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Original Article

Public Health Section

Vitamin D in Treatment-Resistant Carpal Tunnel Syndrome Patients with Hypovitaminosis D

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ABSTRACT

Introduction: Vitamin D significantly effects health. Extraskeletal effects of vitamin D play an important role.

Aim: To study effect of treatment with vitamin D in intractable Carpal Tunnel Syndrome (CTS) patients with hypovitaminosis D referred to the Physical Medicine and Rehabilitation Clinics of Shiraz University of Medical Sciences in 2015.

Materials and Methods: This interventional study investigated 50 intractable CTS patients by electrodiagnostic study and physical examinations who did not respond to standard management of CTS for six weeks with concomitant hypovitaminosis D 25(OH). A dose of 50000 IU vitamin D3 was given orally per week for 12 weeks. Re-evaluation of patients by electrodiagnostic study was done within one week of taking the last dose. A questionnaire was designed to collect data including age, gender, Body Mass Index (BMI), past medical history, drug history, boston score before and after treatment with vitamin D, serum level of vitamin D before treatment. SPSS version 20.0 was used to analyze data.

Results: The mean Boston symptom score prior to the treatment was (3.45±0.90) which reduced to (2.04±0.71) after treatment. The mean Boston function score before treatment was (3.41±0.85) which reduced to (2.08±0.82) after treatment. Mean Slat values before treatment was (4.5±0.57) which reduced to (3.89±0.53) after treatment. Mean Mlat values before treatment was (5.03±0.49) which reduced to (4.66±0.44) after treatment. Mean NCV values before treatment was (27.02±4.64) which reduced to (32.58±4.54) after treatment. There was a significant difference between Boston scores, Slat, Mlat and NCV values before and after treatment with vitamin D (p-value=0.0001).

Conclusion: It is concluded that treatment with vitamin D improves clinical and electrodiagnostic conditions of treatment-resistant CTS patients with hypovitaminosis D.

Keywords: Boston scale, Electrodiagnostic study, Peripheral neuropathy

INTRODUCTION

Vitamin D deficiency in adults is a common problem worldwide [1]. Nonskeletal effects of vitamin D play an important role in growing interest for vitamin D in recent years [2]. Vitamin D should be considered for immune system, cell growth, protein synthesis, muscle function [3, 4] and musculoskeletal pains [5]. Moreover, joint pain is prolonged and gets severe under vitamin D deficiency [6].

Vitamin D, a steroid hormone, which is produced in the body. Exposure to sunlight for 10-20 minutes meets daily need of human body for this vitamin. Serum levels of less than 18 nmol/mL are considered as severe deficiency,18-23 nmol/mL as average deficiency, 23-36 nmol/mL as mild deficiency and over 36 nmol/mL is considered as sufficient level of vitamin D [7,8].

The most recognized function of vitamin D is maintaining the balance of calcium and phosphorus, in three ways : 1) increases calcium and phosphorous absorption. 2) along with PTH and estrogen transport calcium and phosphorus from bones into blood circulation by increasing activity of osteoclasts and increasing the number of new osteoclasts through cell differentiation. 3) increases tubular reabsorption of calcium and phosphate in kidneys [7,8].

Receptor of this hormone (vitamin D) is not only in bone and kidney but also in gonads, pancreas, breast, cardiovascular system, brain and immune cells such as macrophages and lymphocytes B and T and monocytes. All these target tissues can convert 25-hydroxy vitamin D to 1, 25-dihydroxyvitamin D [9, 10].

In addition, there is a significant relationship between low levels of vitamin D and inflammatory markers {including Interleukin (IL)-6 to IL-10 ratio} in middle-aged people [11]. Finally, peripheral neuropathies should be considered as an outcome of vitamin D deficiency [12].

The most common peripheral compressive neuropathy of upper limb is entrapment of median nerve at the wrist. CTS is a painful debilitating condition of the hand and arm. The mechanism of injury is pressure on the median nerve in the wrist which causes irreversible nerve damage leading to intractable pain, numbness, and muscle weakness in the areas supplied by the median nerve if left untreated [12].

Median nerve in the wrist travels under the flexor retinaculum over wrist bones. If the space is narrow, median nerve will experience pressure; this pressure will lead to motor and sensory dysfunction in the fingers [9]. Eight superficial and deep tendons plus flexor pollicis longus (FPL) tendon and median nerve are in the carpal tunnel. Any cause which reduces space of the tunnel or increases volume of tissues inside the tunnel leads to CTS symptoms [12,13].

Risk factors of CTS include obesity, alcoholism, diabetes, hypothyroidism, narrow carpal tunnel, occupational causes and is often a consequence of injury to the wrist and conditions that put pressure on the median nerve at the wrist [14,15].

CTS is mainly characterized by numbness; however, some patients complain about pain and paresthesia in the median nerve branches dermatomes (thumb, index and middle). In some cases, pain

precedes paresthesia and may even spread to forearm and elbow, decreasing quality of life and highlights treatment of this disease [16,17].

In early stages, supportive treatments such as wrist splints, braces, physiotherapy, exercise or non-steroidal anti-inflammatory drugs (NSAIDs) may have an important role in reducing severity of disease. Surgical treatment may be required as the only permanent solution in severe cases [18,19].

However, some patients do not respond well to these treatments. Although Vitamin D can be helpful as an effective factor in improving treatment process, no interventional study has been conducted so far for this purpose.

In 2014 there was a study which investigated the serum level of vitamin D in intractable CTS patients and the result shows low serum level of this vitamin in these patients [20].

Vitamin D can be suggested for improvement and treatment of CTS. This study is planned keeping this goal in mind accordingly, investigates the effect of treatment with vitamin D in intractable CTS patients with hypovitaminosis D referred to the Physical Medicine and Rehabilitation Clinics of Shiraz University of Medical Sciences in 2015. The developed hypotheses of this study include:

1. Is treatment with vitamin D in intractable CTS patients with hypovitaminosis D effective on Boston score?
2. Does treatment with vitamin D in intractable CTS patients with hypovitaminosis D improve Slat ?
3. Does treatment with vitamin D in intractable CTS patients with hypovitaminosis D improve Mlat ?
4. Is treatment with vitamin D in intractable CTS patients with hypovitaminosis D effective on NCV ?

MATERIALS AND METHODS

This was an interventional, study. The study population included 50 intractable CTS patients with hypovitaminosis D; BMI in normal range (19-24 kg/m^2); age: 20-50 years; Intractable CTS Patients who had been six weeks under standard treatment (NSAID, rest, splint and physiotherapy and showed dissatisfaction with treatment such as parasthesia, numbness, pain) and permission of the patients to participate in the study recruited by using convenience sampling method as inclusion criteria. Exclusion criteria included severe CTS, known case of trauma and tumor in the wrist and hand, diabetes mellitus, hypothyroidism, radiculopathy, peripheral neuropathy, known case of chronic liver and renal disease, pregnancy, lactation period, metabolic diseases, patients receiving Vitamin supplements, rheumatoid arthritis, acromegaly and lack of consent to participate.

This study evaluated patients diagnosed to have CTS by electrodiagnostic study and physical examinations including pressure, Phalen's and Tinel tests who have not responded to standard management of CTS for six weeks. They had hypovitaminosis D (25(OH) Vitamin D serum level less than 30 ng/dL) determind by HPLC method and none of the exclusion criteria such as diabetes and hypothyroidism referred to the Physical Medicine and Rehabilitation Clinics of Shiraz University of Medical Sciences in 2015.

Research plan was described for the patients; informed consent was obtained. A questionnaire was recorded for each patient based on personal information, medical history and underlying diseases. Calculation of functional and symptom-related Boston scores and electrodiagnostic data before and after treatment is a key component of this questionnaire.

A dose of 50000 IU Vitamin D3 was given orally per week for 12 weeks [21]. And finally reevaluation of patients was done within one week of taking the last dose of Vitamin D3 by calculating Boston functional and symptom-related scores after treatment and redoing electrodiagnostic study and recording in the boston questionnaire.

All initial and final assessments were done by a doctor blinded to the project and its results (doctor did not know anything about the consumption of Vitamin D supplements). It is noteworthy that all patients continued their supportive treatments during the study.

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences on 2015-10-04 with the reference number of IR.SUMS.REC.1394.120. And also registered in Iranian Registry of Clinical Trials on November 6, 2015 with the registration number of IRCT2015100624384N1.

STATISTICAL ANALYSIS

A questionnaire was designed to collect data including age, gender, BMI, past medical history, drug history, exclusion and inclusion criteria, boston score before and after treatment with Vitamin D, serum level of Vitamin D before treatment. Data was put on the Excel 2013 software. Pairwise t-test (α=0.05) and SPSS version 20.0 were used to analyze data.

RESULTS

[Table/Fig-1] reports distribution of age, BMI and Vitamin D of the studied patients.

Mean age of the patients was 44 years (±8.5); mean level of Vitamin D was 19.1 ng/dL (±6.3). Mean BMI of the patients was 21.8 kg/m^2 (±1.8). Lower and upper bounds of age were 22 and 65 years, respectively. Lower and upper bounds of vitamin D were 28 and 5 ng/dL, respectively. Lower and upper bounds of BMI were 29 kg/m^2 and 19 kg/m^2, respectively.

Based on results and statistical analysis that shows in [Table/Fig-2], the mean Boston symptom score before treatment was (3.45±0.90) which reduced to (2.04±0.71) after treatment. The mean Boston function score before treatment was (3.41±0.85) which reduced to (2.08±0.82) after treatment. Mean Slat values before treatment was (4.5±0.57) which reduced to (3.89±0.53) after treatment. Mean Mlat values before treatment was (5.03±0.49) which reduced to (4.66±0.44) after treatment. Mean NCV values before treatment was (27.02±4.64) which reduced to (32.58±4.54) after treatment. There was a significant difference between Boston scores, Slat, Mlat and NCV values before and after treatment with Vitamin D (p-value=0.0001).

DISCUSSION

It is now well recognized that Vitamin D has many biological functions beyond its classical role in bone metabolism [4]. Some CTS patients did not respond well to standard treatments which were used and to identify effective factors regarding lack of response will be helpful.

The study by Willis KS et al., concluded the need for attention to the epidemic of Vitamin D insufficiency, even in outdoor athletes, and support a possible association between decreased Vitamin D status and one particular marker of inflammation. Regression analysis revealed a significant inverse association between 25-hydroxy

	Age (year)	Vitamin D (ng/dL)	BMI (kg/m^2)
Mean	44.0200	19.1000	21.8100
Sample size	50	50	50
Std. deviation	8.54159	6.34791	1.82357
Median	44.0000	20.000	22.0000
Lower bound	22.00	5.00	19.00
Upper bound	65.00	28.00	29.00

[Table/Fig-1]: Distribution of age, BMI and vitamin D of the studied patients.

Vitamin D and Tumor Necrosis Factor (TNF) but not between 25-hydroxy vitamin D and the remaining cytokines, Interferon gamma(IFN-γ), IL-4, and IL-10 [4].

A study by Moghaddami M et al., showed that arthritis is more severe and prolonged in vitamin-D deficiency, that vitamin-D deficiency

promotes accumulation of CD4(-) DCs in synovium during arthritis and that a gene-expression profile is likely to contribute to the observed increased severity and duration of arthritis [6]

Effect of vitamin D is notable in reducing inflammatory factors such as IL-6 and IL-10 and improving neuropathy caused by CTS which results from vitamin D deficiency [11].

A study by Kulie T et al., showed that vitamin D deficiency is an independent risk factor for diabetic peripheral neuropathy, and further studies are required to confirm if Vitamin D supplementation could prevent or delay the onset. Mean (SD) vitamin D level was significantly lower in those with neuropathy [36.9 (39.9) nmol/L] compared with those without neuropathy [58.32 (58.9) nmol/L] and 81.5% of patients with neuropathy had vitamin D deficiency compared to 60.4% of those without neuropathy [7].

		Mean	n	Std. Deviation	Std. Error Mean	Sig.(2tailed)
Pair 1	Bostons ^{b}	3.4540	50	0.90491	0.12797	0.0001
	Bostons ^{a}	2.0400	50	0.71142	0.10061	
Pair 2	Boston ^{fb}	3.4140	50	0.85117	0.12037	0.0001
	Boston ^{fa}	2.0800	50	0.82239	0.11630	
Pair 3	Slat^{1}	4.5020	50	0.57410	0.08119	0.0001
	Slat^{2}	3.8900	50	0.53347	0.07544	
Pair 4	Mlat^{1}	5.0320	50	0.49670	0.07024	0.0001
	Mlat^{2}	4.6620	50	0.44073	0.06233	
Pair 5	NCV1	27.0200	50	4.46981	0.63213	0.0001
	NCV2	32.5800	50	4.54497	0.64276	

[Table/Fig-2]: Results of pairwise t-test in nerve strip parameters and initial and final points of Boston Questionnaire.
^{b}: Boston symptom score before treatment; ^{a}: Boston symptom score after treatment; ^{fa}: Boston function score after treatment; ^{fb}: Boston function score before treatment; ^{1}: Before treatment; ^{2}: After treatment; NCV1 :Nerve Conducting Velocity before treatment; NCV2: Nerve Conducting Velocity after treatment

Oh YM et al., evaluated six CTS patients and compared them with six controls. They reported down regulation of vitamin-D binding protein (VDBP) in CTS patients compared to controls, suggesting that vitamin D is involved in physiopathogenesis of CTS. This is consistent with the current study [22].

This element, as a fat-soluble vitamin, plays an important role in bone metabolism and seems to have some anti-inflammatory and immune-modulating properties [20]. In addition, recent epidemiologic studies have observed relationships between low vitamin D levels and multiple disease states [20]. Low vitamin D levels are associated with increased overall and cardiovascular mortality, cancer incidence and mortality, and autoimmune diseases such as multiple sclerosis [20].

Considering notable effect of vitamin D in reducing musculoskeletal pain and numbness, these can be considered as a favorable result of vitamin D [5]. A suggested treatment, which uses vitamin D supplement, has not been conducted yet.

Results showed a significant difference between Boston scores, Slat, Mlat and NCV values of median nerve before and after treatment with vitamin D (p-value=0.0001). It has been confirmed that vitamin D has considerdable effect on health promotion; moreover, nonskeletal effects of vitamin D highlight its application. Considering pathogenesis of CTS, it can be concluded that vitamin D can improve CTS in different aspects.

LIMITATION

During the study, some patients quit the supplementation with Vitamin D and some didn't came for follow-up.

CONCLUSION

Treatment with vitamin D improves clinical and electrodiagnostic conditions of intractable CTS patients with hypovitaminosis D. It is recommended to conduct further studies with larger samples in order to confirm current findings. Moreover, comparative interventional studies using clinical trials and comparing with placebo can provide better results.

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