNAPS (digit-wrist segment) and abnormal DML; Extreme severe CTS, absence of thenar sensory and motor response [5].

To quantify symptom severity of carpal tunnel syndrome and patient functional status, all patients completed the Boston Carpal Tunnel Questionnaire (BQ) symptom severity and functional status scales. For this purpose, the Turkish version of BQ previously validated by Sezgin et al. [6] was used. The symptom severity scale (BQ-SSS) consists of 11 questions with multiple-choice responses, scored from 1 point (mildest) to 5 points (most severe). The functional status scale (FSS) consists of 8 questions with multiple choice responses, scored from 1 point (no difficulty with the activity) to 5 points (cannot perform the activity at all). Each score was calculated as the mean of the response points. Thus, a higher score indicates worse symptoms or dysfunction. In addition, the sum score of the

first five questions of the BQ-SSS was calculated to evaluate to severity of pain.

Fasting blood samples were collected from patients and healthy controls for serum 25(OH)D assays. The blood sampling of patients for serum 25(OH)D assay was performed in the same day of electrophysiological examination and of healthy controls in the same months in study period. Plasma and serum samples were stored at −30 °C until the time of analysis. 25(OH)D was determined by the radioimmunoassay method. Patients with 25(OH)D < 20 ng/ml were considered to have vitamin D deficiency.

For statistical analysis the overall patient group, as well as subgroups of patients defined on the basis of electrophysiological results were compared with controls in terms of mean serum 25(OH)D levels and in terms of the proportion of subjects with serum 25(OH)D deficiency. BQ scores were also compared between EP+ and EP− subgroups. In patients with bilateral symptoms, data obtained at the most severely affected side according to the BQ symptom severity scale were used for statistical analyses. The normality of data distribution was verified with the Kolmogorov–Smirnov test. Parametric data were analyzed using independent sample t tests and one-way ANOVA test, nonparametric data were analyzed using Mann–Whitney U test. The correlation between serum 25(OH)D level and BQ scores was examined using Spearman's correlation coefficient. Pearson correlation coefficient was used for analyzing the correlation between serum 25(OH)D level and BMI because of parametric distribution. Probabilities <0.05 were considered significant. All statistical analyses were performed using SPSS 15.0 (SPSS Inc.).

Results

A total of 108 patients (94 female, 14 male) and 52 (46 female, 6 male) healthy controls were included in the study. The mean age of patients with CTS symptoms and controls were 44.7 ± 11.6 (range 18–72) and 41.3 ± 11.7 years (range 20–75), respectively, with no significant difference between the two groups ($p = 0.11$). Body mass index was significantly higher in patients with CTS symptoms compared to healthy controls (28.94 ± 5.09 vs. 26.28 ± 4.25; $p = 0.003$). Patients with CTS symptoms had significantly lower 25(OH) D levels compared to controls (9.21 ± 6.32 vs. 15.76 ± 11.85; $p < 0.001$) (Table 1).

According to the electrophysiological results, 57 patients were classified as EP+ group and 51 patients as EP− group. EP+ patients were significantly older compared to EP− and control group (Tables 2, 3). While BMI was significantly higher in EP+ patients than in controls ($p = 0.002$), the difference between EP+ and EP− groups was not significant (Tables 2, 3). There was a significant difference in 25(0H)D level between EP+, EP− and control subjects ($p < 0.001$) with the lowest levels being in EP− patients (Table 2). 25(0H)D was significantly lower both in EP+ and EP− groups compared to controls ($p = 0.006$, $p = 0.000$, respectively), but the difference between EP+ and EP− groups was not significant (Table 3). 25(OH)D deficiency was present in 96.1, 94.7, and 73.8 % of EP−, EP+, and control subjects, respectively ($p = 0.001$).

BQ symptom severity and functional status scores and BQ pain sum score were not significantly different between EP+ and EP− groups (Table 4). Electrophysiological results of the most severely affected sides showed 15 hands (26.3 %) with minimal CTS, 16 hands (28.1 %) with mild CTS, 21 hands (36.8 %) with moderate CTS and five hands (8.8 %) with severe CTS. 25(OH) D level was not significantly different in EP+ subgroups ($p = 0.13$).

There was no correlation between 25(OH) D levels and BQ symptom severity score (Spearman's rs = 0.06, $p = 0.57$), BQ functional status score (rs = 0.30, $p = 0.76$) and BQ pain sum score (rs = 0.10, $p = 0.29$) and the electrophysiological grade (rs = 0.08, $p = 0.54$). Also there was no correlation between 25(OH)D and BMI (Pearson's $r = 0.93$, $p = 0.26$).

Discussion

In this study examining the association between CTS symptoms and vitamin D levels, our findings point out to the high prevalence of vitamin D deficiency in our country. Despite the uncertainty of the ideal vitamin D levels, a high prevalence of vitamin D deficiency has been found across different populations globally, with even higher prevalence rates in developing countries and also immigrants from developing countries, including Turkey [7, 8]. In a previous study from the same city involving outpatients, vitamin D deficiency was found in 66 % of the participants, with lower levels detected during the spring and winter months [9]. In another study from Izmir province, which is located in the Mediterranean climate zone, 74.9 % of the subjects had 25(OH)D deficiency [10]. Consistent with previous reports, we found 25(OH)D deficiency in 76.9 % of healthy controls during the spring months. However, in patients presenting with CTS symptoms 25(OH)D deficiency was significantly higher.

Several recent studies have indicated the presence of an association between low vitamin D levels and non-specific painful conditions. In a study involving patients with treatment-resistant persistent non-specific musculoskeletal pain, 93 % of the individuals were found to have low

Table 1 Comparison of demographic data and 25(OH)D vitamin level between patients with CTS symptoms and healthy controls

	Patients with CTS symptoms ($N = 108$)	Control ($N = 52$)	p
Age (years)	44.7 ± 11.6	41.3 ± 11.7	0.11
Body mass index (kg/m^2)	28.9 ± 5.1	26.3 ± 4.3	**0.003**
25(OH)D vitamin (ng/ml)	9.2 ± 6.3	15.8 ± 11.9	**<0.001**

p value in bold is statistically significant ($p < 0.05$)

Table 2 Comparison of demographic data and 25(OH)D vitamin level between electrophysiological confirmed CTS patients (EP+), electrophysiological negative symptomatic patients (EP−) and healthy controls

	EP+ ($N = 57$)	EP− ($N = 51$)	Control	p
Age	49.2 ± 10.6	39.7 ± 10.6	41.3 ± 11.7	**0.000**
Body mass index (kg/m^2)	29.7 ± 5.2	28.1 ± 4.9	26.3 ± 4.3	**0.003**
25(OH)D vitamin (ng/ml)	10.5 ± 7.1	7.7 ± 5.0	15.8 ± 11.9	**0.000**

p value in bold is statistically significant ($p < 0.05$)

Table 3 Multiple comparison of demographic data and 25(OH)D vitamin level between electrophysiological confirmed CTS patients (EP+), electrophysiological negative symptomatic patients (EP−) and healthy controls (ANOVA, Tukey test)

		p
Age		
EP−	EP+	**0.000**
	Control	0.76
EP+	EP−	**0.000**
	Control	**0.001**
Body mass index		
EP−	EP+	0.22
	Control	0.17
EP+	EP−	0.22
	Control	**0.002**
25(OH) D Vitamin		
EP−	EP+	0.18
	Control	**0.000**
EP+	EP−	0.18
	Control	**0.006**

p value in bold is statistically significant ($p < 0.05$)

vitamin D levels [11]. In another study with Indo-Asian participants attending to a rheumatology outpatient unit, higher prevalence of hypovitaminosis D was found as compared to healthy controls [12]. Hypovitaminosis D has been reported in 83 % of patients with chronic back pain, with clinical improvement following vitamin D replacement [13]. Also, among a group of patients with lumbar spinal stenosis, vitamin D deficiency was associated with more severe pain [14]. In a cross-sectional population based study from the UK involving 6824 adult patients, chronic widespread pain was found to be related to vitamin D levels [15]. Similarly, in a Norwegian study involving a multi-national ethnic population, a higher prevalence of hypovitaminosis D was found among those with non-specific musculoskeletal pain, fatigue, or headache [16].

Furthermore, an association between diabetic neuropathic pain, diabetic neuropathy and vitamin D levels has been suggested by several studies [17, 18]. A significant association between Vitamin D insufficiency and composite paresthesia has been reported in diabetic patients from 2001 to 2004 National Health and Nutrition Examination Survey (odds ratio 2.12; 95 % CI 1.17–3.85) [19]. In a study from our country using electrophysiological data

Table 4 Comparison of Boston Carpal Tunnel Questionnaire (BQ) symptom severity scale score, functional status scale score and pain sum score between electrophysiological confirmed CTS patients (EP+) and electrophysiological negative symptomatic patients (EP−)

	EP+ ($N = 57$) Mean ± SD (median)	EP− ($N = 51$) Mean ± SD (median)	p
BQ symptom severity score	2.89 ± 0.90 (3.00)	2.62 ± 0.94 (2.55)	0.10
BQ functional status score	2.34 ± 0.88 (2.25)	2.27 ± 0.99 (2.00)	0.45
BQ pain sum score	14.21 ± 5.50 (15.00)	13.47 ± 5.85 (14.00)	0.46

and Douleur Neuropathique 4 questionnaire scores in diabetic patients, those with neuropathy had lower vitamin D levels as compared to those in whom neuropathy could not be identified [20].

To our knowledge, our study is the first of its kind to examine the association between vitamin D levels and an entrapment neuropathy and its symptoms. According to our results, symptomatic patients without electrophysiological abnormalities had the lowest vitamin D levels. Despite the absence of electrophysiological evidence of CTS, the similarity between EP− and EP+ groups in terms of symptom severity, functional status, and pain severity suggest that vitamin D deficiency may overlap with CTS symptoms. This finding may also be associated with small fiber neuropathy with normal electrophysiological results in routine NCSs. The comparable pain severity across the groups may be explained by the reduced anti-inflammatory activity of vitamin D through the regulation of interleukin, tumor necrosis factor, and macrophage activity. Several in vivo and in vitro studies have shown the neurotrophic effects of vitamin D as well as its modulating effects on the neuromuscular functions, and neuronal growth and differentiation [21–23]. In a small study, CTS patients were found to have lower vitamin D binding protein levels in the sera as compared to controls [24]. It is plausible to assume that low levels of vitamin D binding protein levels may increase the free fraction of vitamin D in CTS patients, increasing the amount of vitamin D reaching the target tissues. In support of the previous studies suggesting a link between obesity and CTS, patients with CTS symptoms in our study had significantly higher BMI [25]. Also, obesity and 25(OH)D deficiency has been found to be associated in several studies [26, 27]. However, our results were not consistent with these studies in term of correlation of vitamin D deficiency and obesity.

In our study, we found EP+ CTS relatively lower than expected in symptomatic patients. This could be explained by the likelihood to seek medical attention in earlier CTS stages of patients with severely deficient 25(OH)D, due to complaints of painful paresthesia, because of possibility of prominent vulnerability of small nerve fibers. Increased vitamin D receptor expression prominent in small diameter neurons in dorsal root ganglia has been shown in a diabetic rat model as a supporting finding of the effect of vitamin D receptor signaling system on small nerve fibers [28]. In a previous review, supplementary tests of small nerve fiber function have been recommended to improve early recognition of CTS [29]. In a study Schmid et al. [30] reported a striking reduction in intraepidermal nerve fiber density in CTS, even in patients with normal NCS findings, which was independent of electrodiagnostic test severity. Another possible explanation of low rate of electrophysiologically confirmed CTS could be the selection of patients according to their complaints. We did not evaluate Tinel's sign and Phalen's test in our patients because of previous reports of low sensitivity and spesifity of provocative tests in the diagnosis of CTS [31]. In conflict, a recent study suggested that when both Tinel's and Phalen's tests are positive, the likelihood of abnormality of sensory nerve conductions is higher [32].

One of the limitations of our study is the absence of electrophysiological evaluation of healthy controls, but all healthy volunteers enrolled in the study after detailed clinical evaluation. Other limitations of our study are the absence of an assessment of vitamin D replacement on CTS symptoms and relatively lower number of patients in CTS sub-groups. The failure to detect a significant difference in vitamin D levels between electrophysiological severity of CTS sub-groups may also be related with the latter. A study is planned to examine the efficacy of vitamin D replacement therapy in EP+ or EP− patients with CTS symptoms.

Currently, an increase is noted in the number of studies evaluating the effects of vitamin D replacement on musculoskeletal pain and diabetic neuropathy symptoms. In the study by Lee and Chen, vitamin D replacement therapy of 3-month duration resulted in a 50 % reduction in neuropathy-induced pain in diabetic patients with vitamin D deficiency [21]. In another study, an eight-week course of vitamin D therapy provided a significant improvement in neuropathy symptom scores in Type 2 diabetics [33]. The randomized, double blind, placebo controlled study by Gendelman et al. [34] where 4000 IU of vitamin D was added to the existing therapies, the treatment was associated with significant reduction in VAS scores and in TNF-alpha, leukotriene B4 and prostaglandin E2 levels, as compared to patients receiving placebo. Conversely, in another randomized, placebo controlled study involving 251 patients, 16-week treatment with 25 or 10 μg/day of vitamin D did not result in a significant change in pain scores [35]. Although a 2015 Cochrane review concluded that vitamin D was not associated with a satisfactory effect in adults with chronic pain, a beneficial effect of vitamin D in fibromyalgia or non-specific musculoskeletal pain was proposed in two studies included in this review [36–38].

Our results demonstrate that vitamin D deficiency is a common health problem in Turkey, especially in patients with CTS symptoms. In patients presenting with CTS symptoms, particularly among those with no electrophysiological abnormalities at nerve conduction studies, we recommend the assessment of 25(OH)D level. Further studies are needed to evaluate the effect of vitamin D deficiency on small nerve fiber functions and examine whether correction of hypovitaminosis D improves symptoms and functional status in patients with CTS symptoms.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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