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THE EFFECT OF VITAMIN D TREATMENT ON NEUROPATHIC PAIN AND FUNCTIONAL ACTIVITY IN PATIENTS WITH CARPAL TUNNEL SYNDROME

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ABSTRACT

Background: Vitamin D deficiency is a very common condition throughout the world and is known to be associated with many chronic systemic diseases. It has been shown to have neuroprotective effects in several studies. This study aimed to investigate the effect of vitamin D supplementation on pain, functional activity, and electrophysiological values in patients with carpal tunnel syndrome.

Methods: This study included a total of 50 patients (72 wrists) with vitamin D deficiency and mild CTS. Pre-treatment and post-treatment pain levels of the patients were measured using visual analog scale and painDETECT questionnaire whereas the Boston Carpal Tunnel Syndrome Questionnaire was used to assess the functional status. Furthermore, nerve conduction study was performed in all patients before and after treatment.

Results: There was a significant increase in post-treatment serum vitamin D levels compared to pre-treatment ($p<0.05$). A statistically significant decrease was observed in the visual analog scale, painDETECT, and Boston Carpal Tunnel Syndrome Questionnaire scores after treatment compared to pre-treatment ($p<0.05$). Median nerve distal sensory latency and distal motor latency values decreased significantly after treatment ($p<0.05$). Post-treatment sensory action potential and sensory conduction velocity values increased significantly compared to pre-treatment values ($p<0.05$).

Conclusions: This study shows that vitamin D supplementation improves pain scores, functional activity, and more importantly, electrophysiological findings in carpal tunnel syndrome cases.

KEYWORDS : Carpal tunnel syndrome, vitamin D, neuropathic pain, disability, pain, daily activity, neuropathy, mononeuropathy

INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common peripheral mononeuropathy of the upper extremity and the most common entrapment neuropathy of the median nerve [1]. Its prevalence ranges from 1–5% in the general population but is three times higher in women than men [2]. It occurs commonly in the age range of 30–50 years [3]. While CTS is known to be associated with many risk factors, the followings are the most common ones: chronic repetitive movements of the wrist, high body mass index (BMI), pregnancy, being over the age of 30, diabetes mellitus (DM), thyroid dysfunction, and chronic systemic diseases such as rheumatoid arthritis [4]. The typical symptom is the presence of pain, numbness, and tingling in the first three digits. In addition to these, more severe cases may experience weakness in the hand, thenar muscle atrophy, and loss of sensation [5]. Physical examination and electrophysiological evaluation are the most common diagnostic methods used in clinical practice [6]. Electrophysiological evaluation ensures accurate and definitive diagnosis and is beneficial in determining the severity of CTS. The level of compression severity is an important determinative in the treatment method to be applied [7]. Conservative or surgical approach may be used in the treatment of CTS. Conservative treatment options for CTS include activity modification, splint use, corticosteroid injection, nonsteroidal anti-inflammatory drugs, physical therapy agents including contrast bath, ultrasound, laser therapy and transcutaneous electrical nerve stimulation (TENS). Interventional treatment options include carpal tunnel release surgery [7].

Vitamin D has recently attracted great attention due to its beneficial roles on human health, such as positive calcium balance, immunomodulation, and protection from some systemic diseases, such as cardiovasculer disease, and cancer [8]. On the other hand, vitamin D is further known to have neuroprotective effects. Serum 25-hydroxyvitamin D (25(OH)D) below 20 ng/mL is defined as vitamin D deficiency [9]. Widespread musculoskeletal pain and neuropathic pain are reported to be associated with vitamin D deficiency [9]. Recent studies have shown a significant correlation between CTS and 25(OH)D levels. In these studies, higher incidence of vitamin D deficiency and higher pain severity are reported in patients with CTS [10,11].

This study aimed to investigate the effects of vitamin D replacement on neuropathic pain, functional activity, and electroneuromyography (ENMG) findings among CTS cases with vitamin D deficiency.

MATERIALS AND METHODS

This prospective clinical study included 50 consecutive patients (72 wrists) aged 18–65 years with vitamin D deficiency and an electrophysiologically confirmed diagnosis of mild CTS in Physical Medicine and Rehabilitation outpatient clinic. The study was approved by the local ethics committee (date and decision no: 26.12.2018/18). Written informed consent was obtained from all patients participating in the study. All phases of the study were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines.

Inclusion criteria: Patients aged 18–65 years, volunteering to participate in the study, suffering from numbness or pain in the hands, diagnosed with mild CTS by clinical examination and electrophysiological evaluation, whose serum 25(OH)D was measured and found to be below 20 ng/mL were included in the study.

Exclusion criteria were clinical or electrophysiological evidence of accompanying conditions that have potential to mimic CTS such as polyneuropathy, cervical radiculopathy, brachial plexopathy; history of trauma or fracture of the wrist, previous injection or carpal tunnel release surgery; underlying systemic diseases associated with CTS such as diabetes mellitus, rheumatoid arthritis, acromegaly, hypo/hyperthyroidism or renal disorders; B12 or folate deficiency, pregnancy, lactation, and ongoing systemic corticosteroid therapy for any reason.

Patients with 25(OH)D below 20 ng/mL received a weekly dose of 50.000 IU of vitamin D supplementation for eight weeks. The pain levels of the patients included in the study were evaluated using a visual analog scale (VAS) and neuropathic pain severity was evaluated with the pain DETECT questionnaire (PT-Q) whereas Boston Carpal Tunnel Syndrome Questionnaire (BCTQ) was used to assess the functional status. The correlation between these parameters and the 25(OH)D level was evaluated before and after treatment.

Visual Analogue Scale (VAS)

Pain and numbness for daytime and night were evaluated by VAS at the beginning and at the first and sixth months following either treatment method. Patients were asked to mark the severity of pain on a 100 mm line with "no pain" on one end and "most unbearable pain" on the other end. The distance from the starting point of the pain to the point marked by the patient was recorded.

Pain DETECT Questionnaire (PDQ)

The PD-Q was used to assess the presence of neuropathic pain. Patients receiving a total questionnaire score of ≤12 are considered to have no neuropathic pain component. A score of 13 to 18 is considered uncertain but indicates that the neuropathic pain component is likely to present, and a score of ≥19 indicates the presence of a neuropathic pain component. Alkan et al. conducted the validity and reliability study of the Turkish version of the questionnaire [12].

Boston Carpal Tunnel Syndrome Questionnaire (BCTQ)

The BCTQ comprises two subscales namely Symptom Severity Scale (SSS) and Functional Status Scale (FSS). The level of symptoms is assessed by SSS while the level of hand function was evaluated by the FSS. Turkish validity and reliability study of the questionnaire was conducted [13]. The SSS consists of 11 items and each item is scored on a five-point Likert scale from 1 (no symptoms) or 5 (most severe symptoms). A total score of 11–55 can be obtained from the scale and a higher score indicates increased symptom severity. The FSS includes eight items evaluating the activities of daily living requiring motion of the hand, and the patients are asked to evaluate the items from 'no difficulties' to 'cannot perform the activity at all'. The results obtained are scored from 8 to 40, and higher scores indicate impaired hand functionality [13].

Electrophysiological Evaluation

Nerve conduction studies (NCS) were performed using a Neuropack M1 (Nihon Kohden, Tokyo, Japan) electroneuromyography device in a temperature-controlled room and hand skin temperature was maintained >31°C during all tests.

Median motor nerve conduction was recorded over the belly of the abductor pollicis brevis muscle that was stimulated supramaximally at two different points; the distal one was 2 cm proximal to the volar surface of the wrist, between the flexor carpi radialis and palmaris longus tendons, at least 6 cm away from the active recording electrode and, the proximal one was on the antecubital fossa between the biceps tendon and the medial epicondyle, over brachial artery. The distance between the proximal and distal points was measured in full extension. Distal motor latency (DML), amplitude of compound muscle action potentials (CMAP) and nerve conduction velocity (NCV) were obtained. For examination of the sensory nerve conduction, a pair of ring electrodes were placed on the index finger for recording, and the sensory nerve was stimulated antidromically at the same site used for distal motor stimulation with a distance of 14 cm from the recording electrode. Distal sensory latency (DSL), sensory nerve action potential (SNAP) amplitude and NCV were determined. Together with median NCS, ulnar nerve motor and sensory NCSs were performed to exclude other possible neuropathies such as polyneuropathy of brachial plexopathy [14].

Carpal tunnel syndrome level was classified as "extreme" if no motor and sensory response were obtained from the median nerve, "severe" in case of absent median SNAP and abnormal DML, "moderate" if there were slowing in the sensory median NCV and abnormal DML, "mild" if median DML was normal and there was slowing in the sensory median NCV, and "normal" if there were normal findings in all tests [15]. The patients with mild CTS were recruited to the study.

Serum 25(OH)D level

Patients with serum 25(OH)D level of in the study. Serum 25OHD measurements were performed by chemiluminescence immunoassay methods (Architect, Abbott Park, USA). Serum 25(OH)D levels of all patients were recorded after treatment.

Statistical Analysis

Mean, standard deviation, median, minimum, maximum values, frequency and percentage were used for descriptive statistics. The distribution of variables was checked with Kolmogorov–Smirnov test. Paired samples t-test and Wilcoxon's signed-ranks test were used for the repeated measurement analysis. Statistical analyses were performed using SPSS version 26.0 software.

RESULTS

Of the patients, 68% (n=34) were female and 32% (n=16) were male. The mean age was 44.4±10.1 years. The mean duration of symptoms was 5.3±3.2 months. The mean BMI of the patients was 28.9±4.2 kg/m^2. The mean serum vitamin D level was 11.3±4.5 ng/mL (Table 1).

Table 1. Demographic characterics and vitamin D levels of patients at baseline

		Min-Max	Median	Mean±sd/n-%
Age		22,0 - 61,0	43,5	44,4 ± 10,1
Gender	Female			34 68,0%
	Male			16 32,0%
Body mass index (kg/m^2)		18,3 - 38,9	29,0	28,9 ± 4,2
Symptom Duration (months)		1,0 - 12,0	5,0	5,3 ± 3,2
Before Treatment				
Serum Vitamin D (ng/ml)		4,0 - 19,8	11,1	11,3 ± 4,5

There was a significant increase in post-treatment serum vitamin D levels compared to pre-treatment ($p<0.05$). Total scores obtained from VAS, PD, SSS, FSS, and BCTQ in the post-treatment period showed a significant improvement compared to pre-treatment ($p<0.05$).

The DSL and DML values measured after the treatment were significantly improved compared to the pre-treatment values ($p<0.05$). Post-treatment SNAP increased significantly compared to before treatment ($p<0.05$). There was no significant difference in post-treatment and pre-treatment CMAP values ($p>0.05$). Post-treatment sensory conduction velocity (SCV) increased significantly compared to before treatment ($p<0.05$) while there was no significant difference between the pre- and post-treatment motor conduction velocity (MCV) ($p>0.05$) (Table 2).

Table 2. Nerve conduction studies results, pain and functional activity levels before and after of vitamin D suppplementation in the patients.

	Before Treatment		After Treatment		p	
	Mean±sd	Median	Mean±sd	Median		
Serum Vitamin D (ng/ml)	11,3 ± 4,5	11,1	35,9 ± 7,4	36,0	***0,000***	P
VAS	5,8 ± 1,4	6,0	3,1 ± 1,6	3,0	***0,000***	W
Pain Detect Score	17,8 ± 5,5	17,0	11,5 ± 5,3	11,0	***0,000***	W
Boston Scale Symptom	26,5 ± 8,9	27,0	16,1 ± 6,5	13,0	***0,000***	W
Boston Scale Function	14,4 ± 5,3	14,0	9,9 ± 3,2	9,0	***0,000***	W
Boston Scale Total	40,6 ± 13,2	39,0	25,9 ± 9,1	22,0	***0,000***	W
Median Distal Sensory Oncet Latency (ms)	3,02 ± 0,25	2,99	2,99 ± 0,23	2,95	***0,000***	W
Median Distal Motor Latency (ms)	3,44 ± 0,17	3,45	3,40 ± 0,21	3,45	***0,000***	W
Sensory Amplitude (μV)	25,5 ± 8,9	25,0	26,2 ± 8,5	25,8	***0,001***	W
Motor Amplitude (wrist) (mV)	6,2 ± 1,4	6,3	6,3 ± 1,4	6,4	0,078	W
Median Sensory Conduction Velocity (m/s)	39,0 ± 4,2	39,8	43,3 ± 5,2	44,6	***0,000***	W
Median Motor Conduction Velocity (m/s)	55,9 ± 3,9	55,7	56,3 ± 4,2	55,9	0,055	W

[P] Paired samples t test / [W] Wilcoxon test

VAS: visual analog scala; CTS: Carpal tunnel syndrome.

DISCUSSION

This study evaluated the effects of vitamin D replacement on pain, function, and electrophysiological findings in mild CTS cases with vitamin D deficiency. The results demonstrated that vitamin D replacement improved pain and function levels, as well as electrophysiological findings, in patients with mild CTS.

The vitamin D level of the patients included in the study was observed to be at a very low level (11.3±4.5 ng/mL). The prevalence of vitamin D deficiency is known to be higher in developing countries including Turkey [16]. In the present study, 68% of the patients were females and the mean age of the patients was 44.4±10.1 years. This finding was similar to previous studies [5]. High BMI is reported to be among the risk factors for CTS [5]. The results of the present study are compatible with the literature in this regard. Recent studies have reported that vitamin D has a neuroprotective role and it protects growth factors, particularly neural growth factor (NGF) and suppresses calcium channels in animal experiments, and reduces nerve cell injury by inhibiting neurotoxicity caused by calcium [17,18]. There are studies showing that vitamin D deficiency increases peripheral neuropathy and vitamin D supplementation decreases neuropathic pain [19,20]. In a review involving 1048 patients with type 2 DM (T2DM), vitamin D deficiency was reported to increase the risk of diabetic peripheral neuropathy [19,21-23]. In a study from Turkey (2014), Celikbilek et al. reported that patients with T2DM had lower serum vitamin D levels and statistically significantly higher vitamin D receptor levels compared to the control group whereas no difference was observed between the groups in terms of vitamin D-binding protein levels [24].

Vitamin D supplementation is reported to decrease the severity of neuropathic pain. Lee et al. administered vitamin D replacement to 51 patients with T2DM, who had neuropathic pain, for three months (2000 IU/day) and showed a 50% decrease in neuropathic pain scores after treatment. The authors reported that vitamin D replacement could be used in the treatment of neuropathic pain in patients with T2DM [20]. Furthermore, vitamin D has been found to be involved in the improvement of peripheral nerve injury, axon regeneration, and myelinization [25,26]. These neuroprotective effects of vitamin D can be explained by the facts that vitamin D regulates the expression of NGF, neurotrophin-3 (NT-3), neurotrophin-4 (NT-4), and glial cell-derived neurotrophic factors (GDNF), controls the detoxification process by regulating the activity of gamma-glutamyl transpeptidase (GGTP) enzyme in neurons, and regulates the expression of calcium-binding proteins (CaBP) and L-type stress-sensitive calcium channels, which play an important role in calcium balance [27]. Calcium ion transitions are essential for neuron functions.

There have been few publications investigating the correlation between CTS and vitamin D in recent years. In these studies, vitamin D levels were reported to be lower in patients with CTS than in the control group [28,29]. In a study from Turkey (2017), Demiryurek et al. compared 36 patients with mild CTS with 40 healthy individuals and vitamin D level was found to be lower in the CTS group. The authors further found a significant correlation between vitamin D level and pain severity in patients with CTS [11]. In a study by Tanik et al., the number of patients with mild CTS was found to be significantly higher in the group with vitamin D deficiency compared to the group with normal vitamin D levels and the authors reported that vitamin D deficiency could trigger CTS. In the same study, the severity of vitamin D deficiency was also found to be associated with the severity of CTS in patients with vitamin D deficiency [28]. Similar to previous studies, a

statistically significant improvement was found in the pain level after vitamin D replacement in the present study.

Compatible with the present study, Saçmacý et al. reported statistically significant improvements in pain levels and median nerve DSL, SCV, and DML values after vitamin D replacement in female patients with CTS compared to pre-treatment [30]. In addition to these findings, we further observed a significant improvement in SNAP.

The absence of a placebo group is an important limitation of the study, however the use of objective parameter, electrophysiological data, as well as subjective parameters, might have been partially alleviated this deficiency. Furthermore, the fact that the patients were not examined in the same season may have affected their vitamin D levels since they were exposed to different levels of sunlight. Despite its limitations, the importance of the present study is undeniable due to the limited number of studies on this subject.

In conclusion, the present study has shown that vitamin D replacement improves pain level, neuropathic pain intensity, functional activity, and more importantly, electrophysiological findings in patients with mild CTS. We believe that vitamin D replacement should be included in the management of CTS, which is quite common in the community and affects the quality of life. Future studies with longer duration of follow-up and larger study populations are needed to comment on the long-term efficacy of vitamin D replacement.

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