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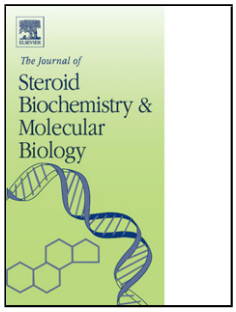

The effect of Vitamin D replacement on spinal inhibitory pathways in women with chronic widespread pain

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The effect of Vitamin D replacement on spinal inhibitory pathways in women with chronic widespread pain

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Highlights:

- Central pain sensitization accompanies chronic widespread pain
- Cutenous silent period (CSP) is an objective measure of central sensitization
- Vitamin D replacement improves pain and quality of life in chronic widespread pain
- Vitamin D replacement does not change CSP parameters

Abstract

Vitamin D replacement helps in pain reduction in patients with chronic widespread pain (CWP). But the current literature lack studies that investigate its mechanism. Cutaneous silent period (CSP) is the electrophysiologic analog of the spinal inhibitory pathways and an objective method to document their involvement. This study aims to show if vitamin D replacement has an effect on the spinal inhibitory pathways through CSP parameters. Female patients who have CWP with vitamin D deficiency were included. Patients received an 8-week replacement therapy of vitamin D. Patients' pain were evaluated using the visual analog scale (VAS) and Leeds assessment of neuropathic symptoms and signs pain scale (LANSS). Quality of life with Nottingham Health Profile (NHP) and CSP parameters were also recorded before and after treatment. A total of 51 patients were included in the final analyses. The mean age of the patients was 44.3 $\pm$ 12.7 (minimum 18-maximum 65). Mean symptom duration was 13.1 $\pm$ 6.7 (minimum3-maximum 24) months. Patients' mean BMI was 21.6 $\pm$ 3.9 (minimum 18.0 maximum 29.1). Patients' median VAS and LANSS scores

decreased significantly ($p < 0.01$) and NHP scores improved significantly in all subsets ($p<0.01$). Vitamin D replacement did not significantly change CSP latency and duration ($p=0.06$ and $p=0.12$).Vitamin D replacement does not seem to work via modifying the spinal inhibitory pathways that are involved in the formation of the cutaneous silent period. This is the first study to objectively investigate the effect of vitamin D replacement on central sensitization mechanisms.

Keywords: central sensitization, chronic widespread pain, cutaneous silent period, pain, vitamin D

Introduction

Chronic widespread pain (CWP) is a condition characterized by the presence of long-standing diffuse musculoskeletal pain and frequently associated with other physical symptoms such as fatigue, psychological distress, and concentration problems [1]. It is defined as pain that lasts more than three months and located axially, above and below the waist, and on both sides of the body [2]. It is the main feature of fibromyalgia but can also accompany other such problems as myofascial pain syndrome, chronic pelvic pain, irritable bowel syndrome, and migraine [3, 4] . The term CWP is more in accordance with the upcoming ICD-11, which classifies CWP under the heading of chronic primary pain [5]. Nowadays, CWP is considered to be the disorder of the mechanisms that process pain in the central nervous system. The impaired central processing decreased modulation, and enhanced peripheral sensitivity causes the patients to be in a constant state of pain, to interpret non-painful inputs as painful (allodynia) and painful inputs at a higher intensity (hyperalgesia) [6]. The pathophysiologic mechanisms are still quite obscure, and the lack of a cure, combined with the constant state of pain make patients' life miserable.

The ongoing debate about the effectiveness and its potential mechanisms keep vitamin D at the center of attention. A recent Cochrane review showed that it might not be superior to placebo in chronic painful conditions in adults [7] . A recent review reflects these results and state that it might play a more critical role in decreasing tissue inflammation, rather than altering sensitivity in the nociceptive system [8]. But it must be kept in mind that the presence of vitamin D deficiency is frequent among patients with CWP [9]. Replacing is still recommended in the current clinical practice as an adjunct therapy to alleviate pain in

patients with CWP [10]. While the exact mechanisms for the effect of vitamin D are still mostly unknown, a recent study showed that vitamin D replacement can work through opioid receptors in rats [11]. In humans it has been shown to have some impact on central pain modulation systems using various methods that assess these processes such as pressure pain sensitivity [12]. These methods are valid but still rely on patient reports. That is why being able to measure the activity of the central nervous system (CNS) on central sensitization an objective, measurable evidence of the change of central pain processing is crucial. Additionally, considering how little we currently know of the pathophysiology of CWP and the full range of effects of vitamin D on the body, we are not still looking for clues to show us the potential pathways of the effectiveness of vitamin D within the context of CWP.

Cutaneous silent period (CSP) is a brief pause in muscle action potentials following strong stimulation of the cutaneous nerve during a sustained voluntary contraction and is considered a protective reflex mediated by the spinal inhibitory circuit and reinforced by parallel modulation of the motor cortex [13]. Since spinal cord is at the center of all pain processing pathways, spinal inhibitory circuit dysfunction is common in all chronic pain conditions [14, 15]. CSP is the body's inhibitory response to painful stimuli, preventing the body to undergo more damage by blocking muscle contraction as the painful stimuli suggest a threat. This will prevent further tissue damage in unpleasant conditions, but when altered, it will fail to impede with the action, creating more tissue damage and causing a paradoxical increase in pain. Elicitation of CSP is minimally discomforting and easy to administer with standard electromyography (EMG) equipment and can show us the state and the changes in pain processing in CNS. Moreover, it gives objective, numeric results as the latency to the

beginning of the response and the entire duration of the response. It has previously been shown to be lengthened in patients with chronic pain syndromes, and it can reflect the state of central pain processing [16]. But the change in its parameters with vitamin D replacement in CWP has never been investigated. If vitamin D replacement has an impact on pain and CSP parameters, it would be logical to conclude that it may be effective on central pain processing mechanisms. This study aims to investigate the effects of vitamin D replacement therapy on the CSP parameters in patients with CWP.

Materials And Methods

Patient selection

Female patients who have been diagnosed in the outpatient pain clinic with CWP with vitamin D insufficiency or deficiency, between the ages of 18-65 have been included in the study between February 2018 and June 2018. Only women were included in the fashion of previous studies on this subject and to have a homogenous patient population[17, 18] . Patients' age, weight, height and duration of their symptoms were recorded. Their body-mass indexes (BMI) were calculated according to their height and weight. The patients were included the study before receiving any other primary medications for their CWP and were excluded if they have been on medications that might alter central pain sensitivity such as selective serotonin reuptake inhibitors, tricyclic antidepressants and/or antiepileptics. Other exclusion criteria were 1) presence of any form of neuropathy such as entrapment syndromes or polyneuropathies 2) co-morbidities that can inherently cause vitamin D deficiency such as cystic fibrosis or intestinal disorders 3) presence or history of any

inflammatory rheumatologic or metabolic diseases such as rheumatoid arthritis or osteomalacia 4) history of any surgery within the last six months 5) presence of central nervous system (CNS) disorders such as stroke or multiple sclerosis 6) presence or previously diagnosed psychiatric disorders such as major depressive disorder and somatoform disorders 7) having a BMI above 30.

The study was undertaken in accordance with the Declaration of Helsinki and the European Medicines Agency Note for Guidance on Good Clinical Practice. Patients provided written informed consent before initiating study procedures. Marmara University ethical committee approved the study. This study is registered to the Clinical Trials Registry with the reference number NCT03420378.

Vitamin D measurement and replacement

Serum 25-hydroxyvitamin D [25(OH)D] levels were determined by chemiluminescence using Nichols Advantage competitive binding assay (San Juan Capistrano, California, USA). A 25(OH)D level between 10- 20 ng/mL was accepted as insufficient, while a vitamin D level below 10 ng/ml was accepted as deficient in this study. Patients received eight weeks of oral 50.000 IU/week of vitamin D3 replacement therapy and re-evaluated at the end of their treatment [19].

Pain Assessment

A 10-centimeter visual analog scale (VAS) was used to determine the overall pain levels of the patients before and after treatment. Along with VAS, Leeds assessment of neuropathic

symptoms and signs pain scale (LANSS) was also used to define the presence of neuropathic component before and after treatment. LANSS was developed by Bennett in 2000 to evaluate the neuropathic components of pain. It has one part of pain questions and a part of assessing touch and pinprick sensation. On the LANSS Pain Scale, a score of 12 or more was classified as neuropathic pain, and a score under 12 was classified as nociceptive pain. It does not reflect the severity of pain or neuropathic pain itself, just the presence and absence of it. It is easily administered and validated in Turkish [20].

Quality of Life Assessment

The first part of the Nottingham Health Profile (NHP) was used as the quality of life assessment. The validity and reliability for the Turkish population were made by Kucukdeveci et al. [21]. The functional status of the patients was measured by requiring a “yes” or “no” answer to 38 questions. It has 6 subheadings: energy (3 items), pain (8 items), emotional reaction (9 items), sleeping (5 items) social isolation (5 items), and physical mobility (8 items). Each dimension has a score in the range between 0 and 100 where zero indicates good health and 100 indicates poor health and each statement is scored using weighted values.

Nerve conduction studies

Electroneurography was applied to rule out possible accompanying pathologies such as carpal tunnel syndrome and polyneuropathies to eliminate these patients before continuing with the CSP. A researcher experienced in electrophysiology who was blinded to the clinical information of the patients performed all electrophysiological testing (GA). Median and

ulnar motor and sensory nerve conduction studies (NCSs) were evaluated bilaterally. NCSs were performed with Medtronic–Keypoint (Skovlunde, Denmark, 2007) device under normal conditions (i.e., standard room temperature was around 25 °C, and limb temperature was approximately 32 °C) with a sweep speed of 5 ms/ division, sensitivity of 5 mV/division, filters set at 2 Hz and 10 kHz, and stimulation duration of 0.1 ms. Sensory nerve conduction study for median nerve was performed from the third finger with a set distance of 14 cms between the stimulation and the recording. Similarly, ulnar sensory nerve conduction studies were performed from the fifth finger with a set distance of 14 cms between the stimulation and the recording. Median and ulnar motor nerve distal latencies, median and ulnar motor nerve conduction velocity, compound muscle action potential (CMAP) amplitudes at the wrist and elbow were measured. Median motor NCSs were recorded with single-use surface electrodes from abductor pollicis brevis muscle, and ulnar motor NCSs were also marked with surface electrodes from abductor digiti minimi. The distance between the recording and stimulation points were set at 8 cms. The latencies were marked at the onset of the first negative peak, and the amplitudes were determined from peak to peak. If there were problems with the sensory or motor conduction studies that would indicate polyneuropathy, lower extremity nerve conduction studies including tibial nerve and peroneal nerve motor conduction studies and sural nerve sensory conduction studies were also performed. Patients who did not have any pathologies in any of the nerve conduction studies were directed for CSP investigation.

Cutaneous silent period

Cutaneous silent period recordings were performed in the right upper extremity using surface recording electrodes. Filters were set at 2 Hz to 10 kHz, sensitivity was set at 200mV,

and sweep speed was set at 200 ms. The stimulating electrode was placed on the index finger, and the surface electrodes were placed on the abductor pollicis brevis (APB) muscle. During steady thumb abduction at approximately 50% of the maximal contraction, 10 consecutive painful electrical stimuli of standard 25 mA intensity and 0.5 ms duration were applied to the index finger and responses were superimposed. The trace of the responses on the screen was considered to provide submaximal constant contraction during voluntary contraction. The beginning and the end of the CSPs were identified visually by the abrupt cessation and the return of the EMG activity. CSP latency was marked as the onset of the silent period. CSP duration was calculated as the time interval between the beginning and end of the CSP.

Statistical analyses

A priori sample size analyses were performed with G-power software package (ver. 3.1.6; Franz Faul, Kiel University, Kiel, Germany). To reach an effect size of 0.7 and a power of 95%, with an a= 0.05, it was calculated that approximately 45 patients needed to be included in the final analyses. All other statistical analyses were performed using the Statistical Package for the Social Sciences version 22.0 (IBM Corp.). Descriptive statistics were calculated and consisted of the mean, standard deviation (SD), 95% confidence interval (CI) and median. Tests of normality were done using the Shapiro-Wilks normality test. According to the distribution of the variable, paired sample t-test or Wilcoxon test were used for continuous variables. The median values were reported to give a better understanding of the data in Wilcoxon analyses. When analyzing the presence of neuropathic pain after the treatment, patients' LANSS scores were calculated, and patients' neuropathic pain were determined

absent or present. The significance of these changes was calculated with the McNemar test since it is a within-subjects change of a dichotomous value. The level of significance was set at $p<0.05$.

Results

A total of 51 patients were included in the final analyses, and patient recruitment flow-chart can be seen in Figure 1.

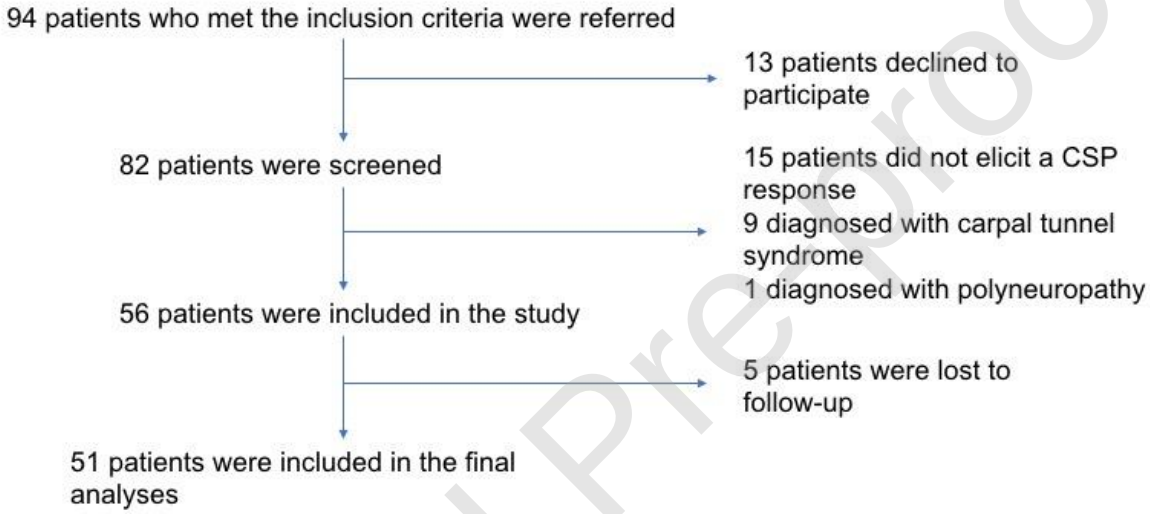

Figure 1: patient recruitment flowchart

The mean age of the patients was 44.3 ± 12.7 (minimum 18 years- maximum 65 years). Mean symptom duration was 13.1 ± 6.7 (minimum 3 maximum 24) months. Patients' mean BMI was 21.6 ± 3.9 (minimum 18.0 maximum 29.1). Patients' vitamin D levels, VAS, and LANSS scores have changed significantly after treatment. Before treatment, mean CSP latency was 74.2 ± 12.5 ms while it was 71.4 ±10.6 ms after the therapy (p= 0.06). CSP duration did not vary significantly either, as median CSP duration was 37.6 ms before the

treatment and 42.1 ms after the treatment (P=0.119). These findings are summarized in Table 1.

Table 1. The change of 25(OH)D levels, VAS and LANSS scores and CSP latency and durations before and after treatment

Parameters	Before treatment	After treatment	Significance
25(OH)D levels (ng/ml) mean ± SD	13.2 ± 4.3	33.3 ± 5.2	Mean ± SD of differance (95% CI) = 19.9 ± 6.3 (18.1 - 21.0) P< 0.001
VAS median	7	3	z= 5.6 P< 0.001
LANSS median	13	5	Z=4.6 P<0.001
Presence of neuropathic pain	30 present 21 absent	7 present 44 absent	P< 0.001
CSP latency (ms) mean ± SD	74.2 ± 12.4	71.4 ±10.6	Mean ± SD of difference (95% CI) = 2.9 ±10.8 (-0.19 – 5.92) P= 0.06
CSP duration (ms) median	37.6	42.1	P=0.12

SD: standard deviation CI: confidence interval VAS: visual analog scale LANSS: Leeds assessment of neuropathic symptoms and signs pain scale CSP: cutaneous silent period

A subgroup analysis was performed for patients with vitamin D deficiency and vitamin D insufficiency. It has shown that there were no significant changes in latency and duration in these subgroups either (Table 2).

Table 2: Change in latency and duration in vitamin D deficiency and insufficiency subgroups.

Parameter / Group	CSP latency before treatment Mean ± SD	CSP latency after treatment Mean ± SD	Change and significance Mean ± SD (%95CI)	CSP duration before treatment Mean ± SD	CSP Duration after treatment Mean ± SD	Change and significance Mean ± SD (%95CI)
Vitamin D deficiency (n=18)	75.6 ± 12.1	72.8± 9.8	-1.8 ± 9.4 (-3.0 - 6.6) P=0.44	41.0 ± 13.5	40.5 ± 9.7	-0.5 ± 16.1 (-8.8 - 7.8) p=0.89
Vitamin D insufficiency (n=33)	74.0 ± 12.0	70.6± 18.1	-3.4 ± 11.5 (-0.7-7.4) p=0.09	Median= 37.6	Median = 47.8	P=0.07 Z= 1.8

CSP: cutaneous silent period

Patients NHP scores showed significant improvements in all subsets except social-life after the treatment (Table3).

Table 3: Changes in Nottingham Health Profile (NHP) subscales after the treatment. All values are median.

NHP subset	Before treatment	After treatment	P and z values
NHP energy	100	60.8	Z= -4.4 P<0.0001
NHP pain	59.8	26.0	Z= -5.3 P<0.0001
NHP emotional	43.5	19.1	Z= 4.7 P<0.0001
NHP sleep	28.7	0	Z= 4.2 P<0.0001
NHP social	0	0	P>0.05
NHP physical	32.5	11.2	Z= 4.8 P<0.0001

Discussion

This study has shown that vitamin D replacement positively affects the pain levels and quality of life in patients with CWP. There were no significant changes in CSP parameters with vitamin D replacement, namely in its latency and duration. These results imply that in whichever way vitamin D is effective in CWP, it does not seem to be via the spinal inhibitory circuit that elicits the inhibition of muscle contraction with painful stimuli. Previously, Känel et al assessed the relationship between vitamin D and central hypersensitivity in patients with chronic pain by using algometry and widespread pain index [12]. They have demonstrated that low vitamin D levels play a role a role in heightened central sensitivity.

However, both of these outcome measures are patient-reported and can be misleading due to being dependent to both the assessor and the subject. Straube et al[22] proposed that current evidence does not allow us to conclude that vitamin D is relevant to chronic pain and to overturn this verdict, Trials should use standardized, validated and objective pain outcomes. And also, Roesel[23] proposed that the relation between vitamin D and chronic pain can be clarified by taking into account of effect of vitamin D replacement on central nervous system because pain inhibition by the central nervous system is dysfunctional in the vitamin D deficient state, and once ascending pain signaling pathways are engaged, simple vitamin repletion may not suppress persistent chronic pain. The present study has investigated the role of vitamin D deficiency and replacement on spinal pain pathways. Considering what little is known about the exact mechanism of vitamin D in pain, the findings of this study are important to rule out its potential effect on spinal inhibitory circuits, and therefore on central pain sensitization mechanism. This is the first study to do so, using objective electrophysiologic measurements. Also, including a patient population with CWP, it has been aimed to find a common ground of pain and investigate vitamin D in this new context of pain as the disease itself. The improvement of pain has reflected as a significant improvement in the patients' quality of life. These findings are in accordance with the existing literature, showing that vitamin D aids in pain reduction in patients with CWP, and this reflects as an improvement in quality of life in other series [18, 24]. Therefore it is important to address vitamin D deficiency in patients with a high risk, such as patients with CWP and the elderly, because they are both groups that benefit from this treatment significantly [25, 26]. This study has centered its outcomes around pain, omitting the muscle wasting changes and fatigue which are seen in patients with CWP. However, changes in NHP sleep, energy, and physical subsets can serve as a proxy. Further research can also focus on

these aspects of CWP and alterations of these domains specifically with vitamin D replacement. The lack of change in the social subset might be attributed to the socio-economical status of the patients recruited, but this aspect is not within the aim of this study.

CSP parameters have already shown to be affected in various kinds of pain pathologies such as myofascial pain syndrome and fibromyalgia. Notably, the increased latency of CSP responses is prominent. The median latency of median nerve CSP in healthy females has been established as 66.0 ms [27]. In this study, the latencies are more prolonged than 66.0 with a mean value of 74.2 ms before the treatment and 71.4 ms after the treatment. These findings are in correlation with the existing literature that involves other patients with chronic pain syndromes [28, 29]. The lengthening of CSP latency has been attributed to the abnormal function of spinal neurons that take part in the polysynaptic pain modulation pathways in medulla spinalis [30]. Vitamin D does not seem to be effective in improving the dysfunction of the spinal inhibitory neurons.

The average values of CSP duration had been depicted as 55.0 ms of the median nerve in healthy females [27]. In this study median values of CSP duration is 37.6 before the treatment and 42.0 after the procedure, which are both shorter than average values. The duration of CSP has been shown to change in previous studies, but not all of them showed decreases in duration. A recent study demonstrated a prolonged CSP duration while another study did not show a significant difference [16, 29]. The duration of the CSP is thought to be affected by the firing of the motor neurons that are controlled by this spinal inhibitory network. The impaired inhibition mechanism caused by the dysfunction of spinal interneuronal networks, which fails to stop firing of these motor neurons, decreases the

duration of CSP [31]. Therefore, it is suggested that these two mechanisms are intertwined and usually occur together. According to this theory, it also makes sense that when vitamin D is ineffective in modulating the inhibitory neurons, it would also fail to change the duration of CSP significantly. But the current literature is not adequate to derive specific results, and more descriptive studies will be helpful to improve the knowledge of these mechanisms and decrease the current discrepancies. Patients who had been using drugs such as gabapentinoids and anti-depressants were excluded from this study to make sure that the effect, or lack thereof, can be attributed to vitamin D. This inevitably limits the usefulness of the results in the clinical setting.

One of the limitations of this study is that a single vitamin D replacement strategy was used without a maintenance period. The negative results of this study can merely be the result of inadequate levels of vitamin D levels within the CNS even though the blood levels of vitamin D is adequate after treatment. However, it is of importance to minimize the seasonal changes of vitamin D, which requires a shorter period of follow-up. Moreover, guidelines on designing a study in patients with chronic pain suggest a 7-week follow-up period is apt [32]. Previous studies that investigated the effect of vitamin D on multiple sclerosis have used different replacement strategies with higher doses [33, 34]. There are understandably no human studies about the tissue concentrations of vitamin D within the CNS after its administration. This study has implemented the most recent guideline, but a different treatment strategy might be warranted for modulating the CNS in patients with CWP as well. But researchers must be cautious in administering higher doses in patients with CWP, because it can worsen the symptoms. It has been documented that high doses of vitamin D can alter gut microbiome, which can in turn increase pro-inflammatory mediators that

increase pain [35]. Another limitation of this study is that it did not have a placebo group due to guideline recommendations for avoiding placebo-controlled trials specifically in patients with pain, because they cause serious discomfort for participants without potential for benefit to the individuals [32]. Although the effectiveness of vitamin D in CWP has been demonstrated in the literature as mentioned before, the mechanisms are not shown appropriately, and data about the potential placebo effect of vitamin D are still unclear. The current data about the effect of vitamin D replacement for patients with CWP are conflicting, with one study showing a superior effect of vitamin D replacement in pain reduction when compared to placebo, and another has not described a significant difference with vitamin D replacement [36, 37].

Conclusion

Vitamin D replacement improves pain and quality of life in patients with CWP, while it does not seem to affect spinal inhibitory pathways. The primary influence of vitamin D may be on other, more peripheral parts of the nervous system, but more data is required to reach a definite opinion about the mechanism of vitamin D on the pain process. To the best of our knowledge, this is the first study that has aimed at showing an effect on CSP by vitamin D replacement in patients with CWP. Future placebo-controlled studies with different replacement strategies are warranted.

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