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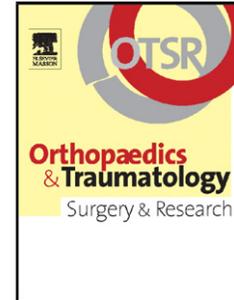
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Original article

The Effect of Vitamin D Levels on Pain In Carpal Tunnel Syndrome

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Abstract:

Background: Carpal tunnel syndrome (CTS) and vitamin D deficiency are two discrete common clinical pictures that can cause chronic pain. In this study, we aimed to evaluate the association of 25 (OH) D deficiency with electrophysiological findings and severity of pain in patients with mild CTS.

Method: The consecutive patients admitted to our laboratory with the symptoms of CTS between May 2016 and August 2016 were enrolled in this study. According to their electrophysiological examination results, only the patients with normal conduction results and ones with mild grade CTS were included. Demographic data, the results of the electrophysiological studies, vitamin D levels (our laboratory normal is > 20 ng / mL), duration of pain and pain intensity due to CTS which was assessed with visual analog scale were collected.

Results: Totally, 76 patients (36 patients with mild CTS and 40 without CTS) were included. In the mild CTS patients, vitamin D levels were significantly lower than those electrophysiologically normal patients ($p = 0.003$). The relationship between gender, duration of pain and vitamin D levels were evaluated in the normal and mild CTS group. There was no significant relationship between the pain and vitamin D levels in the normal group, while vitamin D level was significantly lower in the mild CTS group ($p = 0.730$ and $p = 0.002$; respectively).

Discussion: Vitamin D deficiency increases the pain intensity in patients with CTS. Treatment of vitamin D deficiency in these patients may play a role in pain relief. Further studies involving analyses of post-Vitamin D replacement therapy are warranted to confirm the association between vitamin D deficiency and pain due to CTS.

Key words: carpal tunnel syndrome, vitamin D deficiency, visual analog scale, neuropathy, pain

INTRODUCTION:

Humans get their vitamin D needs from two major sources. One of them is the cholecalciferol (D3) which is synthesized from 7-dehydrocholesterol via the effect of ultraviolet B rays on the skin at the rate of 90-95%, and the other one is the ergocalciferol (D2) which is taken in small amounts via diets. Since the metabolization of vitamins D2 and D3 occurs in the same way, they are known as Vitamin D. 25 hydroxyvitamin D (25 (OH) D), which is the major metabolite of Vitamin D, has a half-life of 15-20 days, and it provides the closest data to the actual entire vitamin D amount in serum (1-2).

Vitamin D has been previously known to be associated with bone metabolism, serum calcium and phosphorus levels. However, as a result of the recent studies, it is anticipated that low vitamin D levels have also many clinical effects, such as gastrointestinal disorders, cardiovascular disorders, neuropsychiatric diseases, autoimmune disorders, cancer, and metabolic syndrome (3). Vitamin D deficiency has also been associated with the development of diabetic neuropathy and various painful syndromes (4).

Carpal tunnel syndrome (CTS) is the most frequent entrapment neuropathy with a high prevalence. It is more common in women and usually begins in adulthood. CTS causes pain, numbness, dysesthesia, and loss of strength in hands impairing the quality of life, and results in social and economic burden. The etiological factors of CTS are systemic diseases, such as diabetes mellitus, thyroid function disorders, rheumatoid arthritis. The most common risk factors for the development of CTS were pregnancy, obesity and recurrent wrist movements (5,6).

In this study, we aimed to evaluate the relationship between 25 (OH) D deficiency and electrophysiological findings and severity of pain in patients with mild CTS symptoms.

METHOD:

Study Population

This study was carried out between May 2016 and August 2016 in the electroneuromyography (ENMG) laboratory of the Neurology Clinic of Sakarya University Training and Research Hospital. According to the nerve conduction studies, 36 patients with

mild CTS and 40 without CTS, a total of 76 patients with the suspicion of CTS were included in the study. Inclusion criteria for the study are being between the ages of 18 and 45, having measured serum 25 (OH) D levels and volunteering to participate in the study. Patients with a history of diabetes mellitus, thyroid disease, wrist fracture, tendon and connective tissue disease, rheumatoid arthritis, osteoporosis, renal failure, and diseases causing chronic pain, or patients with a history of hereditary or acquired polyneuropathy, radiculopathy, or neurological or psychiatric diseases were excluded.

Each participant was informed about the purpose of the study, and each patient read and signed the informed consent form. The present study was approved by the Ethics Committee of Sakarya University.

A demographic data form was used to collect the information about the age, gender, and CTS-induced pain duration. Visual Analog Scale (VAS) was administered in order to assess their pain level. Each participant underwent a detailed systematical and neurological examination by a qualified clinician. During the examination, Tinel's sign and Phalen's maneuver tests were applied to evaluate the sensorial manifestations of CTS. The patients were classified into two groups of normal and mild CTS according to their electrophysiological examination results.

Measurement of vitamin D levels

On the day of the electrophysiological assessment, fasting venous blood samples of the patients were collected in order to measure their serum 25 (OH) D levels. And the samples were stored at -30 °C. The radioimmunoassay method was used to determine the 25 (OH) D levels. Patients with serum levels of 25 (OH) D < 20 ng/ml were defined as having a vitamin D deficiency.

Electrophysiological studies

A nerve conduction study was performed on both arms (a total of 124 arms) using a Nihon Cohden (Tokyo, Japan) electromyograph (EMG) tool at room temperature. The EMG procedure was carried out according to the standard protocol via superficial electrodes using standard nerve conduction techniques (7). Median and ulnar nerve sensory and motor nerve conduction studies were performed and the F responses of both nerves were recorded. In order to exclude cervical radiculopathy, upper extremity needle ENMG studies were conducted

when needed. Nerve conduction studies of the peroneal and tibial nerve of a single extremity and bilateral sural nerve were performed to determine the presence of polyneuropathy. The median and ulnar motor nerve conduction studies of the patients were recorded from the abductor pollicis brevis and the adductor digiti minimi muscles via supramaximal stimulation, and their amplitudes and latencies were assessed. Sensory conduction was assessed from the 2nd and 5th fingers. For the median nerve, the following conduction findings were assessed as abnormal: distal motor latency (DML) >4.2 ms, an amplitude <6.3 mV, a nerve conduction velocity <45 m/sec, sensory distal latency >3.5 ms, a sensory nerve action potential (SNAP) <15 and a nerve conduction rate <45 m/sec. Ulnar and median sensory nerve conduction examinations from the 4th finger were performed in patients with normal standard nerve conduction. A sensory distal latency difference between the median and ulnar nerves on the 4th finger that was > 0.4 ms was accepted as abnormal conduction findings **(8)**. The patients that underwent nerve conduction were further classified into two groups based on the level of CTS, as follows: Patients with no CTS (normal median nerve conduction) and mild CTS group (retarded median nerve sensory conduction rate (by normal standard nerve conduction) or sensory distal latency difference between the median and ulnar nerves on the 4th finger) **(9)**.

Visual Analog Scale (VAS)

All of the patients were asked to mark the pain and paresthesia level on a ruler indicating 0 to 10 points. Turkish version of VAS test has an high validity and reliability for CTS **(10)**.

Statistical Analysis: The Statistical Package for the Social Sciences (SPSS) version 16.0 software program was used for the statistical analysis of the data. Numerical and categorical variables were given as the number, mean, standard deviation, and percentage. The Shapiro-Wilk test was used to determine whether or not the continuous variables had a normal distribution. The Student's t- test was used to compare the continuous variables that showed normal distribution and the Mann-Whitney U test was used to compare the continuous variables that did not show normal distribution. The chi-square test was used to compare the categorical variables. A $p<0.05$ level was accepted as the statistical significance value.

RESULTS:

The mean age of the normal patients was 27 ± 5 , and the mean age of the patients with mild CTS was 28 ± 6 . There was no statistically significant difference between the mean age of two groups ($p= 0.53$). There was no significant difference between sociodemographic parameters and pain duration in both groups ($p=0.2$, $p=0.49$). Besides, in patients with electrophysiologically mild CTS, serum vitamin D levels were significantly lower than those without CTS ($p = 0.003$). Table 1 shows the relationship between gender, duration of pain and vitamin D levels in electrophysiologically normal and mild CTS patients. Table 2 shows the comparison of median nerve conduction study results between healthy subjects and subjects with carpal tunnel syndrome. There was no significant relationship between pain which was evaluated by using VAS and vitamin D levels in the electrophysiologically normal patients, while the serum vitamin D levels were significantly lower in those with mild CTS group ($p = 0.73$, $p = 0.002$) (Figure 1).

DISCUSSION:

This study revealed significantly lower serum vitamin D levels in mild CTS patients, compared to the electrophysiologically normal patients. Additionally, there was no significant association between pain and vitamin D levels in the normal group, while vitamin D levels were significantly lower in those with mild CTS group and high level of pain.

As a result of insufficient exposure to sunlight and nutritional deficiencies, vitamin D deficiency is frequently observed in developing countries especially in the female gender. The prevalence of vitamin D deficiency varies between 60% and 75% in Turkey (11,12). The present study was performed during the summer months and the patients were < 45 years of age, it was found that more than half of the patients had vitamin D deficiency.

Vitamin D deficiency leads to worsening in the non-specific musculoskeletal pain. In a cross-sectional study conducted with 6284 individuals in England, in the patients with chronic widespread pain, vitamin D level was found to be low (13). Similarly, in another study conducted in Norway that included men and women participants of various ethnicities, it was specified that individuals with low vitamin D levels suffered more from widespread musculoskeletal pain (14).

Animal studies have indicated that vitamin D is efficient in protecting neurons and decreasing neuronal toxicity and damage. It has been suggested that Vitamin D reduces free

radical release and blocks calcium channels; therefore, it has an anti-oxidant effect and prevents the neuronal necrosis. Vitamin D prevents nerve growth factor degradation, therefore, it can be effective in the treatment of numerous neurodegenerative and neuroinflammatory diseases by activating myelin-related genes, accelerating myelination and recovery **(16-18)**.

The correlation between vitamin D levels and peripheral neuropathy has been previously examined. A study found a high rate of vitamin D deficiency among the patients with diabetic peripheral neuropathic pain **(18)**. Two other studies reported that replacing vitamin D in diabetic neuropathy patients leads a significant decrease in their neuropathic pain complaints **(19)**. In a study which was conducted in Turkey, electrophysiological examinations were performed on diabetic patients and the lower vitamin D levels were found in the group of patients with diabetic neuropathy **(20)**. The correlation between neuropathy and vitamin D levels in Sjogren's syndrome were evaluated in a study, the vitamin D levels were found to be low in the patients with peripheral neuropathy **(21)**. Another study showed that myelination and recovery increased after vitamin D replacement in rats with peroneal nerve injury **(16)**. However, various studies found no correlation between vitamin D deficiency and neuropathic pain and musculoskeletal pain. For example, a recent review article, it was reported that there was no significant decrease in chronic musculoskeletal pain after vitamin D replacement **(22, 23)**.

A limited number of studies have been evaluated the relationship between CTS and vitamin D levels. One study reported that the serum vitamin D binding protein level was lower in the patients with CTS compared to the control group **(24)**.

In our country, in a study which was conducted among woman, 90 electrophysiologically diagnosed CTS patients were divided into 2 groups according to their serum vitamin D levels. And the severity of CTS was found to be significantly higher in patients with low vitamin D levels than in patients with normal vitamin D levels **(25)**. In another study which has evaluated the vitamin D levels in women with CTS in South Korea, there was no significant relationship between the 135 electrophysiologically detected CTS patients and control group regarding the serum vitamin D levels, however, vitamin D levels were found to be significantly lower in women with CTS below the age of 50 **(17)**. Similar to the both studies, our study revealed significantly lower vitamin D levels in the patients with

mild CTS patients, compared to those without CTS. Unlike these studies, only mild CTS patients were observed in our study.

In a controlled study with a cohort of 108 people in our country, there was no significant difference in serum vitamin D levels between the patients who were electrophysiologically normal and those with mild CTS. The pain and functional capacity of the patients were evaluated using Boston questionnaire (BQ) and no significant relationship was found between BQ and serum vitamin D levels. In contrary to our study, except for pain, other symptoms and functional capacity of the patients were participants in this study were assessed using BQ. Additionally, the majority of patients had low serum vitamin D levels, whereas in our study nearly the half of the patients had normal vitamin D levels. We considered that the results of this study are different from our study as a result of the different methodologies (26).

The main limitation of the present study is that we did not assess whether there was a significant improvement in the CTS symptoms after vitamin D replacement. And we did not include the occupational information of the participants whose relationship with CTS was not known.

In conclusion, patients with mild CTS had a significantly lower level of serum vitamin D than those normal electrophysiological findings. However, low vitamin D levels may increase the severity of the pain due to the CTS. We recommend the assessment of the serum vitamin D levels in patients with CTS-related severe pain who do not have correlated electrophysiologically severe CTS findings. On the other hand, replacing vitamin D deficiency can play a role in reducing CTS related pain in patients. Therefore, we think that large-scale studies are required to analyze the effects of vitamin D replacement and assess the correlation between vitamin D deficiency and the symptoms of CTS.

Declaration of conflicting interests

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	Healthy Subjects (n=36)	Subjects with CTS (n=40)	P :
Sex (female) (N) (%)	18 (%45)	19 (% 52,7)	0.49
Pain Duration (mounth)	9,3±5	10±5	0,2
Low Vitamin D level (vitamin D level < 20 ng/ml) (n) (%)	21 (%52,5)	7 (% 19,4)	0.003

CTS: Carpal Tunnel Syndrome

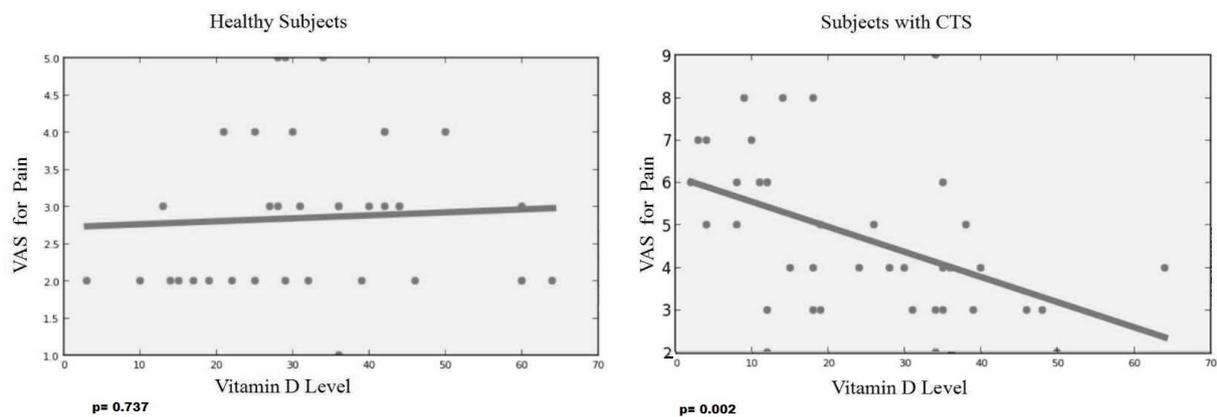
Table 1: Comparison of sex, pain duration and vitamin d level results between healthy subjects and subjects with carpal tunnel syndrome

Parameter	Healthy Subjects (n=36)	Subjects with CTS (n=40)	p
Right Hand Median SNAP Amplitude	33.1±5.8	19.2±11	<0.001
Right Hand Median Nerve Distal Sensory Onset Latency	2.63±0.17	3.24±0.52	<0.001
Right Hand Median Nerve Sensory Conduction Velocity	56.3±2.8	47.5±7.3	<0.001
Right Hand Median CMAP Amplitude	14.9±5.6	12.4±4.6	0.031
Right Hand Median Nerve Distal Motor Latency	3.48±0.30	3.64±0.28	0.021
Right Hand Median Nerve Motor Conduction Velocity	56.5±2.76	55.6±2.82	0.142
Left Hand Median SNAP Amplitude	32.8±6.3	20.9±10.3	<0.001
Left Hand Median Nerve Distal Sensory Onset Latency	2.61±0.15	3.10±0.51	<0.001
Left Hand Median Nerve Sensory Conduction Velocity	56.6±2.4	48.5±7.9	<0.001
Left Hand Median CMAP Amplitude	15.3±3.9	13.2±4.2	0.024
Left Hand Median Nerve Distal Motor Latency	3.52±0.37	3.56±0.36	0.649
Left Hand Median Nerve	57.6±3.6	55.5±2.85	0.007

Motor Conduction Velocity			
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Table 2: Comparison of Nerve Conduction Study Results Between Healthy Subjects and Subjects With Carpal Tunnel Syndrome

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$p = 0.737$

$p = 0.002$

Figure: Correlation of Vitamin D Levels and Scale Scores in Healthy Subjects and in Subjects With Carpal Tunnel Syndrome

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